1470-P

Correlation of Serum Folate Levels with Glucose Levels in Gestational Diabetes Mellitus (GDM) in Relation to Vitamin B12 Levels

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In non-pregnant type 2 diabetes, high serum folate levels have adverse effects on metabolic markers in vitamin B12 deficient setting, whereas folic acid supplementation can improve glycaemic control in some patients.

This study aims to examine the association between serum folate levels and plasma glucose levels in normal and insufficient B12 (<150pmol/l) GDM. This retrospective study included GDM identified between 2009-2012 in a district general hospital, UK. All GDM received folic acid (40ug/day) as routine antenatal care. Serum folate, B12 and homocysteine were measured at 24-28 weeks and compared with glucose levels at diagnostic and postpartum OGTT.

Total of 188 pregnancy included, 60 GDM (31.9%) were B12 deficient and 31 GDM (17%) had high folate levels (>16ug/l). In both normal and B12 deficient GDM, plasma homocysteine had significant negative correlation with folate (r=-0.38 vs. r=-0.44), and not B12 levels. There was a significant inverse association between serum folate and fasting glucose levels at both diagnostic and postpartum OGTT. The association was significant in normal B12 GDM and not B12 deficiency, and was independent of age, BMI and parity.

Our findings suggest that the effects of serum folate levels on fasting glucose levels may differ by vitamin B12 status and highlight the importance of normal vitamin B12 levels for folate to act on glycaemic levels.

Table. Pearson's Correlation-Plasma Glucose Correlates with Serum Folate Levels.

	All GDM		Normal B12GDM		B12 insufficient GDM	
	mid-pregnancy (n=188)	Postpartum (n=67)	mid-pregnancy (n=128)	Postpartum (n=45)	mid-pregnancy (n=60)	Postpartum (n=22)
fasting	-0.17(<0.05)	-0.26(<0.05)	-0.19(<0.05)	-0.36(<0.01)	-0.08 (NS)	-0.02(NS)
2hr postprandial	-0.14(<0.05)	-0.14(NS)	-0.18(<0.05)	-0.20 (NS)	-0.02(NS)	-0.08(NS)
BMI	-0.23(<0.01)		-0.29(<0.01)		-0.04(NS)	
Multiple regression for fasting glucose						
	All GDM		Normal B12GDM		B12 insufficient GDM	
folate	mid-pregnancy (n=188)	Postpartum (n=67)	mid-pregnancy (n=128)	Postpartum (n=45)	mid-pregnancy (n=60)	Postpartum (n=22)
β	-0.04(<0.05)	-0.04(<0.05)	-0.04(<0.05)	-0.06(<0.05)	-0.01(NS)	-0.003(NS)
Adjusted β (Age,BMI,Parity)	-0.03(<0.05)	-0.05(<0.05)	-0.04(<0.05)	-0.07(<0.01)	-0.01(NS)	-0.007(NS)

NS=Not Significant.

1471-P

Sedentary Behavior Is Associated with Improved Cytokine Profile but Not with Glucose or Lipid Metabolism in Obese Pregnant Women

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Sedentary behavior is an independent risk factor for the metabolic syndrome, but the role of sedentary behavior in the development of gestational diabetes is unclear.

This longitudinal cohort study tested the hypothesis that less sedentary behavior is related to better insulin sensitivity, lipid and cytokine profile in obese pregnant women.

Among 46 overweight and obese pregnant women, fasting blood was taken at 15, 24 and 32 weeks of gestation, and a 100 g oral glucose tolerance test was performed at 24 and 32 weeks. Fasting levels of glucose, insulin, total cholesterol, HDL, LDL, triglycerides were measured, as well as cytokines. Insulin sensitivity, first and second phase insulin response were calculated. Sedentary behavior was measured objectively using accelerometers. The relationship between sedentary behavior and metabolic outcomes were assessed using linear regression analysis.

Women spent about 60% of their time sitting throughout pregnancy. In cross sectional analyses, an association of sedentary time at 15 and 24 weeks with increased total cholesterol and HDL was found. Changes in sedentary time were not associated with glucose metabolic or other lipid outcomes, but increased sedentary time was associated with lower CRP and leptin levels, and with higher adiponectin levels at 32 weeks of pregnancy.

In conclusion, no consistent longitudinal relationship between sedentary habits of obese and overweight pregnant women with glucose or lipid metabolism was found. Increases in time spent sedentary in pregnancy were associated with improved cytokine profile. Whether increasing sedentary time is indeed beneficial for metabolism of overweight and obese pregnant women needs to be assessed in further studies.

EPIDEMIOLOGY—AGING

Guided Audio Tour: Diabetes and Aging—It's All the Rage! *(Posters: 1472-P to 1479-P), see page 15.*

1472-P

Disability-Free Life-Years Lost due to Diabetes Mellitus among Older U.S. Adults

BARBARA BARDENHEIER, JI LIN, XIAOHUI ZHUO, MOHAMMED K. ALI, TED THOMPSON, EDWARD W. GREGG, *Atlanta, GA, North Wales, PA*

Increases in diabetes incidence and life expectancy among the diabetes population have led to an increase in the number of years spent with diabetes. However, the effect of diabetes on the quality of those extra years is unknown.

We analyzed longitudinal data from the Health and Retirement Study and modeled disability-free life-years lost due to diabetes over a lifetime in the United States. We estimated incidence of disability, remission from disability, and mortality by self-reported diabetes status among 11,141 adults aged ≥ 50 years with baseline years of 1998 and 2004, followed to 2010. Three measures of disability were examined: severe functional decline (mobility), some difficulty with ≥1 instrumental activities of daily living (IADL), and some difficulty with ≥1 activities of daily living (ADL). Using these estimates, we developed a discrete-time five state Markov model to estimate the numbers of years with and without disability by baseline age and diabetes status. From ages 50 and 60 for all 3 disability definitions, diabetes was significantly associated (p<0.05) with earlier average age of disability onset, reduced total years of life and reduced disability-free life years. Compared to those without diabetics, from age 50 men have 1.5 to 2.2 more disabled years for all 3 disability measures and women have 3.5 more mobility loss disabled years and 2.6 more ADL disabled years. From age 50, men with diabetes have 6-7 years earlier onset of disability (mobility, IADL, ADL) than non-diabetic men, 2-4 fewer total years of remaining life, and have 6-7 fewer disability-free total years of life. From age 50, women with diabetes have a 7-8 year earlier onset of disability (mobility, IADL, ADL) than non-diabetic women, 2-4.5 fewer total years of remaining life, and have 6-7 fewer disability-free total years of life. This study suggests diabetes reduces the quality of life of adults by exposing them to disability at earlier ages and reducing disability-free years remaining compared to adults without diabetes.

1473-P

Incidence of Mobility Loss and Subsequent Recovery by Diabetes Status, 1998-2010

BARBARA BARDENHEIER, JI LIN, XIAOHUI ZHUO, MOHAMMED K. ALI, TED THOMPSON, EDWARD W. GREGG, *Atlanta, GA, North Wales, PA*

Few studies have quantified the incidence of mobility loss or subsequent recovery associated with diabetes. We used generalized estimating equations to analyze prospective data from the Health and Retirement study, a U.S. population-based sample of 11,141 adults aged > 50 years with biennial visits from 1998 through 2010. Compared to non-diabetic persons, incidence of mobility loss was 75% higher (p<0.05) for diabetic men (24.1 vs. 13.8 per 1000 PY) and 83% for diabetic women (34.6 vs. 18.9 per 1000 PY). [Figure 1] Recovery from incident mobility loss was lower for those with diabetes than without, but was similar by sex (226.4 for non-diabetic women, 244.5 for non-diabetic men, 220.0 for diabetic women, 210.8 for diabetic men per 1,000 PY). [Figure 2] Incident mobility loss was higher among diabetic women than men, with little difference in recovery.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Figure 1. Incidence of mobility loss among adults aged ≥ 50 years, with and without diabetes, 1998 - 2010

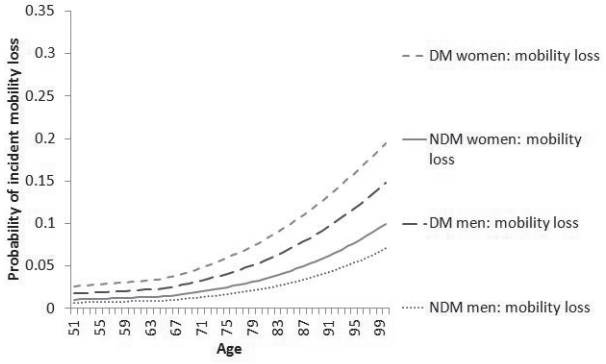
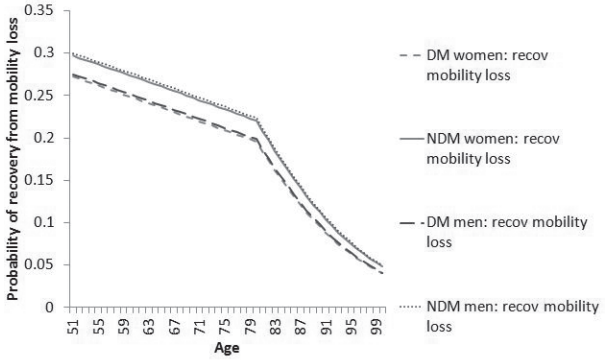


Figure 2. Recovery from incident mobility loss among adults aged ≥ 50 years, with and without diabetes, 1998 - 2010



1474-P

Changes in Hemoglobin A1c and Mortality Risk in Elderly People with Diabetes in the United States

MEDA E. PAVKOV, BARBARA BARDENHEIER, LINDA S. GEISS, *Atlanta, GA*

The association between hemoglobin A1c (A1c) change and mortality was assessed among persons with diabetes in the Health and Retirement Survey (HRS), a population-based survey of persons ≥50 years old. Two sequential A1c measurements were used to define pre-baseline change in A1c. The initial A1c was measured in 2003; a randomly selected half of this cohort had a second A1c measurement in 2006 and the remaining half in 2008. The period at risk started at the second A1c measurement (baseline) and ended at the date of death or final interview in 2012. Association between pre-baseline A1c change and mortality was explored by Cox regression models adjusted for sex, race/ethnicity, and baseline age, blood pressure, cystatin C, and self-reported comorbidities. Inverse probability weighting was used to reduce bias related to missing data. Results are weighted to represent the U.S. population aged ≥50 years with diabetes during 2006-2008. The study included 768 adults with diabetes (51% males) and pre-baseline A1c measurements (352 with A1c remaining <7%, 263 with A1c increasing to or remaining ≥7%, and 153 with A1c declining to <7%). During a median follow-up of 4.3 years (range 0.3 to 6.9 years) 187 participants died. At baseline, median age was 69.7 years [interquartile range (IQR) 62.2-77.5], median blood pressure 94.7 mmHg (IQR 86.0-103.2), and median cystatin C 1.1 mg/L (IQR 0.9-1.5); 88.1% were non-Hispanic white, 10.8% non-Hispanic black, and 1.1% Hispanic/other. Compared with participants with pre-baseline A1c remaining <7%, the adjusted hazard ratio for death was 1.5 (95% CI 1.03-2.3) in those whose A1c increased to or remained ≥7% and 1.4 (95% CI 0.9-2.2) in participants with declining A1c. In conclusion, in this cohort representative of the elderly population with diabetes, persistently high or worsening A1c increased the risk of death. A declining A1c was not associated with reduced mortality, possibly reflecting the high prevalence of comorbidities in this population.

1475-P

Inconsistency in Self-Report of Diabetes in Panel Surveys: The Health and Retirement Study

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Chronic disease data from longitudinal health interview surveys are used often in epidemiologic studies. Yet, these data may be limited by discrepancies in self-report across multiple interview waves. We examined inconsistencies in the self-report of diabetes across 12 years of the Health and Retirement Study (HRS), a nationally representative, longitudinal survey (funded by the National Institute on Aging). We investigated a multistep method of adjudicating discrepancies across waves.

We analyzed HRS waves 1998-2010. The sample included adults ≥51 years (n=24,156) who participated in ≥1 wave. We assessed the extent of problematic responses in the self-report of diabetes, in comparison to 6 other diseases. We examined sociodemographic and geriatric determinants as predictors of problematic response patterns. We then used questions about the diseases (e.g., treatment with oral medication/insulin) and respondent hemoglobin A1c data to devise a multistep adjudication method to resolve discrepancies in respondents' self-report of diseases across successive waves.

28.5% of respondents had inconsistency in their self-report of chronic diseases across waves, with variation by disease, ethnicity, and education. 704 respondents had inconsistency in diabetes self-report (1.2% of all respondents; 11.4% of respondents with diabetes). Using a step-wise method, we adjudicated 63.9% of problematic diabetes responses. Differences in disease prevalence between original and adjudicated data accumulated across succeeding waves (relative difference in diabetes prevalence in 2010, 2.7%).

Discrepancies in the self-report of diabetes accumulate across successive waves of health interview surveys; vary by ethnicity, education, and cognition; and affect disease prevalence. Using survey data internal to the HRS and HbA1c data, we formulated an adjudication algorithm that resolved > 60% of diabetes inconsistencies, enabling a clearer understanding of diabetes among aging Americans.

Supported By: American Diabetes Association (7-13-CD-08 to A.Q.)

1476-P

Proximal Predictors of Discontinuance with Oral Antidiabetic Agents among the Elderly

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Persistence in oral antidiabetic (OAD) therapy is an ongoing clinical concern in treating type 2 diabetes (T2D). Empirical studies of OAD persistence are dominated by small-scale analyses that focus on static rather than dynamic differences between discontinuers and persistent users. Lacking evidence of time-varying prognostic factors for drug discontinuance, clinicians may miss important intervention opportunities. We assessed predictors of OAD discontinuance in a nationally representative 5% sample of Medicare beneficiaries with T2D enrolled in fee-for-service Part D drug plans (2006 - 2008) with discontinuers defined as OAD use in a 12 month baseline period followed by a minimum of 12 months of non-OAD use. Discontinuers (N=7,435) were compared to persistent OAD users (N=65,602) on a series of variables hypothesized to influence discontinuance including static variables (demographics, income, disability, comorbidity burden) and monthly observations for time-varying factors (OAD count, insulin, hospital/SNF admissions, ED visits, Medicare spending, discontinuance with ACEs/ARBs and statins, unique physicians seen, hypoglycemia, uncontrolled diabetes, first use and gaps in OAD therapy). We estimated linear probability models using stepwise regression to identify timing and strength of association to OAD discontinuance. Long-term OHA discontinuation was rare (10%). Static factors explained 1.2% of the variance in probability of discontinuance. Adding dynamic factors increased explained variance to 26% of which 20% was due to co-occurring factors in the OAD discontinuation month (multiple OADs, ACEI/ARB/statin discontinuation, insulin use, and unique physicians seen) and 4% was due to prognostic factors occurring in the second and third month prior to discontinuation (hypoglycemia, hospital discharge, OAD usage gap). In conclusion, dynamic factors proximal to OAD discontinuance were far stronger predictors of non-persistence than traditional static measures.

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1477-P

An Out-of-Range (OOR) Glycemic Population Health Safety Measure

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The ADA recommends a target A1c of 7.5%-8.0% or slightly higher in persons with decreased life expectancy or at risk for serious hypoglycemia. Our objective was to evaluate an OOR measure that assessed both over treatment (OT) (A1c <7%; other cut points: <6.0%, <6.5%) and under treatment (UT) (A1c >9%; cut points: 9.1-9.5%, >9.5%) among high risk, largely elderly patients. This was a cross-sectional study of Veterans Health Administration patients in 2013. The study population was those that received insulin (I) or sulfonylurea (SU) and were considered at high risk for hypoglycemia (being 75 years or older, or with a serum creatinine =>2.0 mg/dL, or having a diagnosis of cognitive impairment or dementia). The national average and facility specific performance for OOR, OT and UT were determined using the last A1c in 2013.

We identified 435,078 patients on I/SU, of whom 133,302 (30.6%) met the inclusion criteria at 130 facilities (average number of patients: 1,017; range 126 - 3,587). The mean age was 75.5 years. The A1c was OOR in 45.2% of patients: OT in 31% of patients (6% with A1c < 6.0%; 16% with <6.5%), UT in 14.2% (4.7% with A1c >9.0-9.5%; 9.5% with >9.5%). Only 27.6% were in the range recommended by ADA (A1c 7.5-8.4%). The OOR measure ranged from 37.6% in the best performing decile (of the 130 facilities) to 53.5% in the worst performing decile. The ranges for OT and UT alone in best and worst performing deciles were 23.4%-41.2% and 9.7%-20.4%, respectively. Facility rankings for OT or UT were poorly correlated (Spearman's rho =-0.44).

We conclude that nearly half of our study population of elderly or ill patients, most of whom would not be included in current HEDIS measures, were OT or UT, and therefore at risk for short term harms. There was significant facility level variation, and even the best performers had more than a third of high risk patients with OOR A1c. We propose that a single measure can be used to simultaneously address multiple ranges of glycemic control in a vulnerable population to improve monitoring of patient health safety.

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1478-P

Clinical Inertia Affects Younger and Older Adults with T2DM Equally, With or Without CKD

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Clinical inertia (CI) is a multifactorial phenomenon with contributory factors from people with diabetes (PwD), their physicians, and the system in which they operate. The Time2DoMore program suggested that physicians believe older PwD and those with chronic kidney disease (CKD) are more susceptible to CI than younger patients with few or no comorbidities, resulting in lower expectations of adherence to lifestyle changes in older PwD. CI has less impact in clinical trials, presumably due to the placebo effect. The difference between routine care and this placebo effect in trials represents a correction of non-pharmacological aspects of CI. We used this method to demonstrate pre-existing CI in older cohorts, those with CKD, and older patients with CKD compared to a younger, non-CKD population.

Placebo-treated subjects (n=3081) from the vildagliptin clinical trial program, comprising 25 studies, were stratified in a factorial design by age (<70 or >70 years) and with or without CKD (eGFR <60 ml/min). HbA1c change was assessed at 24 weeks (ANCOVA).

Baseline HbA1c was similar across the groups (table). The placebo effect was comparable between groups in the base-case, and after adjustment for baseline HbA1c values.

We are able to demonstrate a consistent placebo effect across age groups and presence or absence of CKD, suggesting that the non-pharmacological component of CI in PwD may be independent of age and comorbidities.

Table.

	Younger, non-CKD	Younger with CKD	Older, non-CKD	Older with CKD
	n=2176	n=304	n=338	n=263
Age (years)	54.4	60.6	73.5	74.7
Baseline HbA1c (%)	8.16	7.85	7.95	8.16
Placebo effect (%)	-0.27	-0.20	-0.25	-0.23
After adjustment for baseline HbA1c				
Placebo effect (%)	-0.27	-0.20	-0.25	-0.21

Values are expressed as mean. All comparisons (ANCOVA) between groups: p=non-significant.

Supported By: Novartis

1479-P

Anti-Müllerian Hormone (AMH) Concentrations and Time to Menopause in Women with Type 1 Diabetes in the Epidemiology of Diabetes Interventions and Complications (EDIC) Study

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AMH is a measure of ovarian functioning and predicts response to assisted reproductive technologies as well as age at the final menstrual period (FMP). Cross-sectional studies suggest that insulin resistance may affect AMH levels. Relationships between AMH with age at FMP and insulin dose have not been examined among women with type 1 diabetes, who have ovulatory disorders more often than women without diabetes.

In EDIC, 202 women experienced natural menopause at the mean age of 50 (SD 4.3) years. In a random subsample of 50 women who underwent AMH sampling every 2 years prior to the FMP, logAMH declined linearly prior to the FMP. Therefore, in the remaining women, we performed only 2 AMH measurements prior to the FMP in order to yield values>0 and to represent a range of years prior to the FMP (mean of 10 and 6 years prior to the FMP). AMH coefficients of variation were 5.0% at 3.6 ng/ml and 1.7% at 8.6 ng/ml, and the lower limit of detection was 0.16 ng/ml.

AMH concentrations became undetectable ~1.0 year before the FMP (slope -0.26±0.01, p<0.001). In regression models, younger age at EDIC baseline (p=0.04) and lower insulin dose (per 0.5 units/kg/day) were associated with higher AMH (p=0.008), while randomization arm (p=0.8), body mass index (p=0.6), and HbA1c averaged over EDIC and the preceding Diabetes Control and Complications Trial (p=0.8) were not. Insulin dosing was not associated with more rapid declines in AMH (p=0.8).

These preliminary analyses suggest that AMH can be used to predict age at menopause among women with type 1 diabetes; higher insulin doses may be associated with lower AMH initially but AMH declines; and AMH was not associated with HbA1c over a narrow range. Additional investigation is needed to determine if these associations persist in adjusted models and if AMH predicts additional reproductive outcomes.

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1480-P

Diabetes in the Baltimore Male Hip Fracture Patients Study

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The link between type 2 diabetes (T2D), osteoporosis and fractures in older adults is not well understood. Twenty five percent of U.S. hip fracture patients have diabetes. A prospective cohort study, frequency matched by sex, was conducted to determine whether sex differences exist across multiple outcomes after hip fracture among those 65 and older. The purpose of this secondary analysis was to compare characteristics of patients (n=338) with (n=77) and without (n=261) physician-diagnosed T2D at the time of fracture. In the primary study, participants were enrolled from 8 Baltimore hospitals and assessments done within 15 days of admission and at 2, 6, and 12 months post admission. Assessments included body composition measures of bone mineral density (BMD), lean and fat mass, blood draw, and questionnaires. Data for this analysis came from inpatient medical charts and baseline measures. Participants were equal proportion males (49.4%) and females (50.6%), old (m=80.9 years), mostly white (91.4%), educated (m=13.1 years). Participants with T2D had higher BMI (26.6 vs. 24.7 kg/m2) p=0.007), lower self-reported Yale Physical Activity (2375 vs. 3357 kcals p=0.013), and more IADL impairments (2.30 vs. 1.97 p=0.062) than those without T2D. Participants with T2D also had significantly higher whole body BMD (0.80 vs. 0.75 g/cm^2 p=0.028), total body fat (25.1 vs. 21.5 kg p=0.015) and total body mass (74.0 vs. 66.7 kg p=0.006). No significant differences were observed in history of osteoporosis and previous fracture, depression, and upper and lower extremity ADLS. In conclusion, participants with diabetes and hip fractures were different from typical older hip fracture patients but consistent with the general population with T2D.

For author disclosure information, see page A810.

1481-P

Cognitive Dysfunction and Hypoglycemia in Older Adults with Type 1 Diabetes: Results from the T1D Exchange

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In this study, we aimed to evaluate the frequency of cognitive dysfunction among older adults with type 1 diabetes (T1D) and the factors associated with cognitive dysfunction.

This analysis includes 200 subjects between the ages of 60 and 86 years participating in a study of severe hypoglycemia in older adults with T1D (median age 66 years, median T1D duration 39 years, 47% female, 92% non-Hispanic white). Cognitive assessments included the Montreal Cognitive Assessment (MoCA) and the Trail Making Test part B (TMTB). Participants wore a blinded continuous glucose monitoring (CGM) sensor for 14 days. Spearman correlations were used to assess the association of hypoglycemia measures with cognitive scores.

Median (quartiles) MoCA score was 26 (24, 28) with 87 (44%) having a MoCA score ≤25. Median TMTB time was 95 (71, 120) seconds with 70 (36%) having a z-score<-1.5. There was a weak, but statistically significant, association of poor MoCA and TMTB scores with increased hypoglycemia unawareness (partial r=0.19 and 0.21, respectively). Neither MoCA nor TMTB were associated with fear of hypoglycemia, % CGM values <70 mg/dl or glycemic variation (Table).

Cognitive dysfunction is highly prevalent in older adults with T1D and is associated with hypoglycemic unawareness. Screening for subtle cognitive dysfunction should be performed to assess risk of unrecognized hypoglycemia in this population.

Table.

*Adjusted for Diabetes Duration, Education, Depression, Frailty.

	MoCA (N=200) Lower score indicates worse functioning			TMTB Z-Score (N=195) Lower score indicates worse functioning			
	≤25	≥26	P-value*	<-1.5	–1.5-<1.5	≥1.5	P-value*
Hypoglycemia Unawareness Median (quartiles)	4 (2, 5)	3 (1, 5)	0.007	4 (2, 5)	3 (1, 5)	3 (2, 6)	0.004
Fear of Hypoglycemia Median (quartiles)	34 (23, 45)	35 (25, 46)	0.75	36 (26, 47)	32 (24, 42)	43 (23, 43)	0.09
CGM % Median (quartiles)	0.06 (0.03, 0.10)	0.06 (0.03, 0.11)	0.31	0.07 (0.02, 0.11)	0.06 (0.03, 0.10)	0.07 (0.03, 0.17)	0.89
CGM Coefficient of Variation (CV) Median (quartiles)	0.42 (0.39, 0.48)	0.44 (0.38, 0.49)	0.21	0.44 (0.39, 0.50)	0.43 (0.37, 0.47)	0.48 (0.39, 0.52)	0.41

Supported By: The Leona M. and Harry B. Helmsley Charitable Trust

1482-P

Evidence of a Common Variant in CCDC71L-PIK3CG for Soluble Receptor for Advanced Glycation End-Products

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Importance of glycation has been highlighted in aging processes and glycosylation associated diseases. AGEs and RAGE play a central role in atherosclerosis. Recently, sRAGE has been recognized with a counter-regulatory mechanism, pinpointing sRAGE as a new biomarker of endothelial function or early stage atherosclerosis. To identify loci for circulating sRAGE, we used SNPs imputed from the 1KG project and conducted a GWAS among 3936 nondiabetics of European ancestry in the LLFS. Prior to GWAS, sRAGE was adjusted for age, BMI, smoking status, centers, and 20 principal components, within sex. Linear mixed effects model assuming additive genetic fixed effects was used for association testing with a kinship model to correct for random effects of relatedness. A significant (p<5E-8) intergenic GWAS signal (rs190643062, imputed, AF_T=0.01, β=0.77±0.14, r2=1%, p=3E-8) located between CCDC71L and PIK3CG was identified. This SNP was classified by RegulomeDB with minimal binding evidence and multiple features of regulation. GWAS3D analysis in querying distant cis-/trans-regulatory interactions showed probable interactions of TRIM51GP and 13q31.3 with the top SNP. Several SNPs in CCDC71L-PIK2CG have been reportedly associated with lipids, BP, CIMT, plaque, and pulmonary function, but they were not in LD with the SNP revealed in this analysis. Further, conditional GWAS (on the top SNP) did not yield additional signals. Conditional linkage analysis resulted in a 12% attenuation of linkage strength (LOD from 2.02 to 1.78, the top SNP residing perfectly within the observed linkage peak region 7q22.3), which would suggest an appreciable accountability of this SNP for the promising linkage (LOD>1.75) with other yet unmeasured rare variants being collectively more influential. In conclusion, this first sRAGE GWAS revealed a significant and novel common variant rs190643062 in CCDC71L1-PIK2CG. Replication from a forthcoming independent and large population study is indispensable.

Supported By: National Institute on Aging (U01AG023712, U01AG023744, U01AG023746, U01AG023749, U01AG023755, U19AG023122, K24AG025727, R01AG032319)

1483-P

Early Alzheimer-type Dementia and Type 2 Diabetes: Analysis Using Voxel-based Specific Regional Analysis System for Alzheimer's Disease (VSRAD)

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Purpose: Diabetes is known to be a risk factor for Alzheimer's disease (AD). Voxel-based specific regional analysis system for AD (VSRAD) is the software of automatic image processing which enables statistical analysis of the degree of parahippocampal cortex atrophy and is widely used for early diagnosis of AD in Japan. Our previous study using VSRAD,presented at 71th ADA , has suggested that both hyperglycemia and hypoglycemia were related with the development of early AD in patients with diabetes. The purpose of this study is to assess the treatment related with the development of early AD.

Subjects and Methods: We studied 121 out-patients with type 2 diabetes over 60 years old (Age 71.1±8.8 years, male 58/female 63, HbA1c 6.9±1.0 %) before and after 5 years of ordinal diabetic treatment. We studied medication period of individual diabetic treatment during 60 months.

Results: 81 patients was treated with sulphonylurea (SU), 11 with non SU secretagogues, 27 with α-glucosidase inhibitor (GI), 45 with pioglitazone, 38 with metformin, 52 with dipeptidyl peptidase (DPP)-4 inhibitor, 24 with glucagon like peptide (GLP)-1 receptor agonist (RA), and 60 patients with insulin. The degree of atrophy advanced from 1.59±1.22 to 1.79±1.29 during 5-year study period. Compared with patients with little atrophy, 32 patients with more than 0.2 advanced degree showed significantly shorter period of treatment with GLP-1 RA (16.5±10.7 vs. 22.7±4.1 months, p=0.042). No significant difference was seen between the two groups with SU (52.8±13.6 vs. 57.7±14.3), non SU secretagogues (39.4±16.6 vs. 48.0±13.9), α- GI (39.4±12.3 vs. 42.8±19.4), pioglitazone (38.5±14.7 vs. 57.6±24.0), metformin (52.8±16.6 vs. 45.3±20.6), DPP-4 inhibitor (21.6±5.9 vs. 23.7±4.3), and insulin (49.1±13.5 vs. 49.0±17.1 months).

Conclusion: Treatment with GLP-1 RA was suggested to be useful for prevention of the development of early AD in patients with type 2 diabetes.

1484-P

Are Oral Disposition Index Reduction, Impaired Fasting Glucose, and Impaired Glucose Tolerance All Equally Associated with Age?

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Oral disposition index (DI) reflects the capacity of insulin secretion adjusted for insulin sensitivity, which declined progressively with age in population with NGT. This study aimed to assess whether the risk of DI reduction, impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) all equally associated with age increasing in Chinese population. China National Diabetes and Metabolic Disorders Study was a cross-sectional study conducted from June 2007 to May 2008. Questionnaire and 75g-oral glucose tolerance test (OGTT) was performed. Data from 12060 men and 19165 women with OGTT-diagnosed NGT, IFG or isolated-IGT according to 1999 WHO criteria were included in the data analyses. The participants were divided into four age groups: 20-39, 40-49, 50-59 and 60-75 years. Oral DI was the product of the Matsuda index and 120min AUCins/gluc (the ratio of the area under the insulin curve to the area under the glucose curve for 0-120 min during the OGTT). DI reduction was defined as DI being lower than the 25th percent of the current study population. Logistic regression was used to assess the risk of presence of DI reduction, IFG and isolated IGT with increasing age adjusted for body mass index. Compared with participants aged 20-39 years, the odds ratio (OR) (95% confidence interval) for presence of DI reduction was 1.65 (1.54-1.77), 2.14 (1.99-2.29) and 2.62 (2.42-2.84) in 40-49, 50-59 and 60-75 years age group, respectively. The increasing OR for presence of IGT was 1.82 (1.64-2.01), 2.58 (2.33-2.85) and 3.94 (3.54-4.37) in three age group, respectively. The corresponding OR for presence of IFG was 1.37 (1.17-1.59), 1.27 (1.07-1.53), 1.56 (1.29-1.87) with advancing age. Age is more strongly associated with IGT than with DI reduction and IFG in Chinese populations.

1485-P

Glycemic Control in Skilled Nursing Facilities

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Use of hypoglycemic agents for DM in elderly in skilled nursing facilities (SNF) has led to concerns about hypoglycemia, which might hamper efforts at controlling hyperglycemia. We studied frequency of hypo- and hyperglycemia and associated factors in SNFs. We reviewed charts from 2 SNFs. *Events* were defined as: hypoglycemia BG <70mg/dL, severe hypoglycemia 200mg/dL, and severe hyperglycemia >400mg/dL. *Event-days* were calculated. There were 203 subjects, mean age, BG and A1c±SD: 80.2±8.2 yr, 172.4±40.3mg/dL and 7.46±1.85%. 61 were on insulin alone (I), 67 on insulin + oral hypoglycemic agents (IOHA), the rest on OHA alone (OHA). Percentages of patients with at least one *event* are: 36.9% hypoglycemia, 3.4% severe hypoglycemia, 89.2% hyperglycemia, 14.8% severe hyperglycemia. *Event-days* are: 3.7% hypoglycemia, 0.1% severe hypoglycemia, 52.4% hyperglycemia, 1.16% severe hyperglycemia. Relative risks of hypo- and hyperglycemia based on medication are in Table 1.

Hypoglycemia rates were similar for I vs. IOHA vs. OHA. Among patients on insulin, there was greater risk of hypo- and hyperglycemia for basal±prandial±sliding scale compared to sliding scale alone; A1c 7.7 vs. 6.9%, p=0.059. Among patients on SU, risk of hypoglycemia was higher only if with insulin as well. Overall rates of severe hypoglycemia are low; hyperglycemia rates are high. The association of basal insulin with hypo- and hyperglycemia merits further investigation.

Table.

Parameter		Relative Risk Hypoglycemia (95% CI)	Relative Risk Hyperglycemia (95% CI)
Insulin Use			
	1.Insulin Users	1.62(0.97,2.72)	1.57(1.38,1.78)
	2.Insulin + Oral agents	1.47(0.86,2.53)	1.39(1.21,1.59)
	3.Oral agents only	1.00(REF)	1.00(REF)
Insulin Type			
	1.Basal ± prandial ± sliding scale	1.65(1.14,2.37)	1.33(1.22,1.46)
	2. Sliding scale only	1.00(REF)	1.00(REF)
Sulfonylurea (SU) use			
	SU with Insulin	2.05(1.44,2.91)	1.02(0.92,1.14)
	SU without Insulin	1.32(0.79,2.21)	0.84(0.73,0.97)
	Oral agents alone other than SU	1.00 (REF)	1.00 (REF)

1486-P

A Survey about Management Status of Type 2 Diabetes Mellitus in Elderly Diabetic Patients of China

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This study was aimed to investigate the management status of type 2 diabetes mellitus (T2DM) and diabetic complications in elderly diabetic patients of China, the characteristics of patients who achieved (or did not achieve) target control goals were also determined.

We conducted a multicenter survey, and collected data from elderly type 2 diabetes patients (60 years or older). Control criteria were defined based on the International Diabetes Federation 2013 Global Guideline for type 2 diabetes.

A sample of 2615 patients (male 1317, female 1298), age (60.8±9.2) years, and with a median disease duration of 7.3 years was included. All patients included were functionally independent. Clinical measures Target goals for hemoglobin A1c (HbA1c), blood pressure (BP), and low-density lipoprotein (LDL-c) were based on the latest IDF Guideline, including HbA1c < 7.5%, BP < 140/90mmHg and LDL-c<2.0 mmol/L. ABC goal referred to achievement of treatment targets for HbA1c, BP and LDL-c at the same time. The mean HbA1c, systolic BP, diastolic BP and LDL-c were 8.4%, 131.4mmHg, 76 mmHg, and 2.6mmol/L respectively. 36.7% patients achieved HbA1c target goal, 68.7% achieved BP target goal, 25.7% achieved LDL target goal and only 6.9% achieved ABC goal. In order to find independent risk factors associated with attainment of ABC goals, Logistic regression analysis was used in variables such as gender, age, history of diabetes and BMI. But all these variables were not associated with attainment of ABC goals significantly. In all patients, 31.3% of which had hypertension, 74.3% had dyslipidemia, 14.5% had coronary heart disease , 6.7% had cerebrovascular disease, 15.2% had diabetic retinopathy, 13.2% had nephropathy, 26.1% had diabetic peripheral neuropathy, and 2% had diabetic foot.

In conclusion, we used the latest standards and firstly examined the management status of T2DM in China's elderly. The gap between guideline and current status reality in of diabetic treatment in china was demonstrated to some extent.

1487-P

Oral Health Related Quality of Life in Diabetics with Oral Problems

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Periodontal problems and tooth loss have high impact on Oral Health Related Quality of Life (OHRQoL). To identify if periodontal problems and edentulism have a higher OHRQoL in diabetic elder persons in Mexico City. Household survey in a representative sample of elders' ≥70 years living in one district of Mexico City. Sample size =1294, 1124 were interviewed, 834 were clinically evaluated. Variables: OHRQoL evaluated with the Oral Health Impact Profile validated in Mexico (OHIP14_sp), gender, age, dental conditions (edentulism/healthy-mild gingivitis/moderate periodontitis/severe periodontitis), self-report of diabetes and treatment (Yes with treatment/yes no treatment/no diabetes), self-rate of oral health (good/fair/bad), self-rate of general health (excellent-good/bad-very bad), xerostomia, depression (Geriatric Depression Scale) and cognitive impairment (Mini Mental State Examination). Univariate analysis and logistic regression model (LRM) were performed. Mean age was 79 years, 54.4% women. Diabetes prevalence = 21.8%, edentulism= 23.5%, severe periodontitis = 23.1%. Diabetics have higher prevalence of severe periodontitis (29.7%). Mean OHIP14_sp = 6.9, median = 4. OHIP14_sp was dichotomized. Variables with p<.20 were included in the LRM (age, diabetes, dental condition, GDS, MMSE, xerostomia, self-perception of oral and general health). The LRM showed that diabetic persons receiving treatment had 1.89 (95% CI1.1-3.4) higher probability of having bad OHRQoL than non-diabetics, edentulous persons have more probability (OR=7.3 95% CI 2.9-18.1) than those with severe periodontitis, persons with no diagnosis of cognitive impairment (OR=8.8 95% CI 1.1-51.5) have more probability than those with no cognitive impairment and those with bad self-perception of general health (OR=1.6 95% CI 1.1-2.5) have more probability of bad OHRQoL. Tooth loss in diabetic persons is associated with higher probability of bad OHRQoL. Oral health care in elder diabetics will improve OHRQoL.

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EPIDEMIOLOGY—CARDIOVASCULAR DISEASE

Guided Audio Tour: Epidemiology of Cardiovascular Disease in Diabetes *(Posters: 1488-P to 1495-P), see page 13.*

1488-P

Risk Factors for Lack of Statin Therapy in Patients with Diabetes and Coronary Artery Disease

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Although guidelines recommend statin therapy for all adult patients with coronary artery disease (CAD) and diabetes, many of these patients are not being treated with statins. The reasons for lack of statin therapy in this high-risk population remain obscure. We studied risk factors for lack of statin therapy in a retrospective cohort of patients with diabetes and CAD treated in primary care practices (PCP) affiliated with two academic medical centers between 01/01/2000 and 12/31/2011.

Among 10,085 study patients (Table), 89.0% received statins during the study period and 73.7% had persistent statin therapy (active statin prescription at the last PCP visit). In multivariable analysis of all subjects, patients who were older (OR 1.023 / year), with no history of smoking (OR 1.476), or no cardiologist evaluation (OR 2.315) were less likely (p < 0.001 for all) to have initiated statin therapy. In patients who had initiated statins, lack of history of smoking (OR 1.223), younger age (OR 1.015 / year), lack of cardiologist evaluation (OR 1.344), no family history of CAD (OR 1.474), history of adverse reaction to a statin (OR 1.457) (p < 0.001 for all five), or higher income (OR 1.003 / $1,000, p =0.008) predicted lack of persistent statin therapy.

In a large study of patients with clear indications for statins, lack of cardiology evaluation, lower cardiovascular risk and older age were strong risk factors for lack of statin therapy.

For author disclosure information, see page A810.

Table. Characteristics of All Patients with Diabetes and CAD.

Variable	All Patients	Women	Men	p-value (For difference between men and women, based on Chi-square test)
N (%)	10,085	3,661 (36.3)	6,424 (63.7)	
Age, years (SD)	69.3 (11.3)	71.3 (11.5)	68.1 (11.0)	< 0.0001
History of smoking (%)	6,231 (61.8)	1,844 (50.4)	4,387 (68.3)	< 0.0001
Cardiology evaluation (%)	6,353 (63.0)	2,214 (60.5)	4,139 (64.4)	< 0.0001
Statin initiated (%)	8,922 (88.5)	3,205 (87.5)	5,717 (89.0)	0.03
Adverse reaction to statin (%)	2,105 (20.9)	843 (23.0)	1,262 (19.7)	< 0.0001
Persistent statin therapy (%)	7,430 (73.7)	2,699 (73.7)	4,731 (73.7)	0.93

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1489-P

Obesity and Cardiovascular Risk: Effects of Dual Therapy Intensification with a DPP-4 Inhibitor Compared with Insulin

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Large observational studies have raised concerns about the CV safety of insulin therapy in type 2 diabetes (T2DM) after monotherapy with metformin (MET) has failed to maintain glycaemic control[1,2]. We therefore analysed the time to non-fatal acute myocardial infarction, non-fatal stroke or all-cause mortality in patients with T2DM who had their treatment intensified with a DPP-IV inhibitor or insulin following dual therapy failure with MET and SU. A retrospective cohort study was conducted in 8,654 patients who were newly treated with a DPP-IV inhibitor or insulin following dual therapy (MET+SU) failure between 2007-2014. Data was sourced from UK General Practices via The Health Initiative Network (THIN) database[3]. The risk of the composite outcome (CV events) was compared between 2 treatment groups: MET+SU+DPP-IV inhibitor (reference group, n=3,654) and MET+SU+ insulin (n=1,584). Follow-up was 5 yrs (total of 988 person-yrs), and propensity score matching analysis and Cox proportional hazard models were employed.

Overall, the number of CV events was 171 vs. 231 for patients who added DPP-IV inhibitor vs. insulin respectively (39 vs. 42 events per 100 person-years). Compared to the reference group, there was no significant difference in the hazard of CV events among insulin users (adjusted hazard ratio, aHR [95% CI]: 1.06 [0.86, 1.29], p= 0.6). A subgroup analysis of obese patients (BMI 30-34.9 vs. BMI ≥35kg/m^2) also showed no significant difference in the incidence of CV events between the reference group and insulin (42 vs. 39 events per 100 person-yrs). Therefore, in this large cohort study tracking outcomes in routine clinical practice, intensification of dual oral therapy by adding insulin is not associated with a higher or lower risk of CV events compared with adding a DPP-IV as the third oral agent.

[1] Rournie CL et al. JAMA 2014:311:2288-2296.
[2] Currie CJ et al. J Clin Endocrinol Metab. 2013;98:668-77.
[3] Idris I et al. Arch Intern Med. 2012;172:1005-11.

1490-P

Predictors and Outcome of Heart Failure Complicating Type 2 Diabetes: The Fremantle Diabetes Study

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There have been no detailed contemporary population-based studies of heart failure (HF) complicating type 2 diabetes (T2D). To investigate predictors/outcome of hospitalization or death from HF in T2D, we analyzed prospective data from the community-based longitudinal observational Fremantle Diabetes Study Phase I (FDS1) which included 1296 representative T2D subjects recruited from 1993 to 1996. This cohort and 5159 age-, gender- and postcode-matched non-diabetic residents were followed, through validated data linkage, from recruitment to death or census at end-June 2012. At baseline, FDS1 patients had a mean±SD age of 64.0±11.3 yrs, 49% were male, and their median diabetes duration was 4.0 yrs. Of 1185 patients without prior hospitalization for HF at entry, 377 (31.8%) were hospitalized/died of HF during 14,393 patient-years (12.1±6.2 years) of follow-up. In Cox proportional hazards modelling, independent predictors of HF hospitalization/death comprised sedentary lifestyle, central obesity, lower systolic blood pressure, higher serum triglycerides and urinary albumin:creatinine ratio, eGFR ≥90 ml/min, known ischemic heart disease, retinopathy and schizophrenia (P≤0.046). The age-adjusted hazard ratio (95% CI) for HF hospitalization/death in T2D vs. non-diabetic subjects was 2.36 (2.09-2.66) (P<0.001). Further adjustment for sex and co-morbidities did not attenuate this ratio. T2D patients were 4.8 yrs younger vs. non-diabetic controls at first HF event (P<0.001), and these patients were also 4.4 yrs younger at time of death (P<0.001). T2D more than doubles the risk of HF hospitalization/death. Renal hyperfiltration appears a novel risk factor while albuminuria/retinopathy may be surrogates for microangiopathy-related cardiomyopathy. HF complicating T2D presents relatively early and is associated with early death.

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1491-P

Independent Predictors of Cardiovascular Disease (CVD) Events Identified in a Cohort of Type 2 Diabetes (T2D) Patients in China

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The aim of this study is to determine the incidence of CVD complications in a large Chinese T2D cohort with high risk of CVD.

This was a multi-center, prospective and longitudinal cohort study. Patients with high risk of CVD were enrolled and followed up for 3 years at every 6-month interval. The inclusion criteria were: 1) ≥40 years old; 2) T2D diagnosis ≥6 months; 3) with confirmed hypertension and dyslipidemia, and one or more other CVD risks (overweight, microalbuminauria/proteinuria, previous CAD or stroke history, and ≥65 years old). The primary endpoint was the composite of CVD events (defined as the first occurrence of acute myocardial infarction, stroke or death from cardiovascular causes). All statistical analyses were done using SAS 9.4.

In year 2011 to 2014,4722 patients from 68 hospitals were recruited and followed up. 45.2% were male and the mean age was 65.9 years old. The median duration of diabetes was 7.2 years. The 1-year, 2-year, and 3-year cumulative incidence rates of the composite of CVD events were 2.0%, 3.9%, and 6.2%, respectively. Multivariate Cox models showed that age ≥65 yrs (Hazard Ratio [HR]=2.19; 95% confidence interval [CI]: 1.54-3.12; p<0.001) and prior CVD history (HR=1.65; 95% CI: 1.25-2.19; p<0.001) were associated with the higher risk of the composite CVD events; while the adequate control of HbA1c<7.0% (HR=0.68 (95% CI: 0.52-0.90; p<0.01) and blood pressure < 140/80 mmHg (HR=0.57; 95% CI: 0.43-0.75; p<0.0001) were associated with lower risk of the composite CVD events. Adequate control of LDL-c<2.6% was not significantly associated with the outcome.

This was the first report on CVD outcome of T2D patients from prospective cohort study in Chinese individuals with T2D in China. Age and presence of CVD history were independent predictors of CVD complications; while adequate glycemic control and blood pressure control were associated with lower risks of CVD complications.

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1492-P

Incidence of Cardiovascular Disease and All-Cause Mortality in Subtypes of Type 2 Diabetes

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The oral glucose tolerance test (OGTT) is seldom used for diagnosis of diabetes in clinical practice, but the OGTT may identify asymptomatic patients with a poor prognosis, who would not be diagnosed by the simpler fasting glucose test. We compared the incidence of cardiovascular disease (CVD) events and all-cause mortality in individuals diagnosed with diabetes by fasting glucose only or by OGTT. We analysed data from 7,537 participants in the longitudinal British Whitehall II study (91.3% of White ethnicity). Diabetes diagnosed by OGTT was subdivided into diabetes by fasting glucose only (F-DM, n=86), 2-hour glucose only (2h-DM, n=172) or combined fasting and 2-hour glucose (F-2h-DM, n=107). Median follow-up time was 20.1 years for all-cause mortality and 17.5 years for CVD. In White participants, the 10-year rates of CVD (Figure 1A) and all-cause mortality (Figure 1B) were 2-4 folds higher in F-2h-DM (26.0 and 18.7, P<0.05) than in individuals with F-DM (6.8 and 6.6) or 2h-DM (15.3 and 7.8), but not different in the F-DM and 2h-DM groups compared with the diabetes free population (P≥0.05). In non-Whites there were no differences in rates between diabetes groups, but the entire non-White population had a 72% higher rate of CVD than the entire White population. Diagnosis of diabetes based on OGTTs is more effective in predicting premature CVD and death than the use of fasting glucose only, at least in White individuals.

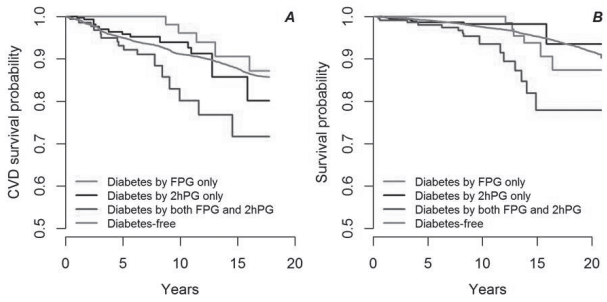

Figure 1. Age and sex adjusted Kaplan-Meier survival curves for fatal and non-fatal CVD events (A) and all-cause mortality (B) in subtypes of type 2 diabetes in the White population of Whitehall II

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1493-P

A Decision Tree for Predicting Coronary Artery Disease (CAD) in Type 1 Diabetes (T1D)

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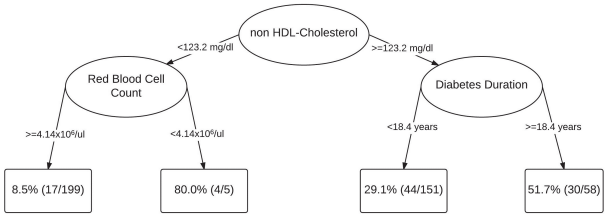
CAD risk is greatly increased in T1D, but the reasons for this increase are not well understood. Our objective is to use tree-structured survival analysis (TSSA) to formally assess the presence of subgroups for CAD risk in the Pittsburgh Epidemiology of Diabetes Complications (EDC) study of T1D.

EDC study participants diagnosed with T1D from 1965-1980 were included in the current analyses (n=413 free of CAD at baseline, mean T1D duration 15 yrs, age 23 yrs, 50% male) and followed for 25 yrs to ascertain CAD incidence (fatal CAD, MI, revascularization procedure/blockage ≥50%, ischemic ECG (MN codes 1.3, 4.1, 4.3, 5.1, 5.3, 7.1), or EDC physician diagnosed angina). TSSA was used to fit a regression tree for time to CAD event by determining optimal cut-points of baseline covariates to discriminate level of CAD risk.

There were 95 (23%) cases of incident CAD. In those with higher nonHDLc, longer T1D duration additionally improved CAD prediction. A small high-risk subgroup with low nonHDLc and low red cell count was identified. Further exploration of this group showed that they are all women with a relatively good profile of other CAD risk factors.

Our results suggest that there may be threshold effects of combinations of these risk factors on absolute CAD risk. Further study, including external validation in other T1D cohorts, is needed to better determine the prognostic utility of TSSA for CAD in T1D.



Supported By: R01DK034818

1494-P

Incident Diabetes, Subclinical Atherosclerosis, and Cardiovascular Events in Apparently Healthy Adults—A Longitudinal Study

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Epidemiological studies have addressed the association between impaired fasting glucose and poorer outcomes, with mixed results. We aimed to estimate incidence of diabetes and occurrence of cardiovascular outcomes after a 10- to 12-year follow-up, according to fasting plasma glucose (FPG) levels. We included 1545 civil servants without diabetes in 1998 (age range, 23 to 63 years), who participated in both a worksite screening assessment (in 1998) and in the Longitudinal Study of Adult Health (ELSA-Brasil) (in 2008-2010). According to FPG levels in 1998, participants were classified as euglycemic (<100mg/dl), impaired fasting glucose (IFG) level 1 (100-109mg/dl) or level 2 (110-125mg/dl). In 2008-2010 participants informed about cardiovascular outcomes and underwent oral glucose tolerance test, carotid intima-media thickness (IMT) and coronary artery calcium score (CAC) measurements. We used crude and adjusted regression models to determine the risk of incident DM, cardiovascular events and higher IMT and/or CAC values. We found an age and sex-adjusted diabetes incidence rate of 10.3/1000 person-years (95% confidence interval [95% CI]: 8.1-14.0) in the sample. The risk for incident diabetes was higher among individuals with IFG level 1 (Hazard ratio [HR]=3.16; 95% CI: 2.18-4.59) and level 2 (HR=7.40; 95% CI: 4.84-11.31) compared to euglycemic participants. IFG level 2 was associated with higher IMT values (β=0.030; 95% CI: 0.005-0.056) and more frequent clinical events (HR=2.56; 95% CI: 1.11-5.90). Incident DM was associated with higher IMT values (β=0.033; 95% CI: 0.014-0.051) and a CAC > 400 (Odds ratio=2.67; 95% CI: 1.10-6.49). In conclusion, IFG was an independent predictor for incident diabetes. IFG level 2 in 1998 and incident DM during follow-up were associated with higher cardiovascular burden.

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1495-P

Reduction in Calcium Density of Coronary Artery Plaque over Time Predicts Progression of Coronary Artery Calcification

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Individuals with type 1 diabetes (T1D) experience higher rates of coronary artery disease (CAD) and mortality than people without diabetes, and CAD occurs earlier in life. Coronary artery calcification (CAC) is a marker for subclinical atherosclerosis and the Agatston score is the standard measurement. Recently plaque calcium density has been shown to predict clinical outcomes, but there are limited data on how it changes over time. The aim of this study was to examine how changes in plaque calcium density over a period of 6-years relate to CAC progression in adults with T1D.

The Coronary Artery Calcification in Type 1 Diabetes (CACTI) cohort consists of 1416 subjects (T1D n=652 and non-diabetic n=764) age 38 ± 9 (SD) years at baseline. CAC was measured by electron-beam computed tomography at baseline and after 6.2 ± 0.6 years of follow-up. CAC density was calculated by dividing the Agatston score by the plaque area accounting for slice thickness. Linear mixed model was used to examine the change in calcium density over time. Progression of CAC, defined as a change ≥ 2.5 in the square root-transformed volume score, was examined using logistic regression, adjusting for the change in density score as well as baseline volume and density scores, age, diabetes status, sex, HDL-c, LDL-c, triglycerides, systolic blood pressure, and BMI.

In those with a positive CAC score in one or more vessels at baseline (n=433), CAC progressed in 224 subjects. CAC density decreased by 1.54 in the non-DM (baseline: 3.71 vs. follow-up 2.17, p<.0001) and 0.98 in the T1D adults (baseline: 3.56 vs. follow-up 2.58, p<.0001) over the 6-year study period, adjusting for plaque volume. Additionally, adjusting for both baseline CAC volume and CAC density, the reduction in CAC density over time predicted progression of CAC in all subjects (OR 2.37, 95% CI 1.44-3.92, p=0.001).

In conclusion, the risk for progression of CAC is increased as the density of plaques decreases, independent of baseline CAC volume and density.

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1496-P

Pericardial Adipose Tissue Is Associated with Coronary Artery Calcification in Adults With and Without Type 1 Diabetes

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Pericardial adipose tissue (PAT) surrounds the coronary arteries and is associated with cardiovascular disease (CVD) and coronary artery calcification (CAC). Adults with T1D are at higher risk of CVD. No studies to date have examined the association of PAT with CAC in those with type 1 diabetes (T1D). The purpose of this study was to test whether PAT was associated with the prevalence and progression of CAC over 6 years in the CACTI study.

CACTI is a prospective cohort study of adults with and without T1D. PAT volume was measured from EBCT scans at baseline. Logistic regression was used to examine the association between PAT and CAC. Progression of CAC was defined as a change in volume of ≥2.5 square-root transformed units. PAT data were available on 1319 subjects, with CAC progression data on 952. PAT volume was log transformed. The relationship between PAT and progression of CAC was not linear, so PAT was categorized into quartiles for this model. BMI and visceral adipose tissue (VAT) were correlated (r=0.66), and were included in separate models.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Results are shown in Table 1. These findings demonstrate that PAT is significantly associated with CAC prevalence and progression, independent of BMI and VAT.

Table 1. Multiple Logistic Regression of PAT on Prevalence and Progression of CAC.

	Model 1*	Model 2†	Model 3‡
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Prevalence of CAC			
Log PAT	2.9 (2.1, 4.0)	1.7 (1.2, 2.5)	2.2 (1.5, 3.3)
Progression of CAC			
PAT quartiles			
1st	Ref	Ref	Ref
2nd	1.7 (1.0, 2.8)	1.6 (0.91, 2.7)	1.7 (1.0, 2.9)
3rd	1.1 (0.63, 1.9)	1.0 (0.56, 1.8)	1.1 (0.62, 2.0)
4th	2.0 (1.1, 3.6)	1.7 (0.89, 3.3)	2.1 (1.0, 4.1)

*Adjusted for age, sex, diabetes, HDL, and hypertension; +CAC prevalence in progression model.
†Model 1 + BMI.
‡Model 1 + VAT.

Supported By: American Diabetes Association (7-13-CE-02 to A.C.A.)

1497-P

Cardiovascular Safety of GLP-1 Receptor Agonists (GLP-1-RA) vs. Other Antidiabetic Agents in Routine Care

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GLP-1-RA may reduce the risk of major adverse cardiovascular events (MACE) in patients with type 2 diabetes mellitus (T2DM). Among metformin users, we compared intensification with GLP-1-RA vs. other antidiabetic agents with regard to MACE risk. Within a large commercial U.S. health insurance database, we identified T2DM patients who intensified metformin with new use of GLP-1-RA, DPP-4 inhibitors (DPP-4i), sulfonylureas, or insulin between 2005 and 2013. Propensity score (PS) matched analyses were used to balance more than 100 baseline characteristics and evaluate MACE risk (i.e. hospitalization for non-fatal acute coronary syndrome, stroke, or cardiac revascularization) in 3 separate PS-matched cohorts (Table 1). Follow-up started on the day following intensification and ended at a MACE event, insurance disenrollment, or the end of a 365-day period. GLP-1-RA initiators had no significant difference in MACE risk vs. initiators of DPP-4i (Cox HR= 1.01, 95% CI = 0.81, 1.26) or vs. sulfonylureas (HR= 0.85, 95% CI = 0.66, 1.11), but had decreased risk vs. insulin initiators (HR= 0.72, 95% CI=0.65, 0.80). Sensitivity analyses censoring at treatment discontinuation produced consistent results. In this study, intensification with GLP-1-RA was associated with a lower MACE risk than insulin, but a similar risk to DPP-4i and sulphonylureas.

Table 1. Characteristics and Outcomes in 3 PS-Matched Cohorts.

	1. PS-matched Cohort GLP1-RA vs. DPP-4i		2. PS-matched Cohort GLP1-RA vs. Sulfonylureas		3. PS-matched Cohort GLP1-RA vs. Insulin	
Baseline characteristics	**GLP1-RAs (N=17,763)**	**DPP-4i (N=17,763)**	**GLP1-RA (N=14,091)**	**Sulfonylureas (N=14,091)**	**GLP1-RA (N=23,729)**	**Insulin (N=23,729)**
Age, Mean (SD)	51.5 (9.5)	51.5 (10.1)	50.8 (9.6)	50.7 (10.3)	51.9 (9.5)	52.0 (10.2)
Females, N (%)	9189 (51.7)	9154 (51.5)	7914 (56.2)	7942 (56.4)	11267 (47.5)	11260 (47.5)
Charlson comorbidity index, Mean (SD)	1.3 (0.7)	1.3 (0.6)	1.2 (0.6)	1.2 (0.6)	1.3 (0.7)	1.3 (0.7)
Outcomes	**GLP1-RAs (N=17,763)**	**DPP-4i (N=17,763)**	**GLP1-RA (N=14,091)**	**Sulfonylureas (N=14,091)**	**GLP1-RA (N=23,729)**	**Insulin (N=23,729)**
MACE, N (IR per 1000 person-years)	157 (10.9)	156 (10.8)	104 (9.2)	120 (10.8)	239 (12.5)	326 (17.7)
Hazard Ratio (95% CI)	1.01 (0.81-1.26)	Ref.	0.85 (0.66-1.11)	Ref.	0.71 (0.60-0.84)	Ref.

1498-P

Trends and Disparities in Hospitalization Rates of Heart Failure among Adults with Diabetes, United States, 1998-2012

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Heart failure (HF) is more prevalent in patients with diabetes than in those without. Cardiovascular risk factors and glycemic control have improved during the past decade among U.S. adults with diabetes. However, no recent studies have examined whether rates of HF and disparities in HF among people with diabetes have paralleled these improvements. Rates were calculated using the number of discharges among adults aged ≥35 years with diabetes-related HF (ICD-9-CM 250 as any listed diagnosis and 428 as primary diagnosis) from the National Inpatient Sample and the U.S. diabetic population from the National Health Interview Survey. Joinpoint regression was used to calculate an annual percentage change (APC) for trend segments and an average APC (AAPC) for the entire time period with 95% confidence interval (CI) to assess trends. The total number of diabetes-related HF hospitalizations increased from 345,535 in 1998 to 426,205 in 2003, and then declined to 374,560 in 2012. The overall age-adjusted rate per 1,000 diabetic population did not change from 1998 to 2003 [24.7, 95% CI (22.7, 26.8) to 23.2 (21.4, 25.0)] ($p>0.05$), and then decreased by 5.4% per year to 13.8 (13.0, 14.6) in 2012 ($p<0.01$). Across the entire study period, rates declined by 4.2% (3.4%, 5.0%) per year. From 1998 to 2012, those aged ≥45 years, men, women, and whites experienced significant declines in hospitalization rates, with AAPC ranging from -5.9% to -3.4%. However, rates among adults aged 35-44 years did not change [AAPC= -1.2% (-2.9%, 0.5%)], and rates among blacks declined at a slower rate than others [AAPC= -1.1% (-2.3%, 0.0%)]. Thus, the absolute difference in HF rates between whites and blacks increased from 6.9 to 9.3 per 1,000 diabetic population. From 1998 to 2012, HF hospitalization rates among people with diabetes declined with an annual decline of 4.2%. The declines were observed for all demographic groups examined except for younger patients. However, black-white disparities in HF rates are widening.

1499-P

WITHDRAWN

1500-P

WITHDRAWN

1501-P

Cardiovascular Risk Factors after Lifestyle Intervention in Prediabetes: Findings from the D-CLIP Trial

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Lifestyle interventions to prevent diabetes may impact cardiovascular disease (CVD) risk factors. The Diabetes Community Lifestyle Improvement Program (D-CLIP) is a randomized, controlled, translation trial of lifestyle modification to prevent diabetes among overweight Asian Indians with impaired fasting glucose and/or impaired glucose tolerance in Chennai, India (n=599). We report (a) proportions achieving CVD risk factor goals (b) changes in HbA1c, systolic blood pressure (SBP), plasma triglycerides (TG), total cholesterol (TC), and low- and high-density lipoprotein (LDL, HDL) across trial groups. After three years, loss to follow-up was 9%. The proportion reaching 1 or 2 CVD goals was statistically greater in the intervention vs. control group at most time points (Table 1). At 6 months, mean reductions from baseline were greater in the intervention for HbA1c (difference between groups: 0.13%, t-test p=0.0002), TG (16.18 mg/dL, p=0.0007), TC (8.68 mg/dL, p=0.0004), and LDL (5.84 mg/dL, p=0.007), but not SBP (1.22 mmHg, p=0.2) or HDL (0.04 mg/dL, p=0.9). After 3 years, differences dissipated (HbA1c 0.09%, p=0.2; TG 1.93 mg/dL, p=0.9; TC 3.66 mg/dL, p=0.6; LDL 0.96 mg/dL, p=0.8). Comprehensive lifestyle programs to prevent diabetes can have beneficial effects on cardiometabolic factors in Asian Indians with prediabetes, but maintaining improvements remains a challenge.

Table 1. Percent of D-CLIP Participants Reaching and Maintaining CVD Risk Reduction Goals.

	Months Follow Up	6	12	18	24	30	36
Reached At Least One CVD Risk Reduction Goal	Intervention	73.5*	68.6*	61.5*	57.6*	44.5*	26.9*
	Control	62.8*	52.9*	47.1*	47.8*	33.1*	17.1*
Reached At Least Two CVD Risk Reduction Goals	Intervention	40.6*	33.6*	33.6*	29.3	23.0*	13.1
	Control	25.3*	22.2*	21.2*	24.9	16.4*	8.5
Reached Three CVD Risk Reduction Goals	Intervention	6.0	3.9	4.6	5.7	3.1	1.4
	Control	3.1	3.1	2.7	2.7	1.0	1.0

*Group percentages are significantly different at p<0.05.

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1502-P

Declining Hospitalization Rates for Hemorrhagic and Ischemic Stroke among U.S. Adults With and Without Diagnosed Diabetes, 1998-2012

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Stroke hospitalization rates have declined among U.S. adults with diabetes but the trends by type of stroke compared to people without diabetes have not been evaluated. Using 1998-2012 Nationwide Inpatient Sample data, we estimated the number of discharges among adults aged ≥35 years with hemorrhagic stroke (HS) (ICD-9 430-432) or ischemic stroke (IS) (ICD-9 433-434) as first-listed diagnosis. ICD-9 250 listed as a secondary diagnosis was used to identify those with diagnosed diabetes. Rates were calculated using diabetic and nondiabetic population estimates from the National Health Interview Survey and age-adjusted to the 2000 U.S. standard population. Joinpoint regression was used to analyze trends and calculate an average annual percentage change (AAPC) in rates with 95% confidence intervals. In 2012, 236,735 discharges for stroke (82% of which were IS) were diabetes-related, and 490,435 discharges (74% of which were IS) were nondiabetes-related. From 1998 to 2012, in both populations, age-adjusted rates for HS decreased at a similar rate, from 1.4 to 1.1 per 1,000 diabetic population (AAPC =-1.1% [-1.6%, -0.5%]), and from 0.8 to 0.6 per 1,000 nondiabetic population (AAPC =-1.5% [-2.0%, -1.0%]) (both AAPCs p<0.01). For IS, age-adjusted rates decreased from 10.0 to 7.0 per 1,000 diabetic population (AAPC =-2.6% [-4.0%, -1.2%]), and from 3.3 to 2.6 per 1,000 nondiabetic population (AAPC =-1.0% [-1.5%, -0.6%]) (both AAPCs p<0.05). Hospitalization rates for HS and IS in both diabetic and nondiabetic populations have declined. However, the rate of decline for IS was greater in the diabetic population compared with the nondiabetic population (AAPC: -2.6% vs. -1.0%, p<0.05). The declining trends may be due to a number of factors, including a reduction in prevalence of risk factors, new and or more aggressive treatment of cardiovascular risk factors, or other factors.

For author disclosure information, see page A810.

1503-P

Association of Sleep Duration with Stroke in Diabetic Patients: Analysis of the National Health Interview Survey

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Abnormal sleep duration (both short and long) is increasingly being recognized as an important risk factor for stroke. We sought to describe the association between abnormal sleep duration and stroke in a cohort with diabetes.

Data from the National Health Interview Survey (2004-2013) was examined. Only those answering "yes" to the question "Have you EVER been told by a doctor or other health professional that you have diabetes or sugar diabetes?"; and females answering "yes" to the question "Other than during pregnancy, have you EVER been told by a doctor or other health professional that you have diabetes or sugar diabetes?" were included in the analysis. Sleep duration was categorized as short (≤ 6 hours), normal (7-8 hours), or long (≥ 9 hours). Self-reported diagnosis of stroke was the main outcome of interest.

A total number of 27,223 self-reported diabetic patients (mean age (±SEM)= 36.9 (±0.03) years, and mean BMI (±SEM)=30.4 (±0.04) Kg/m2; 50.3% female; 6.6% Asians, 15.3% Blacks, and 76.1% Whites) provided valid data for the analysis. Stroke was reported in 8.7% of short sleepers, 15.9% of long sleepers and 7.9% of normative sleepers ($p<0.05$). Based on logistic regression analysis, adjusting for effects of age, gender, race/ethnicity, socioeconomic status, smoking, alcohol intake, physical activity and medical comorbidities, diabetic patients with both short sleep and long sleep had an increased odds of stroke when compared to normal sleep duration (OR=1.14, 95% CI: 1.11 – 1.18, $p<0.01$; and OR=1.71, 95% CI: 1.47 – 1.99, $p<0.01$; respectively).

In diabetic patients, abnormal sleep duration was associated with increased risk of stroke, and diabetic patients reporting long sleep duration had an almost twofold greater likelihood of having a stroke. Incorporating a sleep history into routine clinic visit examination may help healthcare providers optimize efforts to prevent or manage stroke in diabetic patients.

1504-P

The Combined Effect of Visit-to-Visit Variability in HbA1c and Systolic Blood Pressure on the Incidence of Cardiovascular Events in Patients with Type 2 Diabetes

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Visit-to-visit variability in HbA1c or blood pressure (BP) is an independent predictor of diabetic complications. However, no study has examined the risks simultaneously. This study investigated the association between long-term visit-to-visit variability in HbA1c and systolic BP (SBP) and the incidence of cardiovascular disease (CVD) in patients with type 2 diabetes.

We retrospectively enrolled 650 patients with type 2 diabetes and no history of CVD, who first visited our hospital between 1995 and 1996 and had at least four hospital visits, with at least one visit per year. Patients were followed through June 2012, at the latest. The median follow-up period was 15.4 years.

CVD occurred in 85 patients. Multivariate Cox regression analysis showed that the coefficients of variation (CV) for both HbA1c and SBP were significant predictors of the incidence of CVD independent of the mean HbA1c and mean SBP. Patients were classified into four groups according to the median CV of HbA1c and SBP. Hazard ratios were highest for the high HbA1c CV and high SBP CV group, and significantly higher for the low HbA1c CV and high SBP CV group and high HbA1c CV and low SBP CV group than for the Low HbA1c CV and low SBP CV group (Table).

Long-term visit-to-visit variability in both HbA1c and SBP represented a combined and additive risk for the incidence of CVD simultaneously.

Table.

	Incidence of CVD			
	Model 1		Model 2	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Continuous variables				
HbA1c CV	**1.07 (1.01-1.13)**	**0.017**	–	–
SBP CV	**1.09 (1.01–1.19)**	**0.032**	–	–
Categorical variables				
Low HbA1cCV and Low SBPCV	–	–	1	
Low HbA1cCV and High SBPCV	–	–	**1.99 (1.01–3.95)**	**0.048**
High HbA1cCV and Low SBPCV	–	–	**2.37 (1.06–5.31)**	**0.037**
High HbA1cCV and High SBPCV	–	–	**2.93 (1.44-5.94)**	**0.003**
Covariates				
Mean HbA1c (%)	1.14 (0.86-1.53)	0.366	1.16 (0.86-1.55)	0.334
Mean SBP (10 mmHg)	**1.20 (1.02-1.42)**	**0.032**	**1.21 (1.02-1.44)**	**0.034**
Age (10 years)	**1.63 (1.19-2.22)**	**0.002**	**1.53 (1.12-2.10)**	**0.008**
Male gender	1.19 (0.56-2.51)	0.650	1.19 (0.56-2.51)	0.650
Duration of Diabetes (5 years)	**1.34 (1.16-1.55)**	**<0.0001**	**1.32 (1.14-1.52)**	**0.0002**
Mean BMI	0.97 (0.89-1.06)	0.500	0.96 (0.89-1.05)	0.369
Mean TC/HDL-C	**1.58 (1.26-1.98)**	**<0.0001**	**1.59 (1.26-1.99)**	**<0.0001**
eGFR (mL /min/1.73 m^2)	0.99 (0.98-1.00)	0.087	**0.99 (0.97-1.00)**	**0.046**
Current smoking	1.08 (0.65-1.79)	0.781	1.12 (0.67-1.87)	0.666
Alcohol use	0.59 (0.33-1.03)	0.064	**0.55 (0.32-0.97)**	**0.037**
Number of visits (ln-transformed)	**0.31 (0.24-0.41)**	**<0.0001**	**0.31 (0.23-0.40)**	**<0.0001**

1505-P

The Alanine Aminotransferase Ratio/Aspartate Aminotransferase Ratio Is a Strong Predictor of Cardiovascular Events in Insulin Resistant Patients with Established Coronary Artery Disease

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Non-alcoholic fatty liver disease is an important feature of the metabolic syndrome and is characterized by an elevated alanine aminotransferase/aspartate aminotransferase (ALT/AST) ratio. The association of the ALT/AST ratio with cardiovascular events in insulin-resistant patients with established coronary artery disease (CAD) is unclear and is addressed in the present study.

The ALT/AST ratio was measured in a high-risk cohort of 1063 patients with angiographically proven CAD. Patients with a homeostatic model assessment index of insulin resistance >2.5 were considered insulin resistant. Prospectively, vascular events were recorded over 10 years.

At baseline, the ALT/AST ratio was significantly higher in insulin resistant patients than in subjects who were not insulin resistant (HOMA-IR 1.1±0.4 vs. 0.9±0.4;$p<0.001$). Prospectively, cardiovascular events occurred in 34.7% of our patients. The ALT/AST ratio after multivariate adjustment strongly and significantly predicted vascular events among insulin-resistant patients (standardized adjusted hazard ratio (HR) 1.37 [1.10-1.70]; p=0.004) but not among subjects without insulin resistance (HR 1.10 [0.95-1.39]; p=0.158).

We conclude that the ALT/AST ratio in insulin-resistant CAD patients is elevated and is significantly predictive of cardiovascular events.

1506-P

Evaluation of Finnish Diabetes Risk Score (FINDRISC) and Cambridge Diabetes Risk Score as Supplements to 10-Year ASCVD Scores for Predicting Atherosclerotic Burden in South Asians

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10-year ASCVD scores were recently shown to be useful in South Asians, but there are still concerns that they underestimate atherosclerotic burden in this group because they do not take into account pre-diabetic markers. The purpose of this study was to determine the efficacy of the FINDRISC and Cambridge Scores in predicting atherosclerotic burden in South Asians. 298 South Asian men between 40-79 underwent coronary artery calcium (CAC) scoring. They were then assigned a FINDRISC and Cambridge Score and divided into two groups of tertiles according to score severity. For each tertile, mean ASCVD and CAC scores were calculated. Mean ASCVD scores increased across FINDRISC (6.1±0.5 (0-4), 10.4±0.9 (5-8), 13.3±1.1 (9-19)) and Cambridge tertiles (6.1±0.5 (.98-5.1), 8.7±0.8 (5.2-16.2), 14.5±1.1 (16.3-82.0). Mean CAC scores also increased across FINDRISC (17±5.6 (0-4), 68±20.5 (5-8), 96±24.8 (9-19)) and Cambridge tertiles (17±5.4 (.98-5.1), 55±20.7 (5.2-16.2), 106±23.5 (16.3-82.0). Moreover, subjects with a FINDRISC score >=9 and Cambridge Risk score >=16.3 were both found to be more likely to have a non-zero CAC score: OR 2.5 (95% CI 1.4-4.6) and 2.5 (95% CI 1.4-4.4). Finally, for those whose ASCVD Risk Scores were <7.5%, mean CAC scores still increased across FINDRISC (19±7.1 (0-4), 19±7.6 (5-8), 54±24.9 (9-19)) and Cambridge tertiles (15±16.5 (.98-5.1), 23±8.7 (5.2-16.2), 52±22.5 (16.3-82.0). These results suggest there is a positive correlation between FINDRISC and Cambridge Scores and 10-year ASCVD and CAC scores. They also imply ASCVD scores underestimate atherosclerotic burden in South Asians because mean CAC scores of subjects whose ASCVD scores were <7.5% still increased across FINDRISC and Cambridge tertiles. In the future, both FINDRISC and Cambridge Scores could be useful supplements to 10-year

ASCVD scores for identifying South Asians at high risk of developing coronary artery disease.

1507-P

Effects of Body Mass Index on Mortality Risk in the General Population and in Subjects with Chronic Disease: The National Sample Cohort (2002-2010) in Korea

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Background: The association between body mass index (BMI) and mortality is not conclusive, especially in East Asian populations.

Methods: We evaluated the relationship between BMI and all-cause or cause-specific mortality, using data from the national sample cohort provided by the National Health Insurance Service in Korea. A total of 153,484 Korean adults over 30 years of age without pre-existing cardiovascular disease or cancer at baseline of 2003 and 2004 were followed-up until 2010 (mean follow-up period=7·91±0·59 years). Study subjects repeatedly measured body weight 3·99 (±2·01) times, on average.

Results: During follow-up, 3,937 total deaths occurred; 557 deaths from cardiovascular disease, and 1,224 from cancer. U-shaped associations were found between BMI and mortality after adjustment for age, sex, smoking, alcohol, physical activity, socioeconomic status, and weight change. Subjects with a BMI of less than 23 kg/m2 and more than 30 kg/m2 had elevated risks of mortality compared with the reference group (BMI 23-24·9 kg/m2). The lowest risk of all-cause mortality was observed in subjects with a BMI of 25-27·5 kg/m2 among the general population (adjusted hazard ratio [HR] 0·88; 95% confidence interval [CI] 0·80-0·97). Meanwhile, subjects with a BMI of 25-29·9 kg/m2 (moderate obesity) had a lower risk of mortality than those with a reference range in subgroups prominently in the elderly, and those with chronic diseases such as diabetes mellitus, hypertension, and chronic kidney disease. However, this association has been attenuated in younger individuals, those of higher socioeconomic status, and those without chronic diseases.

Conclusions: Moderate obesity was associated more strongly with a lower risk of mortality than with normal, underweight, and overweight groups in the general population of South Korea. This obesity paradox was prominent in not only the elderly but also individuals with chronic disease.

1508-P

Left Ventricular Dysfunction in Nonhuman Primate (NHP) Model of Diabetes

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Diabetes is one of the major risk factors for heart failure with reduced EF, and is highly associated with left ventricular (LV) dysfunction. This study was designed to noninvasively assess LV function using echocardiography in 89 cynomolgus macaques with or without diabetes based on their metabolic statues (Table 1). The present results demonstrated for the first time that pre-diabetic and diabetic monkeys are associated with LV systolic (increased ESV, decreased EF, etc.) and diastolic (decreased EDV and E/A ratio, DT prolongation, etc.) dysfunctions similarly to that in diabetic patients (Table 2). Thus, the spontaneously developed diabetic monkey model is a highly translatable tool not only for studying the pathogenic mechanisms of human diseases, but also for testing the novel therapies for both the cardiovascular and metabolic disorders.

Table 1. Animals Characteristics.

	Control	Pre-Diabetes	Diabetes
Number of animals (%)	28 (31.5%)	20 (22.5%)	41(46.1%)
Age (year)	11±4.4	12±4.8	18±4.3*#
Fasting Blood Glucose (FBG, mg/dL)	66±13	99±9*	227±87*#
HbA1c (%)	4.7±0.62	5.2±2.4	9.1±3.2*#
Cholesterol (CHO, mg/dL)	120±28	113±37	167±6*#
High-density lipoprotein (HDL, mg/dL)	54±14	48±15*	48±20*
Low-density lipoprotein (LDL, mg/dL)	41±17	41±23	69±37*#

Table 2. Echocardiography Parameters.

	Control	Pre-Diabetes	Diabetes
LV end-diastolic volume (EDV, ml)	14±7.4	13±5.8	12±5.7*
LV end-systolic volume (ESV, ml)	4.2±1.9	4.0±1.8	4.4±2.5
LV ejection fraction (EF, %)	68±10	69±10	63±13*#
Peak early diastolic E velocity (cm/sec)	85±17	76±16	79±20*
Peak late diastolic A velocity (cm/ sec)	64±18	69±22	70±18
E/A (ratio)	1.4±0.45	1.2±0.4	1.2±0.5*
Deceleration time (DT) of E wave (ms)	78±26	77±35	80 ±41*

1509-P

ProBNP Strongly Predicts Future Macrovascular Events in Angiographied Coronary Patients With as well as in Those Without Type 2 Diabetes

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Pro-B-type natriuretic peptide (proBNP) is a prognostic biomarker in various patient populations including those with congestive heart failure. The power of proBNP to predict cardiovascular events in patients with type 2 diabetes (T2DM) undergoing coronary angiography is unclear and is addressed in the present study.

We measured serum proBNP in 737 patients undergoing coronary angiography for the evaluation of established or suspected stable coronary artery disease (CAD). Significant CAD was diagnosed in the presence of coronary stenoses with lumen narrowing ≥50%. T2DM was diagnosed according to the ADA criteria. Prospectively, we recorded vascular events over 5.6±2.1 years.

ProBNP was significantly higher in patients with (n=391) than in subjects without significant CAD at baseline (720±1358 vs. 674±1606 pg/ml; p=0.001). Prospectively, we recorded 183 cardiovascular events. The incidence of vascular events significantly increased over tertiles of proBNP in patients with T2DM (21.3%, 30.2%, and 43.5% respectively; p=0.028) was well as in subjects without T2DM (16.9%, 21.2%, and 29.3%, respectively; p=0.015). Concordantly, serum proBNP significantly predicted the incidence of major cardiovascular events after adjustment for age, gender, BMI, smoking, systolic and diastolic blood pressure, LDL cholesterol, HDL cholesterol and the eGFR both in patients with T2DM (standardized adjusted HR 1.50 [1.25-1.78]; p <0.001) and in subjects without T2DM (HR 1.15 [1.03-1.29]; p=0.015). These results were not attenuated after further adjustment for the angiographically determined baseline CAD state (HRs 1.49 [1.24-1.79]; p <0.001 and 1.27 [1.13-1.43]; p <0.001 in patients with T2DM and in subjects without T2DM, respectively).

We conclude that serum proBNP predicts cardiovascular events independently of established cardiovascular risk factors and of the baseline CAD state both in patients with and in subjects without T2DM.

1510-P

Comorbid Type 2 Diabetes and Low Renal Function Does Not Further Increase Risk of Cardiovascular Disease in a Cohort of Older Mexican Americans

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Hispanics are almost twice as likely as non-Hispanic Whites to be diagnosed with diabetes. Although low renal function (LRF) and diabetes are both associated with increased risk of cardiovascular disease (CVD) and CVD-related deaths, little is known how having both conditions affect CVD risk among Hispanics.

We evaluated the risk of CVD due to LRF and determined the effects of interaction between type 2 diabetes and LRF. We hypothesized that having both conditions would lead to an increased CVD risk versus having LRF alone.

Participants came from the Sacramento Area Latino Study on Aging (SALSA), a longitudinal cohort study (n=1789) of Mexican Americans aged 60–101 years at recruitment. Participants were enrolled in 1998 and followed annually until 2008. Outcome was incident fatal and non-fatal CVD. Main predictor was baseline cystatin C eGFR, dichotomized to <60 or 60+ mL/min/1.73m^2. Cox models were used to evaluate the association between eGFR status and incident CVD, stratified on baseline diabetes status. We adjusted for BMI, age, and gender at baseline.

Table 1. Cox Regression Models for the Association between Low Renal Function and CVD, Stratified on Diabetes, n=905.

Predictors	All				Fatal				Non-Fatal			
	With Diabetes		Without Diabetes		With Diabetes		Without Diabetes		With Diabetes		Without Diabetes	
	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value	hazard ratio	p-value
Baseline cystatin C eGFR <60	0.99	0.96	1.53	0.01	2.18	0.04	2.20	0.07	0.85	0.52	1.53	0.02
Baseline BMI	1.01	0.30	1.02	0.25	0.98	0.54	0.98	0.62	1.02	0.22	1.02	0.19
Baseline age	1.04	0.01	1.04	<0.001	1.07	0.01	1.07	0.01	1.04	0.02	1.04	<0.001
Female	0.99	0.95	0.86	0.29	0.66	0.26	0.48	0.06	1.13	0.57	0.92	0.58

For author disclosure information, see page A810.

Guided Audio Tour poster

ADA-Funded Research

As shown in Table 1, LRF appears to increase the risk of CVD for non-diabetics. Interestingly, for diabetics having LRF is not associated with CVD risk greater than that found among non-diabetics. LRF is a strong predictor of mortality from CVD, with the risk of death twice as likely for both groups.

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1511-P

To Determine the Individual Effect of Age, Duration of Diabetes, BMI, and HbA1c on Parameters of Arterial Stiffness in Patients with Type 2 Diabetes

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Arterial Stiffness (AS) has been used as a measure of vascular health. However limited number of studies exist to determine which parameter of a patient has more effect on AS measures. The indices for measuring AS we used are Augmentation Index (Ag), Augmentation Index adjusted for heart rate75 (AgI-75), augmentation pressure (AP) and Pulse Wave Velocity (PWV). We used the Pearson product-moment correlation as a statistical method for analysis. We analyzed 18 patients to investigate which of the above parameters affect AS most. Only one time point was taken for this study. Subjects were enrolled with DM ≤ 8 years, age 40-70, with HbA1C of 6-9 and BMI 25-39.9. We enquired: a) whether age or duration of DM has more impact on the AS and; b) whether BMI or HBA1c level has more impact on AS.

Results that we obtained: a) AI and PWV c-f from the group of patients with DM duration of 0-4year duration [P correlation (Pc) =0.83; 0.93 n= 10] has linear relationship with age. AI and age has a linear relationship Pc=0.75; n=18 with DM duration 0-8yrs; b) relationship between AP and age is linear, Pc = 0.82; n=18; c) PWV c-r and year of DM in the group of people age 40-55 has a linear relationship with Pc = 0.93; n=5; d) HbA1c has direct effect on AI 75 in the patients with BMI 25.0-29. Pc = 0.89; n= 18; AND HbA1c has linear impact on PVW c-f in the patients with BMI 25.0-29.9. Pc= 0.96; n=4. We summarize that: A) Arterial stiffness measures in diabetes subjects appear to be reliable and reproducible using multiple measurement indices. B) PWV appears to be more informative than PWA, C) age can affect AS more than duration of DM; D) Level of HbA1c has more effect on AS than BMI, particularly in patients with BMI 25.0-29.9. In conclusion, we note that AS measurement is a robust indicator of vascular health. Though diabetes is considered a CVD risk equivalent, age appears to play a bigger role in AS development. Degree of diabetes or HbA1C seems to impact more than BMI on AS particularly in overweight subjects.

1512-P

Testosterone, Cardiac Magnetic Resonance Imaging (CMR), and Common Carotid Intima-Media Thickness (cIMT) in Men with Type 1 Diabetes in the Epidemiology of Diabetes Interventions and Complications Study (EDIC)

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Low endogenous testosterone (T) levels are associated with increased risk of cardiovascular events, but the mechanisms are unclear. We examined the relationship between endogenous T and measures of cardiac function obtained upon CMR, as well as the relationship between T and subclinical atherosclerosis obtained upon carotid ultrasound. Participants were men in EDIC, the observational follow-up of Diabetes Control and Complications Trial (DCCT); 628 men had T measurements at year 10 of EDIC, CMR measurements at years 14/15, and cIMT at year 12.

At EDIC year 10, the participants were 45±7 years old, had diabetes for 22±5 years, and had a time-weighted DCCT/EDIC mean HbA1c of 7.7± 1.2%. Adjusted for age, low levels of T were associated with lower end-diastolic volume index values (p=0.03) and with lower stroke volume index values (p=0.03). T was not associated with cIMT.

Lower endogenous T levels are associated with CMR measures but not with cIMT among men with type 1 diabetes. Additional analyses are needed to determine if low T contributes to cardiac dysfunction in men with type 1 diabetes, specifically, if BMI and insulin dosing confound the association between T and CMR measures.

Table. Age-adjusted measures obtained using endogenous testosterone levels at EDIC year 10 with cardiac magnetic resonance imaging (EDIC year 14/15) and carotid ultrasound imaging (EDIC year 12).

	T< 300 ng/dl N=39‡	T≥ 300 ng/dl N=589‡	p-value*
LV mass index, g/m^2	74.6 ± 11.6	76.6 ± 12.4	0.5
End-diastolic volume index, ml/m^2	**67.9 ± 9.5**	**73.6 ± 12.7**	**0.03**
End-systolic volume index, ml/m^2	27.3 ± 6.5	29.3 ± 7.8	0.2
Stroke volume index, ml/m^2	**40.6 ± 7.1**	**44.2 ± 8.1**	**0.03**
Cardiac index, L (min^{-1}xm^{-2})	2.9 ± 0.5	3.1 ± 0.6	0.1
LV mass/volume ratio, mg/ml	1.1 ± 0.2	1.1 ± 0.2	0.1
Ejection fraction, %	59.9 ± 7.3	60.4 ± 6.2	0.7
Common carotid intima media thickness (mm)	0.71 ± 0.14	0.71 ± 0.17	0.9
Ankle/arm ratio <0.9%	11%	8%	0.6

‡ Sample sizes vary depending on sample availability.
*p-values based on models adjusted for age and machine type (MRI) or reader and machine type (IMT).

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1513-P

Study of Cardiovascular Risks in Adolescents—ERICA: Epidemiological Aspects of the Pilot

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The risk factors of cardiovascular (CV) diseases in youth is growing up. We aimed to determine the frequency of CV risk factors (obesity, elevated blood pressure [BP], dyslipidemia and dysglycemia) and association between obesity and insulin resistance [IR], dyslipidemia, dysglycemia and elevated BP in adolescents.

Methods: This is a cross-sectional study with brazilian adolescents, selected by convenience, from public and private schools from five different cities, which formed the pilot study of the Study of Cardiovascular Risk Factors in Adolescents - ERICA. The measurements included: anthropometry, BP and laboratory tests. Overweight and obesity were defined using body mass index (BMI), IR by Homeostasis model assessment of IR (HOMA-IR), dysglycemia and dyslipidemia according to Brazilian Society of Diabetes and Cardiology, respectively.

Results: The sample was consisted by 976 subjects (13.8±1.5 y; 527 [54%] girls; 434 [44.5%] white; 20.9±4.2 BMI). It was found 156 (16.3%), 523 (54.5%), 186 (19.4%) and 94 (9.8%) adolescents classified as underweight, eutrophic, overweight/obese respectively. The prevalence of elevated BP, dyslipidemia, hyperglycemia, and IR in the overall sample were, respectively, 23.4%; 15.7%; 5.4% and 24.1%. The bivariate analysis, between obese and eutrophic, showed these prevalences: IR of 71.1% and 15.2% (PR: 4.7; p<0.001); elevated BP of 51.1% and 16.4% (PR: 3.1 and p<0.001); hypertriglyceridemia 17.5% and 4.7% (PR: 3.7 and p=0.002) and reduced HDL-c 38.1% and 18.7% (PR: 2.0 and p=0.005) respectively. A positive relationship was seen between obesity and IR (p<0.001), low HDL-c (p=0.005) and hypertriglyceridemia (p<0.001) and BP (p<0.001). There was no significant association between excess weight and hyperglycemia (p=0.862) and increased LDL-c (p=0.862).

Conclusion: Observed high prevalence of CV risk factors in early stages of life and close association between obesity and factors such as IR, dyslipidemia and elevated BP in all analyzed cities.

1514-P

Mortality Rates in Type 2 Diabetes Declined to the General Population Level in the Netherlands: A 19-Year Cohort Study

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The improvements in diabetes care and a more stringent treatment of cardiovascular risk factors appear to result in a decline in mortality rates in patients with type 2 diabetes (T2D). We described trends in mortality rates between 1994-2012 in Dutch patients with T2D, and examined whether these trends are explained by changes in cardiovascular risk management. We performed a retrospective cohort study using data of 4,020 T2D patients from 9 general practices. Mortality rates for both sexes, and for men and women separately, were compared to standardized mortality rates of the general Dutch population. Cox-proportional-hazards regression was used to analyze whether these trends are associated with changes in systolic blood pressure, low-density-lipoprotein, and glycated hemoglobin, corrected for age and smoking. The results show that the total mortality rates in T2D patients declined from 4.7 (95% CI 3.1-6.3) in 1994 to 2.5 (95% CI 1.9-

3.1) in 2012. Mortality rates declined from 4.3 (95% CI 1.9-6.7) to 2.4 (95% CI 1.6-3.2) in men and from 5.0 (95% CI 2.8-7.1) to 2.6 (95% CI 1.8-3.5) in women. A decrease in low-density-lipoprotein was associated with a significant lower risk of mortality with respective hazard ratio's of 0.683 (95% CI 0.597 - 0.780) in men and 0.749 (95% CI 0.663 - 0.848) in women. The results indicated gender-differences, i.e., female patients had slightly higher mortality rates, less statins prescribed, and a higher risk for smoking, than male patients. However, these gender-differences did not reach statistical significance. We conclude that mortality rates in patients with T2D in the Netherlands declined to a level that is comparable to the general population. This decline is probably due to the increased prescription of statins. Future research should focus on gender-differences.

1515-P

Study of the Variability of Heart Rate in Type 2 Diabetes Mellitus Patients with Diabetic Autonomic Neuropathy

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Diabetic autonomic neuropathy (DAN) is a severe and common complication of diabetes mellitus (DM). The balance between the sympathetic and parasympathetic nervous system, called autonomic balance, is an alternation of tachycardia and bradycardia. This is evaluate in the electrocardiogram (ECG) by measuring the variable intervals between heartbeats (RR intervals). This alternation between RR intervals seen in the ECG allows visualizing the variability of heart rate (HR) during a day. The autonomic imbalance caused by sympathetic hyperactivity and reduced vagal tone can develop arrhythmias and sudden death. Analyze of the cardiac autonomic profile is an important element for cardiovascular (CV) stratification in type 2 DM (T2DM) with DAN.

The utilization of the Holter system, analazying changes of the cardiac cycles considered normal, allows to extract indices that assess the prevalence of autonomic activity (sympathetic or parasympathetic) heart. From normal measured RR cycles (NN) in 24 hours, we removed indices such as the SDNN (standard deviation of all RR cycles). The lower this ratio, the higher sympathetic activity on the heart and therefore greater cardiac risk. In the study, 126 patients with T2DM performed Holter, 61 women (mean age = 54.32 ± 3.3). Excluded from the study patients on b-blockers and psychostimulants.

Using the SDNN index, stratified patients into 3 cardiac risk groups: Group A- high risk - SDNN ≤ 50ms - sympathetic predominance (23 patients with SDNN = 44 ± 5), M-medium risk - 50<SDNN<100ms - sympathetic-parasympathetic balance (66 with SDNN = 78 ± 14) and Group B - low risk - SDNN≥100ms - parasympathetic predominance (37 with SDNN = 136 ± 14).

The Holter is an easy way to assess cardiac risk. In this study we could stratify the CV risk in T2DM. The group A had higher risk for fatal arrhythmias. The data of the most recent clinical studies shows that neuropathy has been gaining attention as an important complication determing cardiovascular events.

1516-P

WITHDRAWN

1517-P

How to Measure the Effect of Diabetes on Cardiovascular Events during a Clinical Trial? A Meta-analysis of 330,376 Patients from 47 Landmark Trials

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Diabetes is known as a major cardiovascular risk factor. However, its influence on the rate of occurrence of cardiovascular (CV) events during a clinical trial that includes a sub-cohort of diabetics is rarely measured.

The purpose of this work was to determine the extent to which having diabetes at baseline, individually or at a sub-group level, increases as such residual CV risk over the course of a clinical trial.

We performed a meta-analysis of primary outcomes (PO) rates of key prospective trials, for which the baseline proportion of diabetics was reported, including studies having specifically reported CV outcomes within their diabetic subgroups.

Forty-seven studies, representing 330,376 patients (among whom 124,115 diabetics), were analyzed as regards the relationship between CV outcomes rates (including CHD) and the number of diabetics enrolled. Altogether, a total of 18,445 and 16,156 events occurred in the comparator and treatment arms, respectively. There were significant linear relationships between diabetes prevalence and both PO and CHD rates (%/year): $y=0.0299*x + 3.12$ [PO] ($p = 0.0128$); and $y=0.0531*x + 1.54$ [CHD] ($p = 0.0094$), baseline diabetes predicting PO rates between 3.12%/year (no diabetic included) and 6.11%/year (all patients diabetic); and CHD rates between 1.54%/year (no diabetic) and 6.85%/year (all patients diabetic).

In conclusion, the contribution of absolute and relative residual CV risk associated with the presence of diabetes at baseline during a clinical trial can be readily predicted from the linear equations relating diabetes prevalence to primary outcomes or CHD rates.

1518-P

Invasively Measured Aortic Blood Pressure Predicts Stroke in Diabetic Patients Followed in the Western Denmark Heart Registry during 2001-2012

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Diabetic patients are at high risk of stroke. Office blood pressure (BP) conventionally is used to assess hemodynamic load on the cerebral circulation. The prognostic impact of invasively measured aortic BP, which more closely represents the hemodynamic cerebral burden, remains unknown.

Office BP, invasively measured aortic BP, and aortic pulse pressure (PP) were recorded in 3113 diabetic patients (median age 65 years (IQR: 58-71 years), 63% male) with stable angina pectoris undergoing elective coronary angiography during January 2001-December 2012. The association with incident stroke during follow-up was assessed using Cox regression analyses. The predictive power of aortic BP vs. office BP was assessed by Harrell´s C .

In total, 85 (2.7%) patients had a stroke during a median follow up period of 3.1 years (IQR: 1.5-5.1 years). Aortic systolic BP and PP, but not office BP, were associated with incident stroke in both crude and adjusted analyses (Table). Harrell´s C increased non-significantly when aortic BP, compared to office BP, was used to predict stroke (Table).

We conclude that aortic systolic BP and aortic PP were associated with risk of incident stroke in diabetic patients. However, aortic BP did not significantly improve predictive power compared to office BP.

For author disclosure information, see page A810.

Table. Incident Stroke Per 10 mmHg BP Increase.

Hazard ratio (95% CI)			Harrell´s C
	Aortic systolic BP	Office systolic BP	Aortic vs. office BP
Model 1 (Crude)	1.15 (1.06; 1.15), p=0.001	1.07 (0.97; 1.19), p=0.15	0.60 vs. 0.56, p=0.28
Model 2	1.14 (1.05; 1.24), p=0.002	1.06 (0.96; 1.18), p=0.22	0.67 vs. 0.66, p=0.32
Model 3	1.13 (1.04; 1.23), p=0.003	1.06 (0.96; 1.17), p= 0.26	0.69 vs. 0.67, p=0.44
	Aortic PP	Office PP	
Model 1 (Crude)	1.19 (1.09; 1.30), p<0.001	1.10 (0.99; 1.23), p=0.08	0.61 vs. 0.58, p=0.40
Model 2	1.16 (1.05; 1.28), p=0.002	1.06 (0.94; 1.19), p=0.31	0.68 vs. 0.66, p=0.13
Model 3	1.15 (1.04;1.27), p=0.005	1.05 (0.94; 1.18), p=0.39	0.69 vs.0.67, p=0.20

Model 2: Model 1 plus age, gender, smoking, previous stroke, antihypertensive treatment, lipid-lowering treatment, and atrial fibrillation.
Model 3: Model 2 plus extent of coronary vessel disease (0/diffuse without significant stenoses/1/2/3).

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1519-P

Individualized Treatment in Patients with Comorbid Type 2 Diabetes and Heart Failure: Insights from the DIALOGUE Registry

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Patients with type 2 diabetes (T2DM) and hypertension have an increased risk of heart failure (HF) and HF itself complicates the treatment and outcomes of diabetes. We aimed to assess treatment strategies and outcomes in this patient group.

DIALOGUE is a prospective, multi-center registry in patients ith both T2DM and hypertension. Heart failure was recorded at baseline (physician assessment) and patients grouped into those with or without HF.

Out of 8392 patients included, 1123 (13.4%) were diagnosed as having HF at baseline. Patients with HF were older and had a >1 year longer diabetes duration. They had a significantly higher comorbidity burden, with the increase in coronary heart disease and strokes being pronounced. Consequently, they were more often assigned to less strict BP and HbA1c targets. Antihypertensive treatment was more intense as reflected in a higher number of patients receiving respective drugs (see Table). Consequently, achieved BP values after 6 month more closely match the individual target values. The overall mortality at 6 and 12 months follow-up was low, but significantly higher in HF than in non-HF patients.

Assigned individual treatment targets reflect the comorbidity status. Patients with HF were more likely to receive ACE-inhibitors and betablockers probably due to the additional proven benefit in heart failure treatment.

Table.

	Heart failure (n=1123)	No heart failure (n=7269)	p-value
Age (years)	72.3±9.6	63.9±11.2	<0.0001
Diabetes duration (median months)	79.8	66.1	<0.0001
Clinical variables			
HbA1c (%)*	7.7±1.4	7.8±2.2	0.13
Tx target HbA1c ≤6.5% (%)	33.7	40.0	<0.0001
Tx target HbA1c >7.0% to ≤7.5% (%)	23.1	17.3	<0.0001
Fasting blood glucose (mmol/l)*	8.3±2.8	8.5±2.8	<0.05
SBP at baseline (mmHg)*	140.4±16.3	140.3±15.6	0.45
SBP target ≤130 mmHg (%)	33.4	39.6%	<0.0001
SBP target >135 to ≤140 mmHg	34.1	26.1	<0.0001
Comorbidity			
Coronary heart disease (%)	60.0	18.3	<0.0001
Prior stroke (%)	16.2	4.6	<0.0001
Neuropathy (autonomous) (%)	22.2	11.3	<0.0001
Proliferative Retinopathy (%)	2.8	0.9	<0.0001
Antidiabetic treatment			
Metformin after BL (%)	72.4	81.1	<0.0001
DPP-4 inhibitors after BL (%)	62.4	62.2	0.90
Sulfonylurea after BL (%)	19.2	17.3	0.11
Glitazones after BL (%)	0.5	0.5	0.97
Insulin, short acting (%)	5.9	4.0	<0.01
Insulin, long acting (%)	14.7	12.3	<0.05
Insulin, mixed (%)	2.4	1.5	<0.05
Antihypertensive treatment			
ACEi/ARBs (%)	87.1	78.5	<0.05
Betablockers (%)	67.1	43.3	<0.0001
Calcium channelblockers (%)	33.7	25.9	<0.0001
Diuretics (%)	66.8	38.8	<0.0001
Events during follow-up period			
Death at 6 months (%)	0.7	0.1	<0.0001
Death at 12 months (%)	0.9	0.2	<0.0001

*mean±SD.

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1520-P

Impact of Metabolic, Hemodynamic, and Inflammatory Factors on Target Organ Damage in Healthy Subjects

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We wanted to test the impact of metabolic, hemodynamic and inflammatory factors on target organ damage (TOD) defined as cardiac hypertrophy (CH), atherosclerosis, arterioclerosis and microvascular damage (MD). In a population based cohort study of 2115 healthy subjects (1049 male 1066 female) with a mean age of 53,1±10.5 without known diabetes or cardiovascular disease we measured fasting plasma glucose (FPG), serum insulin, lipid profile, soluble urokinase receptor (suPAR), c-reactive protein (CRP), urine albumin/creatinine ratio (UACR), 24-hour ambulatory systolic (24hSBP) and diastolic blood pressure (24hDBP), left ventricular mass index (LVMI) by M-mode echocardiography, carotid plaques (CP) by ultra sound and carotid-femoral pulse wave velocity (PWV). To establish best model for association of LVMI, CP, PWV and UACR we used multiple linear regression analysis starting with inclusion of all variables without co-linearity taking away one by one non-significant variables.

CH assessed by LVMI was primarily associated with gender (β=0.37), 24hSBP (β=0.26) and HR (β=-0.15). Insulin resistance (IR) and inflammation only had minor albeit significant impact on LVMI assessed by HOMA (β=0.09) and CRP (β=0.05). Atherosclerosis assessed by CP was primarily associated to age (β=0.31), 24hSBP (β=0.13) and smoking (β=0.13). Arteriosclerosis indicated by PWV was primarily associated to age (β=0.39), 24hSBP (β=0.31), gender (β=0.14) and HR (β=0.15). FPG (β=0.04), total cholesterol/high density lipoprotein ratio (TC/HDL) (β=0.04) and CRP (β=0.03) had independent impact on PWV. Microvascular damage assessed by UACR was associated to gender (β=-0.16), 24hSBP (β=0.09) suPAR (β=0.09), smoking (β=0.05) and age (β=0.05).

We conclude that 24hSBP was independently associated to CH, arteriosclerosis, atherosclerosis as well as MD, whereas IR and inflammation were only weakly, independently associated to MD, arteriosclerosis and microvascular damage in healthy subjects.

1521-P

Target Values of Cardiovascular Risk Factors Are Not Associated with All-Cause Mortality in Patients with Type 2 Diabetes Mellitus

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Aim of our study was to investigate in a real life clinical set the relationship between target values of glycated hemoglobin, blood pressure and LDL-cholesterol, as considered in a combined fashion, and all-cause mortality in patients with type 2 diabetes mellitus. Two cohorts of patients with type 2 diabetes mellitus, the Gargano Mortality Study (GMS, n=810 patients) and the Foggia Mortality Study (FMS, n=929 patients), were investigated. A target risk score was built as a weighted linear combination of the recommended targets reached by each patient. In the GMS and in the FMS (follow

up=7.4 and 5.5 years, respectively), 161 (19.9%) and 220 (23.7%) patients died, with an age and sex adjusted mortality annual incidence rate of 2.1% and 2.8%, respectively. In both study samples the target risk score tended to be linearly associated with all-cause mortality (HR for SD increment 1.08, 95% CI: 1.03-1.14, p=0.001, and HR 1.02, 95% CI: 0.98-1.07, p=0.243, respectively). When the two cohorts were pooled and analyzed together, a clear association between target risk score and all-cause mortality was observed (HR for SD increment 1.05, 95% CI:1.02-1.08, p=0.004). This counterintuitive association was no longer observable in a model including age, sex, body mass index, smoking habit, estimated-glomerular filtration rate, albuminuria and anti-diabetic, anti-hypertensive and anti-dyslipidemic treatment as covariates (HR for SD increment 1.00, 95% CI: 0.96-1.04, p=0.852). In conclusion, in a real life clinical set of patients with type 2 diabetes mellitus, the combination of recommended target values of established cardiovascular risk factors is not associated with all-cause mortality.

EPIDEMIOLOGY—CLINICAL—DIAGNOSIS AND SCREENING

Guided Audio Tour: Diabetes Advances in Clinical Diagnosis and Screening *(Posters: 1522-P to 1529-P), see page 13.*

1522-P

Irisin and Vaspin as Novel Markers to Predict Metabolic Syndrome in Patients with Type 2 Diabetes

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Metabolic syndrome (MS) is a popular public health issue currently, for which insulin resistance and obesity are considered as the major causative factors. Energy metabolism dysfunction with enhanced reactive oxygen species (ROS) production may contribute to the metabolic abnormality of adipose tissue in obesity and diabetes. Irisin, a newly identified myokine and adipokine, can increase energy expenditure and improve insulin sensitivity and glucose tolerance. Vaspin as an adipocytokine was identified with insulin-sensitizing effects. Our aims were to examine the serum irisin and vaspin levels in type 2 diabetes (T2D) patients, investigate the correlation of irisin and vaspin with clinical parameters pertaining MS, and evaluate the performance of irisin and vaspin as markers to predict MS in T2D patients.

A total of 260 T2D patients were enrolled. Age, gender, anthropometry, biochemistry parameters, HOMA-IR, and levels of irisin, vaspin and ROS in fasting serum were assessed.

Compared to T2D patients without MS, T2D patients with MS had lower serum level of irisin, higher level of vaspin and ROS (P<0.05). Multiple logistic regression analysis revealed that vaspin and ROS were associated with MS (OR=1.39, 95% CI, 1.23-1.57; OR=1.38, 95% CI, 1.07-1.79; P<0.01, respectively). Multiple linear regression analyses showed that irisin and vaspin were significantly correlated with BMI, WC, TG and HOMA-IR (P<0.01). And irisin and vaspin were negative (OR=-0.41, P<0.01) and positive (OR=0.41, P<0.01) correlated with ROS, respectively. ROC analysis demonstrated that irisin and vaspin had significantly higher area under the curve (AUC=0.93, P<0.01; AUC=0.78, P<0.01, respectively) for the detection of MS.

Irisin and vaspin were associated with clinical presentations of MS and the serum ROS level in T2D patients, which suggests that irisin and vaspin might be involved in the development of MS partly via affecting energy metabolism, and may be valuable markers for predicting MS in T2D patients.

Supported By: National Natural Science Foundation of China (819471200591, 81471025); Fund Program for the Scientific Activities of Selected Returned Overseas Professionals in Shanxi Province, China (2013-251)

1523-P

Prediction of Incident Diabetes in the Jackson Heart Study Using Random Forests

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Statistical models for prediction of incident diabetes are often based on a few variables selected by experts. Here we pursued two main goals: 1) Investigate relative performance of a machine learning method such as Random Forests (RF) and a logistic regression (LR) model for detecting incident diabetes, and 2) Uncover potential predictors of diabetes. The Jackson Heart Study collected data at baseline and in two follow-up visits from 5,301 African Americans. We excluded those with baseline diabetes and no follow-up, leaving 3,633 for analyses. Over a mean 8-year follow-up, 584 participants developed diabetes. Diabetes was defined as current use of insulin or oral antidiabetic agent, self-report or physician's diagnosis, fasting glucose > 126 mg/dl, or HbA_{1C} > 6.5%. We used a LR model published by ARIC (Schmidt et al., Diabetes Care 2005) which included BMI, waist circumference, systolic BP, age, sex, glucose, HDL cholesterol, triglycerides, and parental diabetes history. The RF model evaluated 95 variables (including those provided to the LR model) from demographic, anthropometric, blood biomarkers, medical history, and echocardiogram data. The dataset was partitioned into training and testing sets 100 times. Each training dataset included 400 participants who developed diabetes during follow-up and 400 who did not. Both RF and LR were estimated for the training sets; the testing sets were used to evaluate performance based on accuracy, sensitivity, specificity and area under the curve (AUC). We also used RF measures to rank the importance of the variables to the model. RF produced Accuracy = 77%, Sens. = 70%, Spec. = 76% and AUC = 0.81 (mean values) versus, for LR, Accuracy = 71%, Sens. = 67%, Spec. = 71% and AUC = 0.76. Among the top-ranked variables HA_{1C}, glucose, renin and waist were detected. This work shows the potential of RF for incident diabetes prediction and detecting subtle patterns in data. Our findings confirm well-known predictors of diabetes and suggest a role for renin in prediction of diabetes.

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1524-P

Novel Mutations in GCK and HNF1A-MODY in a Large Cohort of Brazilian Diabetic Families

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Maturity-Onset Diabetes of the Young (MODY) is the most common form of monogenic diabetes. To date, there are few cohorts investigated for MODY in Brazil. The aim of this study was to report novel mutations related to MODY 2 (GCK) and 3 (HNF1A) in Brazilian diabetic families and describe clinical characteristics of those patients. Recently, our group has initiated molecular screening for MODY using Sanger's sequencing method. A total of 54 Brazilian families (102 subjects) were screened for GCK or HNF1A mutations: 26 families with clinical suspicion of MODY 2 and 28 families with MODY 3 phenotype. All exons and flanking intronic regions of GCK and HNF1A genes were studied. We found 10 GCK mutations (8 missense, 2 splice site) in 26 families (38%). Two of these variants were novel: c.580-3C>A/IVS5-3C>A and c.505A>G/p.K169E. HNF1A mutations were found in 5 families (18%): 2 missense, 1 nonsense and 2 frameshift-insertion. One was a novel mutation: c.1558C>T/p.Q520*. All 3 novel heterozygous mutations in GCK and HNF1A genes segregated in family members with diabetes phenotype. All variants were absent in healthy individuals databases (1k genomes, ESP-6500) and were predicted to be damaging using in silico analysis (Polyphen-2, MutationTaster, SIFT, HSF). In variant K169E, the substitution occurred in a codon already associated with MODY. All 3 subjects have diabetes onset before age of 25, BMI below 25, family history of diabetes, detectable fasting C-peptide (range 1,1 - 2,2 ng/mL) 3 years after diagnosis of diabetes, and negative beta cell pancreatic antibodies (GADA, IA2, IAA). In summary, we found 3 novel MODY mutations that are predicted to be pathogenic. Those genetic variants were present in subjects with clinical features of MODY. Since most of the MODY mutations are private, it is important to study different ethnicities. This is one of the largest cohorts of MODY patients in Brazil. Our molecular study has identified unpublished mutations, expanding the number of variants associated to this phenotype.

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1525-P

The Influence of Sickle Cell Trait on the Relationship between A1c and Fasting Glucose: The Jackson Heart Study

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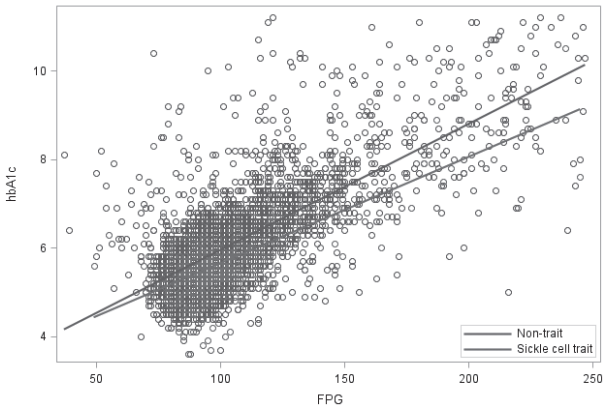
Current guidelines recommend the use of hemoglobin A1c (A1C) as a diagnostic and screening parameter for diabetes. Because of decreased presence of HbA and shortened lifespan of red blood cells in those with sickle cell trait (SCT), A1C may systematically underestimate levels of glycemia in those with SCT, particularly African Americans (AA) who have a much higher prevalence of SCT than whites. This analysis examined the relationship between concurrent measures of A1C and fasting plasma glucose (FPG) among AA with and without SCT using data collected across 10 years (3 clinic visits between 2000 and 2010) on 3,221 participants from the Jackson Heart Study. Using generalized linear mixed models to account for correlation of repeated measures, we estimated the effect of SCT on the association between A1C and FPG. Overall, 270 participants had SCT (8.4%). Participants with SCT did not differ by sex, age, or hemoglobin levels. Using assays available from 2000-2010, at the same FPG, participants with SCT had A1C measures that were, on average, 0.32% lower than participants without SCT (95% CI: 0.28%-0.36%; p<0.01). Given the threshold of A1C ≥6.5% for diagnosis of diabetes, a difference in A1C of 0.32% at the same FPG represents a substantial difference that may result in under-diagnosis of diabetes among AA with SCT. It remains to be determined if newer A1C assays continue to present this diagnostic challenge.

Figure 1. Relationship between fasting plasma glucose and hemoglobin A1c by sickle cell trait status: The Jackson Heart Study



1526-P

The Effect of Fasting Status on 23 Cardiometabolic Biomarkers in 96,000 Subjects

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Fasting requirements for blood collection present practical challenges for clinicians during routine patient assessment. Better understanding of the effects of fasting would enhance clinical decisions about appropriate ordering and interpretation of tests. De-identified data were obtained from blood samples submitted for initial testing to Health Diagnostic Laboratory, Inc. (Richmond, VA) between May 1, 2012 and Nov 1, 2014 as part of routine care. The effects of fasting vs. non-fasting state on measurements for individual patients were tested using linear regression models adjusted for age, gender, and BMI; absolute mean percent differences were reported. 95,860 independent subjects were studied with mean (SD) age 54 (15) and BMI 30 (6.9); 56% were female and 80% reported fasting for at least 8 hours. As expected, the biomarkers most sensitive to fasting status were all insulin-related, with mean differences ranging from 15% to 52%. Other biomarkers very sensitive to fasting (>10% variation) included: L-GPC (14%), triglycerides (14%), and oleic acid (-17%). Percent differences in CRP, leptin, and AHB were influenced by BMI and/or gender differences. These comparisons suggest that many biomarkers used to assess cardiometabolic risk are surprisingly unaffected by fasting status in a routine clinical setting, and highlight the possibility of risk assessment approaches that do not have rigid fasting requirements.

Table 1. Percent Differences in Biomarkers by Fasting Status (N = 95,860).

Biomarker	Median (1st Quartile, 3rd Quartile)		Geometric Mean Percent Difference**	
	Non-Fasting N = 19,151	Fasting (Reference) N = 76,709	Unadjusted	Adjusted for age, gender, & BMI
Proinsulin [pmol/L]	18 (10, 35)	12 (8.0, 21)	49.4	52.0
HOMA-IR	3.2 (1.7, 6.9)	2.5 (1.5, 4.2)	39.6	40.8
Insulin [uU/mL]	14 (8.0, 26)	10 (6.0, 16)	40.4	40.2
C-Peptide [ng/mL]	3.5 (2.4, 5.4)	2.8 (2.0, 3.8)	30.3	31.9
Oleic Acid [ug/mL]	41 (24, 63)	52 (37, 71)	-16.7	-17.0
Proinsulin / C-Peptide	5.2 (3.9, 7.4)	4.5 (3.4, 6.3)	14.6	15.2
L-GPC [ug/mL]	19 (14, 24)	16 (13, 21)	14.1	14.5
Triglycerides [mg/dL]	122 (83, 183)	107 (75, 156)	13.2	13.9
Adiponectin [ug/mL]	11 (7.0, 16)	10 (7.0, 15)	8.4	8.5
Free Fatty Acid [mmol/L]	0.48 (0.32, 0.69)	0.57 (0.43, 0.74)	-8.3	-7.5
hs-CRP [mg/L]	2.0 (0.8, 4.8)	1.8 (0.8, 4.2)	9.2	5.9
AHB [ug/mL]	4.3 (3.1, 6.1)	4.7 (3.5, 6.4)	-11.2	-4.9
Ferritin [ng/mL]	79 (41, 149)	91 (47, 167)	-1.4	-3.9
Leptin [ng/mL]	23 (11, 48)	22 (10, 45)	4.8	-3.0
Glycation Gap	-1.2 (-1.8, -0.6)	-1.2 (-1.8, -0.6)	1.2	3.3
LDL-C	105 (81, 132)	106 (82, 133)	-1.4	-2.3
NonHDL-C [mg/dL]	120 (94, 148)	119 (94, 148)	-0.8	-1.5
PPGI	5.7 (4.5, 7.9)	5.9 (4.7, 8.1)	-2.1	-1.1
Total Cholesterol [mg/dL]	176 (149, 206)	176 (148, 207)	-0.1	-0.9
Fructosamine [umol/L]	290 (260, 324)	292 (263, 326)	-0.4	0.5
Glucose [mg/dL]	92 (84, 105)	95 (87, 105)	-0.5	0.4
HDL-C [mg/dL]	53 (44, 65)	53 (44, 65)	0.6	-0.4
HbA1c [%]	5.4 (5.1, 5.8)	5.5 (5.2, 5.8)	-0.5	0.1

L-GPC = Linoleoyl-GPC; PPGI = [1/1,5 AG (µg/mL)]*100, Post Prandial Glucose Index]; AHB = alpha-hydroxybutyrate. ** All biomarkers were log transformed except: LGPC, Glycation Gap, HDL-C, LDL-C, and Oleic Acid.

1527-P

Impact of Diabetes Definition on Global Surveillance of Diabetes Prevalence

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During the past few decades diabetes definition has changed several times including most recently by adding haemoglobin A1c (HbA1c) as a diagnostic test. HbA1c has the advantages that no fasting is needed and there are now handheld devices that facilitate its use in large population-based studies. However, the debate over usefulness of HbA1c and its optimal diagnostic cut-off continues. Prior studies were based on small cohorts and few covered different regions.

We used data from 74 population-based surveys (217,408 participants in 27 countries) and compared prevalence of diabetes based on HbA1c ≥ 6.5% with prior definitions using fasting plasma glucose (FPG) ≥ 7 mmol/L or either FPG ≥ 7 mmol/L or post-prandial glucose (PPG) ≥ 11.1 mmol/L. Participants who reported prior diagnosis or treatment for diabetes were assigned to the diabetes group. We estimated sensitivity and septicity of HbA1c vs. FPG, PPG, or combined FPG and PPG among participants who did not have diabetes and pooled these using random-effect meta-analyses.

HbA1c-based prevalence of diabetes was on average 4% lower than those based on FPG alone and 16% lower than those based on FPG or PPG. FPG-based prevalence was on average 4% lower than that based on FPG or FPG. Pooled sensitivity of HbA1c ≥ 6.5% was 52.2% when compared with FPG and 36.2% when compared with PPG. Specificity of HbA1c ≥ 6.5% was ≥ 99.8% for both comparisons. Lowering the diagnostic threshold for HbA1c to 5.9% would increase the sensitivity of HbA1c vs. FPG to 82.8% while specificity would still be acceptable at 97.5%.

HbA1c with the proposed 6.5% threshold preforms relatively well in estimating diabetes population prevalence but would miss about half of the undiagnosed diabetes cases, making it unsuitable as a screening test. A lower threshold at 5.9% would increase the sensitivity while maintaining a high specificity.

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1528-P

Progression to Diabetes among U.S. Medicare Fee-for-Service Enrollees

KAI MCKEEVER BULLARD, SHARON SAYDAH, EDWARD W. GREGG, GIUSEPPINA IMPERATORE, *Atlanta, GA*

In the U.S., nearly 40% of the population will develop diabetes (DM) in their lifetime, and almost 3 in 4 older adults have some form of dysglycemia. We examined time to progression to DM from normal- and prediabetic glycemic status among a nationally representative sample of Medicare fee-for-service (FFS) enrollees. We used data from 1,091 men and women without diabetes aged ≥54 years who were examined in the 1999-2004 National Health and Nutrition Examination Survey (NHANES), a nationally representative survey. Incident DM was ascertained using 1999-2007 Medicare claims records. We excluded individuals at baseline with self-reported diagnosed DM, fasting plasma glucose (FPG)≥126 mg/dl, or A1c≥6.5%, and included those with normal glycemic status [FPG <100 mg/dl or A1c <5.7%] or prediabetes [IFG, FPG 100-125 mg/dl; or, impaired A1c (IA1C), 5.7-6.4%]. Progression to DM from time of NHANES examination date to first DM diagnosis was examined using cumulative probabilities and proportional hazards models. During a mean follow-up of 5.4 years, 144 participants progressed to DM, representing an overall incidence rate per 1000 person-years [PY] of 22.6 (95% CI: 17.4, 27.8) in the general Medicare FFS population. At baseline, cases had higher prevalence of obesity, central obesity, physical inactivity, and hypertension than non-cases. DM incidence rates per 1000 PY were 11.0 (5.7, 16.4) for those with normoglycemia and 34.4 (25.2, 43.6) for those with prediabetes. The incidence rate for those with combined IA1C + IFG was 62.3 (40.0, 84.7). Adjusted hazard ratios (normal glycemic status = reference) were 2.54 (1.57, 4.13) for prediabetes and 3.98 (2.07, 7.68) for combined IA1C + IFG. In the Medicare FFS population of older adults, those with prediabetes were two and a half times more likely to progress to DM than those with normoglycemia, while those with combined IA1C + IFG were almost 4 times more likely to progress to DM. Our findings suggest a need to target prevention programs to older adults on Medicare who have prediabetes.

1529-P

Causal Factors for Development of Diabetes Mellitus over the Course of 10 Years in the Korean Genome and Epidemiology Study: Serum Aryl-hydrocarbon Receptor Binding Activity

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Many epidemiologic studies showed serum levels of persistent organic pollutants (POPs) are linked to type 2 diabetes (T2D). Taking advantage of the fact that most of the POPs actby binding the aryl-hydrocarbon receptor (AhR), we developed a novel cell-based AhR ligand activity (CALA) assay for serum POPs and found serum AhR binding activity (AHR binding) is increased in T2D (Park WH et al. Biofactors, 2013). In this study we tested if AHR binding is predictive of future development of T2D.

Total of 1,537 sera collected in 2008 from the Ansung cohort, a part of Korea Genome and Epidemiologic Study (KoGES) was tested. KoGES was started in 2001 and followed upto 2012 (Cho NH et al. Acta Diabetol, 2013). About half, or 919 cases, had normal glucose tolerance (NGT), 244 cases had impaired glucose tolerance (IGT), and 374 were diabetic (DM).

The mean AHR binding was significantly higher in those subjects who developed IGT or DM within 4 years than who remained NGT. Subjects with IGT or DM had higher AHR bindings than NGT. Many clinical parameters associated with metabolic syndrome are quantitatively correlated with AHR bindings. From a ROC analysis, the estimated cut-off value of AHR binding predicting progression to DM within 4 years was 2.04 fold, with AHR binding area 82.1%, sensitivity 66.7%, and specificity 83.6%. In the Cox proportional hazards model, cutoff ≥2.04 fold predicted incident diabetes with a RR of 7.5 (95% CI 3.0-18.8) in the unadjusted model and increased risk remained highly significant (RR=4.8, 95% CI 1.6-14) after additional adjustment for other confounding factors, including sex, age, family history of diabetes, smoking and others.

We conclude that the high AhR ligand binding activity in serum predicts the development of T2D, suggesting a pathogenetic role of AhR ligands, probably POPs. CALA assay might be useful as a diagnostic test predicting T2D.

1530-P

Decreased Glycaemic Difference between Diabetes and Non-diabetes in the Elderly Leads to the Reduced Diagnostic Accuracy of Haemoglobin A1c for Diabetes Screening in Aged Chinese Population

XIANTONG ZOU, HECHAO LI, YUFENG LI, XIAOLING CAI, SIMIN ZHANG, XIUYING ZHANG, XUEYAO HAN, XIANGHAI ZHOU, LINONG JI, *Beijing, China*

This study aims to investigate the impact of age on the accuracy of haemoglobin A1c (HbA1c) for diabetes screening and explore the underlying mechanism. Data from 3050 Chinese participants without a prior history of diabetes in a cross-sectional survey in Beijing were analyzed. Diabetes was diagnosed by oral glucose tolerance test (OGTT). The performance of HbA1c for detecting OGTT defined diabetes in tertile groups according to age was evaluated by the area under the curve of receiver operating characteristic curve (ROC AUC). The effect of age on the difference of glycaemic levels between diabetes and non-diabetes participants and the impact of age on the ROC AUC of HbA1c was evaluated.

Results: In the lowest, medium and highest tertile age group (participants aged 25-41, 42-53 and 54-75 years), the ROC AUC (95% confidence interval) of HbA1c for detecting OGTT diagnosed diabetes was 0.958 (0.915, 1.000), 0.891 (0.852, 0.930) and 0.861 (0.821, 0.901), respectively (P=0.005). Sensitivity of HbA1c at the optimal cut-off point was 94.2, 82.9 and 75.4%, respectively. In the three tertile groups, the difference of fasting plasma glucose (FPG) between non-diabetes and diabetes participants decreased with increasing age (3.01 (2.80, 3.22), 2.90 (2.71, 3.09) and 2.33 (2.16, 2.50) mmol/l in the three consecutive age groups, respectively). This was also true for 2 hour postprandial plasma glucose. The impact of age on the diagnostic accuracy for detecting glucose defined diabetes with HbA1c disappeared after the data was transformed to diminish the difference of glucose level between non-diabetes and diabetes individuals. In conclusion, the accuracy of HbA1c for detecting OGTT defined diabetes is age dependent with decreased accuracy in individuals with more advanced age. This is associated with narrowed difference between glucose level of non-diabetes and diabetes individuals in aged groups.

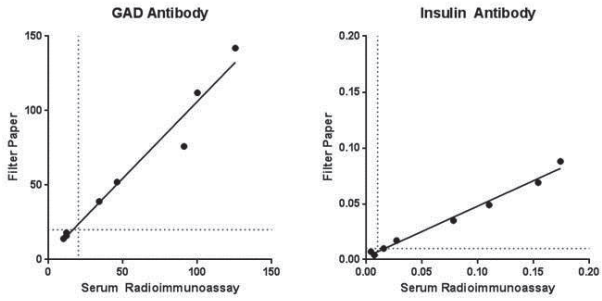
Supported By: National Key Technology R&D Program of China (2012AA02A509); National Basic Research Program of China (2011CB504000); Beijing Science and Technology Committee

1531-P

Islet Autoantibody Measurements from Dried Blood Spots Strongly Correlate with Serum Radioimmunoassay Levels

KIMBER M. SIMMONS, AIMON ALKANANI, LIPING YU, DONGMEI MIAO, AARON W. MICHELS, *Aurora, CO*

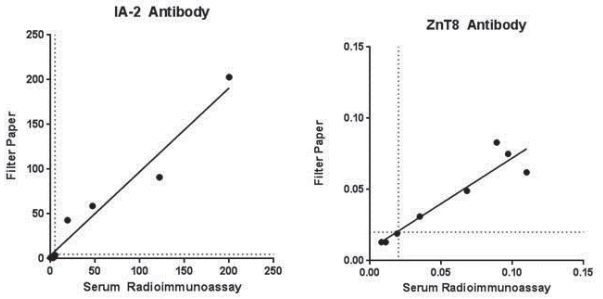
Type 1 diabetes (T1D) is predictable in first degree relatives (FDR) and genetically at-risk individuals, as having ≥2 islet autoantibodies (IA) defines preclinical disease. Screening for IA reduces diabetic ketoacidosis and allows for secondary T1D prevention studies. FDRs can be screened for IA through research studies; however, ~85% of T1D cases have no family history and screening is not available to the general population. Barriers to general screening include low feasibility of collecting blood samples, cost, and difficulty measuring IA, especially insulin which is prevalent in young children developing T1D. We hypothesize that measuring IA from dried blood spots (DBSs) on filter paper will begin to address these barriers. To establish methodology for screening IA from DBS, we performed titrations using IA positive serum spiked into IA negative whole blood. A 6mm DBS was transferred to each well of a nonbinding 96 well plate in elution buffer, agitated, and IA measured by sensitive radioimmunoassays (RIA). As shown in the figure, serum RIA antibody levels correlate with DBS eluate (r^2=0.96 GAD, 0.98 mIAA, 0.95 IA-2, 0.89 ZnT8; p<0.01); dotted lines denote positive cutoff for serum RIA. We are enrolling new onset T1D (n=14) and controls (n=10) with no false positives for insulin, GAD, or IA-2 from DBS measurements. Measuring IA from DBS may allow for screening the general population for T1D risk.



For author disclosure information, see page A810.

Guided Audio Tour poster

ADA-Funded Research



1532-P

Lifetime Risks for Type 2 Diabetes Mellitus: The Rotterdam Study

SYMEN LIGTHART, THIJS T.W. VAN HERPT, MAARTEN J.G. LEENING, ALBERT HOFMAN, BRUNO H.C.H. STRICKER, MANDY VAN HOEK, ERIC SIJBRANDS, OSCAR H. FRANCO, ABBAS DEHGHAN, *Rotterdam, Netherlands*

Data on the lifetime risk of type 2 diabetes and the use of blood glucose lowering medication are scarce. Little is known about the lifetime risk of type 2 diabetes in relation to measures of adiposity. We calculated lifetime cumulative incidences for diabetes and the use of blood glucose lowering medication adjusted for competing risk of death free of diabetes in 10,050 participants aged 45 years and older of the prospective population-based Rotterdam Study. Incident diabetes was diagnosed as fasting glucose level ≥ 7.0 and/or the use of blood glucose lowering medication. All analyses were stratified by sex and anthropometric measures. The mean (SD) age of the population was 64.7 (9.7) years and 57.7% were female. During a mean follow-up of 7.9 (4.0) years, 828 participants developed diabetes and 1709 deceased. At the age of 45, the lifetime risk for type 2 diabetes was 31.3% [95% CI 29.3 to 33.3] (30.5% [27.5 to 33.5] for men and 31.9% [29.3 to 34.6] for women). The lifetime risk was lower with increasing age and declined to 8.9% [6.9 to 10.9] at age 85. Lifetime risks were increasing with body mass index (BMI) and waist circumference (WC) both in men and women. At age 45, those with a BMI <25 kg/m2 had a lifetime risk of 18.8% [15.8 to 21.7], whilst 56.6% [46.7 to 66.6] of those with a BMI ≥35 kg/m2 developed diabetes. In addition, those aged 45 with a WC <80cm for women and <94cm for men had a lifetime risk of 19.5% [16.0 to 23.1], whereas 60.9% [51.0 to 70.9] of those with a WC >108cm for women and >122 for men developed diabetes. The lifetime risk for the use of oral antidiabetic medication was 28.5% [25.0 to 32.0], whereas 9.1% [7.8 to 10.3] became insulin dependent. In conclusion, almost one in three individuals aged 45 will develop type 2 diabetes and will be medication dependant during their remaining lifespan. Our study underscores the importance of lifestyle by showing the effects associated with obesity on lifetime risk of type 2 diabetes.

1533-P

Longitudinal Trajectories of Glucose, Insulin Sensitivity, and Insulin Secretion during Development of Type 2 Diabetes in Japanese: Toranomon Hospital Health Management Center Study

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Evidence is limited about long-term trajectories revealed by assessments of insulin and glucose concentrations before development of type 2 diabetes (T2D). To clarify the time point of deteriorating insulin sensitivity and β-cell function during the development of T2D, we investigated 515 individuals without T2D using various measures of glucose and insulin concentrations during a 3-h oral glucose tolerance test over 10 y. Individuals who did not develop T2D (n=454) had consistently low mean fasting values (<97 mg/dL) and postprandial glucose concentrations at 30 min (<155 mg/dL), 60 min (<151 mg/dL), 90 min (<133 mg/dL), 120 min (<122 mg/dL) and 180 min (<97 mg/dL) over 10 y. Those who later developed T2D (n=61) had higher glucose concentrations at 0 to 120 min even 10 y before diagnosis than those who did not develop T2D; incident cases of T2D also experienced a sharp increase in these glucose measures 3 y before diagnosis. A large difference between cases and non-cases was observed for glucose measurements at 60 min over the total observational period while glucose concentrations at 180 min specifically deteriorated only 1-2 y before diagnosis. Interestingly, those who later developed T2D had constantly reduced insulinogenic index values as a marker of early insulin secretion and reduced whole body insulin sensitivity index levels; these values remained low and did not markedly increase in the late stage before diagnosis. A sharp increase in the homeostasis model assessment index of insulin resistance in the late stage before diagnosis predicted T2D. Results suggested that persons who later developed T2D had clearly elevated glucose concentrations at 60 min rather than other glucose measurements even 10 y before diagnosis. Those who developed T2D also had consistently reduced β-cell function and whole body insulin sensitivity over 10 y before diagnosis, values similar to those observed at diagnosis.

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1534-P

Family History of Diabetes, Presence or Absence of Metabolic Risk Factors, and 5-Year Incident Risk of Type 2 Diabetes in Japanese Men: Toranomon Hospital Health Management Center Study

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A positive family history (FH) of diabetes is a risk factor for diabetes. We investigated the impact of the combination of FH and a number of metabolic risk factors on the development of diabetes in 8821 persons without diabetes at a baseline examination. Diagnosis of diabetes was made by fasting glucose ≧126 mg/dl, HbA1c ≧6.5% or a self-reported history of clinician-diagnosed diabetes. FHs of grandparents, parents or siblings having diabetes were assessed by a questionnaire. Metabolic risk status was assessed by hypertension, dyslipidemia, low HDL cholesterol concentrations and impaired fasting glucose. A metabolically abnormal (MA) state was indicated by having ≥2 of these conditions. During a 5-year follow-up, 305 individuals developed diabetes. Compared with individuals with no FHs, those with parental FH had an odds ratio (OR) of 2.61 (95% CI 1.99, 3.42) for developing diabetes. Persons with a bi-parental FH had an OR of 6.65 (2.87, 15.43) for diabetes compared to those with no parental FH of diabetes. Persons with a FH in 2 generations (grandparents and parents) had an OR 4.76 (2.01, 11.32) compared to those without FHs in both generations. In comparison with no FH of diabetes, individuals with FHs in parents and siblings had an OR 5.05 (2.68, 9.52) for diabetes. We investigated the individual and combined effect of metabolic risk factors and FH clustering. MH persons with a FH of diabetes in ≥2 relatives (grandparents, parents, siblings) had an increased risk of developing diabetes with an OR 5.61 (2.72, 11.59) for diabetes compared with MH individuals without FHs. However, MH persons with a FH in only one relative did not have a significantly increased risk of diabetes (OR 1.35 (0.77, 2.38)). Although the association of FH with developing diabetes varies according to the presence or absence of MA, we found that individuals with FHs of diabetes in parents or 2 generations were at high risk for developing diabetes.

1535-P

Combined Effects of Sex Hormone-binding Globulin and Sex Hormones on Risk of Incident Type 2 Diabetes

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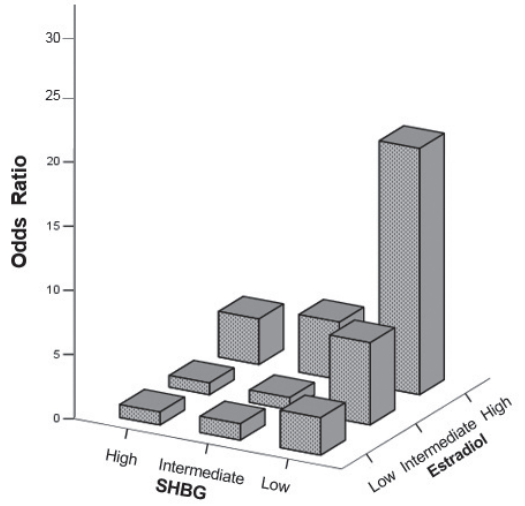
To investigate combined effects of sex hormone-binding globulin (SHBG) and sex hormones on risk of type 2 diabetes (T2D).

This was a nested case-control study among Chinese who participated in the Diabetes and Inflammation Study (2008-2013). Of the 3349 subjects who were free of diabetes, 145 men and 87 women developed diabetes during five-year follow-up. One control subject was selected for each case and matched for age and gender. The distributions of SHBG, estradiol, testosterone and dehydroepiandrosterone-sulfate (DHEA-S) at baseline were split by the tertile and subjects were stratified into those with low, intermediate and high levels accordingly.

After multivariable adjustment, men with low SHBG levels compared to those with high SHBG levels exhibited a four-fold increased risk of T2D, whereas men with high estradiol levels exhibited a four-fold increased risk of T2D compared with those with low estradiol levels. Men with low SHBG and high estradiol exhibited a nineteen-fold increased risk of T2D compared to men with high SHBG and low estradiol (odds ratio [OR] 19.18 [95% CI 3.74-53.46]). In men or women, these risk associations were not observed for testosterone or DHEA-S, alone or in combination with SHBG.

Low SHBG in conjunction with high estradiol exerts an additive detrimental effect on risk of T2D in men.



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1536-P

Testing and Validation of Quality Measures for Childhood Obesity

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National quality measures for pediatric overweight/obesity were commissioned as part of the Children's Health Insurance Program Reauthorization Act (CHIPRA). Quality measures were developed through a comprehensive literature review and a national expert panel convened by the Quality Measurement, Evaluation, Testing, Review, and Implementation Consortium (Q-METRIC) at the University of Michigan in 2012. We tested the performance of 5 quality measures via medical chart review (M1-4) and parent survey (M5) in a national sample of children aged 2-18 with a routine outpatient encounter in 2013 with a specialty of pediatric or general practitioner/family practitioner from a longitudinal database of medical and pharmacy claims from 14 U.S. Blue Cross/Blue Shield Health Plans. We anticipate a total of 750 medical charts and 1350 surveys to be completed. We present preliminary data based on 50 charts and 971 completed surveys for this abstract. For the medical record review (n=50), 11% of children had documentation of body mass index (BMI) percentile, and 28% had documentation of weight classification (M1). For children identified with a BMI≥85th%, none had documentation of communication of weight status in the medical record (M2), blood pressure percentile or classification (M3), nor subsequent outpatient visit where weight was addressed (M4). Based on a separate sample of children from a parent survey, 30% of children were classified as overweight or obese based on parent reported height and weight, but only 20% of parents reported that their provider discussed concerns/worries about their child's weight. The quality of care for identification, classification, and management of childhood overweight and obesity in U.S. children is suboptimal. Given the large burden of overweight and obesity in the U.S., further work is needed to improve care for these children.

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1537-P

AHB and LGPC Are Selective Biomarkers of Impaired Glucose Tolerance (IGT)

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IGT is a high-risk state for the development of type 2 diabetes. Novel biomarkers of IGT may help identify subjects with IGT without performing the currently underutilized OGTT.

A targeted metabolomic analysis of fasting plasma samples from the RISC study 3-year follow-up taken at time=0 of an OGTT was performed. Quantitative measurements of 23 metabolites previously associated with prediabetes and type 2 diabetes were made. This panel of metabolites included the branched-chain amino acids, glycine, tyrosine, and 2-aminoadipic acid. The data was rank normalized using the GenAbel package in R to create a normal distribution. Disease states were classified as normal (normal glucose tolerance & fasting glucose, n=623), isolated impaired fasting glucose (iIFG), n=220), and isolated IGT (iIGT, n=56). The associations of metabolites for normal vs. iIFG or iIGT were made using logistic regressions controlling for age, sex, and BMI. Odds ratios for a one SD change in the metabolite level, 95% confidence intervals, and p values (adjusted with a false discovery rate of 0.1) were calculated for each metabolite.

alpha-Hydroxybutyrate (AHB) was found to be the metabolite most strongly associated with iIGT (2.54 (1.86-3.48), 5E-9) while having no significant association with iIFG. The second most strongly associated metabolite with iIGT was linoleoylglycerophosphocholine (LGPC) (0.48 (0.35-0.66), 5E-6) which was also modestly associated with iIFG (p =0.03). These analyses were replicated for α-HB and LGPC using an identical protocol in the Botnia cohort at baseline (normal n=1105, iIFG n=938, iIGT n=128). AHB was strongly associated with iIGT (2.03 (1.65-2.49), 2E-11) with no significant association with iIFG. LGPC also with strongly associated with iIGT (0.49 (0.40-0.61), 6E-11) and modestly associated with iIFG (1.17 (1.06-1.29), 3E-3).

In summary, in two different cohorts totalling more than 3,000 nondiabetic subjects, AHB and LGPC were shown to be selective biomarkers of IGT with respect to normal or iIFG.

1538-P

Development of Salivary Transcriptomic Biomarkers for Insulin Resistance

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Insulin resistance (IR) is a condition in which cells become less sensitive and eventually resistant to the activity of insulin; subsequently glucose accumulates in the blood instead of entering the body cells, leading to hyperglycemia. While simple glucose tests are used routinely, IR testing is challenging because there are no standard clinical tests. Hence, IR status is rarely evaluated or used for screening, diagnosis, or to inform decisions for preventive interventions or treatment. Availability of IR test would facilitate early detection and prevention. A prospective sample collection and retrospective blinded validation was conducted to evaluate the performance of salivary transcriptomic biomarkers for screening and detection of insulin resistance. Overweight and obese Puerto Ricans adults who were recruited in the San Juan Overweight Adult Longitudinal Study (SOALS) were asked to provide a saliva sample at their baseline visit. Based on the homeostasis model assessment of insulin resistance (HOMA-IR), participants were classified into high risk group (HOMA-IR value ≥2.5) and low risk group (HOMA-IR value <2.5). The Affymetrix HG U133 Plus 2.0 array was used to profile transcriptomes and discover altered gene expression in saliva supernatant from 23 IR high risk subjects and 16 low risk subjects. Forty two messenger RNA (mRNA) were found to be significantly differentially expressed between two groups ($p<0.05$). The top 10 ranking mRNA biomarkers (PRKCB, ADL1, S100A12, KSR, LUZP6, IL1R2, CAMP, COX17, VPS4B and CAP1) were validated in an independent cohort of 40 IR high risk subjects and 40 low risk subjects by droplet digital PCR. After validation, a logistic regression model combing 4 mRNA biomarkers (KSR, LUZP6, IL1R2, CAP1) and body mass index (BMI) could differentiate high risk subjects from low risk subjects, yielding AUC value of 0.93 with 88% sensitivity and 83% specificity. Our study demonstrates that salivary biomarkers possess discriminatory power for the detection of Insulin Resistance.

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1539-P

Test to Identify Patients at High Risk of End-Stage Renal Disease for Clinical Trials in Type 1 Diabetes Using Diagnostic Tree Analysis

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There is a great need to develop diagnostic tools to efficiently select patients with diabetes at high risk of end-stage renal disease (ESRD) for enrollment into clinical trials testing effectiveness of novel therapies. To provide an example of such a tool, we performed a regression tree analysis in 285 patients with type 1 diabetes from Joslin Proteinuria Cohort with impaired renal function (eGFR: 15-60 ml/min/1.73m2). The cohort has been followed for 7 to 18 years to ascertain ESRD and we focused on the events within 5 years from enrollment. We used baseline levels of three "legacy markers": urinary albumin/creatinine ratio (ACR), estimated glomerular filtration rate (eGFR) and glycated hemoglobin (HbA1c), together with new markers: serum tumor necro-

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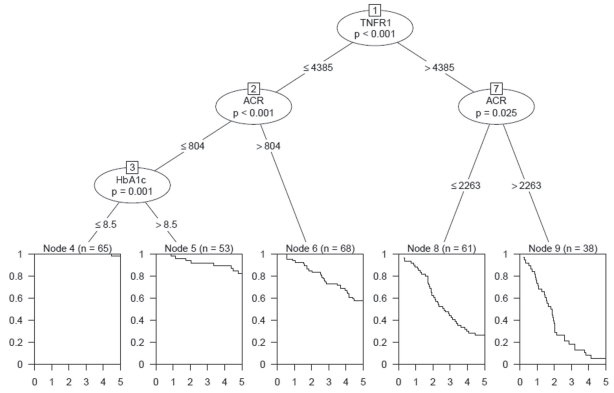
sis factor receptor 1 and 2 (TNFR1, TNFR2). 5-year risk of ESRD in the study group was 43.5%. A single measurement of TNFR1 > 4,385 pg/ml allowed to select 99 (35%) patients with 80.8% risk of ESRD within 5 years, while the risk in patients with TNFR1 below this cutoff was 19.9%. Patients with TNFR1 ≤ 4385 pg/ml, ACR ≤ 804 mg/g and HbA1c ≤ 8.5% had only 2% risk of ESRD in 5 years (Figure). In conclusion, using TNFR1 for eligibility screening in a putative clinical trial can produce a study group with nearly 90% 5-year risk of ESRD.



1540-P

10-Year Diabetes Incidence among Individuals Participating in a Diabetes Screening Program: The ADDITION-DK Study

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Screening programs for type 2 diabetes inevitably find more persons at high risk for diabetes than persons with undiagnosed prevalent disease. The long term incidence of clinically diagnosed diabetes in this group is unknown. In 2001-2006, a pragmatic screening program for diabetes in Danish general practices identified 22,726 persons at high risk of diabetes based on the Danish diabetes risk score but without clinical diabetes (WHO 1999) on subsequent measures of glucose. Persons were categorized into 6 groups of increasing diabetes risk and followed for incident diabetes in the Danish National Diabetes Register until December 2012. For each group, progression rates and risk ratios were estimated by poison regression. During 10 years of follow-up, 1,041 persons were diagnosed with diabetes. Compared to persons with high estimated diabetes risk but normal glucose regulation, the lower estimated diabetes risk groups had a 55% and 39% lower diabetes incidence, whereas persons with impaired glucose regulation had a markedly higher diabetes incidence (Table). In the presence of diabetes risk factors, persons who progress further in a stepwise diabetes screening program are at increased risk of future diabetes. In addition to impaired glucose regulation, clinicians should pay attention to persons with screen-detected high estimated diabetes risk, even when glucose regulation is normal.

Table. Diabetes Incidence and Incidence Rate-Ratio in the Risk Stratified Population.

Risk group	N	Cumulative diabetes incidence, N (%)	Person years	Diabetes incidence per 100 person years (95% CI)	Diabetes incidence rate-ratio with high risk NGT as reference group (95% CI)
Moderate diabetes risk	13,037	237 (1.82)	124,621	0.19 (0.17;0.22)	0.45 (0.36;0.57)
Elevated diabetes risk	4,220	97 (2.30)	37,646	0.26 (0.21;0.31)	0.61 (0.46;0.80)
High risk NGT	2,628	100 (3.81)	23,590	0.42 (0.35;0.52)	reference
iIFG	913	108 (11.83)	7,464	1.45 (1.20;1.75)	3.41 (2.60;4.48)
IGT	1,306	286 (21.90)	9,936	2.88 (2.56;3.23)	6.79 (5.41;8.53)
1 diabetic glucose value	622	213 (34.24)	4,053	5.26 (4.60;6.01)	12.40 (9.78;15.72)

Moderate diabetes risk: diabetes risk score ≥ 5, HbA_{1c} < 5.8%, RBG < 5.5 mmol/l; Elevated diabetes risk: diabetes risk score ≥ 5, HbA_{1c} < 5.8%, RBG ≥ 5.5 mmol/l, FBG < 5.6 mmol/l; High risk NGT, normal glucose tolerance: diabetes risk score ≥ 5, HbA_{1c} ≥ 5.8%, FBG < 5.6 mmol/l, 2hBG < 7.8 mmol/l; iIFG: isolated impaired fasting glucose: diabetes risk score ≥ 5, 5.6 mmol/l ≤ FBG < 6.1 mmol/l, 2hBG < 7.8 mmol/l; IGT, impaired glucose tolerance: diabetes risk score ≥ 5, FBG < 6.1 mmol/l, 7.8 mmol/l ≤ 2hBG < 11.1 mmol/l; RBG: random blood glucose (capillary); FBG: fasting blood glucose (capillary); 2hBG: 2-hour blood glucose (capillary).

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1541-P

Findings from a Universal Gestational Diabetes Mellitus Screening Feasibility Program in Lima, Peru

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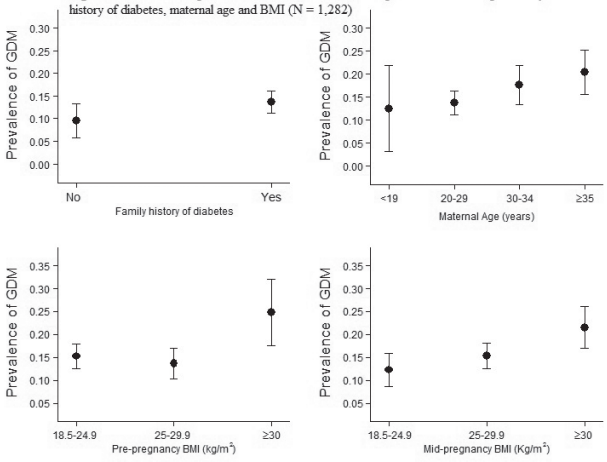
We sought to estimate the prevalence of gestational diabetes mellitus (GDM) using the International Association of Diabetes Pregnancy Study Group (IADPSG) criteria; and assess the association of GDM with maternal pre-pregnancy and mid-pregnancy body mass index (BMI). A 75-g 2-hour oral glucose tolerance test was administered at 24-28 weeks gestation to 1,282 women attending antenatal care at the Instituto National Materno Perinatal in Lima, Peru. Associations of GDM with maternal BMI were estimated. Overall, the prevalence of GDM was 16% (95% CI 14-18%). The prevalence of GDM among lean (mid-pregnancy BMI <25 kg/m^2), overweight (25-29.9 kg/m^2) and obese women (≥30kg/m^2) were 12%, 15% and 22%, respectively. Compared with lean, the prevalence ratio (PR) of GDM for severely obese women (mid-pregnancy BMI ≥35 kg/m^2) was 2.3 (95% CI 1.3-3.8). Compared with younger mothers (<20 years), those aged ≥35 years had 1.6-fold higher prevalence of GDM (PR= 1.6; 95% CI 1.1-1.8). Additionally a positive first-degree family history of diabetes was associated with an increased prevalence of GDM (PR= 1.4; 95% CI 1.2-2.5) (Figure 1).

GDM prevalence in Lima is comparable to estimates reported internationally using IADPSG criteria. Evidence documenting the burden of GDM and its association with maternal obesity has important clinical and public health implications.

Figure 1. Prevalence of gestational diabetes mellitus according to maternal first degree family history of diabetes, maternal age and BMI (N = 1,282)



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1542-P

Glycated Albumin May Be Superior to Fructosamine in Detecting Glucose Intolerance: The Africans in America Study

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A1C, a form of glycated hemoglobin, is approved for diagnosis of glucose intolerance. However, anemia and hemoglobinopathies, common in Africa, can compromise interpretation of A1C. Alternatives include glycated proteins such as fructosamine and glycated albumin (GA). As research on their potential as screening tests is still preliminary, diagnostic cut-offs are not available. In the absence of established cut-offs, we analyzed the diagnostic potential of GA and fructosamine in 189 African immigrants from the Africans in America study (68% male, age 39±10y (mean±SD), BMI 27.8±4.6 kg/m2) by dividing the cohort into quintiles of A1C, GA and fructosamine. Fasting glucose, 2h glucose and prevalence of glucose intolerance were compared in the highest and lowest quintiles. Glucose intolerance was defined as the presence of either pre-diabetes or diabetes based on OGTT criteria for fasting and 2h glucose. Glucose intolerance was discovered in 33% (63/189) as pre-diabetes occurred in 27% (51/189) and diabetes in 6% (12/189). For A1C and GA but not fructosamine, glucose levels and the prevalence of glucose intolerance were higher in the highest quintile than the lowest quintile (Table). As the quintile analyses revealed significant differences in glucose

parameters for GA and A1C but not fructosamine, GA may be more likely than fructosamine to join A1C as a diagnostic test for glucose intolerance.

Table. Glucose Parameters in Lowest & Highest Quintiles of A1C, Glycated Albumin & Fructosamine.

Glucose Parameters	A1C			Glycated Albumin			Fructosamine		
	Quintile		*P*-value	Quintile		*P*-value	Quintile		*P*-value
	Lowest	Highest		Lowest	Highest		Lowest	Highest	
0h Glucose (mg/dL)	87±7	98±21	<0.01	89±7	97±25	0.057	90±6	95±25	0.24
2h Glucose (mg/dL)	121±29	151±60	<0.01	118±31	148±67	0.01	130±30	144±65	0.27
% Glucose Intolerant	23%	77%	<0.01	32%	68%	0.03	44%	56%	0.87

1543-P

Anthropometric Predictors of Type 2 Diabetes among White and Black Adults

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We compared 6 anthropometric screening predictors for type 2 diabetes (T2DM) in white and black males and females, and determined optimal cut-points for A Body Shape Index (ABSI), body adiposity index (BAI), body mass index (BMI), waist circumference (WC), waist to height ratio (WHtR), and waist to hip ratio (WHR). We used a cross-sectional study design with baseline data (1987-1989) from the Atherosclerosis Risk in Communities study. Our analyses consisted of 15242 participants/1827 diabetes cases (5320/543 white males, 1527/285 black males, 5936/479 white females, and 2459/520 black females) aged 45-64 years. All anthropometric predictors were converted to Z scores. Logistic regression odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, physical activity, and family history of diabetes were used to present relationships. The Akaike Information Criterion and Receiver Operating Characteristic C-index were used to calculate best fit model indices. Multivariate odds ratios were highest for WHR (white females: OR=2.68; 95% CI:2.39-3.01) and lowest for ABSI (white males: OR=1.18; 95% CI:1.02-1.37). The best anthropometric predictor of T2DM for the total male population and white males was WHtR. WHR was the best predictor for black males and females. Other anthropometric predictors with comparable predictive ability were BMI, WC, and WHR for males and white females; and WC and WHtR for the total female population. For black females, WHR was better than other predictors at predicting T2DM. In most race-sex groups, ABSI was the poorest predictor of T2DM. In general blacks had lower optimal cut-points compared to their counterparts. For example, cut-points for WHR were 0.92 for black females, 0.94 for white females, 0.93 for black males, and 0.97 for white males. In summary, WHtR and WHR were the best anthropometric screening predictors of T2DM among whites and blacks, with differences observed by race and sex. Optimal cut-points for anthropometric predictors were lower for blacks than whites.

1544-P

WITHDRAWN

1545-P

Prediabetes Screening in High Risk Population with HbA1c

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Symptom-free prediabetes is an optimal time to introduce diabetes prevention measures. Therefore, an effective screening strategy for prediabetes is urgently needed. 5,276 diabetes-free individuals (2,963 women; 56%), aged 45-55 years, who had at least one risk factor for diabetes development took part in a nationwide diabetes screening programme. Participants had fasting blood glucose (FBG) repeatedly measured and HbA1c assessed with the point-of-care device A1cNow (Bayer, Germany). FBG was used for diagnosis of impaired fasting glucose (IFG; 100-125 mg/dl) or diabetes (>125 mg/dl) and served as "gold standard". HbA1c 5.7-6.4% diagnosed prediabetes, >6.4% - diabetes (Table 1). Sensitivity and specificity of HbA1c used for diagnosis of pooled prediabetes and diabetes was 0.324 (95%CI 0.308-0.339) and 0.942 (0.936-0.948); when used only for the diagnosis of prediabetes: 0.382 (0.365-0.398) and 0.833 (0.814-0.850), respectively. Sensitivity and specificity of HbA1c used for diagnosis diabetes only was 0.704 (0.695-0.713) and 0.792 (0.777-0.807), respectively (table). In conclusion, HbA1c measurement is a significantly better tool for diagnosis of diabetes than prediabetes in a high risk population. Were it to be used for prediabetes screening or diagnosing, majority of individuals with this condition would be missed.

Table 1. Distribution of glucose intolerance conditions in the studied cohort.

Diagnosis *(according to FBG or HbA1c)*		FBG (mg/dl) <100 *(normal)*	100-125 *(IFG)*	>125 *(diabetes)*	Total
HbA1c (%)	<5.7 *(normal)*	461	185	39	685
	5.7-6.4 *(prediabetes)*	747	921	375	2043
	>6.4 *(diabetes)*	216	756	1576	2548
Total		1424	1862	1990	5276

FBG – *fasting blood glucose*

Supported By: Bayer Diabetes Care

1546-P

Investigation of Diabetes Risk in Troponin Negative Chest Pain Admissions

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Patients admitted with chest pain are risk stratified and troponin blood tests are performed for those deemed at high risk. Usually cardiac disease is further assessed however this is not the case for metabolic disease despite a large proportion of these patients being at risk of diabetes.

We investigated whether patients admitted with troponin negative chest pain are at a greater risk of developing diabetes with a view to providing evidence for more rigorous screening in this subgroup.

We analysed a retrospective cohort of patients admitted with chest pain to a district general hospital between January to April 2009 and with a negative troponin test. Patients with pre-existing diabetes were excluded. Patients' blood tests were analysed during the subsequent 5 years to establish further glycaemic testing and any abnormalities. American Diabetes Association (ADA) guidance on blood test values for diabetes and pre-diabetes were utilised.

257 patients (156 male, 101 female, mean age 56.2 years) were reviewed for 5 years post admission.

92 (35.8%) patients subsequently developed pre-diabetes; 83 patients had impaired fasting glucose (IFG), 8 patients had Hba1c in pre-diabetes range and 1 patient had impaired glucose tolerance according to ADA criteria.

Of the patients with pre-diabetes, 28 (30.4%) developed diabetes and of the 165 remaining patients without glycaemic abnormalities, 1 developed diabetes. This gave a relative risk of developing diabetes if troponin negative and having pre-diabetes of 50.

32.7% of our study population had impaired fasting glucose which is higher than previously suggested data in the general population. We also found that patients who developed diabetes were more likely to present with higher blood sugar levels (mean blood glucose 6.7 mmol/l vs. 6.5mmol/l, p= 0.05).

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Our findings suggest that focussed screening of troponin negative chest pain patients for diabetes or pre-diabetes is necessary to target patients in this "at risk" subgroup and reduce the healthcare burden.

1547-P

Fatty Liver Index (FLI) Is Independently Associated with Cardiovascular Disease (CVD) and Chronic Kidney Disease (CKD) in Patients with Type 2 Diabetes

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NAFLD is independently related to CVD and CKD. Our aim was to assess whether FLI, a surrogate marker of NAFLD (based on BMI, waist, GGT, fasting serum triglycerides), was associated with micro- and macro-vascular complications of type 2 diabetes. Among the 1,621 diabetic patients in stable clinical conditions who attended our secondary care diabetes clinic at least twice in 2013, FLI was obtained in 870 patients (whose features were not different than those of the entire population). Patients were segregated in three categories based on a FLI score lower than 30 (n=100), between 30-60 (n=213) and higher than 60 (n=557) as originally proposed. Age was higher in those with the highest FLI score but duration of the disease (9±8 years), insulin use, anti-diabetic, anti-cholesterol and anti-hypertensive drugs were not different with the exception of GLP1 receptor agonists, ARB and allopurinol which were more common in those with the highest FLI score. Fasting plasma glucose, HbA1c, blood pressure, heart rate, uric acid, total cholesterol, HDL cholesterol, AST and ALT but not LDL-cholesterol were all higher in those with the highest FLI score regardless of drug therapy. CVD (24%, 46% and 37% in those with FLI lower than 30, between 30-60 and higher than 60 respectively; p<0.001), microalbuminuria (11%, 38%, 49%; p<0.0001), eGFR < 60 mL/min (12%, 26%, 23%; p=0.03), but not retinopathy (14%, 19%, 16%; p=0.65), were more prevalent among patients within higher FLI score and this association was independent of age, sex, duration of the disease, parameters of the metabolic syndrome and therapy. In conclusion, the demonstrated independent association of FLI with CVD and CKD in patients with long lasting type 2 diabetes supports the hypothesis of a prognostic role of fatty liver, to be assessed as a continuous variable, in the natural history of the disease.

1548-P

The Diagnostic Validity of Nervecheck: From Functional and Structural Damage of Small and Large Nerve Fibres to Neuropathic Pain

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Quantitative sensory testing (QST) to assess thresholds for vibration and thermal sensation can quantify nerve dysfunction and may have relevance to painful symptoms and foot ulceration in diabetic patients. However, current QST devices are expensive and can be complex to use.

NerveCheck is a new device (cost $700) for QST assessment. We have assessed its reproducibility and diagnostic validity against established QST devices and its diagnostic ability to detect large (LFN) and small fibre neuropathy (SFN) as well neuropathic pain symptoms.

143 subjects (18 with painful, 55 with painless diabetic neuropathy and 70 controls) underwent QST assessment with NerveCheck; large fibre testing (vibration perception threshold (VPT) (Neurothesiometer), Sural Sensory Nerve Action Potential (SNAP)) and small fibre testing (cold (CPT) and warm (WPT) perception thresholds (TSA-II-NeuroSensory Analyzer), IENFD and Corneal Nerve Fibre Length (CNFL) and density (CNFD) using CCM and McGill pain questionnaire).

NerveCheck's intra correlation coefficient was: VPT 0.95 (-7.6 to 9.22); CPT 0.63 (-6.55 to 10.62); WPT 0.74 (-6.24 to 6.02). NerveCheck showed a diagnostic efficiency of 86%, 79% and 71.5% for VPT, CPT and WPT, respectively for VPT (Neurothesiometer) and thermal thresholds (TSA-II). The AUC of VPT for SNAP (82.2%) was significantly higher than for IENFD (60.5%, P=0.028). There was a significantly greater nerve dysfunction in subjects with painful compared to painless neuropathy (VPT: 2.51 vs. 5.01, P= 0.006, CPT: 3.17 vs. 4.72, P= 0.005 and WPT: 3.61 vs. 4.78, P=0.001).

NerveCheck, a new inexpensive QST device has comparable diagnostic ability to established QST equipment, detects damage to the correct fibre subtype and differentiates patients with and without neuropathic pain.

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1549-P

Exosome-associated microRNA Profiling in Type 1 Diabetes

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Type 1 diabetes (T1D) is a disease characterized by an autoimmune-mediated total or near-total destruction of the pancreatic beta cells, leading to a substantial or complete loss of insulin secretion. There is a need for biomarkers of T1D for assessment of the risk of developing the disease, for monitoring progression and the response to clinical treatments. Exosomes are microvesicles released by most of cell types and found in biological fluids including blood, saliva, and urine. Exosome miRNA profiling has emerged as a powerful tool to accelerate biomarker discovery. The goal of this study was to identify plasma exosome-derived microRNAs as new biomarkers and the consequent relation of those with T1D. We used a microarray containing 800 miRNAs in order to profile the exosome miRNA content of T1D patients (n= 12) and gender and age matched control subjects (n=12). The microRNA array identified one up-regulated miR-25-3p (p=0,0014) and six down-regulated miRNAs miR-16-5p (p=0,0105), miR-302d-3p (p=0,0461), miR-378e (p<0,0001), miR-570-3p (p<0,0001), miR-574-5p (p=0,0082) and miR-579 (p=0,0013) in T1D patients compared to the controls. These results were validated by real-time PCR in an additional cohort of T1D patients and control individuals (n=12 per group) that confirmed the significant down-regulation of miR-378e (fold change 1,75, p= 0,0003), miR-570-3p (fold change 4,45, p<0.0001) and miR-574-5p (fold change 2,24, p=0.0458). The miRNAs identified that were differentially expressed in T1D patients versus healthy individuals were assigned to a possible target by informatics tools, showing that the majority of identified targets were involved in metabolic pathways. In conclusion, our study indicates that exosome miRNA profiling may provide potential biomarkers of T1D but also new insights in the disease.

1550-P

Application of New Cholesterol Guidelines to the Korean Adult Diabetic Patients

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The 2013 guidelines of the American College of Cardiology and the American Heart Association (ACC-AHA) for the treatment of cholesterol expand the indication s for statin therapy. The aim of this study is to evaluate how many diabetic patients have received appropriate statin therapy and to estimate how many patients would be indicate for statin therapy according to Third Adult Treatment Panel (ATP-III) of the National Cholesterol Education Program guideline and new ACC-AHA guideline in Korea.

We analyzed the data from the Korea National Health and Nutrition Examination Survey (KNHANES) 2010-2012. We estimated the number of diabetic patients who already had treated dyslipidemia and for whom statin therapy would be recommended according previous guideline and new guideline.

Of the total 1,975 diabetic patients, 377 (19.1%) were receiving drug for dyslipidemia. Among 1,598 patients who had not taken any medicines for dyslipidemia, 65.6% (1,048) would be indicated for statin therapy according to ATP-III guideline. When we apply to new ACC-AHA guideline, 94.3% (total=1,506, 72.8% (n=1,163) need moderate-high intensive and 21.5% (n=343) need moderate intensive) would be eligible for statin therapy. Among the total diabetic patients, as compaired with the ATP-III guidelines, the new guidelines would increase the number of eligible for statin therapy 53.1% to 76.2%.

In present practical situation, many diabetic patients have not received appropriate statin therapy. The new ACC-AHA guidelines would increase the number of diabetic patients who would be eligible for statin therapy in Korea.

1551-P

New Fasting Index Improves Detection of Impaired Glucose Tolerance

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Oral glucose tolerance testing (OGTT) defines impaired glucose tolerance (IGT, i.e. 2-hour plasma glucose ≥ 140 mg/dL post 75 gm oral glucose); however, OGTT is time-consuming, inconvenient, and difficult to perform in routine clinical practice. We sought to determine whether novel fasting

biomarkers could improve detection of patients with IGT. De-identified data were obtained from blood samples sent to a national reference laboratory (Health Diagnostic Laboratory, Inc., Richmond, VA) of 352 patients at-risk for diabetes who underwent OGTT between Mar 2012 and Jan 2014. Multivariable logistic regression was used to test the association, discrimination, calibration, and reclassification of IGT patients by a new fasting index that included glucose, free fatty acids, linoleoyl-GPC, and myeloperoxidase, in addition to the usual clinical risk factors of age, gender, BMI, HbA1c, glucose and insulin. Subjects' mean (SD) age was 46 (15); BMI was 31 (8); 36% were male; and 18% met IGT criteria. Considering the index alone, a subject was 6.7 times as likely to have IGT for each 1 SD increase (odds ratio 95% CI: 4.1 to 11.0); the association increased to 8.1 (4.0 to 16.5) after adjustment for clinical risk factors; and the models were well calibrated. The area under the ROC curve (c-statistic) increased from 0.79 to 0.88 (p=0.0001) when the index was added to the above list of clinical factors. The Integrated Discrimination Improvement showed increases in both average sensitivity (12%) and specificity (3%); in addition, the continuous Net Reclassification Indexes were 52% and 45% for cases and controls, respectively (all p<0.001). Therefore, a model that included biomarkers for insulin resistance, lipid metabolism, and inflammation produced an index with excellent capability for IGT detection. Using this index may provide a novel strategy to improve the ease and cost-effectiveness of screening for IGT and prediabetes in large populations. An independent validation study is in progress utilizing the IRAS and ACTNOW cohorts.

1552-P

Excess in Hemoglobin Glycation and Glycemic Variability in Obese Individuals without Known Dysglycemia

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We previously showed that, in obese individuals without known dysglycemia, age was a determinant of hemoglobin glycation. A mathematical relation has been proposed (ADAG) between HbA1c and mean glucose levels given by continuous glucose monitoring (CGM). We aimed to assess in overweight or obese patients the difference between the HbA1c level predicted by this relation and the measured HbA1c level and the determinants of this difference.

Seventy patients (age 46.5±14.3 years, BMI 35.2±6.8 kg/m2) without known dysglycemia had a CGM during 24h in stable condition. Mean glucose and MAGE (mean amplitude glycemic excursion) were calculated. Predicted HbA1c was calculated using the formula mean glucose=1.649xHbA1c-2.645 and compared to measured HbA1c (ΔHbA1c). An OGTT was performed.

Measured HbA1c was 5.1% to 7.4%. According to the OGTT 24 patients had prediabetes (fasting hyperglycemia and/or glucose intolerance) and 13 had diabetes. The population was separated into quartiles of measured HbA1c (Q1 to Q4). In each quartile, measured HbA1c was higher than predicted HbA1c (p<0.01 to <0.0001). ΔHbA1c increased significantly from Q1 to Q4 (0.60±0.23/0.77±0.34/0.85±0.25/1.13±0.31%; p<0.008). In the overall population, ΔHbA1c correlated with age (r=0.536, p<0.0001) and MAGE (r=0.494, p<0.0001). In multivariate analysis ΔHbA1c remained associated with age, MAGE and HbA1c quartiles (p=0.002, 0.017, 0.006, respectively; adjusted r2 of the model=0.43).

In obese individuals with normal or mildly elevated HbA1c levels and dysglycemia on OGTT for half of them, HbA1c levels are higher than predicted by mean glucose. This possible excess of hemoglobin glycation is determined in particular by 24-h glycemic variability.

1553-P

Progression to Diabetes and Prediabetes among Nondiabetic Asian Indian Subjects Based on Baseline Glycated Hemoglobin Levels

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We report on the 10-year progression to diabetes or prediabetes based on baseline glycated hemoglobin (A1c) in 975 adults aged ≥20 years from the baseline survey of Chennai Urban Rural Epidemiology Study (CURES) conducted between 2001-2003. We excluded individuals with self reported diabetes and those who were detected to have diabetes at baseline. Oral glucose tolerance tests and A1c estimations were performed at baseline, and after a median follow-up period of 8.9 years. On follow up, diabetes was diagnosed if fasting plasma glucose was ≥126mg/dl or 2hr post glucose was ≥200 mg/dl or A1c ≥6.5% [48 mmol/mol]. When subjects were stratified according to baseline A1c, the overall incidence rates of diabetes were 14.1, 30.1 and 54.6 per 1000 person-years and the age and gender adjusted hazard ratios (95% CI) for diabetes were 1.0 (reference), 2.0 (1.4-2.8) and 3.5 (2.4-5.1) for those with A1c <5.5% [37 mmol/mol], 5.5-5.9% [37-41 mmol/mol] and 6.0-6.4% [42-46 mmol/mol] respectively. ROC curves showed that baseline A1c of 5.7% [39 mmol/mol] had 62.9% sensitivity, 66.2% specificity and AUC of 0.685 to predict development of diabetes.

Table 1.

HbA1c Category (Baseline)			
	<5.5% [<37 mol/mol]	**5.5-5.9%** [37-41 mmol/mol]	**6.0-6.4%** [42-46 mmol/mol]
n	407	389	179
Cases of incident diabetes	49	103	77
Cases per 1000 person years	14.1	30.1	54.6
Hazard Ratio for Diabetes (95% CI, p value)			
HbA1c Category	**Model 1: Unadjusted**	**Model 2: Age and Gender Adjusted**	
<5.5% (reference)	1.0	1.0	
5.5- 5.9%	2.0 (1.4-2.9, <0.001)	2.0 (1.4-2.8, <0.001)	
6.0-6.4%	3.6 (2.5-5.2, < 0.001)	3.5 (2.4-5.1, <0.001)	

1554-P

Prediction Model for Developing Impaired Glucose Tolerance: The Insulin Resistance Atherosclerosis Study (IRAS)

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Prediction of diabetes has attracted considerable interest. However, there are no prediction models for early worsening of glucose tolerance status. Therefore, we aimed to develop a prediction model for developing impaired glucose tolerance (IGT) using a stepwise forward selection procedure. A 75 g OGTT was administered at baseline and follow-up visits among 559 IRAS participants who had normal glucose tolerance at baseline. A total of 120 participants developed incident IGT during a mean follow-up period of 5 years. Insulin sensitivity index (S_I) and acute insulin response (AIR) were directly measured by the frequently sampled intravenous glucose tolerance test. Model fit was improved by adding AIR and S_I (Model 3) to commonly used diabetes predictors (Model 1), but was not changed by homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β cell) (Model 2). In addition to a greater area under the ROC curve, Model 3 added predictive value to Model 1. AIR was required for model improvement. In summary, insulin secretion is a stronger predictor of short-term progression to IGT than insulin resistance (as is true of diabetes). Direct measures of insulin sensitivity and secretion optimize the prediction of early worsening of glucose tolerance status. However, this is less practical in usual care settings.

Table. Models Predicting Progression to IGT Using a Stepwise Forward Selection Procedure.

	Model 1		Model 2		Model 3	
Independent variables	OR	p-value	OR	p-value	OR	p-value
- Hispanic vs. non-Hispanic white	1.21	0.450	1.20	0.483	1.75	0.018
- Family history of diabetes (yes vs. no)	1.43	0.098	1.43	0.100	1.46	0.106
- 2h glucose (× 1 SD)	1.91	<0.001	1.91	<0.001	1.78	<0.001
- Log HOMA-IR (× 1 SD)	–	–	1.10	0.777	–	–
- Log HOMA-β cell (× 1 SD)	–	–	0.84	0.606	–	–
- Log AIR (× 1 SD)	–	–	–	–	0.55	<0.001
- Log S_I (× 1 SD)	–	–	–	–	0.71	0.012
Overall model				p-value		p-value
- Area under the ROC curve *	0.692	Ref.	0.695	0.193	0.728	0.008
- Integrated discrimination improvement	-	Ref.	0.001	0.509	0.046	<0.001
- Net reclassification improvement (%)	-	Ref.	0.5	0.736	16.1	0.005

Age, sex, African American, waist circumference, and fasting glucose were not retained in any model.
* Estimates of area under the ROC curve given by *bootstrap method.*

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For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1555-P

Serum Preadipocyte Factor 1 Concentrations and Risk of Developing Diabetes: A Nested Case-Control Study

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Preadipocyte factor 1 (Pref-1) is a preadipocyte secreted protein that plays an inhibitory role in adipogenic differentiation and is also involved in the proliferation and differentiation of various precursor cells. It has been associated with various metabolic parameters, but with inconsistent results. This study aimed to determine whether Pref-1 could be a predictive marker for the development of diabetes in people without diabetes. A population-based, nested case-control study of individuals who progressed to diabetes (n=43) or prediabetes (n=345) and age, sex, and fasting plasma glucose (FPG) matched control participants who maintained normal glucose tolerance (n=389) during a 4-year follow-up was performed using data from the Chungju Metabolic disease Cohort Study. Circulating levels of Pref-1 were measured by ELISA assay. Baseline serum Pref-1 levels showed a stepwise decrease across the glucose tolerance status at follow-up. Individuals whose FPG level had increased or whose homeostasis model assessment of beta-cell function had decreased at follow-up showed significantly lower levels of Pref-1 compared to their control group counterparts. After adjusting for age, body mass index, FPG, serum insulin levels, systolic blood pressure and triglycerides, the incidence of diabetes was nearly threefold higher in the lowest vs. the upper three quartiles of circulating Pref-1 (relative risk, 2.794; 95% CI, 1.188-6.571; *P*=0.0185). Of note, these findings were significant in women but not in men. In conclusion, levels of circulating Pref-1 may be a useful biomarker for identifying women at high risk for developing diabetes.

1556-P

Incidence of Childhood Type 1 Diabetes in Italy during 2004-2013

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Childhood type 1 diabetes has been shown an increase in Italy of 3.0% during 1990-2003. Aim of this study was to describe the incidence for type 1 diabetes in children 0-14 years in the same geographical area, during 2004-2013, according to gender, age and area of residence.

Registry for type 1 diabetes mellitus in Italy (RIDI) is a coordination of local registries established in 1997. Eleven registries, distributed throughout the country, contributed to this analysis, covering more than 25% of the total Italian population. Cases were grouped into four macro-area of residence at diagnosis: North, Centre, South, and Sardinia.

The incidence rates were age-standardized on the World Standard Population. 95% Confidence intervals (95% CI) were estimated assuming the Poisson distribution of cases. Rates were expressed per 100,000 person-years. Trend analysis of incidence was performed using a Poisson regression model.

Ascertainment exceeded 90% in all registers. During the 10-year period 3643 subjects under 15 years of age developed type 1 diabetes. The highest incidence occurred in Sardinia for both males and females [41.8 (95% CI: 36.3-48.0) and 42.1 (95% CI: 36.4-48.7), respectively]. In the Peninsular Italy, the overall incidence was 14.5 (95% CI: 13.6-15.4) for males, and 13.1 (95% CI: 12.3-14.0) for females. No significant differences were found between the three geographical macro-areas and gender. A significant positive time trend was found in Sardinia and in South Italy, with an average increase of 2.6% (95% CI 0.6%-4.7%) and 3.9% (95% CI: 2.2%-5.6%) of new cases per year, respectively.

During 2004-2013 the incidence rates of childhood diabetes were stable in North and Central Italy, whereas South Italy and Sardinia showed significantly increased rates. This pattern of change suggests that important risk exposures differed over time in different geographical area. Further time trend analysis and comparison of the patterns in defined regions is warranted.

1557-P

Development and Validation of a Prediction Model for Future Type 2 Diabetes in Japan

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A periodic health check-up system for metabolic syndrome has been annually conducted in Japan since 2008. Using the data from the system, we developed a prediction model for future diabetes, by incorporating the change in glucose in addition to other factors, since glucose in incident cases increased steeply during a few years before the incident of diabetes. The study included 17,905 non-diabetes (fasting plasma glucose [FPG] <126 mg/dl and HbA1c <6.5%) subjects aged 40-75 years who had undergone check-ups since 2008 and been followed up for 4 years in J hospital, Tokyo. Incident diabetes was defined as FPG ≥126 mg/dl, HbA1c ≥6.5% or clinician-diagnosed diabetes. Logistic regression analysis was performed to construct a prediction model using the data from non-laboratory assessment and FPG in year 2008 as well as the coefficient of variation of FPG between year 2009 and 2012 (FPG-CV). The prediction model was externally validated using the data of 4,931 non-diabetes subjects from S hospital, Saitama. The 4-year incidences of diabetes were 2.4 and 2.2% in the two hospitals. Age (odds ratio 0.90), sex (0.64), body mass index (1.22), family history of diabetes (1.08), FPG (3.63), FPG-CV (1.52), FPG*FPG-CV (0.82), and weight gain ≥10 kg vs. that at age 20 (1.26) were identified as independent variables for future diabetes. Area under the receiver operating characteristics curve (ROC-AUC) of the model was 0.858, and this was non-significantly higher than that of the model without FPG-CV. Sensitivity, specificity, and positive (PPV) and negative predictive values (NPV) at the optimal cut-off of 0.025 were 78, 79, 9, and 99%, respectively. External validation showed a ROC-AUC of 0.940. Sensitivity, specificity, PPV, and NPV at a cut-off of 0.025 were 91, 78, 6, and 99%, respectively. Similar trends were shown in the analysis where FPG was replaced with HbA1c. Our prediction model combining baseline information with subsequent glucose change may help to identify subjects at high risk for future diabetes in Japan.

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1558-P

Poor Performance of Risk Factors-Driven Screening for Prediabetes

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Prediabetes is a clinically silent condition, therefore its diagnosis remains a challenge. We conducted a study aiming at assessing the use of risk factors-based screening for impaired fasting glucose (IFG). 5,276 diabetes-free individuals (2,963 women; 56%), aged 45-55 years, who had at least one risk factor for diabetes development took part in a nationwide diabetes screening programme. IFG was found in 1860 individuals, while normal fasting glucose (NFG) was noted in 1421 persons. The prevalence of well established risk factors for glucose metabolism disturbances is presented in the table. Sedentary lifestyle, family history of diabetes and newly diagnosed hypertension were similarly prevalent in both studied groups, however even when differences in prevalence of other risk factors reached statistical significance, the actual difference was relatively small, with the exception of the history of IFG as it was found almost twice as often in persons with IFG as compared to those with NFG. In conclusion, prediabetes screening programmes conducted in high risk populations should not be risk factors driven; particularly they must not be based on family history of diabetes or sedentary lifestyle as these factors are equally often present in persons with prediabetes as well as normal fasting glucose.

Table.

	IFG (n=1860)		NFG (n=1421)		Absolute prevalence difference (APD)	Relative prevalence difference (APD/IFG in %)	p
	n	%	n	%	%	%	
Waist circumference ≥80 cm (women) or ≥94 cm (men)	1666	89.6	1133	79.7	9.9	11.0	<0.001
BMI ≥25 kg/m²	1653	88.9	1167	82.2	6.7	7.5	<0.001
Sedentary lifestyle	1473	79.2	1109	78.1	1.1	-	NS
Family history of diabetes	1188	63.9	920	64.7	0.8	-	NS
Lipid disorders	1185	63.7	827	58.2	5.5	8.6	<0.01
Hypertension – treated	810	43.5	503	35.4	8.1	18.6	<0.001
Cardiovascular disease	737	39.6	456	32.1	7.5	18.9	<0.001
Hypertension – newly diagnosed	458	24.6	349	24.6	0	-	NS
History of IFG	443	23.8	175	12.3	11.5	48.3	<0.001

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1559-P

Redefining Reactive Hypoglycemia from a Population Study

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Whipple Triad currently serves as the standard for reactive hypoglycemia diagnosis. However, repeated hypoglycemia could induce automatic dysfunction causing unawareness of symptoms. Furthermore, the glucose level of reactive hypoglycemia is still undefined. We used the data from NHANES to redefine reactive hypoglycemia.

We included adult non-diabetic subjects (≥20 y/o) with data of fasting plasma insulin available from the NHANES 1999-2010. Diabetes was defined as established diabetes, fasting plasma glucose (FPG) ≥126 mg/dL, 2-hour plasma glucose (2hPG) ≥200 mg/dL or HbA1c 6.5%. Linear regression analysis was applied with the data of FPG and fasting plasma insulin (FPI) predicting the plasma glucose at zero insulin. Non-diabetic subjects with 2hPG were examined for reactive hypoglycemia prevalence accordingly.

After excluding diabetic subjects, there are 11,483 subjects in the study (52.72% female, age 47±18 y/o, BMI 28.07±6.23 kg/m2, A1c 5.3±0.4 %, FPG 98 ±10 mg/dl, FPI 11.56 ± 9.84 mU/l, mean ± STD). With linear regression analysis, FPI=-13.0216+(0.2510xFPG), (r=0.2568; p<0.0001). When insulin secretion approaches near zero, plasma glucose was estimated to be 51.88mg/dl. Accordingly, 50mg/dl was chosen to define reactive hypoglycemia. Among the non-diabetic subjects, there were 1.11% subjects with 2hPG <50mg/dl. The subjects with 2hPG <50mg/dl are fewer female, younger, smaller BMI, lower fasting plasma glucose, higher insulin resistance, and with fewer glucose intolerant subjects (All p<0.001). The delta plasma glucose obtained from 2hPG subtracting FPG was -50±11 mg/dl in subjects with 2hPG <50mg/dl compared to 21±42 mg/dl in subjects with 2hPG ≥50mg/dl (p<0.0001).

From our observation, FPI approaches zero when FPG approaches 50 mg/dL which we used as our definition of hypoglycemia. Prevalence of reactive hypoglycemia is 1.11%. Based on characteristics of the reactive hypoglycemia population, delta plasma glucose could be a good screening test for reactive hypoglycemia in non-diabetic subjects.

1560-P

Self-Perceived Distress and Diabetes Risk among Young Men

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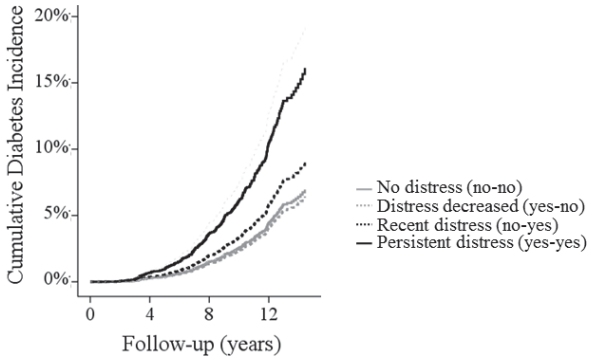
Our goal was to assess the effect of self-perceived emotional distress on T2D incidence among young adults.

Incident diabetes was assessed among 32,586 men (mean age 31.0±5.6 years) with no history of T2D from the prospectively followed young adults of the MELANY cohort (mean follow-up 6.3±4.3 years). Distress level was assessed repeatedly by asking participants, "Are you preoccupied by worries that affect your overall wellbeing?" as part of a computerized questionnaire. The association between reported distress and incident T2D was determined using time-dependent Cox proportional hazard model.

There were 732 cases of T2D during 206,382 person years. The presence of distress was associated with a 53% higher incidence of T2D (95% CI=1.1-2.2, p=0.017) after adjustment for age, BMI, fasting glucose, family history of diabetes, triglyceride and HDL levels, education, white blood cell count, physical activity and a sleep quality assessment score. These results persisted when distress, BMI, physical activity and smoking status were treated as time-dependent variables (HR=1.7, 95% CI=1.2-2.2, p=0.002). An adjusted HR of 2.1 (95% CI=1.1-4.5, p=0.041) for incident T2D was observed among participants consecutively reporting psychological stress compared to those denying it ("yes-yes," and '"no-no" groups, respectively in figure). Thus, sustained self-perceived distress is an important factor in stratifying T2D risk among young men.



Cumulative type 2 diabetes (T2D) risk for participants of the MELANY study with two consecutive assessments of distress level, lifestyle and biochemical risk factors for T2D. The model was adjusted for age, BMI, fasting glucose, family history of diabetes, triglyceride and HDL levels, education, white blood cell count, physical activity and a sleep quality assessment score.

1561-P

HbA1c Is a Poor Predictor of Cardiometabolic Risk and Abnormal Glucose Tolerance in Latinos

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Diagnosis of prediabetes includes impaired fasting glucose (IFG, fasting glucose 100-125 mg/dl), impaired glucose tolerance (IGT, 2 hour glucose 140-199), or HbA1c (5.7-6.4%). These criteria have distinct pathophysiology and may show ethnic differences. This study was done to determine the presence of prediabetes by HbA1c, IFG, or IGT in Latino patients in the Mayo Clinic Sangre por Salud Biobank at Mountain Park Health Center and the association of these categories with cardiometabolic risk. Otherwise healthy patients (707) without diabetes diagnosis were assessed for anthropometrics, HbA1c, fasting/2-hour glucose (75 g OGTT) and blood lipids. Of these, 44 had type 2 diabetes and were omitted, leaving 663 nondiabetics (F/M 75/25%, 41±0.5 yr., BMI 30.4±0.2, FPG 91±0.3, 2-h glucose 108±1, HbA1c 5.6±0.3). Prediabetes was present in 56% (IFG 10%, IGT 10.6%, IFG+IGT 5.3%, HbA1c alone 30.2%). Prediabetes by HbA1c, regardless of OGTT, was present in 47%. Patients with prediabetes by HbA1c alone were compared to those with IFG and/or IGT and normoglycemic controls for blood pressure (BP), plasma lipids, and insulin levels (BMI and age as covariates). Systolic and diastolic BP, VLDL, HDL, cholesterol, triglycerides, and fasting insulin for patients prediabetic by OGTT criteria were worse than normoglycemic values (P<0.05 or better), but did not differ between patients prediabetic by HbA1c alone and those with normoglycemia. VLDL was higher in HbA1c prediabetics compared to normoglycemia (26±0.9 vs. 22±0.7 mg/dl, P=0.012). For other cardiometabolic variables, patients with prediabetes by HbA1c had values between normoglycemia and prediabetes by OGTT. We conclude that prediabetes diagnosis by HbA1c is more common than by OGTT criteria in these Latino patients. Patients diagnosed with prediabetes by HbA1c alone do not differ from normoglycemic patients for most cardiometabolic variables, but may represent a stage on a continuum between normoglycemia and abnormal glucose tolerance.

1562-P

Glycated Albumin May Be a Useful Indicator for Beta-Cell Dysfunction and Impending Diabetes in Prediabetic Condition

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Prediabetes is known as a pre-clinical stage of increased risk for overt diabetes mellitus (DM) and cardiovascular disease. Because glycated albumin (GA) has been suggested to have more potential for assessing insulin secretory dysfunction and glycemic fluctuation than HbA1c, we studied the clinical significance of GA in this stage.

We enrolled 1,379 anti-diabetic drug naïve subjects in a retrospective, multi-center, cross-sectional manner. According to 75-g oral glucose tolerance tests (OGTTs), the subjects were separated into normal glucose tolerance (NGT), isolated impaired fasting glucose (i-IFG), isolated impaired

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glucose toloerance (i-IGT), combined glucose intolerance (CGI), and DM groups. The clinical characteristics of these five groups were measured, including GA, insulin sensitivity index (HOMA2%S), and insulin secretory index (HOMA2%B).

Mean GA was 11.6±1.4, 12.3±1.8, 12.3±1.9, 13.0±1.9, and 18.8±7.9 mg/dL in the NGT (n=295, 21.4%), i-IFG (n=257, 18.6%), i-IGT (n=103, 7.4%), CGI (n=257, 18.6%), and DM (n=466, 34%) subgroups, respectively. After adjusting covariates, the adjusted mean GA levels were 12.2±0.1, 12.2±0.2, and 13.1±0.1 in the i-IFG, i-IGT, and CGI subgroups, respectively; post-hoc analysis revealed that levels were significantly higher in the CGI group ($p<0.001$). The Adjusted mean HbA1c levels were also significant, respectively, but were not distinguished from each subgroup by post-hoc analysis. Moreover, the correlation coefficients between GA and HOMA2%B ($r=-0.567$, $p<0.001$), and between GA and HOMA2%S ($r=-0.013$, $p=0.325$) were higher than those between HbA1c and HOMA2%B, and between HbA1c and HOMA2%S. And these results were remained significant after adjusting covariates.

We suggest that GA might be a better indicator for screening impending diabetes and assessing β-cell dysfunction in prediabetic subjects.

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1563-P

Pancreatic Beta-Cell Function, Insulin Sensitivity, and Metabolic Phenotypes in Type 2 Diabetes at the Time of Diagnosis—The Verona Newly Diagnosed Type 2 Diabetes Study (VNDS)

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Presence and frequency of beta cell (BC) dysfunction (BCD) and insulin resistance (IR) in patients with newly diagnosed type 2 diabetes mellitus (NDT2D) are imperfectly known, because previous studies used small cohorts and/or only surrogate indexes of BC function and IR. We assessed BC function and IR with state-of-art methods in the VNDS. In 712 GADA-negative, drug naïve, consecutive Italian NDT2D patients we assessed: 1. standard parameters; 2. insulin sensitivity (IS) by the euglycaemic insulin clamp); 3. BC function by state-of-art modeling of prolonged (5 hours) OGTT-derived glucose/C-peptide curves. Thresholds for BCD and IR were the 25th percentiles of BC function and IS assessed with the same methods of the VNDS in Italian subjects with normal glucose regulation of the GENFIEV (n=340) and GISIR (n=386) studies, respectively. In the VNDS, 89.8% [95% C.I.: 87.6 - 92.0%] and 87.8% [85.4 - 90.2] patients had BCD and IR, respectively. Patients with only one defect were 19.7% [16.8 - 22.6]. Isolated BCD and isolated IR were present in 10.9% [8.6 - 13.2] and 8.9% [6.8 - 11.0] patients, respectively. Coexistence of BCD and IR was observed in 78.9% [75.9 - 81.9] of the patients. 1.4% [0.5 - 2.3] of the patients had no detectable alterations in BC function and IS. Patients (19.7%) with only one metabolic defect had lower BMI, fasting glucose, HbA1c, triglycerides and BC function, and higher HDL-cholesterol and IS than patients with both BCD and IR ($p<0.01$ or less after Bonferroni's correction). In conclusion, in NDT2DM patients: 1. at least 75.9% have both BCD and IR; 2. At least 87.6% and 85.4% have BCD and IR, respectively; 3. At least 16.8% have only one defect and a significantly different (milder) metabolic phenotype compared to patients with both defects. These findings may be relevant to therapeutic strategies centered on the metabolic phenotype of the patient. ClinicalTrial.gov Identifiers: NCT00879801, NCT01526720.

1564-P

Glycemic Status and Metabolic Features of Patients with Adrenal Incidentalomas With or Without Subclinical Cushing's Syndrome

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The aim of this study was to examine the clinical characteristics of adrenal incidentalomas discovered by computed tomography (CT) and to investigate glycemic status and metabolic features of subclinical Cushing's syndrome (SCS) in patients with adrenal incidentalomas in a tertiary hospital in Korea. This retrospective study examined clinical aspects of 268 patients with adrenal incidentalomas discovered by CT at Soonchunhyang University Bucheon Hospital. Clinical data and endocrine function of the patient as well as histological findings were obtained from medical records, while the anatomic characteristics were analyzed by reviewing the imaging study. Hormonal tests for pheochromocytoma, Cushing's syndrome, and aldosterone secreting adenoma were carried out. Most (n=218, 81.3%) cases were nonfunctioning tumors. Of the 50 patients with functioning tumors (18.7%), 19 (7.1%) were diagnosed with SCS, 9 (3.4%) with overt Cushing's syndrome, 12 (4.5%) with primary aldosteronism, and 10 (3.7%) with pheochromocytoma. Malignant tumors (both primary and metastatic) were rare (n=2, 0.7%). Body mass index, fasting glucose, HbA1c, and total cholesterol were significantly higher in patients with SCS in comparison with those with nonfunctioning tumor. The prevalences of type 2 diabetes mellitus and hypertension were significantly higher in patients with SCS compared to those with nonfunctioning tumors. Functioning tumors, especially those with subclinical cortisol excess, is commonly found in patients with adrenal incidentalomas although malignancy is rare. In addition, patients with SCS in adrenal incidentalomas have adverse metabolic and cardiovascular profiles.

1565-P

Serum Uric Acid: As a Strong and Independent Predictor of Metabolic Syndrome after Adjusting Body Compositions

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Some observational studies have reported that serum uric acid (SUA) levels are one of the determinants of the metabolic syndrome (MetS). However, several previous studies reported combined results for men and women after adjusting for sex and there were few studies that body compositions were taken into account. Therefore, we performed this sex-specific follow-up study to investigate how the longitudinal effects of baseline SUA levels influence the incident MetS including body compositions as an adjusting factor in a large number of subjects. A total of 15,247 participants (9,291 men and 5,956 women) taking a medical health check-up program without diagnosed MetS at baseline were enrolled. Separate analyses were performed for men and women including body compositions as a confounding factor. Cox proportional hazards models were used to quantify the independent association between SUA levels and incident MetS. During 68709 person-years of follow-up, there were 4483 (3174 in men, 1309 in women, respectively) incident cases of MetS between 2006 and 2012. After full adjustment for multiple potential confounders, glucose metabolic confounders, lipid metabolic confounders and body compositions, SUA levels were significantly associated with incident MetS (per 1mg/dl, hazard ratio (HR)=1.076, 95% confidence interval (CI): 1.034-1.120, $p < 0.001$ in men, HR=1.114, 95% CI: 1.015-1.222, $p=0.023$ in women, respectively). This study demonstrated that SUA levels are strong and independent predictor of MetS and this result remained after full adjustment for multiple associated confounders including body compositions, both men and women.

1566-P

Skin Advanced Glycation End Products (AGE) Fluorescence Identifies Abnormal Glucose Tolerance Independent of Levels of HbA1c and Soluble Receptor for Advanced Glycation End Products (sRAGE)

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Skin AGE fluorescence has been widely studied and linked to the development of diabetic complications. Recent studies suggest their utility in screening for abnormal glucose tolerance (AGT). Using Scout DS, a non-invasive, point-of-care (POC) diabetes screening device, we have recently demonstrated that SCOUT is an effective tool for AGT screening in Asian Indians. In this study, we evaluated the clinical utility of SCOUT in picking up AGT and analyzed its relationship with HbA1c (both by autoanalyzer and POC device) and serum levels of soluble receptor for advanced glycation end products (sRAGE). Subjects (n=139) without previous diagnosis of diabetes or impaired glucose tolerance in Chennai, India were subjected to oral glucose tolerance test (OGTT). They were classified as normal glucose tolerance (NGT) and abnormal glucose tolerance (AGT) which includes those with prediabetes or diabetes. Along with SCOUT DS score and HbA1c, circulatory levels of sRAGE were also measured by ELISA. SCOUT DS score was significantly ($p<0.001$) higher in subjects with AGT (52.2±6.3 AU) compared to subjects with NGT (42.5±5.3 AU). SCOUT DS score was positively correlated with BMI ($r=0.404$; $p<0.001$), fasting plasma glucose ($r=0.285$; $p<0.001$), post-prandial plasma glucose ($r=0.483$; $p<0.001$), autoanalyzer-based HbA1c ($r=0.305$; $p<0.001$) and POC-based HbA1c ($r=0.341$; $p<0.001$) and negatively correlated to sRAGE ($r= -0.221$; $p<0.001$). Logistic regression analysis revealed that the association between increased SCOUT DS score and AGT remained statistically significant (OR=1.47; $p<0.001$) even after adjusting for age, BMI, HbA1c and sRAGE levels. Our study underscores the clinical utility of SCOUT DS score as a non-invasive POC tool to identify the subjects at high risk for diabetes.

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1567-P

Concordance of Glucose-based and of HbA1c-based Diagnoses of Diabetes in Patients with Established Coronary Atherosclerosis: A Comparison between Men and Women

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Concordance between glucose based and HbA1c based diagnoses of diabetes differ between populations. Here, we aimed at investigating their concordance in men and in women with stable coronary artery disease (CAD).

We measured fasting glucose as well as HbA1c and performed standard 75g oral glucose tolerance tests in a consecutive series of 711 patients, 513 men and 198 women, who had angiographically proven coronary artery disease (CAD) but not previously diagnosed diabetes. Based on glucose values, diabetes was diagnosed with a fasting plasma glucose (FPG) ≥126 mg/dl or a postchallenge glucose ≥200 mg/dl 2 hours after the oral glucose load; based on HbA1c values diabetes was diagnosed with an HbA1c ≥6.5%.

Among men, 33 had diabetes based on fasting or postchallenge glucose values, of whom 26 also had diabetes according to the HbA1c criterion. Of the 480 men who did not have diabetes based on glucose values, 446 also did not have diabetes according to HbA1c criteria; among women, 3 had diabetes based on glucose values, of whom 2 also had diabetes according to the HbA1c criterion. Of the 195 women who did not have diabetes based on glucose values, 185 also did not have diabetes according to HbA1c criteria. Concordance of Glucose and HbA1c criteria was similar in men and women (92% and 94%; p=0.335). Applying glucose criteria as a standard, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the HbA1c criterion for men were 78.8%, 92.9%, 43.3%, and 98.5%, respectively. For women, sensitivity, specificity, PPV and NPV of the HbA1c criterion were 66.7%, 94.9%, 16.7%, and 99.5%, respectively.

We conclude that concordance of glucose and HbA1c criteria among patients with stable CAD is high and is similar in men and women with CAD. However, for both sexes the sensitivity of the HbA1c criterion is poor in this patient population.

1568-P

Weight Gain and Progression to Type 2 Diabetes in Korean Women with History of Gestational Diabetes Mellitus

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We investigated the effect of longitudinal BMI change on the development of type 2 diabetes in Korean women with a history of gestational diabetes mellitus (GDM).

Women with a history of GDM or gestational impaired glucose tolerance (GIGT) were recruited and underwent a 75 g oral glucose tolerance test at postpartum 6 weeks and annually thereafter. Changes in BMI were calculated between the initial postpartum visit and the last follow-up or at the onset of diabetes. The risk of diabetes was analyzed according to the tertiles of BMI change.

A total of 418 subjects were included for analysis, with a median follow-up duration of 4.0 years. The BMI change in each tertile was -1.8, -0.2, and 1.6 kg/m^2, respectively. We observed an increased risk of incident diabetes as the tertile of BMI change increased (8.6%, 12.6%, and 16.9%, P=0.039). Postpartum BMI change was an independent predictor of diabetes in multivariate analysis (hazard ratio 1.19, 95% confidence interval 1.03-1.39, P=0.020). In the highest tertile group in which BMI increased, there was a significant deterioration in blood pressure, 2-hour glucose, insulin sensitivity, and lipid profiles.

This prospective study demonstrates that an increase in BMI during the 4-years of follow-up after parturition is significantly associated with an increased risk of diabetes and deterioration of metabolic phenotypes in Korean women with a history of GDM.

Table. Cumulative Incidence of Type 2 Diabetes and Changes of Metabolic Phenotypes by Postpartum BMI Change.

	First tertile (n=139)	Second tertile (n=143)	Third tertile (n=136)	*P*-value
BMI (kg/m^2)	-1.8 ± 1.1	-0.2 ± 0.3	1.6 ± 1.1	<0.001
Fasting glucose (mg/dL)	5.4 ± 24.5	5.4 ± 15.3	10.6 ± 23.9	0.073
2-hour glucose (mg/dL)	5.1 ± 59.8	9.0 ± 46.9	26.2 ± 59.6	0.004
Type 2 diabetes	12 (8.6%)	18 (12.6%)	23 (16.9%)	0.039
Matsuda index	0.0 ± 3.4	0.0 ± 3.4	-1.4 ± 3.2	<0.001
Insulinogenic index	0.10 ± 0.52	0.03 ± 0.38	0.04 ± 0.50	0.441
Disposition index	1.0 ± 3.7	0.0 ± 2.6	-0.6 ± 6.1	0.013

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1569-P

Self-Reported Diabetes in Brazil: Prevalence Trends and Related Factors

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Diabetes is increasing globally, particularly in low and middle income countries, posing a great challenge to health systems. Brazil is currently ranked 4th in the world in terms of the absolute number of persons with diabetes. Our aim was to estimate the trend (2006 to 2013) in self-reported diabetes in Brazilian adults, using representative data from the national telephone monitoring system (VIGITEL) which samples yearly more than 40,000 individuals ≥18 years old residing in Brazilian state capitals and the Federal District. Estimates are weighted to represent the surveyed population. We analyzed tendencies with a linear regression model and adjusted prevalences with a probability predictive margins model using as reference categories men, age 18 to 24 years, ≥12 years of schooling and lean/normal weight. As expected, the prevalence of self-reported diabetes was always higher among those with greater age, in women and in those with excess weight and less schooling. From 2006 to 2013, the overall prevalence increased from 5.7% to 6.9%, a net raise of 0.22%/year (p=0.0004). The increase was higher in men (0.24%/year), in those ≥65 years (0.51%/year), and in those with ≤8 years of schooling (0.49%/year). After adjusting for changes in sex, age, school achievement and nutritional status over the period, the trend decreased only slightly to 0.20%/year, suggesting that factors beyond increasing age and excess weight in the population may be at play. The adjusted increase was higher in men (0.26%/year) and in those ≥65 years (0.47%/year), ≤8 years of schooling (0.26%/year) and overweight (0.25%/year). Regardless of the possible causes (higher incidence, increased diagnosis or decreased mortality) of the increasing prevalence, implications for the health system are enormous, representing >300,000 newly diagnosed cases requiring care for diabetes yearly, including many, given their age and schooling, with limited health literacy and multiple co-morbidities.

1570-P

Clinical Decision Support to Enhance Prediabetes Screening in Primary Care

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Despite evidence that diabetes can be prevented or delayed, there is a gap in identifying patients at high risk of diabetes, or prediabetes, within primary care. Barriers include busy clinic schedules, competing priorities, and conflicting guidelines. We hypothesized that an embedded clinical decision support system (CDSS) within the Electronic Health Record (EHR) would facilitate identification of patients with prediabetes. 20 primary care practices within MedStar Health were randomized by cluster to usual care (no CDSS), CDSS following ADA guidelines for prediabetes/diabetes screening, or CDSS following the U.S. Preventive Service Task Force guidelines for a pilot period of 2 months. The CDSS was embedded within a View All Protocols function, which providers had the option to activate or ignore, generating screening prompts for patients meeting criteria. Screening and prediabetes diagnosis rates were compared (Table).

CDSS following either guideline resulted in higher screening of patients at risk and prediabetes identification compared to usual care. Despite the low CDSS review rate, the CDSS prompts reinforced screening behaviors, resulting in greater diabetes screening even when providers did not invoke the CDSS. Embedding CDSS within EHR workflow to enhance identification of patients at high risk of diabetes is feasible and effective, and may allow for greater diabetes prevention efforts within primary care.

Table.

	Usual Care	CDSS per ADA Guidelines	CDSS per USPSTF Guidelines
Number of Practices	6	7	7
Number of Patients Seen	9,556	12,540	15,046
Number of Patients Eligible for Screening	3,713 (per ADA criteria, 38.9%); 2846 (per USPSTF criteria, 29.8%)	5,177 (41.3%)	4203 (27.9%)
CDSS Protocol Activation and Review Rate	NA	22.0%	9.6%
% Screening Rate After CDSS Protocol Reviewed	NA	49.4% (563/1,139)	37.4% (154/412)

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% Declined Screening (via CDSS)	NA	0.25% (13/5,177)	0.17% (7/4,203)
Screening rate (%) of Patients Eligible and Willing to be Screened	12.4% (per ADA criteria); 13.3% (per USPSTF criteria)	19.8%* (1022/5164)	22.2%* (932/4196)
Newly Diagnosed Prediabetes (incidence, %)	2.04% (195/9,556)	3.69%* (463/12,540)	4.15%* (624/15,046)
% of at Risk Patients where Educational Handout given (via CDSS)	NA	7.8% (404/5177)	8.9% (375/4203)

*p<0.0001 compared to usual care, NA = not applicable.

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1571-P

Tracking Type 2 Diabetes Using Sparse Coding

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Tracking methods (TRACK) are used to diminish the drawbacks and costs related to the complications of type 2 diabetes (T2DM). Here we propose a noninvasive method for classifying TRACK based on the sparse coding (SC). SC is a statistical technique to estimate the *primary* causes of the disease. Tests were conducted using with the Brazilian database HIPERDIA, composed of 14 noninvasive disease markers of 1001 pacients: (1-Age, 2-SBP, 3-DBP, 4-waist circumference (cm), 5-weight (kg), 6-height (m), 7-family history, 8-tobacco use, 9-physical inactivity, 10-overweight, 11-heart attack, 12-stroke, 13-other coronary heart diseases, 14-amputation). All possible combinations of these characteristics were tested and removed successively using a one-class SVM type classifier. Table 1 shows the results for all combinations. It was observed that the removal of characteristics related to the age and high rates of body fat decreased the accuracy of the results, which was also observed for its influence on the disease. It is believed that the process of SC can attain the fundamental patterns of disease formation, minimizing the search space for the classifier. In this way, SC achieved results close to the physical results, because a high rate of body fat and old age is directly related to T2DM.

Table 1. Tests Performed Using the Proposed Method Removing the Markers Successively and Testing the Possible Combinations.

Combinations	Possibilities of Disease Markers Combinations	Mean of Accuracy	Standard Deviation	Order of importance of disease markers set for each test
C(14,6)	3003	93.24%	16.13	1>14>6>4>3>9>5>7>8>2>10>13>11>12
C(14,7)	3432	92.79%	16.47	1>13>10>9>8>2>4>5>7>6>3>12>11>14
C(14,8)	3003	95.16%	12.40	1>7>9>4>5>3>8>10>2>6>11>12>14>13
C(14,9)	2002	97.69%	7.5	1>10>7>3>8=9>2>4>13>6>12>5>11>14
C(14,10)	1001	98.67	4.79	1>5=8=12>4=11=13>2=3=10>9>6>7
C(14,11)	364	99.24	3.40	1=2=7=8=14>3=4=5=6=9=10=11=12=13
C(14,12)	91	99.65	1.74	1=5>2=3=4=6=7=8=9=10=11=12=13=14

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1572-P

Rates of Polypharmacy among Type 2 Diabetics in Greece

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Aim: Polypharmacy is a common problem in diabetic patients and a significant barrier to the achievement of glycemic control. Since there are no data in our country regarding polypharmacy among diabetic patients we conducted the present study in order to estimate the rate of polypharmacy among patients attending a diabetic outpatient clinic.

Material and Methods: 205 diabetic patients [98 women/107 men, mean age (± standard deviation, SD): 64.1±11.9 years, mean HbA1c: 7.5±1.5] were included in the study from January to May 2014. Data were collected by the medical files. Only chronic medications given for at least 1 month prior to data collection, were recorded for each patient. Two types of polypharmacy were determined: polypharmacy defined as >5 drugs/day and >7 drugs/day.

Results: Mean rates of polypharmacy>5 drugs and >7 drugs were 79.0% and 54.1%, respectively. From the study patients, 83.9% were on oral antidiabetic medications (OAM) and 48.8% on insulin treatment. The majority of study patients were on antihypertensive (96.6%) and lipid lowering medication (71.2%), followed by antiplatelet drugs (47.3%), H2 blockers and proton-pump inhibitors (22.4%), benzodiazepines (14.6%) and levothyroxine (12.2%). The number of drugs per patient varied from one to 13 while the mean number was 6.6±2.5. Regarding OAM, the number of drugs per patient varied from one to 4 while the mean number was 1.7±1.1. Regarding antihypertensive medication, the number of drugs per patient varied from one to 6 while the mean number was 2.1±1.5. Only, two independent variables for polypharmacy >5 drugs were found: age [odds ratio (OR): 1.06, 95% confidence interval (CI): 1.03-1.09, P<0.001] and OAM (OR: 2.59, 95% CI: 1.15-5.83, P=0.02). No significant associations were found between polypharmacy >5 and sex, HbA1c, duration of T2D, body mass index and insulin therapy.

Conclusions: Greek diabetic patients show high rates of polypharmacy with unknown implications for the achievement of therapeutic targets, especially for arterial hypertension and diabetes.

1573-P

Height in Adolescence and Incident Diabetes among Young Men

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Our goal was to assess the association between height and type 2 diabetes (T2D). Incident T2D was assessed among 32,055 men with no history of T2D from the prospectively followed young adults of the MELANY cohort. Height was measured at two time points; at adolescence (mean age 17.4±0.3 y) and was grouped according to the U.S. CDC percentiles; at enrolment (mean age 31.0±5.6 y). Cox proportional hazards models were applied controlling for clinical and biochemical risk factors for T2D that were assessed at enrollment.

There were 702 new cases of T2D during a mean follow-up 6.3±4.3 y. There was a graded increase in crude T2D incidence rate for decreasing height (see Table); 4.23 vs. 2.44 cases/104 person years for the 1st-10th (162.9±2.9 cm) and 75th-100th (184.4±3.2 cm) height percentiles.These results persisted in when various T2D risk factors were added to the model (See Table). Compared to the 75th-100th percentiles, height at 25th-50th percentiles was associated with HR of 1.5 (95% CI=1.0-2.1, p=0.04) for incident T2D after adjustment for age, BMI, fasting glucose, HDL and triglyceride levels, WBC count, socioeconomic status, country of origin, family history of T2D, sleep quality and physical activity. Every 1 cm decrement in height at age 30 was associated HR of 1.025 for T2D (95% CI=1.01-1.04, p=0.001) controlling for the latter model. These results suggest that height may be added to diabetes risk calculators in stratifying T2D risk among young men.

Table.

	Height at age 17 (CDC-adjusted percentile)					Total
	1-10	10-25	25-50	50-75	75-100	
N	4,335	6,876	8,854	7,501	4,489	32,055
Height at age 17 (cm)	162.9±2.8	168.8±1.2	173.3±1.4	178.1±1.4	184.5±3.1	173.6±6.7
Range (cm)	148-167	165-172	169-176	174-181	180-207	148-207
New cases of diabetes	116	173	194	152	67	702
Mean follow-up	6.33±4.25	6.51±4.29	6.29±4.25	6.30±4.28	6.11±4.30	6.32±4.28
Person years of	27,421	44,760	55,658	47,290	27,419	202,549
Rate (1/1,000 person	4.23	3.86	3.48	3.21	2.44	3.46
Mean age of diabetes	38.67±6.9	37.99±6.8	37.26±6.7	36.80±6.7	35.81±6.5	37.30±6.81
Model 1: Age, birth year						
HR	1.42	1.37	1.30	1.23	Ref	
95%CI	1.05-1.92	1.03-1.82	0.93-1.71	0.92-1.64	-	
P	0.023	0.028	0.065	0.156	-	
Model 2: Age, birth year, BMI						
HR	1.66	1.51	1.37	1.26	Ref	
95%CI	1.28-2.25	1.14-2.01	1.03-1.81	0.95-1.69	-	
P	0.001	0.004	0.029	0.11	-	
Model 3: Age, birth year, BMI, fasting glucose, HDL-c, Triglycerides, WBC count						
HR	1.67	1.52	1.37	1.25	Ref	
95%CI	1.22-2.27	1.14-2.04	1.04-1.83	0.93-1.68	-	
P	0.001	0.004	0.027	0.14	-	
Model 4: Age, birth year, BMI, physical activity, smoking status, MSQ score, breakfast consumption						
HR	1.76	1.70	1.45	1.18	Ref	
95%CI	1.19-2.68	1.18-2.44	1.02-2.09	0.82-1.73	-	
P	0.005	0.004	0.040	0.371	-	
Model 5: Age, birth year, BMI, family history, country of origin, cognitive performance, socioeconomic status, education						
HR	1.44	1.35	1.29	1.20	Ref	
95%CI	1.05-1.96	1.01-1.80	0.98-1.72	0.89-1.61	-	
P	0.023	0.043	0.075	0.216	-	
Model 6: Age, birth year, BMI, fasting glucose, HDL-c, Triglycerides, WBC count, socioeconomic status, country of origin, family history, cognitive function,						
HR	1.64	1.69	1.48	1.17	Ref	
95%CI	1.09-2.46	1.17-2.44	1.03-2.12	0.81-1.72	-	
P	0.017	0.005	0.036	0.39	-	

ADA-Funded Research Guided Audio Tour poster

For author disclosure information, see page A810.

1574-P

Potential Covariables and Pathophysiological Mechanisms Resulting in Elevated HbA1c Levels without Dysglycemia

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Prior studies found an elevated mean HbA1c for Non-Hispanic Black (NHB) compared to Non-Hispanic White (NHW) populations without yielding a physiological mechanism. This study sought to use NHANES data to determine if covariates influence HbA1c levels but not other glycemic measures, and if any of these covariates are known to have differences for likelihood of exposure between racial groups. Once covariates were identified, potential physiological mechanisms related to these covariates were proposed and studied. NHANES data from 2007-2012 was analyzed using logistic regression to determine the odds ratio (OR) for HbA1c > 5.6% without dysglycemia (elevated FPG or OGTT) in non-diabetic subjects. Levels of cadmium in blood above the population mean were found to be significantly associated with elevated HbA1c levels without dysglycemia, and mean HbA1c for NHW with lower Cd exposure was less than those with higher Cd exposure. This was not true for NHB. Cd is known to impede acetylation, and N-acetyltransferase 2 (NAT2) is polymorphic with slow and rapid acetylator phenotypes with a distribution favoring rapid acetylation in NHW and slow in NHB populations. Acetylation may compete with glycation of the hemoglobin β-chain, so a subsample of NHANES subjects was evaluated for acetylator phenotype using caffeine metabolite data. In this subsample, slow acetylators were associated with lower HbA1c levels, which was the opposite of expectations. Further evaluation of this data found that CYP1A2 activity had a greater association with Cd level, and CYP1A2 was associated with decreasing NAT2 activity, thus Cd is suspected of acting through CYP1A2 to decrease NAT2 activity. Tobacco use is known to increase CYP1A2 activity and expose users to lead (Pb) and Cd. When controlling for both tobacco use and blood Pb levels in the statistical model, the significantly elevated OR for HbA1c > 5.6% with normoglycemia in NHB was ameliorated.

1575-P

Causal Factors for Development of Diabetes Mellitus over the Course of 10 Years in the Korean Genome and Epidemiology Study: Serum Mitochondrial Function Inhibiting Activity

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Many epidemiologic studies showed serum levels of persistent organic pollutants (POPs) are linked to type 2 diabetes (T2D). POPs are known to inhibit mitochondrial function. Having reported that serum AhR binding activity (thus serum POPs level) is increased in T2D and diabetic sera as toxic as dioxin to the cultured cells (Park WH et al. Biofactors, 2013), we tested if serum mitochondrial inhibitor activity (MIA) is predictive of future development of T2D.

Total of 1,537 sera collected in 2008 from the Korea Genome and Epidemiologic Study (KoGES) was tested. KoGES was started in 2001 and followed up to 2012 (Cho NH et al. Acta Diabetol, 2013). About half, or 919 cases, had normal glucose tolerance (NGT), 244 cases had impaired glucose tolerance (IGT), and 374 were diabetic (DM). MIA was measured by intracellular ATP level (ATP) after the C2C12 mouse myoblasts were cultured with the heat inactivated serum. Serum AhR binding is measured with previously reported method.

The mean ATP was significantly lower in those subjects who developed IGT or DM within 4 years than those who remained NGT. Subjects with IGT or DM had lower ATP than NGT. From a ROC analysis, the estimated cut-off point of ATP predicting progression to DM within 4 years was 87.4% of control value, with ATP area 82.1%, sensitivity 76.8%, and specificity 61.9%. In the Cox proportional hazards model, cut-off ≥87.4% predicted new diabetes with a RR of 4.3 (95% CI 1.8~10.3) and increased risk remained highly significant with RR=2.9 (95% CI 1.1~8.0) after adjustment of confounding factors. Correlation between serum AHR binding and ATP was highly significant (R=0.34, p<0.001). These results suggested the diabetogenic role of POPs acting through AhR and by causing mitochondrial dysfunction.

1576-P

High Level of Glycated Albumin May Allude to Worsening Insulin Secretory Functions in Prediabetes

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Background: It is well known that the positive correlation between HbA1c and glycated albumin (GA), which has potentials for assessing insulin secretory dysfunction and glycemic fluctuation than HbA1c. Recent studies showed a steeper incline gradient of GA during increasing HbA1c after Impaired glucose tolerance state. We aimed to assess whether insulin secretory function made the slop change in association between HbA1c and GA.

Methods: A total of 298 drug antidiabetic drug naïve subjects underwent 75-g oral glucose tolerance test (OGTT) was performed and A1c and GA were measured, also we calculated the insulin secretory functions. The participants were divided into 2 groups according to A1c < 6.26% (Group I) and A1c ≥ 6.26% (Group II). HbA1c, GA and FCGR, PCGR, 1st phase insulin secretory function, C-pepAUC30/GluAUC30, InsAUC30/GluAUC30, insulinogenic index (IGI) were compared between groups.

Results: In Group II, GA were significantly higher correlations with indices of beta-cell function, compared with HbA1c but not in Group I. These correlations were maintained after adjusting age, BMI in Group II. Binding data were fitted by nonlinear regression, the values of insulin secretory functions were significantly higher correlations with GA than HbA1c .

Conclusions: High GA relative to HbA1c might infer that insulin secretory functions accelerate worsening and diabetes is impending. GA reflects the clinical implications as a marker to identify subjects with impaired b-cell function than HbA1c.

1577-P

Evaluation of HbA1c as a Screening for Type 2 Diabetes Mellitus in Korea

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An HbA1c test result ≥ 6.5% has recently been recommended as the defining criterion for diabetes by the American Diabetes Association (ADA). The aim of the study was to assess the screening test properties of HbA1c for undiagnosed diabetes mellitus (DM) according to the ADA criteria.

Oral glucose tolerance test (OGTT) and HbA1c were performed among 163 subjects without previously diagnosed diabetes at Taeyoung 21 Hospital, Korea between January, 2009 and June, 2014. The OGTT is considered to be the gold standard for diagnosing diabetes. Based on a ROC curve, optimal sensitivity and specificity were derived for identifying the HbA1c threshold. The level of agreement (κ statistics) between OGTT and HbA1c were calculated.

The prevalence of prediabetes and diabetes were 27.6% and 56.4%. The area under the receiver operating characteristic curve for undiagnosed DM was low in HbA1c (0.814 [95% CI: 0.750-0.879]) compared to fasting plasma glucose (0.924 [0.884-0.964]) and 2-h plasma glucose (0.924 [0.884-0.964]). HbA1c of 6.5% gave a sensitivity of 70.7%, a specificity of 76.1%. The level of agreement between two diagnostic criteria was low (κ = 0.448).

The findings in this study demonstrate that the discordance between the OGTT and HbA1c criteria in the diagnosis of diabetes in some Koreans is large. The measurement of HbA1c alone may be inefficient to screen undiagnosed DM. Further large-scale, population-based studies are needed to evaluate the HbA1c threshold for diagnosing diabetes in Korea.

EPIDEMIOLOGY—DIABETES COMPLICATIONS

Guided Audio Tour: What's New in the Epidemiology of Diabetes Complications? *(Posters: 1578-P to 1585-P), see page 13.*

1578-P

Relationship between Cigarette Smoking and the Risk of Proteinuria in New-Onset Type 2 Diabetes Men

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We prospectively examined the relationship between daily and cumulative cigarette consumption and the risk of proteinuria during the 11-years follow-up period in men with new-onset type 2 diabetes. Study subjects were 494 Japanese new-onset type 2 diabetes men aged 40-55 years, with normal estimated glomerular filtration rate (≥60 ml/min/1.73 m^2) and no proteinuria who were not taking hypoglycemic or hypertensive medications at entry. Proteinuria was defined as 1+ or higher on urine dipstick. Daily cigarette consumption was divided into four groups: nonsmokers, past smokers, 1-24, and ≥25 cigarettes/day. Cumulative cigarette consumption was divided into four groups: nonsmokers, past smokers, 1-32.9, and ≥33.0 pack-years. During the 3493 person-years, we confirmed 152 cases of proteinuria. The incidence rates per 1000 person-years for nonsmokers, past smokers, 1-24, and ≥25 cigarettes/day were 25.4, 38.3, 46.6, and 54.1, respectively. After adjustment for age, BMI, systolic and diastolic blood pressure, HbA1c, daily alcohol consumption (nondrinkers, 0.1-22.9, 23.0-46.0, or ≥46.1 g ethanol/day), and regular leisure-time physical activity

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

(yes/no), hazard ratios were 1.82 (95% CI, 1.00-3.31) for 1-24 cigarettes/day and 2.06 (1.15-3.70) for ≥25 cigarettes/day, compared to nonsmokers. Regarding cumulative cigarette consumption, the incidence rates per 1000 person-years for nonsmokers, past smokers, 1-32.9, and ≥33.0 pack-years were 25.4, 38.3, 48.1, and 53.1, respectively. The multiple-adjusted hazard ratios were 1.80 (1.00-3.27) for 1-32.9 pack-years and 2.10 (1.17-3.78) for ≥33.0 pack-years, compared to nonsmokers. P for trend across daily and cumulative cigarette consumption were both significant (p=0.017 and 0.014, respectively). In conclusion, both daily and cumulative cigarette consumption were associated with an increased risk of proteinuria in a dose-response relationship in men with new-onset type 2 diabetes.

1579-P

Inflammation Accelerates Declines in Cerebral Vasoregulation and Cognitions in Type 2 Diabetes

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Older adults with type 2 diabetes mellitus (T2DM) have been showed to have more impaired cerebral perfusion and greater cognitive decline than non-diabetic adults. We aimed to investigate the relationships between cerebral vasoregulation and the progression of cognitive dysfunction in T2DM.

In this two-year prospective study, 40 participants (age 66.8 ± 8.8 years, 19 with T2DM, 22 women) were enrolled. Participants completed medical, neuro-physiological and neuropsychological examinations and continuous arterial spin labeling MRI to measure global and regional cerebral perfusion and vasoreactivity.

After the two years of follow-up, T2DM participants showed diminished global and regional cerebral vasoreactivity and a decline in multiple cognitive tasks as compared to baseline ($p < 0.0001$-0.012). T2DM participants with lower cerebral vasoreactivity at baseline had a greater decrease in the daily living activities score ($r2adj = 0.35$, $p = 0.04$). T2DM participants with lower global vasodilation had a greater decline in the executive function ($r2adj = 0.6$, $p = 0.047$). In the T2DM group, higher baseline serum inflammatory markers, including cortisol, C-reactive protein, soluble intercellular and vascular adhesion molecules, were associated with greater decreases in cerebral vasoreactivity and vasodilation ($r2adj = 0.16$-0.53, $p = 0.007$-0.048), independent of diabetes control. These relationships were not observed in non-diabetic controls.

Inflammation may exaggerate the long-term adverse effects of T2DM on cerebral vasoreactivity that may accelerate to cognitive decline older diabetic adults.

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1580-P

Neuropathy Prevalence Compared with Other Complications in Longstanding T1DM: Preliminary Analysis of the Canadian Study of Longevity in Diabetes Cohort

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T1DM subjects can survive for extreme duration without retinopathy or nephropathy. Though lifetime risk of neuropathy is thought to approach 100%, estimates are uncertain. In a cohort with ≥50y of T1DM, we aimed to assess the prevalence of microvascular complications and other indicator variables. In the questionnaire phase of the Cohort, 303 participants were recruited (2013-2014) across Canada by public advertisement and mailings to health professionals. Participants answered a comprehensive questionnaire and provided recent laboratory results. We assessed complications objectively by eye specialist fundus examinations, Michigan Neuropathy Screening Instrument score ≥3/15, chronic kidney disease (CKD) by age-adjusted CKD Stage 3 or urine albumin-to-creatinine ratio, and self-report of cardiovascular disease (CVD). In preliminary analysis, 190 participants (54% female) had median diabetes duration of 55 (range 50 to 81y), age 66 (range 51-93), BMI 25.8±4.3 kg/m2, and A1c 7.6±1.0%. 98 (52%) attended ≥3 annual physician visits, and 141 (77%) reported endocrinologist care. 131 (69%) reported renin angiotensin system inhibitor use and 139 (74%) statins. Retinopathy was most prevalent at 71% compared to neuropathy (39%), nephropathy (42%) and CVD (36%; p<0.001 for all comparisons with retinopathy). 34 (18%) lacked evidence of any complication. In linear regression, greater number of complications was independently associated with longer diabetes duration (p=0.02), higher A1c (p=0.04), and lower GFR (p<0.001). Despite presence of salutary factors such as frequent specialist care, medication adherence and good glycemic control, only a small proportion of patients with longstanding T1DM were resistant to all complications. Retinopathy - and not symptomatic neuropathy - was the dominant complication indicating a need to better understand mechanisms that could promote resistance to specific complications.

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1581-P

Nonalcoholic Fatty Liver Disease Is Associated with Heart Valve Calcification in Type 2 Diabetes

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Aortic valve sclerosis (AVS) and mitral annulus calcification (MAC) are powerful predictors of adverse cardiovascular outcomes in patients with type 2 diabetes (T2D), but the aetiology of valvular calcification is uncertain. Nonalcoholic fatty liver disease (NAFLD) is an emerging cardiovascular risk factor commonly present in T2D patients, but its association with valvular calcification is unknown. We sought to investigate whether NAFLD is associated with AVS and/or MAC in T2D patients. We conducted a cross-sectional study by performing a conventional echocardiography and liver ultrasonography in a sample of 247 consecutive outpatients with T2D (179 men; mean age 68 years) free of known liver diseases, prior history of chronic heart failure and moderate-to-severe valvular heart disease. Overall, 139 (56.3%) patients had no calcification at both aortic and mitral valve (HVC-0), 65 (26.3%) had one valve affected (HVC-1) and 43 (17.4%) patients had both valves affected (HVC-2). NAFLD was present in 175 (70.8%) patients and its prevalence markedly increased in patients with HVC-2 compared with either HVC-1 or HVC-0 (86.1% vs. 83.1% vs. 60.4%, respectively; p<0.001). NAFLD was associated with AVS and/or MAC (unadjusted-odds ratio [OR] 3.51, 95% CI 1.89-6.51, p<0.001). Adjustments for age, sex, smoking history, alcohol consumption, diastolic blood pressure, hemoglobin A1c, LDL-cholesterol, estimated glomerular filtration rate, use of hypoglycemic, lipid-lowering and anti-hypertensive medications and echocardiographic variables did not substantially attenuate the strong association of NAFLD with AVS and/or MAC (adjusted-OR 2.97, 95% CI 1.31-6.70, p<0.01). In conclusion, these results show for the first time that NAFLD is a strong and independent predictor of cardiac calcification in both aortic and mitral valves in patients affected by T2D. Further research is needed to better elucidate the mechanisms underlying this association.

1582-P

Health Disparity in Zuni Indians as Reflected in Progression of Metabolic Risk Factors

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The Zuni Indians are socioeconomically disadvantaged population faces a major public health challenge from growing health disparities. The Zuni Kidney Project (ZKP) has described the epidemic of kidney disease and the subsequent investigation of Genetics of Kidney Disease in Zuni Indians (GKDZI) described the heritability of kidney disease and its intermediate phenotypes. Recently, through PCORI funded home-base kidney care (HBKC), we rescreened 314 Zuni participants.

In order to test the hypothesis that the metabolic risk factors including diabetes and chronic kidney disease would progress over time, we performed an analysis of subjects in HBKC who participated in both ZKP and GKDZI.

Individuals (n=314) who participated in HBKC were studied at 3 time points at a mean interval of 8.6 years (range 2.5-13 years). 46% of this cohort was female; mean age at the 1st study point was 30.8 years. The table shows the progression of metabolic risk factors over time.

Table.

	Time Point 1		Time point 2		Time point 3		
	Mean (SD)	% abnormal	Mean (SD)	% abnormal	Mean (SD)	% abnormal	P-value*
A1C	6.2 (1.7)	20.13%	6.1 (1.6)	22%	7.0 (2.0)	39.05%	<0.0001
UACR**	11.9 (36.2)	31.21%	30.1 (72.1)	54.88%	57 (220)	71.5%	0.0163

This analysis of a cohort of individuals from the ZKP/GKDZI/HBKC studied at 3 time points over up to 14.3 years shows a progression of CKD and its risk factors including diabetes and obesity. These findings reinforce the need for interventions to modify these risk factors for CKD progression as supported by and PCORI pilot HBKC care in this high risk population, particularly amongst the young adult Zuni.

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1583-P

Relationship between Diabetes Complications and Health Related Quality of Life among an Elderly Population in the United States

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Type 2 diabetes mellitus (T2DM) is associated with increased risk for morbidity and mortality. Health related quality of life (HRQOL) has become an increasingly important component of quantifying the health of patients. The objective of this study is to understand the relationship between complications of T2DM and self-reported HRQOL.

The Health Outcomes Survey (HOS), a cohort study spanning 2 years that is administered to a sample of Medicare Advantage members from all plans in the U.S. each year, includes a 4-question HRQOL instrument called Healthy Days. This instrument measures the number of physically and mentally unhealthy days (UHD) within the past 30 days. Using the results of the 2011-2013 HOS survey from the Humana Medicare Advantage population, members' responses were matched to their claims data. Analysis of variance (ANOVA) was used to examine the correlation between the presence of complications and UHD. To measure the impact of the severity of complications a linear regression model was used to assess the association between the diabetes complication severity index (DCSI) and UHD.

Of the 12,105 people who completed the 2011-2013 HOS, 3,120 (25.3%) had T2DM (mean age=75.8 years, 54.0% female, mean UHD=11.3). Two individual complications associated with large increases in UHD were limb amputation (9.4 more UHD, p=0.002), and depression (7.9 more UHD, p<0.001). After controlling for age and gender, every one-point increase in the DCSI score was associated with an increase of 1.2 average UHD (p<0.0001). Increases in the number of HbA1c tests during the study period and HbA1c control (<8.0%) were associated with lower UHD, though not statistically significant.

Patients with more diabetes-related complications report worse HRQOL. There seems to be a significant opportunity to improve HRQOL of patients by improving targeted care and thereby preventing complications.

1584-P

Increased 10-Year Risk for Cardiovascular Disease Assessed by Pooled Cohort Equation in Subjects with HbA1c Lower than 6.5%

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In 2013, new risk calculator, called "Pooled Cohort Equation" has been released with a new cholesterol guideline. We calculated 10-year cardiovascular risk in non-diabetic Korean subjects with HbA1c lower than 6.5%. In 17519 participants (mean age 40 years, men: 79.3%) in a health screening program, 10-year risk for cardiovascular disease (CVD) was calculated with Pooled Cohort Equation (PCE). The subjects with underlying diabetes or HbA1c≥6.5% were excluded from the study. In all subject, HbA1c and fasting blood glucose (FBG) were measured and subjects were divided into four groups according to FBG and HbA1c levels; category I: FBG<100, 100≤FBG<110, 110≤FBG<120, FBG≥120, category II: HbA1c <5.5, 5.5≤HbA1c<5.6, 5.6≤HbA1c<5.8, HbA1c≥5.8. Mean 10-year cardiovascular risk calculated by PCE was 2.9%. FBG and HbA1c showed significant positive correlation with 10-year CVD risk in bivariate correlation analyses (r=0.161, p<0.01; r=0.145, p<0.01). Mean 10-year CVD risk significantly increased as FBG increased in four groups from lower than 100 mg/dL to higher than 120 mg/dL (2.6, 3.3, 3.8, 4.1%; p<0.01 by one-way ANOVA test), and as HbA1c increased in four groups from lower than 5.5% to higher than 5.8% (2.4, 2.7, 3.0, 3.6%; p<0.01 by one-way ANOVA test). Risk for 10-year CVD risk being equal to or higher than 10% significantly increased from the 1st group to 4th group divided by FBG and HbA1c after adjustment for BMI and fasting insulin level (1.349, 1.955, 2.535 vs. 1.0 in the lowest FBG group; 1.846, 1.646, 4.019 vs. 1.0 in the lowest HbA1c group). 10-year CVD risk calculated by the new calculator significantly increased as the FBG and HbA1c increased even in Korean subjects without underlying diabetes.

1585-P

Phosphodiesterase Type-5 Inhibitor Use in Type 2 Diabetes Is Associated with a Reduction in All-Cause Mortality

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Objectives: Phosphodiesterase type 5 inhibitors (PDE5i) are cardioprotective in animal models of acute myocardial infarction (MI) although few supporting clinical data are available. We sought to investigate whether PDE5i use in a cohort of patients with type 2 diabetes (T2DM), and therefore high attendant cardiovascular risk, was associated with altered mortality.

Design: Population based cohort study.

Setting: The anonymised records of 5,956 men (mean follow-up of 6.9 years) aged 40-89 years diagnosed with T2DM before 2007 were identified from 42 GP practices in Cheshire UK. Baseline clinical characteristics and PDE5i treatment data were obtained.

Main Outcome Measure: We used hazard ratios (HR) from Cox regression models to describe the association between PDE5i use and all cause mortality.

Results: A lower percentage of deaths (18% vs. 25%), and a significantly reduced risk of all-cause mortality from unadjusted Cox regressions [HR=0.69 (95% confidence interval: 0.60, 0.79); P<0.0001], was observed amongst the 1,359 (22.8%) men prescribed a PDE5i, compared to those without such a prescription. This reduction in risk remained after adjusting for age, eGFR, smoking status, history of myocardial infarction, systolic blood pressure (per 5 mmHg), use of a statin, metformin, aspirin and beta-blockers: hazard ratio=0.83 (0.70-0.98); p 0.038. The pattern of lower mortality (unadjusted HR=0.69. P=0.009) was similar in those with a history of acute MI (25.7%, (49/191) vs. 40.1% (337/840) deaths). After multiple adjustments, users of PDE5is were less likely to suffer an acute MI event (HR 0.74. P=0.036).

Conclusion: In a population of men with T2DM, on-demand use of PDE5is was associated with decreased risk of both overall mortality and mortality in those with a history of AMI. Further studies are required to characterise these potential cardio-protective effects.

1586-P

Self Report of Low Blood Sugar Symptoms among Adults with Diabetes 50 Years and Older in the United States

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Although there is an increased focus on preventing hypoglycemia events among adults with diabetes, few studies have looked at factors associated with hypoglycemia events outside of a hospital setting. We used data from the Health and Retirement Survey 2003 supplemental diabetes questionnaire that included questions related to low blood sugar. Diabetic participants ≥ 50 years (n=1628) responded to "How many days in the last month have you had symptoms of low blood sugar, such as sweating, weakness, anxiety, trembling, hunger, or headache?" Responses were categorized as 0 days, 1 to 3 days and 4 days or more. We aimed to determine the factors associated with low blood sugar symptoms (LBSS). Overall, 50.6% participants reported 0 days, 32.6% reported 1-3 days and 16.6% reported 4 or more days in the past month with LBSS. Greater frequency of LBSS was reported by women, adults 51-64 years, type 1 diabetes or type 2 diabetes taking insulin, participants reporting having a target A1c, visiting the doctor more frequently, more ER visits in the past year and self report of CVD. Race/ethnicity, education level, mean A1c, hypertension and use of sulfonylureas were not associated with increased LBSS. Adjusting for age, sex and duration of diabetes, the odds ratio for 4 + LBSS compared to 0 days was 3.6 (95% CI 1.4, 9.8) for adults with type 1 diabetes and 2.0 (95% CI 1.3, 2.9) for adults with type 2 diabetes taking insulin compared with adults with type 2 diabetes not on insulin. In adjusted analyses, visiting the doctor more frequently, more ER visits, proteinuria, and CVD remained significantly associated with greater number of compared to 0 LBSS while there was no significant association with being able to specify a target A1c. Among adult with diabetes, LBSS occur more frequently among women, younger older adults, those using insulin for treatment and those reporting CVD history. These groups may benefit from increased diabetes education to recognize and prevent hypoglycemia.

1587-P

Mortality in Youth-Onset Diabetes: The SEARCH for Diabetes in Youth Study

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Few studies have examined mortality risk among youth with diabetes. We estimated all-cause mortality in youth with incident type 1 (T1D) and type 2 diabetes (T2D) diagnosed before age 20 yrs. T1D (n=6840) and T2D (n=1518) cases diagnosed from 1/1/02-12/31/08 were assessed for vital status through 12/31/10 using the National Death Index. Standardized mortality ratios compared observed vs. expected numbers of deaths based on age, sex and race for the comparable general U.S. population. We used Cox proportional hazards regression to assess effects of demographics and diabetes type on mortality. Mean age at diagnosis was 10.7 yrs. During follow-up (mean 5.3 yrs) there were 41 deaths. Overall mortality did not differ significantly from expected (Table). However, compared to the general population, mortality was higher

For author disclosure information, see page A810.

among those with T2D, females, 15-19 yr olds, and NHBs. In Cox regression analysis, mortality was higher for NHBs vs. NHWs and those who were older at diagnosis. Although mortality was higher among those with T2D vs. T1D, the excess was accounted for by differences in age and race. Among youth with T1D, diabetes (n=11) was the most frequent underlying cause of death. Among youth with T2D, accidents/injuries (n=8) were the most frequent causes. Our results show excess mortality in youth with T2D, NHBs, females, and older youth with diabetes compared to the general population. Further study of mortality in youth with diabetes is warranted.

Table. Age-, Sex-, Race-Standardized Mortality Ratios (SMRs).

	No. Person-Years	No. Deaths Observed	No. Deaths Expected	SMR	95% CI	P-value
Overall	44,893	41	31	1.3	1.0, 1.8	0.0815
Diabetes Type						
T1D	36,810	26	25	1.1	0.7, 1.6	0.8435
T2D	8,083	15	6	**2.4**	**1.3, 3.9**	**0.0011**
Sex						
Female	22,489	22	10	**2.2**	**1.3, 3.3**	**0.0004**
Male	22,404	19	21	0.9	0.6, 1.4	0.8060
Race/Ethnicity						
Non-Hispanic White (NHW)	27,766	12	17	0.7	0.4, 1.2	0.2634
Non-Hispanic Black (NHB)	6,897	16	8	**2.1**	**1.2, 3.4**	**0.0043**
Hispanic	7,138	9	5	1.9	0.9, 3.6	0.0894
Other	3,091	4	1	3.1	0.8, 7.9	0.0539
Age at death or end of follow-up						
<14 years	16,436	8	10	0.8	0.3, 1.6	0.6379
15-19 years	15,481	23	9	**2.7**	**1.7, 4.0**	**<0.0001**
20-24 years	11,283	9	11	0.8	0.4, 1.6	0.7049
25-29 years	1,693	1	2	0.6	0.0, 3.6	0.9712

1588-P

Infection and Pathogen Burden among Medicare Beneficiaries with Diabetes, 2012

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Diabetes (DM) is associated with increased risk of mortality and morbidity from various infections and their complications. Infection is among the 10 most frequent indications for use of health care services and accounts for 2 of the top 3 conditions with the largest number of 30-day hospital readmissions among Medicare enrollees aged ≥65 years. In 2011, costs for 30-day-readmissions due to septicemia, pneumonia, and urinary tract infection totaled U.S. $ 3.2 billion. We analyzed data from the Centers for Medicare & Medicaid Services (CMS) to assess the frequency of receipt of medical care for infection among Medicare beneficiaries with DM in 2012.

We used the CMS chronic condition algorithm to identify beneficiaries with DM. We identified infections in persons with DM who had at least one reimbursement claim with the *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD9 CM) diagnosis code for a specific anatomic site or pathogen. We estimated the frequency of anatomic site with infection and pathogen burden among beneficiaries with DM.

Of the 10.3 million beneficiaries with DM in 2012, 82% were ≥65 years of age, 54% female, 28% minority racial-ethnic groups, and 38% had ≥3 comorbidities known to predict infection-related mortality. One in 5 (21%) beneficiaries (n=2.2 million) had at least one infection. Pneumonia (n=1,065,386), septicemia (n=492,813) and urinary tract infection (n=381,373) were the top 3 conditions. Overall, 4.5 million beneficiaries had pathogen-specific infections: Dermatophytosis (n=2,207,129), Candidiasis (n=377,775), Viral hepatitis (n=168,280), Herpes zoster (n=165,012), and Streptococci or Meningococci infections (n=45,608).

In 2012, among Medicare beneficiaries with DM, the lower respiratory tract, urinary tract, blood, and skin were the most commonly involved anatomic sites with infections; viruses and fungi were the most common pathogens.

1589-P

Effects of Hypertension and Diabetes on Myocardial Infarction, Stroke, and Mortality in the Chinese Population Participating in 23-Year Follow-up of Da Qing IGT and Diabetes Study

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Diabetes (DM) and hypertension (HTN) are risk factors for myocardial infarction (MI), stroke and mortality, but little information is available on the long-term excess risks attributable to these factors in the Chinese population. We estimated the excess risks for DM and HTN alone, and in combination, from 23-year follow-up of the population-based Da Qing IGT and Diabetes Study.

In 1986, 110,660 adults aged 25-74 years were screened for newly diagnosed diabetes (DM) in Da Qing, China. 630 people with DM were identified and 519 with normal glucose tolerance (NGT) were selected for comparison. 285 with DM and 248 with NGT had HTN. In 2009, we tracked all study participants to compare their risks of first MI, stroke, and all-cause mortality.

Diabetes and hypertension each lead to substantial excess risk for MI, stroke and mortality. The combination of the two further increases the risk of MI and mortality. Diabetes alone appears to increase the risk of MI and death more than HTN alone, whereas the risk for stroke is similar.

Table. Age-Sex Adjusted Annual Incidence for MI, Stroke and All-Cause Mortality and Hazard Ratios.

	NGT without HTN	NGT with HTN	DM without HTN	DM with HTN
No. of participants	271	248	345	285
MI incidence Hazard Ratio	2.7 (1.7-4.3)1	5.7 (3.9-8.4) 1.9 (1.0-3.8)*	11.3 (8.5-14.9) 4.6 (2.6-8.3)***	12.0 (8.9-16) 4.3 (2.3-7.8)***
Stroke incidence Hazard Ratio	11.1 (9.1-13.5)1	19.3 (16.0-23.0) 1.6 (1.2-2.3)**	17.3 (4.0-21.1) 1.6 (1.2-2.3)**	31.3 (27.1-35.7) 2.7 (2.0-3.7)**
Mortality incidence Hazard Ratio	8.3 (6.6-10.5)1	15.1 (12.3-18.3) 1.9 (1.3-2.6)**	26.1 (22.7-29.6) 3.4 (2.5-4.7)**	32.5(29.0-36.0) 4.2 (3.1-5.7)**

1590-P

Hypoglycemia and Glycemic Variability Are Associated with Mortality in Non-Intensive Care Unit Hospitalized Infectious-Disease Patients with Diabetes Mellitus

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It has been reported that hypoglycemia and glycemic variability (GV) are associated with mortality in intensive care unit (ICU) patients. Reactive inflammatory biomarkers (RIB) and vital signs in infectious-diseases such as pneumonia have also been associated with mortality. However, it is not well known which factors—glycemic control, RIB, or vital signs—are most associated with mortality in non-ICU hospitalized infectious-disease patients with diabetes mellitus (Non-ICU-IP-DM). In this study, we investigated the association between those factors and mortality in non-ICU-IP-DM. We retrospectively analyzed 631 Non-ICU-IP-DMs who underwent glucose monitoring more than twice per day. We extracted RIB and vital signs data on the first day of glycemic control, and calculated hypoglycemia, GV (coefficient of variation (CV), standard deviation (SD)) and mean glucose level (MGL) from all glycemic values. We analyzed the association between those factors and mortality by using logistic multivariate regression analysis. We found a mortality rate of 10.1%. RIB and vital signs were not associated with mortality. However, hypoglycemia, CV, SD, and MGL were independent risk factors for increased mortality. Glycemic control (especially hypoglycemia and GV), rather than RIB or vital signs, is associated with mortality in Non-ICU-IP-DM.

Table.

(n = 631)	Mortality	
Variable	*OR (95% CI)*	*p*
Age, years	*1.02 (0.98-1.07)*	*0.34*
Male sex, n	*1.91 (0.81-4.49)*	*0.14*
Body mass index (BMI), kg/m^2	*0.93 (0.83-1.03)*	*0.15*
HbA1c (NGSP), %	*0.64 (0.47-0.86)*	*0.003*
White blood cell (WBC), mg/dL	*1.00 (1.00-1.00)*	*0.51*
C-reactive protein (CRP), mg/dL	*1.03 (0.99-1.07)*	*0.22*
Body temperature (BT), °C	*0.61 (0.33-1.12)*	*0.11*
Systolic blood pressure (SBP), mmHg	*1.01 (0.99-1.03)*	*0.51*
Diastolic blood pressure (DBP), mmHg	*1.02 (0.98-1.05)*	*0.38*
Heart rate (HR), times/minute	*1.02 (0.99-1.05)*	*0.18*
Arterial oxygen saturation (SpO2), %	*0.84 (0.70-1.01)*	*0.06*
Mean glucose level, mg/dL	*1.07 (1.03-1.12)*	*0.0005*
Standard deviation (SD), mg/dL	*1.16 (1.03-1.29)*	*0.01*
Coefficient of variation (CV), %	*1.31 (1.06-1.61)*	*0.01*
Hypoglycemia, n (%)	*5.90 (2.19-15.84)*	*0.0004*
R^2	*0.33*	
Significance		*<0.0001*

ADA-Funded Research Guided Audio Tour poster

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1591-P

HbA1c Variability and HDL-cholesterol Might Be Associated with Diabetic Kidney Disease in Type 2 Diabetic Patients with Advanced Diabetic Retinopathy

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Diabetic kidney disease (DKD) is often accompanied by diabetic retinopathy (DR). However, some patients do not develop any sign of DKD in the presence of advanced DR. We have therefore investigated the presence and characteristics of DKD in type 2 diabetic patients with advanced DR.

A total of 317 patients with advanced DR, defined by the presence of moderate/severe nonproliferative DR or proliferative DR on the basis of the worst eye, were retrospectively studied. DKD was defined by the presence of the urine albumin/creatinine ratio (uACR) (mg/g) ≥30 or the estimated glomerular filtration rate (eGFR) (ml/min/1.73m^2) <60. They were divided into the following 3 groups: No DKD (uACR <30 and eGFR ≥60), Early DKD (uACR ≥30 alone or eGFR <60 alone), and Late DKD (uACR ≥30 and eGFR <60). Mean systolic and diastolic blood pressures, mean HbA1c levels and HbA1c variability (HbA1c SD; SD of serial HbA1c values) were calculated during the preceding 2 year.

Prevalence rates of the No DKD, Early DKD, and Late DKD groups were 37.2%, 37.0%, and 25.8%, respectively. The No DKD group had lower HbA1c SD and mean systolic blood pressure, and higher HDL-cholesterol and hemoglobin levels as compared with the Late DKD group. However, diabetes duration, age, mean HbA1c and LDL-cholesterol levels were not different. HbA1c SD or HDL-cholesterol levels were correlated with uACR as well as eGFR. Multiple linear regression showed that HbA1c SD or HDL-cholesterol levels was a significant predictor of eGFR after adjusting for other confounding variables. Multiple logistic regression showed that HbA1c SD and HDL-cholesterol levels were significant predictors of the late DKD group after adjusting for other confounding variables.

In conclusion, DKD was present in approximately 60% of type 2 diabetic patients with advanced DR. HbA1c variability and HDL-cholesterol might be associated with the development and progression of DKD in these patients.

1592-P

A Genome-Wide Association Study of Lower Urinary Tract Symptoms (LUTS) in Men with Type 1 Diabetes in DCCT/EDIC

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Lower urinary tract symptoms (LUTS) are commonly reported by men with diabetes. There is evidence that LUTS risk is heritable, and candidate gene studies have identified several potential risk variants. We aimed to identify genetic predictors of LUTS in men with type 1 diabetes (T1D) in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications using a genome wide association study (GWAS). We characterized LUTS severity with the American Urological Association Symptom Index (AUASI) at EDIC year 17, using a standardized 7 item questionnaire that quantifies the presence and frequency of the following symptoms: nocturia, frequency, urgency, weak urinary stream, intermittency, straining, and the sensation of incomplete emptying, with scores ranging from 0 to 35. Standardized definitions of LUTS were used (0-7 none/mild, ≥8 moderate/severe). Genotypes were collected with an Illumina 1M chip and imputed to the 1000 Genomes data. A GWAS with 474 controls and 156 cases was performed with a model adjusting for age, BMI, HbA1c, former DCCT treatment group, and diabetes duration. Age, but none of the other covariates, was associated with LUTS in a logistic regression: p=3x10^{-8}, OR=1.09 (1.06-1.12). Genomic control lambda for GWAS = 1.02. Two regions reach suggestive significance: An intergenic region on chromosome 10 between a microRNA and *SH2D4B*: p=1.7x10^{-7}, OR=2.0 (1.8-5.0), MAF=5.9%, and on chr 2 in an intron of *GPR39*: p=1.9x10^{-7}, OR=2.2 (1.6-2.9), MAF=25.3%. *GPR*s are involved in signaling. Our preliminary data demonstrates a potential role for a genetic contribution to LUTS in men with T1D. If validated in other cohorts, these SNPs could help risk stratify the large proportion of men with T1D who will develop significant LUTS.

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1593-P

In Morbid Obesity Type 2 Diabetes Is Associated with Raised Liver Enzymes and Predicts Chronic Liver Disease—A 15-Year Prospective Study

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To explore in morbid obesity the role of type 2 diabetes (DM) and liver enzymes (AST and ALT) in the development of chronic liver disease (CLD) and long-term mortality, we planned a prospective cohort, record-linked study, and we considered morbidly obese subjects first seen during the period 1995-2001 [divided in two groups: 221 with DM and 748 without DM)]. Data included: gender, age, anthropometric and blood pressure measurements, metabolic parameters (blood glucose, HbA1c, cholesterol, HDL and LDL cholesterol, triglycerides, AST and ALT). Personal identification codes of subjects were entered into the Regional Database of the Italian National Health System to identify alive and dead subjects, and subjects developing DM or CLD at the date 30.09.2012. Despite similar body mass index (BMI), ALT (34.6±22.15 vs. 48.7±44.74 U/L, means ± SD, p=0.001) and AST (25.2±12.56 vs. 32.2±21.26 U/L, p=0.001) were lower in non-DM than in DM subjects; ALT and AST did not correlate with BMI, but correlated with blood glucose levels (r=0.266, p=0.0001; r=0.19, p=0.001, respectively), and inversely with HDL-cholesterol (r=0.24, p=0.0001; r=0.11, p=0.013, respectively). ALT and AST were significantly higher in DM subjects even after group matching for age and sex (107 vs. 197 subjects). Data from Regional Database showed that CLD developed more frequently in DM (n=10) than in non-DM subjects (n=11, p=0.006); in addition more deaths were recorded among DM than non-DM subjects (50 vs. 42, p=0.0001).

We conclude that an increase of ALT and AST is more frequent in DM subjects among morbidly obese subjects; ALT and AST correlate with other known metabolic risk factors; after a mean 15 years follow-up analysis, DM patients are at increased risk of mortality and of chronic liver disease.

1594-P

Does Long-Term Use of Low-Dose Aspirin Develop Proteinuria in Diabetic Patients?

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Low-dose aspirin is widely recommended for those with higher risk of cardiovascular diseases (CVD); however, there is not enough evidence for renal toxicity in long-term use of aspirin. We analyzed whether long-term use of low-dose aspirin affects incidence of proteinuria, as an early phenomenon of renal dysfunction in diabetic patients. We have conducted JPAD trial to evaluate originally whether low-dose aspirin prevents CVD in type 2 diabetic patients without previous CVD. 2,536 patients were randomly assigned to aspirin (81 or 100 mg daily) or no aspirin groups. We followed the cohort of JPAD trial for a median of 8.5 years, and evaluated incidence of proteinuria. The analysis included 2,173 patients without proteinuria at baseline. Proteinuria was developed in 297 patients of aspirin group and 270 patients of no aspirin group. Kaplan-Meier curves by the intention-to-treat principle showed that aspirin did not increase incidence of proteinuria (hazard ratio [HR], 1.17; 95% confidence intervals [CI], 0.995-1.38; Figure A). On-treatment analysis showed similar results (HR, 1.08; 95% CI, 0.92-1.28; Figure B). Cox proportional hazard model showed that incidence of proteinuria was increased by elderly, high blood pressure, high levels of serum creatinine, or A1C, not by taking aspirin (HR, 1.12; 95% CI, 0.95-1.32). The findings indicated that long-term use of low-dose aspirin did not affect proteinuria in diabetic patients.

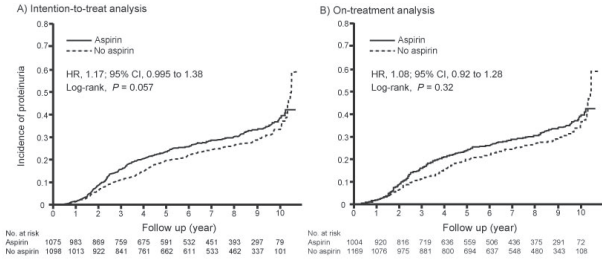

Figure. Effect of low-dose aspirin on incidence of poteinuria

For author disclosure information, see page A810.

Guided Audio Tour poster

ADA-Funded Research

1595-P

Longitudinal A1c Patterns and Their Associations with Outcomes in Type 2 Diabetes

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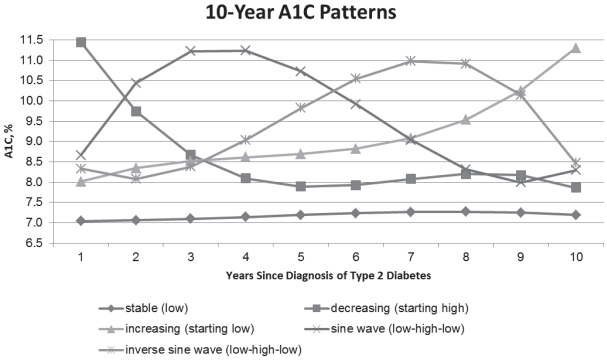
Results from the United Kingdom Prospective Diabetes Study suggest that achieving good A1C control early in type 2 diabetes reduces complications. However, little is known about A1C varies over time and how A1C patterns affect outcomes. We studied 28,016 patients with newly diagnosed type 2 diabetes from Kaiser Permanente Northern California from 1997-2001. Using latent growth mixture and Cox proportional hazard models, we categorized 10-year A1C patterns and examined their associations with time to post-10 year incident complications and death, adjusted for age, gender, race, hemoglobin, eGFR, 10-year average A1C, cardiovascular risk factors and comorbidity. We identified 5 A1C patterns: stable (81%), decreasing (5%), increasing (5%), inverse sine (4%) and sine (4%). Compared to stable, increasing, inverse sine and sine patterns were associated with increased microvascular disease (hazard ratio (HR), 1.17 (1.01-1.35); 1.17 (1.01-1.35); 1.21 (1.05-1.41)), and the decreasing pattern was associated with increased death (HR, 1.28 (1.04-1.59)). Macrovascular disease risk did not differ by A1C pattern. During the first 10 years after diabetes diagnosis, the majority of patients have stable A1C levels. Those with non-stable A1C patterns had a greater risk of worse outcomes. In addition to achieving good A1C control, maintaining a stable A1C level may be an important goal for long-term outcomes.



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1596-P

Association of New Plasma Biomarkers (TNFR1, Adrenomedullin, and Copeptin) with Rapid Renal Function Decline in French Type 2 Diabetes Patients

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We assessed the predictive value of 3 biomarkers on renal function decline. Three recently-reported peptides were considered: mid-regional pro adrenomedullin (MR-proADM), copeptin and TNF receptor 1 (TNFR1). Patients with type 2 diabetes (T2D), estimated GFR≥30ml/min at baseline and no history of renal replacement therapy were prospectively followed in a French hospital-based cohort. Biomarkers were measured on the same baseline plasma sample. Annualized GFR slope was individually determined by linear regression. Rapid renal function decline (RRFD) was defined by a GFR annual slope ≤ -5 ml/min/year, according to KDIGO guidelines. The added prognostic value of biomarker was estimated with integrated discrimination improvement (IDI).

Median duration of follow-up of the 1135 patients was 5.8 years (IQR, 3.2-8.8 years); the prevalence of RRFD was 21%. In univariate analysis, each biomarker was significantly associated with eGFR slope and with RRFD (p<0.0001 for all). After multiple adjustment only TNFR1 remained a significant predictor of RRFD (Table). Addition of TNFR1 in the multi-adjusted model improved prediction of RRFD (IDI index = 0.0063, p<0.0001). In addition to the usual risk factors TNFR1 is an independent prognostic risk factor for RRFD in T2D patients.

Table. Univariate and Multiple Logistic Analysis (Odds Ratio and 95% CI) of Determinants of Rapid Rena.

Baseline Parameters	Univariate	P value	Multivariate	P value
Age (per 1 year)	1.02 (1.01-1.03)	0.006	0.99 (1.01-1.04)	0.93
Sex (female vs. male)	0.69 (0.51-0.93)	0.015	0.70 (0.49-0.97)	0.034
HbA1c (per 1 %)	1.10 (1.01-1.20)	0.037	1.12(1.02-1.23)	0.021
Log uACR	2.34 (1.94-2.83)	<0.0001	1.81(1.47-2.23)	<0.0001
Log copeptin	1.13 (1.08-1.18)	<0.0001	1.00(0.95-1.06)	0.98
Log MR-proADM	1.45 (1.33-1.62)	<0.0001	1.17(0.98-1.389)	0.08
Log TNFR1	1.53 (1.41-1.77)	<0.0001	1.24(1.04-1.48)	0.017

Supported By: French Ministry of Health (PHRC-Poitiers 2004); Association Française des Diabétiques (2003); Groupement pour l'Etude des Maladies Métaboliques et Systémiques

1597-P

Systolic Blood Pressure Variability and Lower Extremity Amputation in Non-elderly Diabetic Veterans

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To examine the association between systolic blood pressure variability (SPBV) and lower-extremity major amputation (LEA). We hypothesize that excessive SBPV is associated with increased risk of LEA.

This is a nested case-control study of a cohort of individuals age <60 years with diabetes and an LEA in the U.S. Department of Veterans Affairs hospitals from 2003-2008. SBPV were based on all BP measures taken during a year before LEA. Conditional logistic regression was used to model LEA risk as a function of SBPV, mean SBP, demographic factors, and other known risk factors of LEA (e.g., PAD, foot ulcers, peripheral neuropathy, osteomyelitis, and history of vascular procedure).

The cohort included 262,954 patients, 1129 experienced an LEA during follow-up. We randomly selected 3546 controls, matching on age, sex, race/ethnicity, and duration. The crude incidence rates were 8%, 16%, 32% and 41% in SBP Variability Quartiles 1 (lowest) - 4 (highest). Results from a logistic regression showed graded relationship between SBPV and major LEA. Compared to Quartile 1, odds ratios for Quartiles 2 - 4 were 1.4 (95% CI, 1.01 - 2.07), 2.9 (95% CI, 2.02 - 4.07), and 3.2 (95% CI, 2.22 - 4.48) in a model with all covariates (P for trend < 0.001).

This is the first study showing SBPV as significantly associated with increased risk of LEA in diabetes.

Table: Odds Ratios of Experiencing a Major Amputation Among Non-Elderly Individuals for Systolic Blood Pressure Variability Quartiles 2 - 4 Compared to Quartile 1 (Lowest Variability)

Models	N	Odds Ratios for Quartiles 2 – 4 Compared to Quartile 1			P for Trend
		2	3	4	
1. Unadjusted	4675	2.285	6.062	8.860	< 0.001
2. Adjusted*	4675	1.444	2.868	3.155	< 0.001
3. Sensitivity Analyses*					
BPs within one month excluded†	4473	1.363	2.098	2.278	< 0.001
Night time measures excluded‡	4579	1.150	2.293	2.921	< 0.001
PVD or history of vascular procedures excluded**	1824	1.222	2.117	3.317	< 0.001

* Adjusted for marital status, mean SBP, body mass index, A1c, diabetes duration, LDL cholesterol, comorbidities (diabetic neuropathy, foot ulcers, osteomyelitis, CHF, renal failure, cancer, deficiency anemias), diabetes treatment (none, oral medications only, insulin only, or both), and hypertension treatment (none, calcium channel blockers, or other medications). All of the covariates were taken from a window of 365 days before the event.
† BP measures taken during the 30-day period immediately before the cases' event dates were excluded in computing SBP variability.
‡ BP measures taken at night (8:00 PM – 8:00 AM) were excluded in computing SBP variability.
** All individuals with pre-existing PVD or a history of vascular surgery were excluded from the analysis. When a case or all controls in a set had PVD or previous vascular surgery, the set (the case and all of its matched controls) was excluded from the analysis.

1598-P

A Time-to-Event Genome-Wide Association Study of Erectile Dysfunction in Men with Type 1 Diabetes (T1D) in DCCT/EDIC

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Erectile dysfunction (ED) is associated with diabetes and poor glycemic control. A twin study demonstrated that ED is 30% heritable and suggests that genetics may also influence the risk of early onset ED. We examined longitudinal data to detect a genetic association with onset of ED in men with T1D. Phenotype was defined by report of ED by annual single-item question in men in the Diabetes Control and Complications Trial (DCCT) and during 20 years of follow-up in the Epidemiology of Diabetes Intervention and Complications (EDIC) (n=711). We defined time-to-event as the number of years from

DCCT randomization until the first of at least 2 consecutive years reporting ED. Genotypes were obtained with Illumina 1M chip and imputed to the 1000 Genomes data. We performed a genome wide association study for the time-to-event phenotype using a Cox Proportional Hazards model. 305 individuals had at least two consecutive reports of ED, and 257 never reported ED. The model adjusted for age, age squared, DCCT treatment arm, and primary vs. secondary cohort. Lambda genomic control = 1.06. One region reaches genome-wide significance: chromosome 7 downstream of ZNF282 (p=4.6x10-8, HR=0.48 (0.42-0.55), MAF=10.8%). Another region approaches genome-wide significance: chromosome 12 in an intron of NTN4 (p=1.4x10-7, HR=0.44 (0.37-0.51), MAF=5.3%). Variants associated with the time of onset of ED in DCCT/EDIC men could help assess risk in men with T1D. These findings require replication in other studies.

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1599-P

Clinical Course of Urinary Incontinence in Women with Type 1 Diabetes: Longitudinal Findings from DCCT/EDIC

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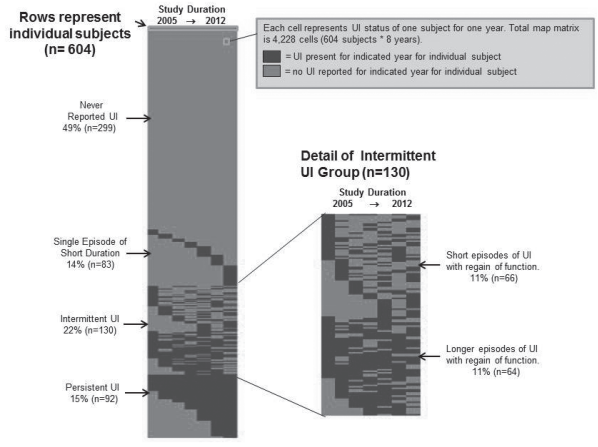
This study describes the long-term time course of urinary incontinence (UI) in women with type 1 diabetes (T1DM). Longitudinal data from 604 females in the Epidemiology of Diabetes Interventions and Complications study defined UI annually over 7 years using a single question querying presence/absence of UI. At first year of longitudinal data collection mean age was 46 (±7) years and mean duration of diabetes was 26 (±5) years. Subjects were categorized into 4 groups: Never Reported UI (controls), Single Episode of ≤2 years duration, Intermittent UI for subjects moving between UI states at least twice, and Persistent UI for subjects never reporting regain of function (Figure 1). Adjusted logistic regression was used to estimate association of covariates with UI behavior groups at the time of the index report. Eligible cases had to have ≤2 years of follow-up from index report of UI and controls were matched by EDIC year. Over the study period prevalence of UI increased from 18.1% to 32.4%. Single episode UI subjects did not differ from controls for measured clinical and demographic factors. Intermittent and persistent cases had higher BMI (p<0.001), longer duration of diabetes (p=0.01), higher insulin dose (p<0.002), and more likely to be parous (p=.005), but did not differ with respect to Hemoglobin A1c. Within this T1DM cohort, UI is a dynamic state with remission linked to diabetic duration, BMI and parity.

Figure 1. Heatmap of UI Status for DCCT/EDIC Females Over Time



1600-P

Prevalence and Factors Associated with Dental Loss among Ambulatory Patients with Diabetes

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Poor dental health is more prevalent among patients with diabetes compared to the general population. Dental loss is associated with periodontal disease (POD) and several diabetes comorbidities. Understanding the prevalence and factors that impact dental loss in the diabetic population will aid with the development of new strategies for prevention and improved care.

In this cross-sectional study of diabetes patients presenting for routine clinic visit at a university medical center, subjects completed a 48-item investigator-administered questionnaire. Data was collected on demographics, duration and control of diabetes, dental care history, dental health status, and presence of microvascular (retinopathy, nephropathy or neuropathy) and macrovascular (heart disease or stroke) complications of diabetes.

Among 202 subjects enrolled, 100 were female, mean age: 58.9 ± 13.2 years, duration of diabetes: 15.8 ± 11.0 years, and A1c: 7.7 ± 1.6%. We found that 31 patients had no teeth, 32 had 1 - 16 teeth, and 126 had 17 - 31 teeth. Only 13 (6.4%) had all 32 of their teeth. Among those with teeth, 87.7% had survey responses suggestive of POD. Using multivariate linear regression, we found that presence of bone disease (history of, or treatment for osteoporosis) was associated with 22 times higher odds of having POD (p = 0.029). In addition, older age (p = 0.001), past or present smoking (p = 0.055), not flossing (p = 0.001) and presence of diabetic retinopathy (p = 0.002) were associated with fewer number of teeth. Current A1c did not predict presence of POD or dental loss.

In conclusion, there is a need for developing innovative approaches to dental care among patients with diabetes given the high prevalence of periodontal disease and dental loss, and the strong correlation between periodontal disease and osteoporosis identified among our patients with diabetes.

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1601-P

Hearing Loss among Hispanic Adults with Diabetes

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National health survey data suggest that diabetes is associated with hearing loss. Few studies have documented correlates of hearing loss among people with diabetes, the results of which could provide insight about pathogenesis and prevention. Using data collected by the Hispanic Community Health Study/Study of Latinos (HCHS/SOL), a multi-site, population-based study, we examined demographic characteristics, cardiovascular risk factors and cardiovascular complications of diabetes for their relationship to audiometrically-determined hearing loss among 3384 Hispanic adults aged 18-76 years with diagnosed or undiagnosed diabetes. Hearing loss was defined as having two conditions: 1) a pure tone average (PTA) of thresholds measured at 3000, 4000, 6000, and 8000 Hz > 25 db HL and 2) a PTA of thresholds measured at 500, 1000, and 2000 Hz > 25 db HL. Using multiple logistic regression, we estimated odds ratios [OR (95% confidence limits)] for independent risk factors for hearing loss while controlling for age and ethnicity and accounting for the complex sample design. Individuals with less than a high school education and those of low income had increased odds of hearing loss [OR=1.43 (1.00, 2.06)] and [OR=2.49 (1.57, 3.96)], respectively. Other groups with elevated odds include current smokers [OR=1.61 (1.09, 2.37)] and those with at-risk drinking behavior [OR=2.11 (1.16, 3.86)]. We observed greater odds of hearing loss among those with high triglycerides [OR=1.46 (1.09, 1.97)] but no association with hypertension, obesity, glycemic control, medication use, duration of diabetes, or other diabetic complications. Diabetes-related hearing loss is socio-economically patterned and correlates with altered lipid metabolism. Behavioral risk factors such as smoking and at-risk drinking suggest the potential for public health prevention.

1602-P

Serum Adiponectin and Glomerular Filtration Rate in Patients with Type 2 Diabetes

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High serum adiponectin has been associated with decreased renal function in the general population. Only sparse and conflicting results, all derived from small studies mainly carried out in non-European populations, have been reported in patients with type 2 diabetes (T2D), a subgroup of individuals who are at high risk of renal dysfunction. The aim of this study was to fill up this gap of knowledge by investigating such association among diabetic patients of European ancestry.

The association between serum adiponectin levels and estimated glomerular filtration rate (eGFR by Modification of Diet in Renal Disease equation) was investigated in 1,212 patients with T2D from two different Italian samples: 847 patients from San Giovanni Rotondo (SGR) and 365 patients from Foggia.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Serum adiponectin was inversely associated with eGFR in SGR [β (SE) for 1 SD of adiponectin = -2.53 (0.69), $p = 2.0*10^{-4}$] and in Foggia [β (SE) = -5.63 (1.66), p = 0.001] samples, as well as in the two studies combined [β (SE) = -3.46 (0.69), $p = 6.0*10^{-7}$]. The association was somehow reduced but still significant after adjusting for sex, smoking habits, BMI, diabetes duration, HbA1c, anti-diabetic, anti-hypertensive and anti-dyslipidemic treatments [β (SE) = -1.79 (0.73), p = 0.015]. For each adiponectin SD increment, the odds of having eGFR < 60 ml/min/1.73m^2 increased by 46% (OR =1.46; 95% CI 1.24-1.71; $p = 3.2*10^{-6}$) in SGR sample, 52% (OR = 1.52; 95% CI 1.19-1.94; p = 0.001) in Foggia sample, and 47% (OR = 1.47; 95% CI 1.29-1.68; $p = 8.7*10^{-9}$) in the two studies considered together. Further adjustment for the above mentioned covariates did not change the observed association (OR = 1.36; 95% CI 1.16-1.59; $p = 9.6*10^{-5}$).

This is the first report of an association between high serum adiponectin and low eGFR in a large study of patients with T2D of European ancestry. Such counterintuitive, paradoxical association deserve further attempts to be deeper understood.

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1603-P

Cardiovascular Risk Factors and Cognitive Performance: A Diffusion Tensor Imaging Study

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Cardiovascular risk factors (diabetes mellitus type 2 (T2DM), hypertension, hyperlipidemia) are associated with worse cognitive performance in older adults. We aimed to determine the impact of cardiovascular risk factors on brain white matter microstructure and cognitive performance. 33 subjects with cardiovascular risk factors (age 65.3 ± 8.3, 57.8% female, 28 T2DM (duration 14.6 ± 8.5 years), 33 hypertensive, 28 hyperlipidemic and 23 age and education-matched nondiabetic normotensive controls completed a battery of cognitive tests (Hopkins Verbal Learning test (HVLT), Verbal Fluency test (VF)). All patients received 3T MRI diffusion tensor imaging. Brain global and regional volumes, white matter fractional anisotropy (FA), mean diffusivity (MD), radial diffusivity (RD) and axial diffusivity (AD) were calculated. Multiple regression analyses were performed adjusting for age, and for the presence of hypertension, hyperlipidemia and diabetes. Global and regional white and gray matter brain volumes were not different between the groups. The risk factor group had worse performance in verbal fluency, learning and memory, compared to controls (VF: t-score (p=0.03), VF: #animals t-score (p=0.0001), HVLT: Total recall t-score (p=0.0001), and HVLT: Delayed recall t-score (p=0.003)). We found a positive association between VF: #animals t-score and R angular gyrus FA (p=0.0003, radj 0.4), and a negative association with MD (p=0.003, radj 0.3), L1 (p=0.01, radj 0.3, and RD (p=0.0001, radj 0.5), independent of age, hyperlipidemia, hypertension diagnosis and HbA1c. The cardiovascular risk factor group had worse performance in verbal fluency, learning and memory. Semantic verbal fluency showed the strongest correlation with R angular gyrus diffusion tensor imaging metrics. Cardiovascular risk factors exert a long-term effect on brain structure manifesting as microstructural white matter abnormalities.

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1604-P

Emergence and Regression of Urological Symptoms in Men and Women with Type 1 Diabetes Mellitus

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Urological complications associated with poor diabetes control are considered to be irreversible, however, longitudinal studies have not determined the cumulative emergence and regression of these complications. UroEDIC, an ancillary study of urological complications in the Epidemiology of Diabetes Interventions and Complications [EDIC] study, was administered in 2003 and 2010. Participants who provided responses to an anonymized survey of sexual and urinary function at both time points were included (n=1059). Emergence, persistence and regression were assessed for lower urinary tract symptoms (LUTS), urinary incontinence (UI), urinary tract infection (UTI), female sexual dysfunction (FSD), and erectile dysfunction (ED). Item completion rates for each domain ranged from 92-99%. Mean age of the cohort in 2003 was 43 years. For subjects with a given urological complication at baseline, approximately two-thirds reported persistence and one-third showed regression of symptoms, with the exception of UTI (Table 1). Incident cases of urological complication led to an overall increase in prevalence at follow-up. Urological symptoms in patients with longstanding type 1 diabetes exhibit significant fluctuation over a seven-year interval. Further investigation into factors influencing regression of urologic symptoms may offer potential for better management.

Table 1. Status of Urological Complications at Follow-Up UroEDIC Survey.

	Entire Cohort* N (%)	Symptomatic at Baseline N (% of entire cohort)	Symptomatic at Follow-up N (% of entire cohort)	Persistence at Follow-up N (% of entire cohort)	Regression at Follow-up N (% of entire cohort)	Emergence at Follow-up N (% of entire cohort)
Women	508					
LUTS	506 (99)	101 (20)	113 (22)	61 (12)	40 (8)	52 (10)
UI	493 (97)	109 (22)	151 (31)	70 (14)	39 (8)	81 (16)
UTI	468 (92)	75 (16)	80 (17)	22 (5)	53 (11)	58 (12)
FSD	472 (98)	75 (16)	122 (26)	46 (10)	29 (6)	76 (16)
Men	551					
LUTS	550 (99)	100 (18)	132 (24)	62 (11)	38 (7)	70 (13)
ED	525 (95)	111 (21)	156 (30)	80 (15)	31 (6)	76 (14)
Low desire	506 (92)	83 (16)	104 (21)	109 (22)	73 (14)	94 (19)
Orgasm	461 (84)	41 (9)	63 (14)	23 (5)	18 (4)	40 (9)

* Subjects with data for both UroEDIC baseline and follow-up surveys
Emergence = Defined as subjects free of disease at UroEDIC baseline but positive at UroEDIC follow-up by the change in score crossing an *a priori* numerical cutpoint.
Persistence = Defined as subjects positive at UroEDIC baseline and positive at UroEDIC follow-up by the change in score crossing an *a priori* numerical cutpoint.
Regression = Defined as subjects positive at UroEDIC baseline but free of disease at UroEDIC follow-up by the change in score crossing an *a priori* numerical cutpoint.

1605-P

Do Prevention Quality Indicators (PQIs) Underestimate Preventable Hospitalizations (PHs)?

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Agency for Health Research and Quality (AHRQ) PQIs have not been recently updated. We evaluated individual and combined rates of 5 AHRQ PQIs (metabolic decompensation (MD): short term, dehydration, and uncontrolled diabetes), lower extremity amputations (LEAs), and urinary tract infections), and 3 proposed PHs (LE ulcers/infections (LEU), hypoglycemia (HYPO), and Acute Kidney Injury (AKI)) among Veterans Health Administration patients (VHA) with diabetes in 2006.

We combined VHA and Medicare records to identify patients with diabetes and determine PHs; we then calculated PH rates (per 1,000 persons) and determine age and sex adjusted rates by race. Following the AHRQ definitions for PQIs, we used principal ICD9CM codes for the proposed PHs: 1) LEU (Harrington C. 2000; excluding co-occurring LEAs)); 2) AKI: diagnosis code 548.9; and 3) HYPO (Ginde 2008). We used AHRQ technical specifications for current PQIs.

There were 975,677 individuals; 57% were 65 years or older, 97% men. Proposed PHs comprised 48% of the total. AKI was the most common PH; lower extremity PHs increased by 41% by including LEU, and MD by 40% by including HYPO. Blacks were more likely to incur all/AHRQ/proposed PHs: 44/24/24 (per 1,000 persons) vs. 32/17/17 (others) vs. 29/16/15 (Whites) based on age and sex adjusted rates.

Current PQIs do not capture about half of diabetes relevant PHs; development of additional PQIs should be considered.

Table. Diabetes Relevant Preventable Hospitalizations (PHs) among Veterans Health Administration Patients with Diabetes in 2006.

	Number of hospital admissions	Rate of admissions (per 1,000 persons)	Number of persons with hospital admissions	Rate of persons with admissions (per 1,000 persons)	Age and sex adjusted rates: Blacks	Whites	Others
All (AHRQ and Proposed) PHs	35,943	36.84	29,875	30.62	44.4	29.0	31.7
AHRQ PQI (combined)	18,874	19.34	16,468	16.88	24.2	16.0	17.2
Metabolic Decompensation (combined)	7,500	7.69	6,802	6.97	10.5	6.6	6.3
Short term diabetes complications	2,028	2.08	1,716	1.76	3.2	1.5	1.8
Dehydration	4,061	4.16	3,876	3.97	4.9	4.0	3.0
Uncontrolled Diabetes	1,411	1.45	1,353	1.39	2.7	1.2	1.5
Amputation	5,244	5.37	4,519	4.63	6.8	4.3	5.1
Urinary Track Infection	6,130	6.28	5,527	5.66	7.6	5.5	6.3
Proposed PHs (combined)	17,069	17.49	15,393	15.78	23.8	14.8	17.0
Lower extremity ulcers/infections	3,583	3.67	3,202	3.28	3.6	3.2	3.9
Hypoglycemia	4,979	5.10	4,713	4.83	9.1	4.2	5.8
Acute Kidney Injury	8,507	8.72	7,850	8.05	11.9	7.6	7.7

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1606-P

WITHDRAWN

1607-P

Visual Acuity Outcomes Associated with Dilated Eye Exams for Patients with Diabetes Mellitus

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ADA guidelines recommend dilated eye exams annually for persons with diabetes mellitus (DM) with diabetic retinopathy (DR) and less frequent exams (every 2 to 3 years) may be considered for persons with DM but no DR. This study investigated the association between best-corrected visual acuity (BCVA) outcomes in DM patients and regular eye exams. This retrospective cohort study identified adults aged ≥18 y with DM from 1/1/2009 to 12/31/2010.

First DM diagnosis or anti-diabetes drug dispense date was defined as the index date. Eligible patients had continuous coverage for 12 mo prior (baseline) and ≥4 y after the index date (follow-up). Both eyes were required to have a BCVA of ≥ 20/40 (Snellen equivalent; ≥70 ETDRS letter score) at baseline. Baseline and follow up BCVA data were extracted from electronic medical records. Noncompliant patients did not conduct dilated eye exams annually (DM with DR) or biennially (DM w/o DR). Associations between BCVA outcomes and dilated eye exams were investigated using multivariate logistic regressions. Among the 15,315 eligible patients (mean age ± SD: 66±11 y; 52% were female), Baseline mean (SD) BCVA ETDRS letter score of the worse-seeing eye was 79.0 (5.2). After 4 y, BCVA worsened to <20/40 (ETDRS letter score 68 or lower) in 22.7% of patients and <20/200 (ETDRS letter score 38 or lower) in 3.5% of patients. In all patients, having an annual eye exam was associated with a reduced risk of VA worsening vs. noncompliance (odds ratio (OR) [95% confidence interval [CI]=0.87 [0.78-0.97]). In patients w/o DR, having biennial exams was not associated with a reduced risk of VA worsening vs. noncompliance (OR=0.90 [95% CI: 0.77-1.05]). Older age, elevated hemoglobin A1C levels, and having other eye diseases (e.g. cataract or age-related macular degeneration) were associated with an increased risk of worsening BCVA. Annual eye exams were associated with a lower risk of worsening BCVA. This analysis emphasizes the importance of routine eye exams for patients with DM.

1608-P

Serum Uric Acid Levels Are Associated with High Risk of Diabetic Nephropathy Progress among Japanese Type 2 Diabetes Patients

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We studied a cohort of Japanese patients with type 2 diabetes from a large-scale registry, to determine the prospective association between baseline serum uric acid level and subsequent risk of development or progression of diabetic nephropathy. Longitudinal data were obtained from 2518 patients in the cohort with type 2 diabetes who were registered in a Japanese diabetes registry. To assess the independent correlations between baseline serum uric acid quartiles and either development or progression of diabetic nephropathy for 2 years, the Cox proportional hazards model was used and adjusted for potential confounders. Mean patient age, body mass index, and HbA1c level was 66.1 years, 24.6 kg/m2, and 7.5% (57.6 mmol/mol), respectively. Baseline serum uric acid levels with mean values of 3.6 mg/dl, 4.9 mg/dl, 5.8 mg/dl, and 7.3 mg/dl for the 1st to 4th quartiles, were significantly associated with urinary albumin-creatinine ratio at baseline ($p < 0.001$). The multivariable-adjusted hazard ratios (HRs) for developing diabetic nephropathy were 0.93 (95% confidence interval (CI), 0.73-2.17; p=0.526), 1.01 (95% CI, 0.74-1.38; p=0.955), and 1.09 (95% CI, 0.73-1.63; p=0.680), respectively, for the 1st, 3rd, and 4th quartiles as compared to the 2nd quartile of uric acid. We did not observe a significant association between baseline uric acid levels and development of nephropathy, while it was significantly associated with progression of nephropathy. Multivariable adjusted HRs for the progression from microalbuminuria to macroalbuminuria were 2.17 (95% CI, 1.15-4.08; p=0.016), 3.04 (95% CI, 1.67-5.53; $p < 0.001$), and 3.56 (95% CI, 1.83-6.93; $p < 0.0011$), respectively, for the 1st, 3rd, and 4th quartile of serum uric acid levels, as compared with the 2nd quartile. Low and high serum uric acid levels, independent of possible confounders, were associated with a subsequent risk of progressing, but not developing, diabetic nephropathy in type 2 diabetes patients.

1609-P

Validation of Serum Biomarker Panel for Prediction of Renal Function Decline in Type 2 Diabetes

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The aim of this study was to validate a previously defined panel of 13 serum biomarkers plus creatinine that in combination with clinical factors improved prediction of rate of renal decline in individuals with type 2 diabetes and chronic kidney disease stage 3 above that based on clinical factors alone. We measured the biomarker panel in 429 samples from the Genetics Audit Diabetes in Tayside Study (Go-DARTS). The biomarkers were measured in baseline serum samples at two labs – Myriad RBM measured Adrenomedullin (ADM), Beta-2 Microglobulin (B2M), Fatty Acid Binding Protein Heart, Fibroblast Growth Factor 21, Kidney Injury Molecule-1 (KIM-1) and N-terminal Prohormone B type Natriuretic Peptide, using Luminex technology and the WellChild lab measured Alpha-1-Antitrypsin, Asymmetric Dimethylarginine, C16-acylcarnitine, Creatine, Creatinine, Hydroxyproline, Symmetric Dimethylarginine (SDMA), and Uracil using mass-spectroscopy. To test the predictive performance of the biomarker panels we used linear regression models and then calculated the correlation between the fitted model's output and the actual output, using 10 fold cross-validation. All data were Gaussianised prior to analysis. The median follow-up for eGFR was 5.6 years. The median annualised eGFR slope was -0.18 (IQR -1.50, 1.06) ml/min/1.73m^2/year. At baseline median age was 73 years, median HbA_{1c} 7.1%, median eGFR 49.3ml/min/1.73m^2, and 30.5% of the subjects had micro or macroalbuminuria. Four biomarkers were significantly associated with the annualised slope of eGFR – B2M (beta coefficient = -0.22), KIM-1 (-0.19), ADM (-0.17) and SDMA (-0.18). Overall the correlation for a model including only clinical covariates (age, sex, baseline eGFR, HbA_{1c}, albuminuria, ACE inhibitor and Angiotensin Receptor Blocker use) was 0.193 which was increased to 0.267 by addition of the 14 biomarkers. We show that the biomarker panel is associated with improvements in prediction of change in eGFR compared to clinical factors alone.

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1610-P

Burden of Urological Complications of Type 1 Diabetes Mellitus: Results from UroEDIC

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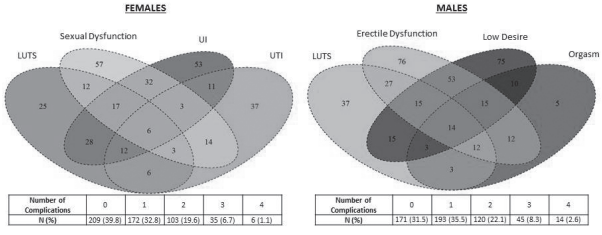
This cross-sectional study assessed cumulative burden of sexual dysfunction, lower urinary tract symptoms (LUTS), urinary incontinence (UI) and urinary tract infection (UTI) in a cohort of men and women with longstanding type 1 diabetes (T1D). In 2010, participants in UroEDIC, an ancillary study of urological complications of T1D in the Epidemiology of Diabetes Interventions and Complications [EDIC] study, completed an anonymized survey of sexual and urinary function. Primary outcome variables were designated a priori for each urological complication based on items derived from validated instruments (International Index of Erectile Function, Female Sexual Function Index, AUA Symptom Index and Sandvik Severity Scale). Survey item completion rates within complication domain ranged from 92-99%. In this cohort (n=1224) mean age was 51 years and mean diabetes duration was 29 years. Of the 580 women, 60% reported at least one of the following: LUTS (22%), Female Sexual Dysfunction (26%), UI (30%) and UTI (17%). Of the 644 men, 68% reported at least one of the following: LUTS (25%), Erectile Dysfunction (46%), Low Desire (41%) and Orgasmic Dysfunction (15%). Overlap of prevalent complications by gender is shown in Fig 1. Of the two-thirds of the cohort reporting a complication, half report two or more complications. Urological complications represent a substantial burden to the TID population and warrant future research.

Figure 1: Overlap of Prevalent Urological Complications by Gender



Number of Complications	0	1	2	3	4
N (%)	209 (39.8)	172 (32.8)	103 (19.6)	35 (6.7)	6 (1.1)

Number of Complications	0	1	2	3	4
N (%)	171 (31.5)	193 (35.5)	120 (22.1)	45 (8.3)	14 (2.6)

1611-P

Prevalence and Risk Factors for Diabetic Foot in Overweight or Obese Patients with Type 2 Diabetes

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This study was aimed to investigate the prevalence and risk factors for diabetic foot in overweight or obese patients with type 2 diabetes. From August 2011 to March 2012, 5241 subjects who were diagnosed as type 2 diabetes with BMI≥24kg/m^2 were enrolled from 60 hospitals in Guangdong Province. Patients with diabetic foot was diagnosed by Wagner's classification. Binary Logistic regression was used to analyze the risk factors for diabetic foot. In our Binary Logistic regression analysis, presence of diabetic foot was positively associated with age (*OR*=1.020, 95% *CI*: 1.004-1.036), female (*OR*=1.784, 95% *CI*: 1.142-2.787), the duration of diabetes (year) (*OR*=1.042, 95% *CI*: 1.017-1.068), BMI(*OR*=1.224, 95% *CI*: 1.156-1.296), HbA1c (*OR*=1.217, 95% *CI*:1.142-1.298), smoke (*OR*=3.657, 95% *CI*: 2.337-5.723) and diabetic nephropathy (*OR*=1.7680, 95% *CI*: 1.192-2.622). The results suggested that prevalence of diabetic foot was relatively high in the overweight or obese patients with type 2 diabetes. For those overweight or obese patients with type 2 diabetes, especially the old female patients, it is important to control the plasma glucose, decrease the level of body weight, quit smoking and screen diabetes chronic complications such as diabetic nephropathy to lowering the risk of diabetic foot.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1612-P

The Characteristics of Dyslipidemia and Hypertension in Elderly Patients with Type 2 Diabetes Mellitus

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Diabetes mellitus is increasingly recognized as an essentially vascular disease, and a principal objective of diabetes care is prevention or reduction of cardiovascular risk. Our aim is to determine the characteristics of dyslipidemia and hypertension in elderly patients with type 2 diabetes mellitus (DM). Two hundred (160 female, 40 male) (mean age 72.8±16.7 yrs) elderly patients with type 2 DM were included in the study. The hypertensive phenotype was defined as systolic blood pressure (SBP) ≥140 or diastolic blood pressure (DBP) ≥90 mm Hg. National Cholesterol Education Programme guidelines were used for definition of dyslipidemia. Sociodemographic, clinical, and biochemical data were taken from medical records, retrospectively. Hypertensive phenotype was found in 50.3% of diabetic elderly patients. Mean levels of systolic and diastolic blood pressures were found to be 169±25.9 mmHg and 100.1±12.1 mmHg, respectively, in elderly patients with hypertension. Seventy percent of the hypertensive patients had isolated systolic hypertension. Hypercholesterolemia was found to be in 60.0%, low HDL cholesterol in 65.1%, high LDL cholesterol in 70.5%, and hypertriglyceridemia in 41.1% of the patients. High LDL-cholesterol was the most common dyslipidemia in combination (78.5%) in all patients. And also, isolated low HDL levels (8.1%) were found in male. There were positive correlations between hemoglobin A1C and LDL-cholesterol levels (r=0.490, p=0.01) and TSH levels (r=0.500, p=0.05) in male. However, a positive correlation between postprandial glucose and triglyceride levels was found in female patients (r=0.400, p=0.01). Isolated systolic hypertension was most common hypertension pattern in elderly diabetic patients. Dyslipidemia patterns such as hypercholesterolemia, low high-density lipoprotein and high low-density lipoprotein levels, and hypertriglyceridemia were common in diabetic elderly.

1613-P

Risk for Bone Fractures in Men and Women with Type 1 Diabetes

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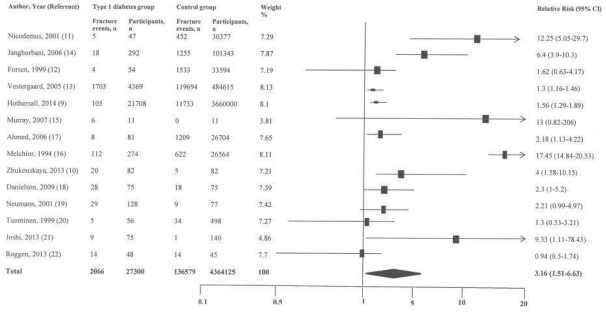
Fracture risk in men and women with type 1 diabetes (T1D) is not well studied. Therefore, a systematic review and meta-analysis of observational studies were conducted to assess the association between T1D and fractures.

Data were selected from Medline and Embase and "Abstracts" from annual scientific meeting of various diabetes and bone and mineral societies. Published studies reporting fracture risk in subjects with T1D in comparison with subjects without diabetes between 1990 and July, 2014 and abstracts from various annual meeting (2005 onwards) were also included for this meta-analysis.

Fourteen studies that met inclusion criteria reported 2,066 fracture events among 27,300 subjects with T1D (7.6%) and 136,579 fracture events among 4,364,125 subjects without diabetes (3.1%). The pooled relative risk (RR) of any fracture in subjects with T1D was 3.16 (95% CI 1.51-6.63, p=0.002) [Figure]. Women with T1D had four times higher risk and men with T1D had two times higher risk for any fractures compared to subjects without diabetes. The pooled RR of hip fractures and spinal fractures were 3.78 (95% CI; 2.05-6.98, p<0.001) and 2.88 (1.71-4.82, p<0.001), respectively, among subjects with T1D.

Our meta-analysis suggests that both men and women with type 1 diabetes might have an increased risk for any fractures. A large prospective epidemiological study is needed to confirm our findings.

Figure : Forest plot for fracture risk in subjects with type 1 diabetes



1614-P

Diabetes-related Complications among American Indians/Alaska Natives—Idaho, Oregon, and Washington State, 2001-2011

JESSICA MARCINKEVAGE, THOMAS WEISER, EDWARD W. GREGG, KERRI LOPEZ, VICTORIA WARREN-MEARS, *Portland, OR, Atlanta, GA*

Diabetes-related complication rates reported in the United States declined during 1990-2010. Whether such improvements have also benefited American Indians/Alaska Natives (AI/ANs), a group disproportionately affected by diabetes, is unknown. We examined incidence of diabetes-related complications for 2001-2011 among Idaho, Oregon, and Washington AI/ANs.

We analyzed data from the Indian Health Service (IHS) National Data Warehouse (NDW), a repository of demographic, clinical, and billing data from IHS, tribal, and urban Indian clinics, with a user population representing ~70% of all Pacific Northwest AI/ANs. Using International Classification of Diseases, 9th Revision codes, we calculated the 2001-2011 prevalence of diabetes diagnoses in the NDW among AI/AN patients in the Pacific Northwest and calculated annual and cumulative incidence overall and individually for 5 diabetes-related complications: acute myocardial infarction (MI), lower-extremity amputation, stroke, end-stage renal disease (ESRD), and sepsis.

During 2001-2011, the prevalence of diabetes within the NDW user population increased from 3.1% (95% confidence interval [CI]: 3.0-3.2) to 5.0% (95% CI: 4.8-5.1). The annual incidence of amputations/10,000 patients with diabetes decreased from 28.6 (95% CI: 13.3-54.2) in 2001 to 1.9 (95% CI: 0.1-9.2) in 2011; no significant change was detected for MI, stroke, ESRD, or sepsis. During 2001-2011, the cumulative incidence of all 5 diabetes-related complications was 1,635.9 (95% CI: 1,568.0-1,705.0)/10,000 patients with diabetes. The 3 conditions with highest cumulative incidence were ESRD (919.2 [95% CI: 866.8-973.8]), followed by stroke (372.2 [95% CI: 338.3-408.4]), and MI (199.0 [95% CI: 174.4-226.1]).

The burden of diabetes persists among Pacific Northwest AI/ANs. Clinical and community programs promoting diabetes management are needed to improve outcomes and prevent complications.

1615-P

A Retrospective Review of Hyperglycemia Management in 79 Patients Admitted to the Medical Intensive Care Unit at Boston Medical Center with Septic Shock

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Rationale: Hyperglycemia is known to increase morbidity and mortality in critically ill patients. Guidelines recommend insulin infusions for hyperglycemia in septic shock. Adherence to these guidelines may be inconsistent. We conducted a retrospective review of 79 patients with septic shock to assess the management of hyperglycemia with the goal of identifying opportunities for improvement.

Methods: All patients admitted to Boston Medical Center's Medical Intensive Care Unit (MICU) in 2013 with a diagnosis of septic shock were identified from the University HealthSystem Consortium database. Manual chart analysis was focused on the first 48 hours of ICU admission.

Results: We found delays in recognition and treatment of hyperglycemia as well as frequent selection of inappropriate treatment. 69.6% of patients had glucose checked by point-of-care testing in the MICU. There was a delay between MICU admission and first glucose check (median 130 min). Glucose was elevated (over 180 mg/dL) in 32.9% of these patients while in the emergency department and in 48% in the MICU. 40.5% had two elevated glucose values in the MICU; of these, only 43.8% were placed on an insulin infusion and 68.8% received subcutaneous insulin. The time between second elevated glucose and order for an insulin infusion was prolonged (median 58 minutes), as was the time between order entry and administration of the insulin (median 112 min).

Conclusions: Management of hyperglycemia in septic shock is variable and presents an opportunity for improvement. An ongoing project seeks to increase early recognition and accelerate appropriate management of this. Our interdisciplinary approach includes a nursing driven protocol to check blood sugars and treat hyperglycemia, new electronic order sets for septic shock patients, and front-line education for nursing and housestaff. Our balancing measures include hypoglycemic events and length of stay.

1616-P

Neutrophil-Lymphocyte Ratio and C-Reactive Protein Levels Are Increased in Patients with Diabetic Kidney Disease

LYDIA A. WONG, GEORGE JERUMS, RICHARD J. MACISSAC, JAS-MINE SEAH, SARA BAQAR, MICHELE CLARKE, FELICITY PYRLIS, RENATA LIBIANTO, SCOTT BAKER, JETHRO WU, ELIF I. EKINCI, *Heidelberg West, Australia, Melbourne, Australia, Heidelberg, Australia*

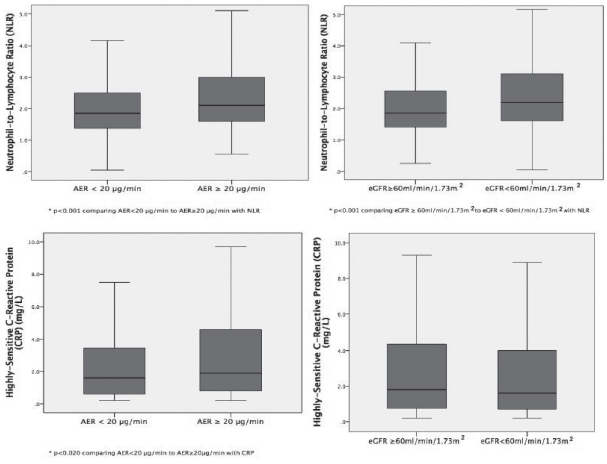
The neutrophil-to-lymphocyte ratio (NLR) and high-sensitivity C-reactive protein (CRP) are reliable measures of systemic inflammation. We hypothesized that a higher NLR and CRP are associated with an increase in albumin excretion rate (AER) and reduced glomerular filtration rate (GFR) in diabetes.

504 patients with type 1 or type 2 diabetes attending Austin Health Diabetes Clinics were recruited in a prospective study. NLR was calculated by dividing total neutrophil count by total lymphocyte count.

NLR values were significantly higher for patients with albuminuria (AER>20ug/min) compared to patients with normoalbuminuria (p<0.001, Fig. 1), as well as in patients with eGFR<60ml/min/1.73m^2 compared to patients with eGFR>60ml/min/1.73 m^2 (p<0.01, Fig. 1). CRP levels were significantly lower in patients with normoalbuminuria compared to those with albuminuria (p<0.02, Fig. 1), but were not related to eGFmR.

Higher NLR values are independently associated with reduced eGFR and increased AER in patients with diabetic kidney disease. Higher CRP levels are only associated with increased AER, with no relationship to eGFR. Whether these findings represent cause, effect, or association, awaits the results of interventional studies.

Figure 1.



1617-P

Association between Serum Zinc Level and Microvascular Complications in Type 2 Diabetes

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Purpose: The aims of our study were to compare serum zinc level in diabetic patients with and without microvascular complications, to investigate the association between zinc level and each microvascular complication and identify clinical and biochemical characteristics related to low level of serum zinc.

Methods: This is a non-interventional, cross-sectional study. We included the hospitalized T2DM patients in our hospital from May 30, 2013 to March 31, 2014. We firstly compared the serum zinc levels between patients with at least one microvascular complications and those without any complications. We also assessed associations between serum zinc level and microvascular complications. We further compared the characteristics between people with high and low serum zinc level.

Results: The study involved 412 patients, 271 with one or more microvascular complications and 141 without microvascular complications. There was a linear relationship between serum zinc level and the number of miacrovascular complications. The serum zinc level was significantly lower in patients with microvascular complications than patients without (P<0.01). Patients with more microvascular complications had lower serum zinc level. In the regression analysis, we found that lower serum zinc level was the independent risk factor for the presence of diabetic nephropathy (OR=0.869, 95% CI=1.04-1.11, P<0.05). As compared to the normal level of serum zinc group, the subjects in the group with low zinc levels had a longer duration of diabetes, higher hemoglobin A1c, higher prevalence of hypertension, higher prevalence of any forms of microvascular complications, lower C-Peptide level.

Conclusions: Lower serum zinc level in T2DM patients was associated with more microvascular complecations. Low serum zinc level is an independent risk factor for diabetic nephropathy. T2DM patients with low serum zinc level were more likely to have a longer duration of diabetes, poorer glucose control, worse β cell fuction.

EPIDEMIOLOGY—NUTRITION

Guided Audio Tour: You Are What You Eat—Nutrition and Diabetes *(Posters: 1618-P to 1625-P), see page 15.*

1618-P

The Association between Breastfeeding and Insulin Sensitivity among Youth with Diabetes

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There is mounting evidence that infant feeding practices are associated with later health outcomes. However, the association between breastfeeding and insulin sensitivity (IS) is unclear, with some studies showing a protective effect while other studies report no association. Further, existing studies have been exclusively conducted in healthy populations, and have not considered youth with diabetes. Participants included in our analyses were youth with type 1 diabetes (T1D; n=1,751; mean age at diagnosis 8.6±4.2 years) and type 2 diabetes (T2D; n=204; mean age at diagnosis 13.8±2.6 years). These data were collected as part of the SEARCH for Diabetes Youth and the SEARCH Nutrition Ancillary studies (SNAS). Mothers of participants were asked to report infant feeding practices, including breastfeeding initiation and duration. IS was estimated using an equation validated for youth with diabetes, which includes waist circumference, A1c and triglycerides levels. Nearly 70% of participants with T1D were ever breastfed in comparison to 35% of participants with T2D. Among participants with T1D, IS was higher in those who had longer duration of breastfeeding (mean IS: never breastfed [9.8±3.581], breastfed < 6 months [10.5±3.5], breastfed ≥ 6 months [10.7±3.4]; p<0.001) in the unadjusted analyses. However, stepwise linear regression analyses showed the association was no longer significant after adjustment for confounders (model 1: adjusted for socio-demographic factors [B=0.006; p=0.5]; model 2: adjusted for socio-demographic factors and diabetes related characteristics [B=0.02; p=0.1]). Interactions of breastfeeding with HLA risk alleles and age at diagnosis were not significant (p≥0.10). Among participants with T2D, breastfeeding was not significantly associated with IS in either unadjusted (B=0.003; p=0.8) or adjusted models (model 1: B=0.01; p=0.2; model 2: B=0.01; p=0.2). In our cohort of youth with diabetes, breastfeeding was not associated with improved IS in later life.

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1619-P

Food Insecurity Is Associated with Poor Glycemic Control among Youth and Young Adults with Type 1 Diabetes Mellitus

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Food insecurity, i.e. limited or uncertain availability of nutritionally adequate and safe foods, has been associated with poor glycemic control, medication underuse, less physical activity, and poorer diet quality among adults with type 2 diabetes, but there are no studies examining food insecurity among U.S. youth and young adults with type 1 diabetes (T1D). Using data from two centers (Washington and South Carolina) in the SEARCH for Diabetes in Youth Study, we evaluated the association between food insecurity and glycemic control among participants ages 3 to 27 years with T1D. During SEARCH visits, parents or adult participants completed surveys including the Household Food Security Survey Module (HFSSM), which asks about conditions and behaviors typical of households unable to meet basic food needs. Participants' HbA1c was measured. The HFSSM yields a standardized score from 0-10, which was dichotomized as food secure (≤2.2) or insecure (>2.2). Of the 168 participants (mean age 15.5 years, T1D duration 77.8 months, and 44.6% Medicaid), 8.1% lived in food-insecure households.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Mean HbA1c was 9.8% for participants living in food-insecure households vs. 8.9% for those living in food-secure households (p=0.009). In a linear regression model adjusted for age, gender, race/ethnicity, health insurance, parent or participant education, T1D duration, and study site, participants from food-insecure households had 0.93% higher HbA1c (95% CI: 0.27, 1.60) vs. peers from food-secure households. In adjusted logistic regression, participants from food-insecure households had 3.95 higher odds (95% CI: 1.65, 9.44) of poor glycemic control, i.e., HbA1c ≥ 9.5%, vs. peers from food-secure households. Our findings suggest that food insecurity may be an important correlate of poor glycemic control. If our results are confirmed by longitudinal studies, targeted efforts should be developed to identify and alleviate household food insecurity among youth and young adults with T1D.

Supported By: University of South Carolina; Seattle Children's Research Institute

1620-P

Diet Quality during Pregnancy and Risk of Gestational Diabetes: The Healthy Start Study

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Poor diet quality during pregnancy may increase the risk of adverse pregnancy outcomes, with consequences for both maternal and offspring health. This study examined whether diet quality in early and mid-pregnancy was associated with gestational diabetes (GDM) or impaired glucose tolerance (IGT). Participants were 1090 ethnically diverse pregnant women enrolled in Healthy Start, a pre-birth prospective cohort study. Dietary intake was assessed using Automated Self-Administered 24-hour dietary recalls prior to 27 weeks of pregnancy (the median gestational age at GDM screening). Participants completed at least 1 and up to 6 dietary recalls, and a glucose challenge test and/or oral glucose tolerance test (OGTT). A USDA Healthy Eating Index (HEI) score was calculated for each participant (range 1-100). GDM (n=50) was defined as either a clinical diagnosis in the prenatal medical record, or 2 abnormal values on a 3-hr, 100g OGTT, using Carpenter-Coustan criteria. IGT (n=102) was defined as a positive result (≥140 mg/dl) on a 1-hr, 50g oral glucose challenge test, and/or 1 abnormal value on the 3-hr OGTT, in the absence of GDM. Multinomial logistic regression, adjusted for potential confounders, was used to estimate associations between HEI score and risk of GDM or IGT. Total HEI score ranged from 30 to 87 (mean: 60, SD: 11). The optimal HEI cutoff for predicting GDM was calculated using Youden's index. Relative to women with HEI greater than or equal to 64, women with HEI less than 64 (63% of participants) had a higher risk of GDM (adjusted OR: 2.19, 95% CI: 1.05, 4.57), independent of daily energy intake and maternal pre-pregnancy body mass index (BMI). There was no evidence of a statistical interaction between BMI and diet quality in their associations with GDM. There was no significant association between HEI<64 and IGT. Our data suggest that improving dietary quality in early and mid-pregnancy may reduce the risk of GDM, independent of maternal obesity.

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1621-P

Serum Nonesterified Fatty Acid (NEFA) Concentration Is Associated with Longitudinal Progression of β-Cell Dysfunction: Prospective Metabolism and Islet Cell Evaluation (PROMISE) Cohort

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Higher NEFA concentrations are associated with incident type 2 diabetes (T2DM), however limited longitudinal data exist regarding the impact of NEFA on the progression of metabolic disorders underlying T2DM. Our aim was to study the longitudinal associations of NEFA with 6-yr changes in insulin sensitivity (IS), β-cell function, and glycemia.

Adults at risk for diabetes in PROMISE had glucose and insulin measured from an oral glucose tolerance test (OGTT) at 3 visits over 6-yrs (n=478). Fasting NEFA were analyzed at baseline with thin layer chromatograhy and gas liquid chromatography coupled to flame ionization detector. The inverse of HOMA-IR (HOMA-IS) and the Matsuda index assessed IS. The Insulinogenic Index over HOMA-IR (IGI/IR) and the Insulin Secretion-Sensitivity Index-2 (ISSI-2) assessed β-cell function. Generalized estimating equations were adjusted for waist, physical activity, alcohol, and sex.

IS and β-cell function decreased over 6-yrs (all p<0.001; Fig. A & B). Higher NEFA were associated with an increased risk for dysglycemia (RR=1.25 (1.03 to 1.52) per SD). Although NEFA were not associated with either IS measure, higher NEFA independently predicted declines in IGI/IR and ISSI-2 over time (both p<0.01, Fig. C). Our findings suggest NEFA influence T2DM risk primarily through β-cell dysfunction.

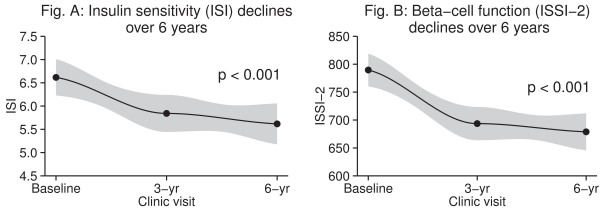
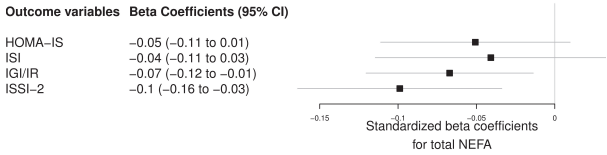


Fig. C: Forest plot of the results from the generalized estimating equations



Supported By: Canadian Diabetes Association; Canadian Institutes of Health Research

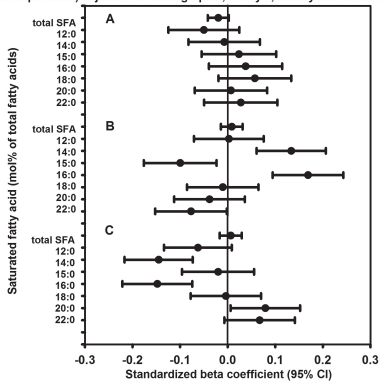
1622-P

Individual Serum Saturated Fatty Acids and Markers of Chronic Subclinical Inflammation: The Insulin Resistance Atherosclerosis Study (IRAS)

INGRID D. SANTAREN, STEVEN M. WATKINS, ANGELA D. LIESE, LYNNE E. WAGENKNECHT, MARIAN REWERS, STEVEN M. HAFFNER, CARLOS LORENZO, ANTHONY J. HANLEY, *Toronto, ON, Canada, West Sacramento, CA, Columbia, SC, Winston-Salem, NC, Aurora, CO, San Antonio, TX*

Despite longstanding dietary recommendations for reduced saturated fatty acid (SFA) intake, recent evidence has highlighted distinct effects of individual circulating SFA on cardiometabolic outcomes, with potential protective effects of odd and longer-chain SFA. Less is known, however, regarding the impact of individual SFA on subclinical inflammation. This study aimed to cross-sectionally investigate the associations of individual SFA with inflammation markers in 624 white, African American, and Hispanic adults, aged 40-69 y from IRAS. Serum SFA were analyzed using gas chromatography. Clinical measures included fasting serum pro-inflammatory markers, adiponectin, and oral glucose tolerance tests. For outcomes, we used Principal Components (PC) Analysis of pro-inflammatory markers, yielding 2 PCs (PC 1: fibrinogen, CRP and white cell count; and PC 2: PAI-1 and TNF-α). In multiple linear regression models adjusted for demographic and lifestyle variables, waist circumference, and glucose tolerance status, 15:0 and 22:0 were negatively associated, while 14:0 and 16:0 were positively associated, with PC 2. Further, 20:0 was positively, and 14:0 and 16:0 were negatively associated with adiponectin (Figure). In conclusion, lower circulating odd and longer-chain, and higher even-chain SFA, were related to worsened subclinical inflammation status.

Figure: Standardized beta coefficients and 95% CI from multiple linear regressions of serum SFA on markers of subclinical inflammation (A-PC 1: fibrinogen, CRP and white cell count; B-PC 2: PAI-1 and TNF-a; and C-adiponectin) adjusted for demographic, lifestyle, dietary and metabolic variables.



Supported By: Banting and Best Diabetes Centre; Dairy Farmers of Canada; National Heart, Lung, and Blood Institute

1623-P

Dietary Acid Load and Type 2 Diabetes Mellitus: Pooled Results from Three Prospective Cohort Studies

JESSICA C. KIEFTE-DE JONG, YANPING LI, MU CHEN, GARY C. CURHAN, JOHN P. FORMAN, OSCAR H. FRANCO, FRANK B. HU, *Rotterdam, Netherlands, Boston, MA*

Low grade metabolic acidosis, which is related to a Western diet, may be associated with the development of type 2 diabetes mellitus (T2DM). We aimed to assess the association between dietary acid load and T2DM.

We studied 67,419 women from the Nurses' Health Study (1994), 84,483 women from Nurses' Health Study II (1999) and 35,585 men from the Health Professionals Follow-up Study (1996) free from diabetes, cardiovascular disease and cancer at baseline. Diet was assessed by validated food-frequency questionnaires every four years. Two indices of dietary acid load were used: (1) energy-adjusted estimated net endogenous acid production (NEAP) and (2) energy-adjusted animal protein to potassium ratio (A/P). Incident cases of T2DM were identified through validated questionnaires.

We documented 15,179 cases with T2DM during 3,976,093 person-years of follow-up. After adjustment for potential confounders, including sociodemographic, medical and lifestyle factors, and BMI, higher NEAP and higher A/P were significantly associated with an increased risk of T2DM (Pooled Hazard Ratio (HR); 95% Confidence Interval (CI): 1.28; 1.21-1.35; P-for trend<0.001 and HR: 1.30; 95% CI: 1.23-1.38; P-for trend<0.0001 for the highest vs. lowest quintile of NEAP and A/P, respectively).

The associations between NEAP and A/P and the risk of T2DM did not substantially differ among those who were overweight or obese compared to those with normal weight or between those with high or low adherence scores on the Alternate Healthy Eating Index (P for interaction>0.05).

In conclusion, this study suggests that high dietary acid load is prospectively and independently associated with an increased risk of T2DM. Further studies are needed to establish whether diet-induced low grade metabolic acidosis is a causal mechanism for the development of T2DM.

Supported By: European Foundation for the Study of Diabetes

1624-P

Alcohol Drinking and 4-Year Changes in Fasting Glucose in the Guangzhou Biobank Cohort Study

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Moderate alcohol drinking is associated with a lower risk of type 2 diabetes (T2DM), whereas heavy drinking is not, but findings from small-scale randomized controlled trials of moderate drinking are mixed. We examined the association of baseline alcohol use (never, former, occasional, moderate and heavy (>210 gram of ethanol per week for men and >140 gram per week for women)) with changes in fasting plasma glucose and with incident T2DM in the Guangzhou Biobank Cohort Study. A total of 13,001 women and 4,862 men aged 50+ years were recruited from 2003 to 2008 and followed up until 2012 (average follow-up 4.1 years). Of 11,537 women and 4,306 men without diabetes at baseline, 11.5% (1,330) of women and 11.3% (485) of men developed T2DM during follow up. The association of alcohol use with changes in glucose and incident T2DM varied by sex (p-values for interaction <0.05). In men, compared with never drinkers, heavy drinking was associated with a glucose increase during follow up (0.25mmol/l, 95% confidence interval (CI) 0.06 to 0.44), whereas no changes were found for occasional drinkers (0.03mmol/l, 95% CI -0.06 to 0.11), moderate drinkers (0.02mmol/l, 95% CI -0.10 to 0.13) or former drinkers (-0.03mmol/l, 95% CI -0.16 to 0.10), adjusted for age, education, physical activity, smoking, body mass index, fasting glucose at baseline and diabetes history. Similarly adjusted, heavy drinkers had a 57% (95% CI 5% to 133%) higher risk of incident T2DM, but not occasional, moderate or former drinkers. For women, no association of alcohol use with changes in glucose was found, but moderate drinking were associated with a lower risk of T2DM (-43% (95% CI -64% to -10%)), although occasional, heavy and former drinking were not. In conclusion, heavy alcohol use was positively associated with T2DM in Chinese men but not women. Further studies are needed to clarify the underlying mechanisms of the sex difference in the association of alcohol with diabetes.

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1625-P

Changes in Macronutrient Intake and Achievement of ABC goals in Adults with Type 1 Diabetes

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Despite therapeutic advances, few patients with type 1 diabetes (T1D) achieve the ADA's ABC goals (A: HbA1c < 7%, B: BP < 130/80mmHg, C: LDL-c <100mg/dL). Diet may contribute to suboptimal ABC control. We hypothesized changes in nutrient intake would impact ABC changes over 6 years in T1D adults.

Dietary intake was assessed by a validated food-frequency questionnaire at baseline in the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study (n=652, age 38 ± 9 years), then at 2.5 ± 0.5, and 6.2 ± 0.6 years of follow-up. Linear mixed models were used to examine how HbA1c, SBP and LDL-c changed over time in relation to changes in dietary macronutrients.

Baseline and 6-year total fat intake (35.5% vs. 36.0%) and saturated fat intake (12.7% vs. 12.8%) did not differ. Protein intake remained similar at baseline vs. 6 years (19.2% vs. 19.6%), but carbohydrate intake decreased (44.6% vs. 43.2%, p=0.002). Increased total and saturated fat intake was associated with an increase in HbA1c and LDL-cholesterol, and increased protein intake was associated with reduced SBP. Changes in carbohydrate intake were not related to the ABC goals (Table).

Increased intake of fat and saturated fat was associated with worsening of lipids and glycemic control and increased protein intake with lower SBP, whereas a decrease in carbohydrate intake was observed in the cohort but was not associated with changes in achievement of ABC goals.

Table.

	Change in HbA1c			Change in SBP			Change in LDL cholesterol		
	Estimate	SE	p-value	Estimate	SE	p-value	Estimate	SE	p-value
Total fat (%)	**0.01**	**0.004**	**0.03**	-0.04	0.04	0.44	**0.40**	**0.11**	**0.0003**
Saturated fat (%)	**0.02**	**0.01**	**0.04**	-0.03	0.11	0.78	**0.72**	**0.25**	**0.004**
Protein (%)	0.003	0.008	0.66	**-0.28**	**0.09**	**0.002**	-0.18	0.19	0.37
Carbohydrate (%)	-0.005	0.003	0.17	0.05	0.04	0.22	-0.11	0.09	0.19

*Macronutrient intake expressed as a percentage of daily energy intake and are time-varying explanatory variables, across the 6-year study period. All models are adjusted for age, sex, and diabetes status. P-value from linear mixed models.

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1626-P

Influence of Sugar, Milk, and Energy Intake on Glucose Metabolism

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Meta-analyses were performed of randomized trials examining the influence of sugar, milk and total energy intake (TEI) on fasting plasma glucose (FPG) concentrations. Sugar was the total amount of mono and disaccharide carbohydrates present in diets. Milk was any liquid milk product. Random effect models were applied to estimate changes in FPG during trials corresponding to changes in the amount of sugar, milk or total energy intake. Results are expressed as change in FPG (mmol/L) per month with 95% CIs.

29 trials were retrieved on sugar conducted in adults and in children, 8 on sugar sweetened beverages that allocated 646 subjects in 21 groups and 21 on sugar from solid foods that allocated 768 subjects in 46 groups. Incremental intake of 100 g/d of sugar was associated with a non-significant 0.10 mmol/L (-0.02, 0.21; p=0.11) increase in FPG. Liquid or solid sugar had the same effect on changes in FPG. A model restricted to 12 trials including 28 groups that also reported TEI showed that when TEI was taken into account, an increment of 100 g/d in intake of sugar was associated with a non-significant 0.06 mmol/L (-0.20, 0.08; p=0.35) decrease in FPG, while an incremental intake of 400 Kcal/d (i.e., the energy of 100 g of sugar) was associated with a significant 0.29 mmol/L (0.11, 0.46; p=0.004) increase in FPG.

Seven trials were performed on milk intake in adults: 507 subjects were allocated to 20 groups. Compared to comparison groups, significant increases in FPG of 0.11 mmol/L (0.02, 0.19; p=0.001) were observed in milk groups. A model restricted to the 3 trials including 7 groups that also reported TEI showed that when TEI was taken into account, allocation to milk groups was associated with a non-significant 0.04 mmol/L (-0.07, 0.16; p=0.23) increase in FPG, while an incremental intake of 100 Kcal/d was associated with a borderline significant 0.04 mmol/L (0.00, 0.08; p=0.06) increase in FPG.

Changes in FPG are driven by changes in total energy intake and not by changes in amounts of specific nutrients. Implications for public health are obvious.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1627-P

Adherence to Low-Carbohydrate Dietary Pattern and Long-Term Risk of Type 2 Diabetes among Women with a History of Gestational Diabetes: A Prospective Cohort Study

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Women with a history of gestational diabetes mellitus (GDM) are at high risk of developing type 2 diabetes mellitus (T2DM) after pregnancy. Carbohydrate restriction may improve short-term glycemic control in patients with GDM, but its long-term impact on the risk of T2DM is unknown. We aimed to examine the association among 4346 women with a history of GDM from the Nurses' Health Study II cohort, as part of the Diabetes & Women's Health Study. These women were followed up from 1991 to 2011. Low-carbohydrate-diet (LCD) scores were calculated from validated food-frequency questionnaires that were collected every four years, including overall LCD score based on intakes of carbohydrate, total protein and total fat, animal LCD score on intakes of carbohydrate, animal protein and animal fat, and vegetable-based LCD score on intakes of carbohydrate, vegetable protein and vegetable fat. A higher LCD score indicates a closer adherence to a low-carbohydrate dietary pattern. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). We documented 703 incident T2DM cases during up to 20 years of follow up. After adjustment for age, race/ethnicity, parity, family history of diabetes, dietary and other lifestyle factors, the HRs (95% CIs) of T2DM comparing the highest versus the lowest quartiles were 1.84 (1.46-2.32) for overall LCD score (P for trend < 0.001), 1.77 (1.40-2.25) for animal LCD score (P for trend < 0.001), and 1.03 (0.82-1.31) for vegetable LCD score (P for trend = 0.48). The associations may be partly explained by BMI. In conclusion, among women with a history of GDM, a low-carbohydrate dietary pattern, particularly with high protein and fat intake mainly from animal-source foods, is associated with higher T2DM risk, whereas a low-carbohydrate dietary pattern with high protein and fat from plant-source foods is not associated with the risk.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development

1628-P

Meta-analysis of Sugar-Sweetened Beverage Intake and Interactions with Genetic Loci Related to Fructose Metabolism on Measures of Fasting Glucose and Insulin in 5 Cohorts

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Animal and human studies suggest that a molecular pathway involving the nutrient-sensing transcription factor carbohydrate responsive-element binding protein (ChREBP) and the metabolic hormone FGF21 influences sugar metabolism and fructose-induced metabolic disease. We examined in non-diabetic adults (1) the relationship between sugar-sweetened beverage (SSB) intake and fasting insulin (FI) or glucose (FG) levels and (2) whether these associations were modified by common genetic variants in *CHREBP-FGF21* pathway related genes. Five cohorts in the CHARGE (Cohorts for Heart and Aging Research in Genomic Epidemiology) Consortium provided association and interaction data from 15,885 participants of European descent. SSB intake (sodas, fruit punches, lemonades, or other noncarbonated fruit drinks) was derived from FFQs. In fixed-effects meta-analyses, we quantified *1*) cross-sectional associations of SSBs with FG and FI and *2*) interactions between SSBs and 18 single nucleotide polymorphisms (SNPs) related to the CHREBP-FGF21 pathway. After adjustment for age, sex, energy intake, and BMI, a daily one-serving increase in SSB was associated with FI [β =0.02 ln-pmol/L (95% CI: 0.00 - 0.05), *P*=0.04], but not FG. A nominal significant interaction was observed with a SNP (rs1542423) in the beta-klotho (KLB) locus on FI (β±SE = 0.03±0.01 ln-pmol/L, uncorrected P =0.008), suggesting a stronger insulin-raising effect with greater SSB consumption in adults with the T (risk) allele. This association did not retain significance after Bonferroni correction for multiple comparisons. We observed that 1) SSB intake was associated with elevations in FI and 2) a genetic variant in the CHREBP-FGF21 pathway may interact with SSB consumption to raise FI in humans. Replication of this observed gene-diet interaction, in addition to examining other candidates in this pathway, is warranted in additional populations.

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1629-P

Sitagliptin Prevents Cardiac Dysfunction in a Diabetic Rat Model via Modulation of the JAK/STAT Pathway

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This study was designed to test the hypothesis that sitagliptin, a member of a class of oral antidiabetic agent called dipeptidyl peptidase 4 (DPP-4) inhibitor, could mediate a cardioprotective effect by reducing the proinflammatory profile in cardiac tissue and that this protective effect is correlated with reduced JAK2/STAT3 expression in heart of streptozotocin diabetic rats. To achieve this aim diabetes was induced in rats by a single intraperitoneal injection of streptozotocin (55 mg kg^{-1}). Diabetic rats were given sitagliptin (10 mg kg^{-1}, p.o). After 12 weeks, cardiac and inflammatory biomarkers were assessed. The expression of phosphorylated JAK2 and STAT3 in cardiac tissue was studied using immunohistochemistry. In addition, a histopathological examination of paraffin-embedded samples was performed. The results indicated that treatment of rats with sitagliptin significantly reduced the heart weight (0.92±0.02 vs. 1.28±0.05 mg) (p<0.05), heart/body weight ratio (0.47±0.03 vs. 0.58±0.02 mg g^{-1}) (p<0.01) and ameliorated the altered cardiac biomarkers [troponin-T (50.67±4.47 vs. 66.4±4.02 ng ml^{-1}) (*P<0.01*); CK (37.3±0.78 vs. 47.5±1.2 U ml^{-1}) (*P<0.001*); and lipid profile (*P<0.01*)] and inflammatory marker [IL-6 levels (372±8.7 vs. 821.0±40.9 pg ml^{-1}) (*P<0.01*)] compared to diabetic control group. Moreover, immunohistochemical and histopathological examinations revealed that sitagliptin administration reduced the expression of JAK2/STAT3 and confirmed the protective effects of sitagliptin against streptozotocin-induced alteration of cardiac structure.

In conclusion, data suggest that the cardioprotective effect of sitagliptin might be due to modulation of JAK/STAT signaling pathway. Thus, sitagliptin may be a useful therapeutic approach to prevent cardiac complications of diabetes mellitus.

Supported By: King Saud University

1630-P

Strawberry Intake, Hemoglobin A1c, and Risk of Developing Diabetes in Women

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Strawberries contain key nutrients that have been inversely associated with incident diabetes. We investigated the association between strawberry intake, hemoglobin A1c, and incident diabetes in the Women's Health Study, a prospective cohort of 37,131 initially nondiabetic middle-aged and older women. Strawberry intake was assessed from a baseline food frequency questionnaire, along with risk factors for diabetes. We identified 2,901 incident cases of diabetes during a mean follow-up of 14.7 years. In addition, 26,206 nondiabetic women returned baseline bloods that were assayed for hemoglobin A1c. At baseline, 25.0%, 42.8%, 24.8%, and 7.4% of women reported strawberry intake of rarely/never, 1-3 servings/mth, 1 serving/wk, and ≥2 servings/wk. Compared with no strawberry intake, the age-adjusted relative risks (RRs) of diabetes were 0.90, 0.89, and 0.91 for strawberry intake of 1-3 servings/mth, 1 serving/wk, and ≥2 servings/wk, respectively (p, trend = 0.43). In models fully adjusted for lifestyle, clinical, and dietary risk factors, the RRs (95% confidence intervals (CIs)) of diabetes were 0.97 (0.88-1.07), 0.89 (0.79-1.00), and 0.81 (0.68-0.97) (p, trend=0.033). After excluding women with baseline obesity, hypertension, or high cholesterol, the magnitude of the RRs for categories of strawberry intake and incident diabetes strengthened. The 26,206 nondiabetic women with bloods had a mean (SD) hemoglobin A1c of 5.03% (0.37), including 291 (1.1%) women with a hemoglobin A1c ≥6.0%. Compared with no strawberry intake, the fully-adjusted RRs (95% CIs) of having an hemoglobin A1c ≥6% were 1.04 (0.77-1.41), 0.71 (0.48-1.05), and 0.67 (0.38-1.21) for 1-3 servings/month, 1 serving/week, and ≥2 servings/week, respectively. In conclusion, modest strawberry intake may be inversely associated with favorable levels of hemoglobin A1c and a lower risk of incident diabetes in middle-aged and older women, for which additional data are needed to clarify any role of strawberry intake.

1631-P

Diabetes Genetic Score, 2-Year Changes in Insulin Sensitivity, and Insulin Resistance in Response to Weight Loss Diets: The Pounds Lost Trial

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Background: Numerous diabetes loci have been identified using genome-wide association studies. However, little is known about whether dietary factors may modify the effects of the genetic variants predisposing to diabetes on insulin resistance.

Objective: We examined interactions between weight-loss diets and diabetes genetic score on 2-year changes in insulin sensitivity and insulin resistance in a randomized controlled trial.

Research Design and Methods: Data were analyzed in the Preventing Overweight Using Novel Dietary Strategies (Pounds Lost) trial. Diabetes genetic risk score (GRS) was calculated based on 36 diabetes single nucleotide polymorphisms (SNP) in 730 (80% Whites) overweight or obese adults.

Results: We found that dietary protein significantly modified the diabetes genetic associations with fasting insulin, HbA1c, HOMA-B, and HOMA-IR (P for interaction=0.02, 0.04, 0.01, and 0.05, respectively) at 2 years in Whites, after adjustment for age, sex, ethnicity, baseline body weight, weight change, and baseline perspective phenotype. The low-GRS was associated with greater decreases in fasting insulin (P=0.04), HbA1c (P=0.0001), and HOMA-IR (P=0.02) among participants with low-protein diet. Opposite genetic effects on changes in fasting insulin (P=0.03), and insulin resistance (P=0.08) were observed among high-protein diet group.

Conclusions: Our data suggest that individuals with low diabetes genetic risk might experience greater benefits in improving insulin resistance when consuming a low-protein weight-loss diet, while high-protein diet may be more beneficial for those with high genetic risk.

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1632-P

Dietary Protein Intake and Risk of Type 2 Diabetes in U.S. Men and Women

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Dietary proteins are known modulators of glucose metabolism. However, longitudinal studies evaluating the association between protein intake and risk of type 2 diabetes (T2D) are sparse and whether type of protein differentially impacts long-term risk of T2D is uncertain.

We aimed to investigate the association between total, animal and plant protein and incident T2D in U.S. men and women.

We prospectively followed 72,992 women from the Nurses' Health Study (1984-2008), 92,088 women from the Nurses' Health Study II (1991-2009) and 40,722 men from the Health Professionals Follow-up Study (1986-2008) who were free of diabetes, cardiovascular disease and cancer at baseline. Diet was assessed using a validated food frequency questionnaire updated every 4 years. Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% CI's.

During 4,146,216 person-years of follow up, we documented 15,580 incident cases of T2D. In pooled multivariate models, intake of percent energy from total and animal protein was associated with 39% (31%, 48%) and 49% (40%, 59%) increased risk for T2D respectively, comparing extreme quintiles. Associations were attenuated after adjusting for BMI (HR (95 % CI): 1.07 (1.01, 1.17) and 1.13 (1.06, 1.21) comparing extreme quintiles for total and animal protein, respectively). Intake of percent energy from vegetable protein was associated with a moderate decreased risk for T2D (0.91 (0.84, 0.98) comparing extreme quintiles in the fully adjusted model including BMI. Substituting 5% of energy from vegetable protein for animal protein was associated with 18% reduced risk for T2D and substituting 1 serving per day of vegetable protein foods for animal protein foods was associated with 10-21% reduced risk for T2D.

Higher intake of total and animal protein was associated with increased risk for T2D, while higher intake of vegetable protein was associated with a modest reduced risk. Substituting vegetable protein for animal protein was associated with reduced risk for T2D.

1633-P

U-Shaped Association between Plasma Manganese Concentration and Type 2 Diabetes in Adults

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Both manganese and manganese-dependent mitochondrial superoxide dismutase (MnSOD) polymorphisms are elucidated to be associated with the activity of MnSOD and type 2 diabetes (T2D). The objective was to investigate the association of plasma manganese with newly diagnosed T2D as well as whether the association could be modified by MnSOD polymorphisms. We conducted a case-control study of 3228 participants: 1614 T2D patients and 1614 controls. All participants were genotyped for MnSOD polymorphism (rs4880) and plasma magnesium was measured by inductively coupled plasma mass spectrometry. Medians of plasma manganese concentration were 5.26 μg/L for controls and 4.37 μg/L for T2D. A U-shaped association was observed between plasma manganese and T2D, with increased ORs in relation to either low or high plasma manganese levels. Compared with middle tertile, the multivariate-adjusted ORs (95% CI) of T2D associated with lowest tertile and highest tertile of plasma manganese were 2.22 (1.81-2.71) and 1.55 (1.25-1.92), respectively. In spline analysis, the U-shaped association was consistently indicated, with the lowest odds of T2D at the plasma manganese concentration of 4.95 μg/L. The MnSOD rs4880 polymorphism was not associated with T2D and no interaction was found between plasma manganese and MnSOD rs4880 polymorphism in relation to T2D. Our results suggested a U-shaped association between plasma manganese and T2D; both low and high levels of plasma manganese were associated with higher odds of newly diagnosed T2D. The U-shaped association was not modified by MnSOD rs4880 polymorphism. Further studies are warranted to confirm this association.

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1634-P

Association between Mediterranean Diet, Metabolic Health, and Obesity among U.S. Adults

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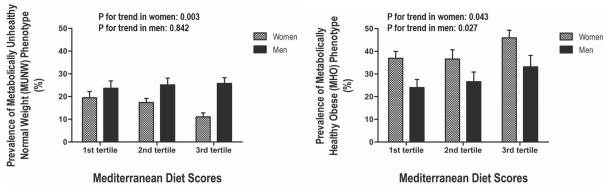
Evidence on the relation between Mediterranean diet (MD) and metabolic health is scarce. Data came from 5,631 adults aged 20-90 years (2,376 men and 3,255 women) without a history of cancer from the NHANES III, 1988-1994. Mediterranean Diet Scores (MDS) were created to assess the adherence to MD using food frequency questionnaires, supplemented by the 24-hr dietary recall data. Metabolic health was defined if subjects had fewer than two metabolic abnormalities (systolic/diastolic ≥ 130/85 mm Hg, triglycerides ≥ 150 mg/dL, HDL-cholesterol < 40 mg/dL in men or < 50 mg/dL in women, fasting glucose ≥ 100 mg/dL, HOMA-IR > 90th pct, hsCRP > 90th pct). Metabolically unhealthy normal weight (MUNW, 18.5 ≤ BMI < 25 kg/m^2) and metabolically healthy obese (MHO, BMI ≥ 30 kg/m^2) individuals were identified. With increasing MDS, there was lower prevalence of MUNW in women and higher prevalence of MHO in men and women (Figure). Lower MDS was associated with MUNW only in women (tertile 2 vs. 1, OR 0.86 [95% CI 0.55-1.37]; tertile 3 vs. 1, 0.49 [0.31-0.80], whereas higher MDS was associated with MHO only in men (tertile 2 vs. 1, 1.03 [0.66-1.60]; tertile 3 vs. 1, 1.89 [1.19-3.02]), after adjusting for age, race, education, income, smoking, physical activity, history of cardiovascular disease, BMI, and energy intake. Adherence to MD is associated with metabolic health among both normal weight and obese individuals in a representative U.S. population.



1635-P

In Peru, Lower Risk of Obesity at Higher Altitudes Extends to Adolescents: A Cross-Sectional Study

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Background: We recently reported a significant inverse association between obesity and altitude in the adult population of the United States, adjusting for several covariates. It is of great interest from a public health perspective whether this relationship develops earlier in life, and in other countries.

Methods: We examined the association between altitude and obesity in the adolescent population of Peru, a country with topographic, socioeconomic, cultural, and ethnic features differing from those of the United States. We utilized data publicly available online from the Food and Nutrition National Center of Peru, CENAN, for 2009-2010, the last period for which data is available. The CENAN used a nationally representative sample selected by the National Home Survey. Body weight and height were measured on-site using standardized methods. Final dataset included 7,618 adolescent subjects (14-19 years old). Odds ratios were estimated using binary logistic regression with clustered robust standard errors, adjusting for risk factors and potential confounders, including age, sex, physical activity, out-migration rate, urbanization, and latitude.

Results: The odds ratios for obesity were as follows: 1.00 between 0–499 meters (reference category), 1.71 (95% confidence interval 1.29 to 2.26) between 500–1,499 m, 0.62 (0.45 to 0.86) between 1,500–2,999 m, and 0.29 (0.17 to 0.50) at ≥3,000 m.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Conclusions: In Peruvian adolescents, living at higher altitude *per se* appears to be associated with reduced odds of having obesity. These findings suggest that geographical elevation is an important factor linked to obesity not only among adults but also among adolescents. The environmental explanation for this interesting relationship, which was also reported for adults, is unknown, but could yield important information regarding the pathogenic environmental causes of obesity *per se.*

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EPIDEMIOLOGY—OTHER

Guided Audio Tour: Diabetes—From Soup to Nuts *(Posters: 1636-P to 1643-P), see page 13.*

1636-P

Metformin Reduces Prostate Cancer Disparity in Men with Type 2 Diabetes?

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Hispanics are at higher risk for type 2 diabetes (T2D). T2D is associated with increased risk for high grade prostate cancer (PCa). The Diabetes Prevention Program suggested that metformin (METF) might modulate T2D risk due to the TCF7L2 polymorphism, which plays a role in the pathogenesis of T2D in Hispanics. This study assesses in men with T2D, whether 1) PCa incidence differs by Hispanic origin, and 2) METF is associated with ethnic difference in PCa incidence.

The retrospective study cohort consisted of 77951 male veterans with T2D but no prior cancer or liver diseases, nor thiazolidinediones or insulin use during 2003-2013. Cox proportional hazard model was used to compute the hazard ratio (HR) of PCa associated with Hispanic, and compare HR associated with METF use for Hispanics vs. non-Hispanics, adjusting for covariates and propensity scores of METF use.

Mean follow-up was 6.4±2.8 years; 5424 (7%) were Hispanics; 13811 (17%) were Black; mean age was 67.8±9.8 years; mean A1c was 6.5±0.9%; 4070 (5.2%) had a PCa diagnosis; 38.9% used METF; 86.6% used statin; 13.4% used finasteride. PCa incidence was 40% greater in Hispanics (HR=1.40, p<.01). METF use alone was associated with 35% PCa incidence reduction in Hispanics (HR= 0.65, p<.01) but not in non-Hispanics (HR=0.92, p=.10). METF+statin was associated with similar PCa incidence reduction between Hispanics and non-Hispanics (p=.06): HR=0.38 (p<.01) in Hispanics; HR=0.57 (p<.01) in non-Hispanics. METF+finasteride was associated with similar PCa incidence reduction between Hispanics and non-Hispanics (p=.46): HR=0.57 (p<.01) in non-Hispanics; HR=0.76 (p=.04) in Hispanics.

In insulin naïve men with T2D: 1) PCa incidence was higher in Hispanics; 2) METF alone could be more effective for PCa prevention in Hispanics than non-Hispanics; 3) METF in combination with finasteride or statin could be equally effective for PCa prevention in both ethnic groups. Prospective studies in multi ethnic groups are needed to confirm if METF reduces ethnic difference in PCa risk.

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1637-P

Mortality and Days at Hospital in Offspring of Diabetic Mothers: Danish Population-based Cohort Study with 8 to 36 Years Follow-up

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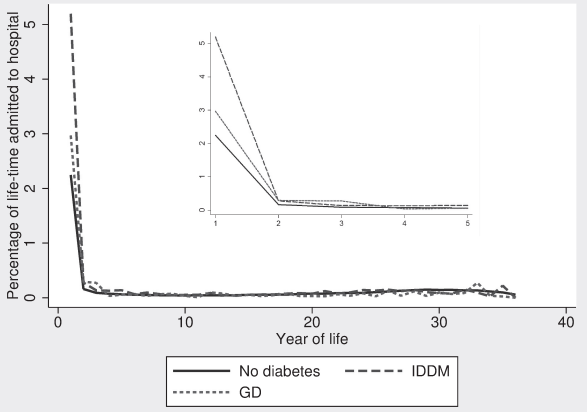
Offspring of mothers with diabetes (ODM) have significantly increased perinatal mortality and morbidity and concerns have been raised about long term prognosis. We assessed mortality and morbidity expressed as percentage of days spent at hospital in the first 8-36 years of life in ODM using Danish Registries. We identified all recorded live-born pregnancies (n=695) in women with diabetes (DM) in a Danish County from 1976-2003. They were categorized as pre-gestational IDDM (n=524) or gestational (n=171) diabetes (GD). Vital status was collected from Statistics Denmark. Percentage of days spent at hospital from day of birth to death, emigration, or December 31 2011 was calculated based on data from the Danish Registry of Patients. Outcomes were compared with offspring in the non-diabetic background population (n=170,335).

Mortality in the first 8 years was 1.2% in ODM compared with 0.9% in the background population, risk difference 0.3% (95% CI: -0.6 to 1.1, p=0.47). The percentage of days spent at hospital from 7-28 days were 14.6% vs. 3.5%; from 29-365 days 1.3% vs. 0.4%. After 1 year there was no difference in hospitalizations, see Figure.

We found no difference in mortality between the ODM and controls. ODM spent significantly more days at hospital in the first year of life, but thereafter no difference was observed.



1638-P

Prediabetes with High 30-Minute Postprandial Plasma Glucose Levels Had β-Cell Dysfunction and Insulin Resistance Similar to Overt Type 2 Diabetes

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Although 30-minute postprandial glucose (PP30) after 75g oral glucose load (75g OGTT) reflects an early phase insulin secretion, PP30 had not been used well for clinical practice as a diagnostic value. The aim of this study was to compare the β-cell function and clinical characteristics in prediabetes and type 2 diabetes (T2DM) according to level of PP30.

A total 1,800 subjects, who had suspected abnormal glucose tolerance or strong family history for diabetes, were performed 75g OGTT at time 0, 30 and 120 min. All subjects were classified as having normal glucose tolerance (n=123), prediabetes (n=663), or T2DM (n=1014). The subjects with prediabetes and T2DM were subcategorized into high PP30 (≥200mg/dl) or low PP30 (<200mg/dl) with cutoff value of 200 mg/dl, which was used in the level of 2-hour postprandial glucose when diagnosing T2DM.

While acute insulinogenic index (0.9 ± 0.7 vs. 0.5 ± 0.5 vs. 0.2 ± 0.2, p<0.001) and HOMA-β (137.0 ± 62.4 vs. 103.7 ± 60.4 vs. 72.1 ± 56.0, p<0.001) significantly decreased, HOMA-IR (2.3 ± 0.9 vs. 3.0 ± 1.8 vs. 4.3 ± 3.0, p<0.001) increased according to the glucose intolerance, NGT, prediabetes and T2DM by order. Prediabetes with high PP30 showed significantly lower HOMA-β (89.1 ± 57.0 vs. 108.5 ± 60.8, p<0.001) and acute insulinogenic index (0.34 ±0.26 vs. 0.59 ± 0.56, p<0.001) than prediabetes with low PP30. However, prediabetes with high PP30 and overt T2DM had similar glycemic parameters including HOMA-β, insulinogenic index and HOMA-IR as well as BMI and lipid profile. 18.9% of prediabetes with low PP30 and 34.3% of prediabetes with high PP30 progressed to T2DM (p=0.001).

Prediabetes with high PP30 (>200mg/dl) showed β-cell dysfunction and insulin resistance similar to T2DM. This study suggested that prediabetic subjects with high PP30 should be considered as proactive management for diabetes and diagnostic criteria for considering the value of PP30 should be reflected.

1639-P

Effect of Lifestyle Interventions on Glucose Regulation among Adults without Impaired Glucose Tolerance or Diabetes: A Systematic Review

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The effectiveness of lifestyle interventions (LI) for diabetes (DM) prevention among persons with impaired glucose tolerance (IGT) is well established but

whether LI is similarly effective in preventing pre-DM among persons without IGT is unclear. We conducted a systematic review to assess effectiveness of LI on glycemic indicators among adults (≥18years) without IGT or DM. Sixty-seven studies met the inclusion criteria (randomized controlled trials of LI that reported: fasting plasma glucose [FPG]; hemoglobin A1C [A1C]; fasting insulin [FI]; or homeostasis model assessment-estimated insulin resistance [HOMA-IR]). LI included physical activity, diet, or their combination with follow-up ≥12 months. We divided studies to two groups: 1) normal glycemia, defined as mean FPG <5.5mmol/L or A1C <5.5%; and 2) high normal, defined as FPG ≥5.5mmol/L or A1C≥5.5%. We synthesized data as a whole and by glycemic status groups using random-effect models. We applied results from meta-analyses to data from the 2005-2012 National Health and Nutrition Examination Survey, and used Monte Carlo Simulation models to estimate potential decreases in the prevalence of pre-DM in the U.S. Compared to usual care, LI achieved significant reductions in FPG (-0.14mmol/L [95% CI -0.19, -0.09]), A1C (-0.05% [-0.08, -0.02]), percent change in FI (-15.26% [-20.22, -10.31]), percent change in HOMA-IR (-22.66% [-29.43, -15.88]), and percent body weight (-3.84% [-4.56, -3.12]). Similar effects were observed among both groups (FPG: -0.08mmol/L [-0.11, -0.04] in normal vs. -0.19 [-0.26, -0.11] in high normal group). Results of the simulation models suggest that if changes in FPG and A1C from all studies were applied to the U.S. population, the prevalence of pre-DM in the U.S. could be decreased by 29% (95% CI, 25, 33) from the current level (34.25%). In adults without IGT or DM, LIs significantly improve FPG, A1C, FI, HOMA-IR, and body weight, and may reduce progression to pre-DM.

1640-P

Prevalence of Acute Kidney Injury (AKI) Is Underestimated Using Administrative Data

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Patients with diabetes have an increased risk for AKI compared to those without. However, the magnitude of this potentially preventable event may differ based upon the method used to ascertain AKI. Our objective was to evaluate the rate of AKI hospitalizations (AKI-Hs) using administrative codes (ICD9CM) vs. laboratory (serum creatinine) values.

This study used Veterans Health Administration (VHA) patient records in 2006. Patients with diabetes were identified based on two ICD9CM codes or prescription of diabetes specific medications. We calculated the number of AKI-Hs and compare two approaches (APPs) of AKI derivation. AKI-Hs were defined by the principal diagnosis code 584.9 (APP 1). We also defined AKI-Hs using combination of ratio and difference from two serum creatinine values (APP 2; (Lafrance 2010)): the peak creatinine value within the first 2 days of a hospital admission and a lowest baseline creatinine value within prior 3 months of discharge of the same admission). We excluded AKI-Hs occurring with dialysis within prior 3 months of admissions.

There were 975,677 VHA diabetes patients incurring 156,813 hospital admissions. The number of AKI-H was 2,637 (3 per 1,000 persons) for APP 1 and 27,146 (28 per 1,000) for APP 2. For comparison of two APPs, we limited the admissions to the 95,379 that had both ICD9CM codes and two serum creatinine values qualified for application of APP 2. This led to 1,773 (864 (33%) reduction) AKI-Hs for APP1. Of the 95,379 admissions, 29% were AKI-Hs based on either APP; 5% of them were AKI-Hs from both APPs, and 94% were from APP 2 only. Similar statistics were observed across various age, sex, and race groups and CKD stages 1-3 (4-6%/91%-94%; CKD stages 4 & 5: 8-9%/88%). Even when adding those 864 AKI-H admissions to the above calculation, we calculated that 91% were determined to be AKI-Hs solely based on APP2.

Administrative codes underestimate AKI-Hs by about 90%. The use of serum creatinine values to determine AKI better estimates the magnitude of this complication.

Supported By: U.S. Department of Veterans Affairs (IIR11-077)

1641-P

Natriuretic Peptide Levels Vary by Race in the Diabetes Prevention Program (DPP)

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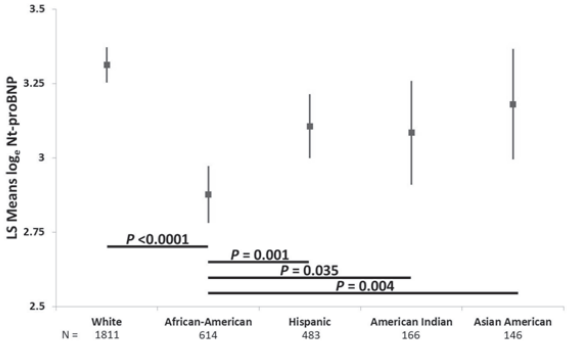
Natriuretic peptides (NP) are cardiac-derived hormones that promote salt excretion, enhance insulin sensitivity, and reduce fat accumulation. Low NP levels have been associated with increased risks of diabetes and hypertension, conditions with variable prevalence across racial/ethnic groups. We hypothesized that NP levels differ according to race and are lowest in African-Americans. We examined plasma N-terminus pro-B-type natriuretic peptide (NtproBNP) levels in 3,220 individuals in the DPP (56% White; 19% African-American; 15% Hispanic; 5% American-Indian; 5% Asian-American) at randomization. Multivariable adjusted linear regression was performed, least square means for natural log NtproBNP were calculated and compared, with Bonferroni corrected $P < 0.005$ considered significant to account for multiple testing. NtproBNP significantly differed by race (ANOVA, $P < 0.001$), with the lowest values in African-American compared with White, Hispanic, and Asian-American individuals (Figure). Hispanics also had lower NtproBNP levels compared with Whites, $P < 0.001$; while NtproBNP levels were similar between White and American-Indian and Asian-American individuals, P=0.014 and P=0.180, respectively. In the DPP cohort, African-Americans had lower NtproBNP levels compared with other racial groups. Further studies should examine the cardiometabolic implications of lower NP levels in African-Americans.



Adjusted least square means (95% CI) determined from linear regression models including age, gender, BMI, systolic BP, diastolic BP, history of hypertension, insulin sensitivity, estimated glomerular filtration rate, education, and income

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1642-P

The Joint Asia Diabetes Evaluation (JADE) Program—A Quality Improvement Program to Treat to Multiple Targets

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Diabetic complications are preventable although clinical inertia and poor self management often lead to suboptimal quality of care.

In 2007, we designed the web-based Joint Asia Diabetes Evaluation (JADE) Program with protocols, risk engines, decision support and personalized reports for detecting silent risk factors and promoting shared decision-making.

In 2007-2014, 21313 diabetic patients [mean±SD: age: 58.5±12.2 years, male: 54.6%, type 1 diabetes: 2%, median (IQR) duration: 7 (2-13) years] underwent structured assessment at 5 nurse-led Diabetes Centres in Hong Kong guided by the JADE Program. Six quality indexes were defined as A1c<7%, blood pressure (BP) <130/80 mmHg, LDL-C<2.6 mmol/L, non-smoking status, use of renin-angiotensin-system (RAS) inhibitors and statins. After 1.25 (1.01-2.02) years, 7502 (35%) patients had repeat assessment with significant improvement in those who were previously not at target: 26% attained A1c<7% (1136/4343); 26% BP<130/80 mmHg (1166/4459); 45.1% LDL-C<2.6 mmol/L (1643/3642), 18.5% smoking cessation (162/877); 11.6% started RAS inhibitors (579/5015), 17.6% started statins (905/5017) with 72-78% attaining ≥1 additional targets or remained stable. There was also improved self care with 38.6% started to perform self-blood-glucose-monitoring (664/1721), 71.9% adhered to balanced diet (586/815) and 24.5% increased physical activity (948/3819). Overall, 20.2% had at least 3% reduction in body weight, 39.1%: 4 mmHg reduction in systolic BP; 15% 1 mmol/L reduction in LDL-C and 22.6% 0.9% reduction in A1c, which were expected to translate into long term clinical benefits.

The use of the JADE Program combining logistics, information technology and team-based care reduced clinical inertia, improved self care and increased attainment of multiple treatment targets.

Supported By: Asia Diabetes Foundation; Merck & Co., Inc.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1643-P

Maternal Pregravid Obesity Accelerates the Timing of Pubertal Onset in Daughters

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Early puberty is associated with a variety of chronic conditions including metabolic syndrome and cancer, therefore identification of modifiable risk factors is essential. Fetal origins of accelerated pubertal development have not been well studied. We investigated whether *in utero* exposure to maternal gestational diabetes (GDM) and pregravid obesity are associated with timing of pubertal onset in a multiethnic population.

This cohort study included 12,222 female members of Kaiser Permanente Northern California (KPNC) age 6-11 y, who were also born at one of the KPNC facilities. Pubertal onset was assessed using pediatrician-based pubertal maturation (Tanner) staging: outcomes were ages of transition from breast stage 1 to 2+ (BR2+) or pubic hair stage 1 to 2+ (PH2+). Maternal glucose levels, height, and weight at AFP test were obtained from the electronic health record (EHR). A proportional hazards model with interval censoring was used for analysis, adjusting for maternal age and race/ethnicity.

Having a mother who was overweight (body mass index (BMI) ≥25 kg/m^2) or obese (BMI ≥30) was associated with earlier transition to BR2+ [hazard ratio (HR)=1.32, 95% confidence interval (CI) 1.19-1.47); HR=1.42 95% CI 1.26-1.60, respectively, vs. BMI <25]. Maternal obesity was also associated with earlier transition to PH2+ [HR=1.42 95% CI 1.25-1.62 for BMI ≥30; HR=1.25 95% CI 1.10-1.41 for BMI ≥25]. These associations were attenuated when adjusted for girl's pre-pubertal age- and sex-specific BMI percentile, but remained significant [HR for BR2+=1.16 95% 1.02-1.32; HR for PH2+=1.19 95% 1.04-1.37, BMI ≥30 vs. <25]. There was no association between the presence of GDM and timing of pubertal onset.

Maternal obesity is associated with higher risk of earlier pubertal onset in girls, independent of their own obesity status. These results suggest the importance of monitoring obesity among pregnant women to prevent ever-accelerating pubertal maturation in girls, which may in turn prevent its long-term sequelae.

1644-P

Ethnic Differences in Body Composition and Adiponectin: Results from the MASALA and MESA Studies

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Possibly due to less favorable body composition and adipokines, South Asians (SA) have higher rates of type 2 diabetes (DM) compared to other ethnic groups. Studies comparing body composition in U.S. SA to other race/ethnic groups are lacking. We performed a cross-sectional analysis of two community-based cohorts, Mediators of Atherosclerosis in South Asians Living in America (MASALA) and Multi-Ethnic Study of Atherosclerosis (MESA) using harmonized data. Generalized linear models were developed to assess ethnic differences in ectopic fat, lean mass, and adiponectin (Table, *p-value <0.01 for pairwise comparison to SA). All models were adjusted for age, sex, site, alcohol use, smoking, and BMI. Additionally, ectopic fat models were adjusted for exercise, hypertension, DM, high-density lipoprotein, and triglycerides; lean mass models were adjusted for exercise; and the adiponectin model was adjusted for visceral fat and intermuscular fat area. Compared to the other ethnic groups, SA had greater intermuscular and visceral fat; and lower liver density, lean muscle mass, and adiponectin. SA have a less favorable body composition and adipokine profile compared to other groups independent of BMI, lifestyle and metabolic factors. Investigation of whether these differences account for higher DM and cardiovascular disease prevalence in U.S. SA is warranted.

Table.

	South Asian (n=903)	White (n=2464)	Chinese American (n=728)	African American (n=1689)	Latino (n=1350)	Overall p-value
Subcutaneous fat area (cm^2)	243 (236-250)	250 (244-256)	236 (225-247)	261 (253-268)*	240 (232-247)	<0.001
Visceral fat area (cm^2)	155 (151-160)	159 (155-163)	138 (131-145)*	119 (114-124)*	148 (143-153)	<0.001
Intermuscular fat area (cm^2)	28 (27-28)	26 (25-26)*	20 (18-21)*	18 (17-19)*	22 (21-23)*	<0.001
Liver attenuation (Hounsfield units)	53 (52-54)	59 (59-60)*	59 (58-60)*	63 (62-63)*	60 (59-61)*	<0.001
Pericardial fat (cm^2)	74 (71-77)	87 (86-89)*	91 (88-93)*	62 (60-64)*	83 (81-84)*	<0.001
Total lean mass area (cm^2)	82 (80-84)	102 (101-104)*	100 (98-103)*	109 (107-110)*	102 (100-104)*	<0.001
Adiponectin (ng/mL)	13 (12-14)	24 (23-24)*	15 (14-17)	17 (16-18)*	21 (20-22)*	<0.001

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1645-P

Serum Potassium Is a Predictor of Diabetes Risk in African Americans with Normal Aldosterone: The Jackson Heart Study (JHS)

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Low-normal potassium (K) is a risk factor for diabetes which may account for some of the racial disparity in diabetes risk. Aldosterone affects serum K and has been associated with metabolic syndrome. We assessed the association between K and diabetes risk in African Americans and the effect of aldosterone on this association.

We studied participants from JHS, a community-based longitudinal cohort of African-American adults from Jackson, MS, who were free of diabetes at baseline. Using logistic regression, we characterized the associations between serum, dietary, and urinary K and diabetes risk, adjusting for traditional risk factors, including anthropometric measures, demographics, biochemical measures, lifestyle factors, hypertension, and use of diuretics. Additionally, we evaluated aldosterone as a potential effect modifier of these associations.

Of 2,004 participants included in our analyses, 376 developed diabetes over 8 years. We found a lower crude incidence of diabetes among participants in the highest serum K quartile compared to the lowest K quartile (16% vs. 24% respectively, p<0.01). Adjusting for all covariates other than aldosterone, those participants in the highest two K quartiles had a lower risk of diabetes compared to those in the lowest K quartile with adjusted OR (95% CI) of 0.66 (0.43, 1.00) and 0.59 (0.36, 0.93) respectively. We found a nearly-significant interaction between serum K and aldosterone (p=0.054). Among those with a normal aldosterone (<9ng/dL) (n=1106), the association between serum K and diabetes risk persisted. Among those with a high-normal aldosterone (≥9ng/dL) the association between serum K and diabetes risk was not significant. We found no significant associations between dietary K or urinary K and diabetes risk.

Conclusions: In this African-American cohort, the association between low-normal serum K and higher diabetes risk exists in participants with normal aldosterone.

Supported By: KL2TR001115-02

1646-P

Cross-Sectional Association between Rheumatoid Arthritis (RA) and Type 2 Diabetes Mellitus (T2DM): Data from Continuous NHANES, 1999-2012

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Data from the Center for Disease Control indicates that more than 50% of all people with diabetes in U.S. have some kind of arthritis. There is no recognized association between T2DM and RA which causes significant disability. While some evidence has been found, RA is not recognized as a co-morbidity related with T2DM and for this reason is not managed as part of the potential hurdles when managing diabetes. The purpose of this study was to identify if any association exists between T2DM and RA for non-institutionalized U.S. adults between 1999 and 2012. A quantitative, cross-sectional investigation was completed using the National Health and Nutrition Examination Survey (NHANES), a nationally representative sample. A logistic regression analysis was performed taking the complex survey methodology into consideration to analyze the U.S. population. The prevalence and adjusted odds ratios for the cross sectional association between T2DM and RA was determined after adjusting for potential confounders (age, gender, ethnicity, education and smoking status). Among all included participants (n=31488), the prevalence of T2DM was 7.63% and the prevalence of RA was 4.03%. The prevalence of RA among patients with T2DM was 9% which was significantly higher than the prevalence of RA among those patients without T2DM (3.62%). Considering the prevalence of T2DM among patients with and without RA, the difference was significantly higher with a prevalence of 17% on those patients with RA versus 7.24% among those without RA (OR 2.63; 95% CI [2.24, 3.10]; p<.0001). The adjusted odd ratios for the cross-sectional association between RA and T2DM were 1.45 (95% CI [1.29, 1.71]; p<.0001). The results of this study demonstrate that there is strong association between RA and T2DM. Important factors to consider in this association are age, BMI and socioeconomic factors. Health care providers may consider these important factors while managing both conditions.

Supported By: Eli Lilly and Company

1647-P

Heavy Metals in Urine and Diabetes in United States Adults =20 Years of Age

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In studies of the general population, lead, cadmium, and arsenic have been associated with various health outcomes including diabetes. The association between environmental exposure to several other metals and diabetes has not been studied. Our objective was to evaluate the relationship of urine metals including barium, cadmium, cobalt, cesium, molybdenum, lead, antimony, thallium, tungsten, and uranium with diabetes prevalence. Data were from 9447 participants of the 1999-2010 National Health and Nutrition Examination Survey (NHANES), a cross-sectional study from a representative sample of the U.S. civilian non-institutionalized population. Metals were measured in urine and diabetes status was determined based on a previous diagnosis or an A1c ≥6.5%. After adjusting for demographics, socioeconomic status, smoking, alcohol, waist circumference, C-reactive protein, liver enzymes, nutrition, and urine creatinine, the odds ratios (95% confidence interval) of diabetes associated with the highest quartile of metal, compared to the lowest quartile, were 0.86 (0.66-1.12) for barium, 0.74 (0.51-1.09) for cadmium, 1.21 (0.85-1.72) for cobalt, 1.31 (0.90-1.91) for cesium, 1.76 (1.24-2.50) for molybdenum, 0.79 (0.56-1.13) for lead, 1.72 (1.27-2.33) for antimony, 0.76 (0.51-1.13) for thallium, 2.18 (1.51-3.15) for tungsten, and 1.46 (1.09-1.96) for uranium. Higher quartiles of barium, molybdenum, and antimony were associated with greater homeostasis model assessment-insulin resistance after multivariable adjustment (each p-trend<0.05). Molybdenum, antimony, tungsten, and uranium were positively associated with diabetes, even at the relatively low levels seen in the U.S. population. Our study provides further evidence that environmental exposure to metals may play a role in the development of chronic diseases such as diabetes.

Supported By: National Institute of Diabetes and Digestive and Kidney Diseases (GS10F0381L)

1648-P

Sleep Characteristics in Association with Type 2 Diabetes Risk and Hemoglobin A1c Levels among Women with a History of Gestational Diabetes: A Prospective Cohort Study

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Women with a history of gestational diabetes mellitus (GDM) are at substantially increased risk of type 2 diabetes mellitus (T2DM). Sleep disorders has been implicated in impaired glucose metabolism and insulin resistance. We aimed to prospectively examine the associations of sleep characteristics with T2DM risk and hemoglobin A1c (HbA1c) levels among women with a history of GDM. We included 2860 women in the Nurses' Health Study II with prior GDM, as part of the Diabetes & Women's Health Study, and followed them biennially from 2001 to 2011. Of them, 304 incident T2DM cases were identified through self-reports and confirmed by supplemental questionnaires. Self-reported sleep characteristics were assessed by questionnaire in 2001. HbA1c was measured by high performance liquid chromatography in a subset of participants (n=581) who donated blood samples in 2012-2013. After adjustment for age, parity, family history of diabetes, and dietary and lifestyle factors, snoring was significantly associated with T2DM risk; the hazard ratio (HR) and 95% confidence interval (CI) was 2.10 (1.44-3.05) for occasional snoring and 2.53 (1.73-3.70) for regular snoring, compared with almost never snoring. The associations were attenuated but remained significant after additional adjustment for body mass index. Moreover, the least squares means of HbA1c levels for women who snored regularly were significantly higher than those who almost never snored (adjusted means [95% CI], 6.48 [6.13-6.86] vs. 6.32 [5.96-6.71], P=0.04). There was suggestive evidence that short sleep duration (<=6 vs. 7 hours/day) was associated with greater risk of T2DM and higher HbA1c levels, but the associations became non-significant after adjustment for other risk factors. In conclusion, snoring is independently associated with greater risk of T2DM and elevated HbA1c levels among women with a history of GDM.

Supported By: Eunice Kennedy Shriver National Institute of Child Health and Human Development

1649-P

Outcomes among Patients with Type 2 Diabetes (T2D) Receiving Basal Insulin with Mealtime Insulin or Exenatide BID: A Retrospective Study Using Real-World EMR Data

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Mealtime insulin and exenatide twice daily (ExBID) are effective as add-on therapies to basal insulin for T2D patients in randomized clinical trials. This retrospective cohort study used electronic medical record (EMR) data to evaluate analogous real-world outcomes.

Adult patients with T2D who initiated mealtime insulin or exenatide BID as an add-on to basal insulin between Jan 1, 2008 and Mar 31, 2013 were identified in a U.S. EMR database, with the date of first prescription defined as index date. Patients were followed for 12-months before (baseline) and 6-months after index. Outcomes included glycemic control (percent with A1C<7%), change in A1C, incidence of hypoglycemic events, and change in body weight. Multivariate regressions adjusted for differences in baseline demographic characteristics and potential confounders.

1,152 ExBID patients (mean±SD age 59±10.4y, 55.0% female) and 23,891 mealtime insulin patients (mean±SD age 61±13.3y, 51.2% female) were identified. Mean baseline A1C was 8.7% and 8.4% (p<0.001) for mealtime insulin and ExBID patients, respectively. During follow-up, mean A1C was 8.1% and 7.9% (p=0.001) for mealtime insulin and ExBID patients, with 25.7% and 29.8% achieving control (p=0.006). Weight decreased with ExBID and increased with mealtime insulin (-3.1 vs. +1.0 lb, p<0.001). Patients initiating ExBID were less likely to have a hypoglycemic event than mealtime insulin (2.5% vs. 5.7%, p<0.001). In multivariate models, ExBID patients were more likely to achieve glycemic control (OR=1.2, p=0.01) and had a similar change in A1C during follow-up (LS mean = -0.27 ExBID; -0.29 mealtime, p=0.74).

In a real-world setting basal insulin plus ExBID was as effective as basal insulin and meal bolus insulin treatment in reducing A1C, but was associated with less weight gain and less hypoglycemia. This study supports use of basal-exenatide treatment in T2D as an alternative to basal-meal bolus therapy.

1650-P

Vitamin D Status in Patients with Type 2 Diabetes Mellitus and Its Relation with Glycemic Control and Cardiovascular Risk Factors

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Emerging data is mounting that hypovitaminosis D is common in type 2 diabetes mellitus (T2DM) and may adversely affect the cardiovascular system. Herein, we aimed to determine the prevalence and predictors of hypovitaminosis D in Brazilian patients with T2DM in a predominantly nonwhite population; and correlate 25-hydroxyvitamin D [25(OH)D] levels with variables representative of glycemic control and cardiovascular risk. We conducted a cross-sectional study with consecutive patients treated at a University Hospital´s Endocrinology outpatient clinic located at 12°58´S latitude, between October 2012 and November 2013. Hypovitaminosis D was defined as 25(OH)D levels <30 mg/dL. We evaluated 119 patients with a history of T2DM for 14.58 ± 8.27 years. Mean age was 58.69 ± 10.43 years. Most subjects were women (70.6%), nonwhite (89.9%), hypertensive (77.3%) and dyslipidemic (76.5%). Insulin (72.3%) and metformin (76.5%) were the most common drugs used to treat T2DM. The prevalence of hypovitaminosis D was 62%. Independent predictors of hypovitaminosis D were female gender (OR 3, 10 p=0,024), dyslipidemia (OR 6, 50 p=0,001) and obesity (OR 2, 55 p=0,072). 25OHD levels were inversely correlated with Body Mass Index (BMI) (r=-0.199 p=0.040), HbA1c (r=-0.217 p=0.029), total cholesterol (TC) (r=-0.395 p=0.000), LDL cholesterol (r=-0.320 p=0.001), triglycerides (r=-0.336 p=0.000) and microalbuminuria (r=-0.235 p=0.020). In multiple linear regression, only TC (β=-0.363 p=0.000) and BMI (β=-0.207 p=0.036) remained associated with 25(OH)D levels. The prevalence of hypovitaminosis D in T2DM patients was elevated, similar to that found in non-tropical regions. The main predictors of hypovitaminosis D were female gender, dyslipidemia and obesity. Low 25(OH)D levels were correlated with elevated levels of BMI and TC. Further studies are needed to determine if vitamin D replacement can improve these parameters.

Supported By: Conselho Nacional de Desenvolvimento Científico e Tecnológico

1651-P

Weight Loss Strategies and Changes in Body Weight among Subjects with Type 2 Diabetes (T2D) in the U.S.

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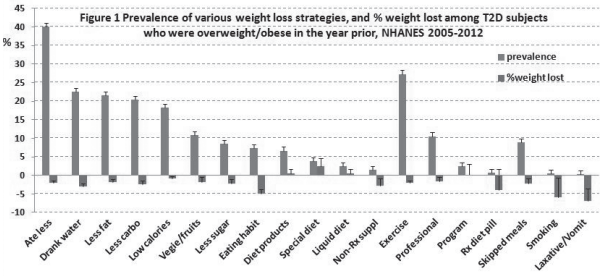
This analysis seeks to understand weight loss strategies, weight changes, attitudes and behaviors in subjects with T2D. We used the 2005-2012 U.S. NHANES data to identify subjects with self-reported T2D diagnosis. Body weight data included measured and self-reported current body weight and height, self-reported weight the prior year, and self-reported desired weight. Analyses were weighted to account for the stratified, multistage probability sampling design and survey nonresponse.

Of the 2,266 subjects identified with T2D, 2,187 (97%) had data to calculate weight change from the prior year. The overall prevalence of overweight/obesity (body mass index ≥ 25kg/m^2) was 86% (95% confidence interval (CI) 84%-88%) in present year, and 88% (95% CI 86%-90%) the prior year. Figure 1 shows the prevalence of various weight loss strategies, and % body weight lost among subjects who were overweight/obese the prior year. Many diet-related methods were used, with average weight lost<5%. Two most "effective" methods reported (smoking, taking laxatives/vomiting) are also potentially the most harmful. Overweight and obese patients would have to lose about 8% and 24%, respectively, to reach their desired body weight.

This study highlights the T2D weight issues, and challenges facing patients and clinicians in seeking to manage it.



Blue bars: prevalence of the weight loss strategies; Red bars: % weight lost in the year prior. Capped spikes (outward for blue bars and inward for red bars): standard errors. NHANES=National Health and Nutrition Examination Survey.

Drank water=Drank a lot of water; Less fat=Ate less fat; Less carbo=Ate fewer carbohydrates; Low calories=Switched to foods with lower calories; Vegie/fruits=Ate more fruits/vegetables/salads; Less sugar=Ate less sugar/candy/sweets; Eating habit=Changed eating habits; Diet products=Ate diet foods/products; Special diet=Followed a special diet; Liquid diet=Used a liquid diet formula; Non-Rx suppl=Took other pills/medicines/herbs/supplements not needing a prescription to lose weight; Professional=Seek help from a health professional; Program=Joined a weight loss program; Rx diet pill=Took prescription diet pills.
Potentially harmful methods: Smoking=Started to smoke or began to smoke again; Laxative/Vomit=Took laxatives or vomited.

1652-P

Trends in Diabetes Control and Insulin Use in the U.S., 1988-2010

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Over the past two decades many new treatment options have been introduced for type 2 diabetes. Increasingly there is debate regarding the effectiveness of insulin as the last-line therapy. We conducted a cross-sectional study of 4,310 participants with diagnosed diabetes in the National Health and Nutrition Examination Survey (NHANES) 1988-1994 and 1999-2010 to examine trends in glycemic control by insulin and oral diabetes medication use. Overall, diabetes control has improved, but those on any insulin are consistently less likely to meet glycemic targets (Table). Over 20 years the duration of diabetes for those on any insulin has increased significantly (13 to 17 years, p<0.0001) compared to that for persons on oral medication (7 to 8 years, p=0.04). In 2005-10, among whites, the prevalence of any insulin use was 33%, compared to 29% in African Americans and only 20% in Mexican Americans. After adjustment for duration of diabetes, age, gender, BMI, and education, Mexican Americans were still significantly less likely to receive insulin therapy as compared to whites. Differences in HbA1c by race have become more notable, with higher HbA1c in Mexican Americans and blacks than whites (Table). Our results suggest improvements are needed in education on insulin use, new insulin formulations and delivery technologies, and/or systems of care to improve glycemic control in patients receiving insulin, with particular attention to racial disparities.

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Table. Trends in Insulin and Oral Diabetes Therapy, US Adults with Diagnosed Diabetes, Weighted Estimates from NHANES 1988-1994, 1999-2004, and 2005-2010.

	1988-1994			1999-2004			2005-2010		
	Any Insulin	Oral Only	None	Any Insulin	Oral Only	None	Any Insulin	Oral Only	None
	Mean or %	Mean or %	Mean or %	Mean or %	Mean or %	Mean or %	Mean or %	Mean or %	Mean or %
N	373	540	292	317	799	201	484	1,079	225
Calibrated A1c, %*	7.9	7.6	6.1	8.1	7.4	6.5	7.8	6.9	6.2
Non-Hispanic white	7.9	7.5	6.1	8.0	7.1	6.2	7.6	6.7	5.9
Non-Hispanic black†	8.1	**8.4**	6.2	8.5	**7.8**	6.7	**8.4**	**7.1**	**6.8**
Mexican American†	8.0	7.9	6.6	8.2	**8.1**	**7.2**	**8.2**	**7.5**	**6.8**
A1c<7%	33.6%	43.9%	82.0%	29.2%	49.4%	78.3%	32.1%	66.5%	82.6%
A1c<8%	52.3%	63.5%	89.5%	53.9%	73.8%	84.6%	62.9%	84.9%	91.6%
Duration of diabetes, yrs	12.7	7.0	9.9	17.5	10.4	6.9	17.1	8.1	8.2
Age, yrs	59.8	61.1	59.1	59.3	60.1	57.1	58.6	60.5	57.0
Male	43.0%	49.3%	42.8%	45.3%	51.5%	48.9%	54.4%	45.7%	47.4%
Race									
Non-Hispanic white	71.8%	73.8%	77.8%	66.2%	63.2%	65.5%	70.5%	59.8%	56.2%
Non-Hispanic black	20.4%	11.7%	11.3%	19.1%	14.1%	11.1%	16.9%	16.8%	16.3%
Mexican American	4.1%	6.7%	5.3%	5.2%	8.4%	5.9%	5.8%	9.1%	11.7%
Other	3.7%	7.9%	5.6%	9.5%	14.4%	17.5%	6.9%	14.4%	15.7%
Education									
HS or less	75.5%	76.6%	68.2%	61.9%	58.8%	54.3%	49.6%	58.4%	46.5%
Some college	16.0%	13.0%	15.6%	24.6%	28.1%	26.9%	33.2%	24.8%	34.9%
College or more	8.6%	10.5%	16.2%	13.5%	13.1%	18.8%	17.2%	16.8%	18.6%
Hypercholesterolemia‡	37.8%	40.3%	35.2%	50.5%	48.1%	37.2%	55.3%	58.4%	38.4%

*A1c values were calibrated to account for laboratory drift over the 20 year period, using 2001-04 as the reference
†Bolded results indicate p<0.05 for comparison of mean calibrated HbA1c compared to Non-Hispanic whites
‡Defined as total cholesterol >=240 mg/dL or taking cholesterol-lowering medications

1653-P

Food Insecurity, Food Deserts, and Hemoglobin A1c: A Multilevel Longitudinal Analysis

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The extent to which food insecurity, defined as limited access to food due to cost, and residence in a food "desert", an area with limited options to purchase fresh foods, are associated with glycemic control is unclear. A random sample of diabetes patients entered our longitudinal cohort study from June 1, 2013 to December 1, 2014. ≥ 2 affirmative responses on the Food Security Survey Module indicated food insecurity. Patient addresses were geocoded to census tracts, and we used the 2014 USDA Food Access Research Atlas to determine if that census tract was considered a food desert. Our primary outcome was hemoglobin A1c (HbA1c). We assessed the association between food insecurity, residence in a food desert, and HbA1c using hierarchical linear models with patient-level and census tract-level random effects. We calculated intraclass correlation coefficients (ICC) to partition the variation in glycemic control between levels. We enrolled 411 patients: mean age was 62 (SD: 12) years, 47% were women, and 79% were non-Hispanic white. 20% reported food insecurity, and 29% lived in a food desert. Those who reported food insecurity were more likely to live in a food desert (36% vs. 27%, p=.04). Based on the ICC, census tract characteristics explained only 6% of the variation in HbA1c over time, while patient-level characteristics explained 74%. In longitudinal hierarchical models adjusted for age, gender, race/ethnicity, education, insurance, Charlson comorbidity score, duration of diabetes, health literacy, language, and medications, food insecurity was associated with greater increase in HbA1c over time (0.24%/year greater increase in those with food insecurity, 95% CI 0.05% to 0.48%), while residence in a food desert was not (-0.12%/year change in HbA1c, 95% CI -0.24% to 0.12%). Variation in HbA1c was largely explained by patient-level factors. Interventions to increase neighborhood food access may have limited impact on glycemic control if they are not coupled with efforts to reduce food insecurity.

1654-P

Factors Associated with Cancer Risk in Type 2 Diabetes

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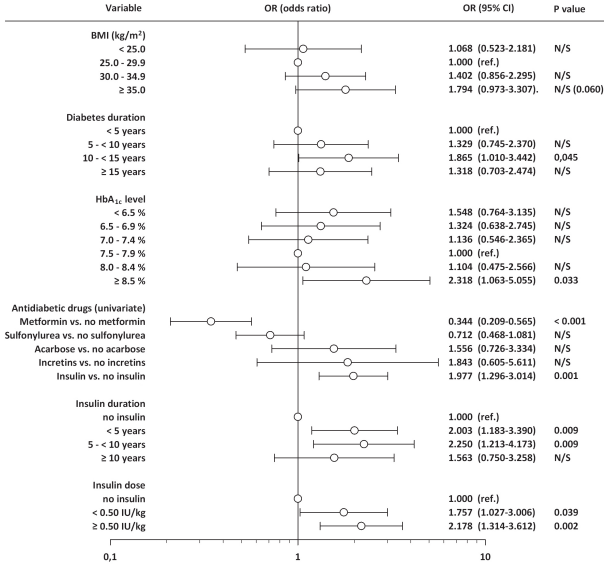
The risk of several types of cancer is increased in type 2 diabetes mellitus (T2DM). The earliest possible diagnosis of cancer - difficult within regular outpatient diabetes care - is of utmost importance for patients' survival. The aim of this multicenter, retrospective (years 1998-2014), case-control study was to identify risk factors associated with malignancy in subjects with diabetes treated in a typical outpatient setting.

In the databases of 3 diabetic and 1 primary care clinics 178 patients (99 women) with T2DM who developed cancer while treated for diabetes were identified. The control group consisted of 178 age- and gender matched subjects with T2DM without cancer. Demographic data, BMI, smoking habits, comorbidities, as well as duration, treatment and metabolic control of diabetes were analyzed.

The most prevalent malignancies were breast cancer in women (40.4%) and colorectal cancer in men (21.3%). HbA1c level ≥ 8.5 %, diabetes duration and insulin treatment in time-varying and dose-dependent manner were significantly associated with increased risk of malignancy (Fig.). Not surprisingly, metformin use was associated with lower cancer risk.

In conclusion, in the outpatient diabetes centers the patients with long-standing, poorly controlled insulin treated T2DM should be rigorously assessed towards malignancies, particularly breast cancer in women and colorectal cancer in men.



Epidemiology/ Genetics **POSTERS**

1655-P

Sex Hormone Binding Globulin (SHBG) and Sex Steroids in the Diabetes Prevention Program (DPP)

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SHBG and sex steroids are associated with dysglycemia and diabetes risk in populations without recognized glucose intolerance. We evaluated these relationships in the DPP, an at-risk population. Diabetes was ascertained over 3.2 years follow-up.

There were no treatment-group effects, so treatment groups were combined. SHBG and sex steroid concentrations were associated with plasma glucose at DPP baseline (Table). Among men, higher levels of estrone (HR 1.09 per 10 nmol/L, p<0.0001) and estradiol (HR 1.09 per 10 nmol/L, p=0.048) predicted diabetes risk after adjustment for age, race/ethnicity, BMI, and HOMA-IR. There was no association between estrogens and diabetes incidence among women. Testosterone and DHEAS were not associated with incident diabetes in any group. SHBG gene polymorphisms were associated with SHBG levels (in men β=0.17 nmol/L SHBG per allele at rs6259, p=0.0002; in men and women β=0.06 to 0.12 nmol/L per allele at rs1799941, p=0.05 to 0.005). Neither SHBG levels nor its polymorphisms were associated with incident diabetes.

In the DPP, SHBG and sex steroids were associated with glucose. Estrogen levels modified diabetes risk in men, but androgen, SHBG levels, or SHBG polymorphisms did not predict diabetes in any group. This suggests that sex steroids have little value in predicting risk for diabetes in women, and SHBG has little value in predicting diabetes in both sexes, in an at-risk population.

Table. Cross-sectional Associations between SHBG, Sex Steroids, and Fasting Plasma Glucose and 2-Hour Glucose among DPP Participants at Baseline. Correlation-Coefficients were Adjusted for Age, Race/Ethnicity, Body Mass Index (BMI), and HOMA-IR. Data are Presented as Pearson Correlation Coefficient (p-value).

	Men (n=969)	Premenopausal women, no estrogen use (n=948)	Postmenopausal women, no hormone use (n=551)	Postmenopausal women, with estrogen use (n=431)
Estrone-S and fasting glucose	0.04 (0.22)	-0.02 (0.41)	-0.09 (0.07)	0.03 (0.64)
Estrone-S and 2-hour glucose	**0.09 (<0.01)**	**0.10 (<0.01)**	0.00 (0.96)	0.05 (0.41)
Estradiol and fasting glucose	0.05 (0.17)	-0.03 (0.41)	-0.06 (0.23)	-0.05 (0.42)
Estradiol and 2-hour glucose	0.05 (0.17)	0.02 (0.47)	-0.06 (0.20)	0.05 (0.39)
DHEAS and fasting glucose	0.00 (0.91)	-0.05 (0.13)	-0.03 (0.57)	-0.06 (0.28)
DHEAS and 2-hour glucose	0.00 (0.99)	0.04 (0.26)	**0.12 (0.02)**	-0.07 (0.28)
Testosterone and fasting glucose	-0.06 (0.05)	0.00 (0.91)	-0.03 (0.48)	-0.02 (0.72)
Testosterone and 2-hour glucose	**-0.07 (0.05)**	**0.10 (<0.01)**	-0.05 (0.34)	0.01 (0.80)
SHBG and fasting glucose	-0.06 (0.10)	**-0.16 (<0.01)**	-0.06 (0.20)	**-0.18 (0.02)**
SHBG and 2-hour glucose	-0.01 (0.82)	0.03 (0.43)	-0.07 (0.12)	0.05 (0.37)

Supported By: American Diabetes Association (1-05-CD-12, 7-02-JF-30 to K.M.); National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases; National Institute of Child Health and Human Development; National Institute on Aging; Office of Research on Minority Health and Health Disparities; Office of Research on Women's Health; Indian Health Services; Centers for Disease Control and Prevention; U.S. Global Change Research Program; National Center for Research Resources; Bristol-Myers Squibb; Lipha; Parke-Davis

1656-P

WITHDRAWN

1657-P

Multiple Healthy Behaviors and Risk of Dysglycemia in Pregnancy: The Healthy Start Study

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Dysglycemia in pregnancy is associated with adverse maternal and offspring health. We examined the cumulative benefit of multiple healthy behaviors during pregnancy on risk of dysglycemia in 760 women from Healthy Start, a pre-birth cohort study in Colorado. Maternal diet, physical activity, vitamin use, and mental health were assessed by self-report in early and mid-pregnancy (< 27 weeks). Women received one point for each healthy behavior: diet (Healthy Eating Index > 64); moderate-vigorous physical activity > 150 min/week; daily multivitamin use; mental health (lowest quartile of Perceived Stress Scale and Edinburgh Depression Scale < 13). Dysglycemia (n=106) was defined as gestational diabetes diagnosis or at least 1 abnormal value on the 50g glucose challenge or 3h OGTT. Logistic regression was used to estimate the odd ratios (OR) for dysglycemia by number of healthy behaviors, with and without adjustment for confounders (BMI, diabetes history, etc). The OR for dysglycemia (Table) significantly decreased with increasing number of healthy behaviors (p for trend = 0.03-0.04 in unadjusted and adjusted models). Compared to women with no healthy behaviors, women with 3+ healthy behaviors had ~60% lower risk of dysglycemia. Our findings suggest that engaging in multiple healthy behaviors during pregnancy may reduce the risk of dysglycemia, with potentially important benefits for mother and offspring.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Table. Odds Ratios for Dysglycemia in Pregnancy According to Number of Healthy Prenatal Behaviors.

Healthy behaviors	Normal n (%)	Dysglycemia n (%)	Unadjusted OR (95% CI)		Adjusted OR (95% CI)	
0	34 (5.2%)	8 (7.5%)	1.00	(ref)	1.00	(ref)
1	218 (33.3%)	40 (37.7%)	0.78	(0.34, 1.81)	0.91	(0.37, 2.22)
2	222 (33.9%)	41 (38.7%)	0.79	(0.34, 1.82)	0.88	(0.36, 2.15)
3-4	180 (27.5%)	17 (16.0%)	0.40	(0.16, 1.00)	0.44	(0.17, 1.17)
p for trend			0.03		0.04	

Supported By: National Institutes of Health (R01DK076648, UL1TR001082, P30DK56350, T32DK07658)

1658-P

Biomarkers for Insulin Resistance and 10-Year Risk of Diabetes: Evaluation of a Novel 92-Protein Assay in Two Large Swedish Community Cohorts

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Insulin resistance (IR) is a major precursor and pathogenic component of type 2 diabetes (T2D) but difficult to measure in the clinical setting. To identify new biomarkers for IR and T2D, we used a novel 92-protein proximity extension assay for cardiovascular and inflammatory markers.

Proteomic profiles of blood samples from non-diabetic elderly Swedish community residents in two longitudinal cohorts (PIVUS n=887, ULSAM n=606; mean age 73.2±0.53 yrs, 30.3% female) were assessed using the Olink Proseek Multiplex CVD 96x96 panel. Outcomes were baseline HOMA-IR, 10-yr incident T2D, and 5-yr risk for worsening fasting glucose category (<5.6 mmol/l, 5.6-6.9 mmol/l, and ≥7 mmol/l or T2D). Linear (HOMA-IR), logistic (5-yr prediction), and Cox regression analyses (10-yr T2D risk) were adjusted for causal confounders (age, sex, BMI, waist circumference, C-reactive protein, and comorbidities) and multiple testing (5% false discovery rate).

At baseline, 15 out of 85 proteins that passed quality control were associated with HOMA-IR in the training sample (PIVUS); five had confirmed positive associations in the validation sample (ULSAM): leptin, tissue plasminogen activator (t-PA), renin, interleukin-1 receptor antagonist (IL-1RA), and hepatocyte growth factor (HGF). Only IL-1RA predicted 10-yr incident T2D (adjusted HR for a log2-scale unit increase 1.35, 95% CI 1.02-1.80). In unadjusted analyses, IL-1RA (HR 1.29, 95% CI 1.08-1.54), t-PA (HR 1.42, 95% CI 1.19-1.70), and HGF (HR 1.38, 95% CI 1.12-1.71) predicted 5-yr worsening in glycaemic state. These associations were no longer significant after confounder adjustment.

Proteomic profiling is valuable for IR/T2D biomarker discovery. The identified risk markers relate to recently implicated pathways in T2D pathogenesis, including endothelial dysfunction, ectopic hepatic lipid accumulation, and imbalance between pro- and anti-inflammatory cytokines.

1659-P

Trends of Hospitalization and Health Care Cost for Type 2 Diabetes Mellitus in the U.S., 2000-2011

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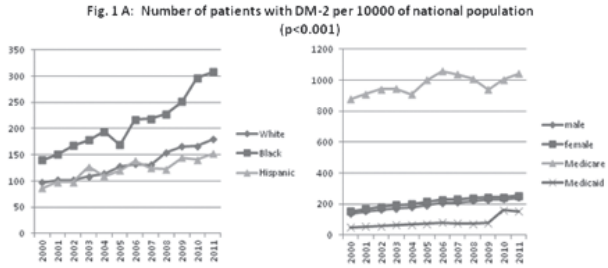
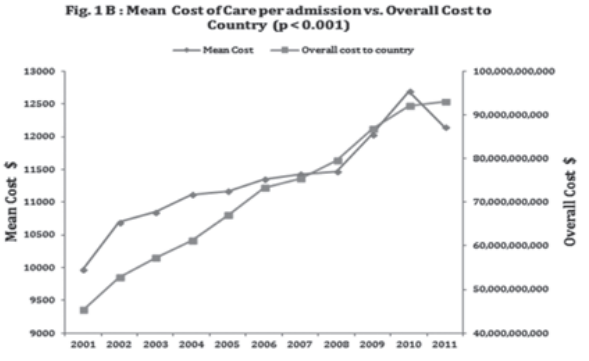
Type 2 diabetes mellitus (DM-2) is a very common primary or secondary diagnosis in hospitalized patients. The purpose of the study was to examine possible trends in the number of hospitalizations and in the health care costs related to DM-2. The data was taken from HCUP's Nationwide Inpatient Sample (NIS) from 2000 to 2011 by using appropriate ICD-9 code in primary or secondary diagnosis field. 14,766,564 admissions were analyzed (Weighted n 72,467,063) (On average: 46.7% male (M), 51.7% White (W), 13.5% Black (B), 8.9% Hispanic (H)) including only the patients ≥ 18 years of age. Cost to charge ratio files were merged with NIS to calculate the cost of care (adjusted for inflation in reference to 2011). In the national population, the study found statistically significant ($p < 0.001$) increase in admissions for M (75.5%), F (64.3%), W (85.1%), B (119.8%), H (75.6%), primary payer - Medicare (19.1%)/Medicaid (301.1%). Overall, DM-2 hospitalizations increased by 87.2% from 2000 to 2011, and mean cost of admission for DM-2 hospitalizations grew from $9,975 to $12,149 respectively (23.4%, $p < 0.001$). The resulting costs to the U.S. healthcare system increased by 116.8% from $45.33 billion to $92.97 billion. We contend that the given increases in cost were significantly impacted by the growth seen in both DM-2 associated hospitalizations and in the percentage of patients covered by Medicare or Medicaid in this subgroup.





1660-P

Use of Health Information Technology and Access to Medical Care among Persons With and Without Diagnosed Diabetes

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Health information technology (HIT) may be effective in improving access to care and quality of care. However, the proportion of U.S. adults (aged ≥18 years) with/without self-reported diabetes (DM) using HIT to access medical care is unknown. We used data from 94,706 adults with/without DM in the 2009, 2011, and 2012 U.S. National Health Interview Survey. We assessed use of HIT to access medical care by: use of the internet for setting appointments; communicating with health care providers; and refilling prescriptions. We calculated adjusted prevalences of HIT use from logistic regression models, controlling for socio-demographic and health status. Adults with DM reported higher age-adjusted prevalences of refilling prescriptions online (11.4% [95% CI: 9.4-13.7] vs. 5.9% [5.6-6.1]) and communicating with health providers online in the past year (7.8% [6.1-10.0] vs. 5.3% [5.0-5.5]) than those without. There was no statistical difference in the age-adjusted prevalence of setting appointments online between those with/without DM (5.3% [3.9-7.1] vs. 4.2% [4.0-4.4]). The adjusted association between DM status and refilling prescriptions and communicating with health providers online differed by selected demographics. For example, among adults with DM, those aged 18-39 y were more likely to refill prescriptions online than those aged 40-64 y (14.3% [11.3-17.9] vs. 9.6% [8.4-11.0]); among adults without DM, adults aged 18-39 y were less likely to refill prescriptions online than those aged 40-64 y (6.0% [5.6-6.4] vs. 7.0% [6.7-7.4]). Diabetes status is associated with HIT use. Among those with diabetes, younger and those with private insurance are more likely to use HIT. Given the potential of HIT to benefit large numbers of people, interventions to motivate people with diabetes to use internet for their medical care needs might be considered.

1661-P

The Temporal Relationship between Diagnosis with Diabetes and Development of Depression: A Registry-based Analysis of the Working-Age Population in Denmark 1996-2010

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The study investigated the temporal relationship between diagnosis with diabetes (Source: Danish Diabetes Register) and first purchase of prescribed antidepressants (Source: Register Medicinal Product Statistics) as a proxy for incident depression. We excluded individuals taking antidepressants in the year prior to baseline. People with diabetes of working age (18-59) were followed for five years after diagnosis. As a proxy of socioeconomic status, subjects were stratified according to occupational status.

9.9% of people with diabetes developed depression within 5 years of the diagnosis of diabetes, of whom 24.1% did so in the first year. Thus, a significantly greater proportion developed depression within the first year. Overall, incident depression in the first year is the same for all occupational groups. After five years differences between the different occupational categories emerge, with those of lower socioeconomic status having the highest incidence. Conversely, those of high socioeconomic status who develop depression are more likely to do so in the first year after diagnosis. The data indicate that diagnosis of diabetes precipitates depression across the workforce, but those with high occupational status have better resilience/coping skills that allow them to adapt better to the demands of diabetes.

Table.

	Depression* within 1 year, %	Depression within 5 years, %	Share with depression within 1 year, % (1)/(2)	Different from randomness, *p*-value	*N*	N with depression within 1 year	N with depression within 5 years
(a) Both men and women							
All	2,4%	9,9%	24,1%	<.0001	33.496	794	3.300
1: Employee at highest level	2,5%	8,6%	29,4%	<.0001	6.288	159	540
2: Executive management	1,6%	6,7%	23,9%	0,105	1.619	26	109
3: Employee at medium level	2,3%	9,6%	23,7%	0,018	5.165	118	498
4: Employee at basic level	2,4%	10,2%	23,8%	0,007	15.159	370	1.553
5: Self-employed	2,2%	9,5%	23,5%	0,193	2.055	46	196
6: Other employee	2,3%	11,7%	19,5%	0,994	2.752	63	323
7: Unemployed	2,6%	17,7%	14,8%	0,316	458	12	81

Notes
N: People with diabetes
p-values: Two-sided Fisher's exact tests.
* Depression defined by purchase of prescribed antidepressant
Antidepressants excluded for potential confounding: Desipramin; Imipramin; Clomipramin; Amitriptylin; Nortriptylin; Duloxetin.

Epidemiology/ Genetics **POSTERS**

1662-P

IDF Diabetes Atlas Estimates of Diabetes Prevalence in the North America and Caribbean Region in 2014

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Diabetes is a serious and increasing global public health burden, and accurate estimates of the burden of diabetes are essential to allocate resources appropriately. The number of people (20-79 years) living with diabetes in the North America and Caribbean (NAC) Region was estimated for 2014 for the International Diabetes Federation (IDF) Diabetes Atlas.

Studies reporting age-specific prevalence of diabetes were identified through a search including PubMed, Google Scholar, WHO, Ministries of Health, and other major health organizations. Studies were then scored by age of study, design, diagnostic criteria, sample representation, size of study, and type of publication. The highest scoring studies for each country were selected for inclusion. Studies were excluded if they did not meet a minimum score. Estimates for countries without source data were modelled from pooled estimates of countries matched for geography, World Bank development classification, ethnicity, and IDF Region. Estimates of undiagnosed diabetes were derived from studies providing such information. The prevalence estimates were applied to 2014 UN population estimates to determine the prevalence of diabetes in 219 countries and territories. The presented estimates for the 28 countries and territories in the NAC region represent a subset of the larger global IDF Diabetes Atlas project.

This study estimated that 9.9% of adults in the NAC region had diabetes in 2014, a total of 38.8 million people. Of these, 10.5 million adults were undiagnosed and 31.2 million were living in an urban setting. Within the NAC region, the majority of people with diabetes were over 40 years of age (88.1%). The age-adjusted prevalence for the region was 11.4%, the highest comparative regional prevalence worldwide.

Approximately one in ten adults in the NAC region had diabetes in 2014. A comprehensive diabetes plan is required to ensure appropriate prevention, identification, management, and education for people living with diabetes.

1663-P

Neck Circumference as Causal Factor for Development of Diabetes Mellitus over the Course of 10 Years in the Korean Genome and Epidemiology Study

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Neck circumference, a proxy for upper-body fat, may be a unique fat depot that indicates additional metabolic risk beyond whole body fat. We investigated whether neck circumference is associated with development of diabetes mellitus (DM). We used a subset of data with Korean Genome and Epidemiology Study, a community-based prospective cohort (n=3521, age range=42-71 years). Nondiabetic subjects at the baseline were categorized into 4 groups (Q1-Q4) in accordance to their neck circumference quartiles. Anthropometric and biochemical parameters related with insulin resistance and β-cell function were investigated. Epworth sleepiness scale for daytime sleepiness and snoring habit were also examined. The development of DM was confirmed biannually as ≥126 mg/dl in fasting glucose or ≥200 mg/dl in postload glucose concentrations based on a 75-g oral glucose tolerance test or antidiabetic medication. The mean±SD neck circumference (cm) was 35.1±0.9, 37.0±0.4, 38.4±0.4, and 40.3±1.1 in men, and 30.7±0.8, 32.2±0.3, 33.5±0.4, and 35.2±1.0 in women, from Q1 to Q4, respectively. During the 10 year-study period, 2623 (74.5%) among 3521 subjects were followed-up. Of these subjects, 632 (24.1%) developed DM. The incidence of DM increased from 17.6% in Q1 to 18.2% in Q2, to 25.4% in Q3, and to 36.0% in Q4 (P<0.001). After adjusting for most risk factors related with DM, the relative risks of DM development were 0.95 (95% confidence interval, 0.66-1.37), 1.50 (1.02-2.22), and 1.63 (1.07-2.50) in Q2, Q3, and Q4, respectively when compared to Q1. This finding indicates negative impact from large neck circumference in the development of DM beyond whole body fat and other risk factors.

1664-P

Changes in Cancer Mortality among U.S. Adults with Diabetes, 1990-2011

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Although mortality in persons with diabetes has decreased, there are evidences that the incidence of certain cancers and related mortality are increased in people with diabetes (DM). It is unclear whether overall cancer mortality has changed among U.S. adults with DM. To examine trends in cancer mortality, we used data from 33,442 adults aged ≥20 yrs with self-reported DM who participated in the 1985-2009 U.S. National Health Interview Survey. Participants were linked to the National Death Index to determine vital status up to 2011. Cancer deaths were classified according to underlying or contributing cause of death. We compared cancer mortality rates of 5 consecutive time periods (1990-1994, 1995-1999, 2000-2004, 2005-2009, and 2010-2011).

During a mean follow-up of 12.5 years, 11,445 adults with DM died. From 1990-1994 to 2010-2011, age-standardized all cause death rates (per 1000 person-years and 95% CI) declined from 23.4 (20.3, 26.5) to 19.4 (17.8, 20.9), and underlying cancer death rates declined from 3.7 (2.8, 4.7) to 3.0 (2.4, 3.7). The age- sex- race/ethnicity-adjusted hazard ratios of underlying cancer mortality for the 5 time periods were 1.0 (1990-1994 used as a reference), 0.9 (0.7, 1.1), 0.9 (0.7, 1.2), 0.8 (0.6, 1.1), and 0.7 (0.6, 0.9), respectively. When classified according to either underlying or contributing cause, cancer death rates decreased by 27% (6%, 42%), and the death rate for selected cancer (combined liver and intrahepatic bile ducts, pancreas, endometrium, colon and rectum, breast, and bladder) decreased by 40% (9%, 60%) (both $p < 0.05$). Among U.S. adults with diabetes, cancer mortality rates are declining. Continued monitoring is needed to assess whether these trends persist over time.

1665-P

Characterizing the Prehospital Response to Diabetic Emergencies

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Pre-hospital diabetes-related emergencies represent an important part of the continuum of diabetes care. Understanding the prevalence of these emergencies is crucial to understanding the efficacy of patient education and home rescue medications. Using the National Emergency Medical Services Information System (NEMSIS) 2011 Public Release dataset, an analysis was conducted to determine the approximate number of diabetes-related 911 calls encountered by pre-hospital EMS each year. Given the database's 11,317,115 primary 911 responses (estimated to represent 40-45% of the actual total responses in the U.S.), it was estimated that 916,273 responses (3.64%) of all calls to 911 were diabetes related, based on dispatch complaint, provider impressions, and/or relevant Medicare condition code. Of these diabetes-related calls to 911, 669,270 (73.04%) resulted in transport to the hospital. Furthermore, as many as 222,991 (33.32%) of those transports received only Basic Life Support (BLS) level care, meaning that invasive treatments such as IV or IM treatments weren't initiated until reaching the emergency department based on various scope of practices for BLS personnel. The NEMSIS database, however, did not allow for differentiation between hyperglycemia- and hypoglycemia-related emergencies, as the database lacked blood glucose level measurements. Records with BGL measurements was obtained from the North Carolina Office of Emergency Medical Services (NC OEMS). Of the 430,623 runs included in the NC OEMS data, 41,174 were found to be diabetes-related (9.65%), and 16,551 (40.19% of

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all diabetes-related responses) were found to be hypoglycemia related. Extrapolating these numbers to the figures obtained earlier, this means as least 368,250 EMS responses (1.46%) annually would be related to hypoglycemia, with as many as 268,970 requiring transport to the hospital.

1666-P

Prevalence of Diabetes among Patients of Safety Net Clinics

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The demographic and socioeconomic characteristics of underserved populations are associated with increased risk of diabetes. Our objectives were to calculate the prevalence of diabetes in three networks of safety net clinics and describe the characteristics of these vulnerable patients.

The Accelerating Data Value Across a National Community Health Center NEtwork (ADVANCE) project is a Clinical Data Research Network comprised of the OCHIN Community Health Information Network, the Health Choice Network, and Fenway Health. Together, these three systems combine data from 97 Federally Qualified Health Center systems with 744 clinics serving approximately 1.6 million safety net patients, many of whom are uninsured. Using electronic medical record data that included visit diagnoses, laboratory results and pharmaceutical orders, we identified 273,835 adult OCHIN patients aged ≥20 years who had at least two visits to a participating clinic in 2012/2013. We defined diabetes as the presence of any two diagnostic events including a clinician-recorded diagnosis of diabetes (ICD-9-CM 250.xx), a diagnostic laboratory value (A1C ≥6.5%, fasting glucose ≥126mg/dl, random glucose ≥200mg/dl), or a prescription for an anti-hyperglycemic agent. We calculated diabetes prevalence overall and by age, sex, race/ethnicity and body mass index (BMI) categories.

Overall, diabetes was present in 16.4% of the study population. Prevalence was highest among older adults (30.5% of those ≥65 years) and race/ethnicity minority groups (18.9% among Hispanics, and 22.0% among non-Hispanic Blacks).) Approximately 50% of the total population was obese. Among patients with diabetes, 72% of whites and 70% of non-Hispanic Blacks were obese, compared with 64% of Hispanics.

The prevalence of diabetes among safety net patients is greater than in the general population, a difference that is driven by a larger proportion of minorities and greater obesity rates. Hispanics had higher rates of diabetes among those overweight but not obese.

1667-P

The SWEET SPOTS Study: A Real-World Interpretation of the 2012 ADA Position Statement Regarding Individualized A1c Targets

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The 2012 American Diabetes Association (ADA) position statement on the management of hyperglycemia in T2DM recommends patient-centered A1C goals based on clinical characteristics. Here we assess physician interpretations of individualized A1C targets based on real-world patient profiles.

In the Summarize Real-world Individualized Treatment Goals and Potential Support Systems in T2DM (SWEET SPOTS) study, patients identified from administrative claims in the HealthCore Integrated Research Environment (October 2012 to October 2013) were stratified into risk segments according to their clinical characteristics, and their treating physicians identified. Physicians were invited to participate in the study and those consenting completed online surveys on A1C targets and factors influencing target-setting, before and after receiving an educational intervention to review the 2012 ADA position statement.

Of 125 physicians who participated in the study (mean age 50 years, 58% group practice, 64% in practice ≥ 15 years, and 13% endocrinologists) and who were linked to 125 patient profiles (42% female, mean age 57 years, mean A1C 7.2%), 83% were somewhat aware of the position statement prior to the intervention and most (61% primary care physicians and 50% endocrinologists) believed it would impact how they set A1C targets. The educational intervention resulted in more stringent or looser goal-setting for lower or higher risk patients, respectively, but changes were not statistically significant. The proportion of physician-assigned targets that were within ADA-recommended ranges increased significantly.

This study found that although physicians treating T2DM are aware of the 2012 ADA position statement and state that it may influence treatment goals, patient-specific A1C targets were not significantly impacted. Further research into optimizing physician education regarding individualized A1C targets in T2DM patients is warranted.

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1668-P

Assessment of Kidney Dysfunction with Cystatin C- and Creatinine-based Estimated Glomerular Filtration Rate and Predicting Future Type 2 Diabetes among Japanese: Toranomon Hospital Health Management Center Study

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Although the prognostic value of the serum cystatin C level compared with the serum creatinine level has attracted attention worldwide, whether early stages of kidney dysfunction assessed by the estimated glomerular filtration rate from cystatin C measurements (eGFRCysC) rather than from creatinine measurements (eGFRCre) would more precisely reflect the risk of developing T2D has not been clarified. We therefore compared the risk of developing T2D associated with renal dysfunction indicated by eGFRCysC or eGFRCre measurements. Studied were 2,131 Japanese individuals without T2D. Hazard ratios (HRs) for the development of T2D over 3 to 5 y were calculated across categories of eGFRCysC and eGFRCre, respectively. Results showed that reduced levels of eGFRCysC were associated with a step-wise increase in the cumulative incidence rate of T2D (log rank test, p=0.007). We did not find such associations across eGFRCre categories. In comparison with the eGFRCysC >85th percentile group (≥117.4 mL/min/1.72m^2), the lowest group, which was the eGFRCysC <15th percentile group (<86.2 mL/min/1.72m^2), had an adjusted HR of 2.30 (95% CI 1.13, 4.68) for T2D. Compared with the eGFRCre >85th percentile group, the lowest eGFRCre group (<15th percentile) had an HR of 1.19 (0.63, 2.24) for T2D. On the other hand, individuals with eGFRCre <60 ml/min/1.72m^2 had a significantly increased risk of developing T2D. We also found that clustering of both low eGFRCysC and low eGFRCre further elevated the HR for T2D in comparison with the presence of either. In conclusion, the early stage of kidney dysfunction assessed by eGFRCysC rather than by eGFRCre would be a marker for predicting the development of T2D. Although mildly-to-moderately reduced levels of eGFR creatinine would also reflect a high risk of developing T2D, eGFRCysC in earlier stages of kidney disease might influence the development of T2D.

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1669-P

Short-Term Total Variability in Nontraditional Biomarkers of Hyperglycemia in Older Adults

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The short-term variability in nontraditional biomarkers of hyperglycemia is relatively uncharacterized. We included 174 ARIC participants (mean age, 76 years; 37% male; 27% black) who had two blood samples collected in 2011-13, 6 weeks apart. We compared 6-week variability in fasting glucose, HbA1c, fructosamine, glycated albumin, and 1, 5-anhydroglucitol (1, 5-AG) in persons with (n=61) and without diagnosed diabetes (n=113). We calculated the within-person coefficient of variation (CV_W), intraclass correlation coefficient (ICC), and Spearman's rank correlation coefficient (r). For all biomarkers, 6-week within-person variability, as measured by CV_w, was greater in persons with diagnosed diabetes (67% of whom took glucose-lowering medication at visit 5). HbA1c had the lowest variability in persons with and without diabetes (CV_W=4.1% and CV_W=3.4%, respectively), and was comparable to that of fructosamine and glycated albumin (Table). In persons with diabetes, the correlation of repeat measurements of 1, 5-AG was high (both ICC and r=0.93) but the within-person variability was also high (CV_w=20.7%) (Table). In persons without diabetes, HbA1c and nontraditional biomarkers of hyperglycemia track well over 6 weeks. In persons with diabetes, 1, 5-AG is highly variable, consistent with its biology as a marker of glucose excursions.

Table. Six-week total variability in traditional and nontraditional glycemic markers in persons with and without diabetes, the Atherosclerosis Risk in Communities (ARIC) Study 2011-2013, N=174.

	Mean* (SD)	CV_w† (95% CI)	ICC (95% CI)	Spearman's rank correlation coefficient (95% CI)
No Diagnosed Diabetes (N=113)				
Fasting glucose, mg/dL	104.3 (16.4)	6.3% (3.9, 8.1)	0.83 (0.76, 0.88)	0.66 (0.54, 0.75)
HbA1c, %	5.7 (0.4)	3.4% (0, 5.2)	0.75 (0.65, 0.82)	0.89 (0.85, 0.92)
Fructosamine, µmol/L	235.7 (21.7)	3.9% (3.3, 4.5)	0.84 (0.78, 0.89)	0.83 (0.76, 0.88)
Glycated albumin, %	13.5 (1.6)	3.7% (3.1, 4.2)	0.93 (0.90, 0.95)	0.89 (0.85, 0.93)
1,5-anhydroglucitol, µg/mL	17.1 (6.2)	6.8% (4.0, 8.7)	0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
Diagnosed Diabetes (N=61)				
Fasting glucose, mg/dL	136.2 (42.9)	14.9% (10.8, 18.1)	0.65 (0.47, 0.77)	0.76 (0.63, 0.85)
HbA1c, %	6.7 (1.2)	4.1% (2.0, 5.5)	0.94 (0.90, 0.96)	0.94 (0.90, 0.96)
Fructosamine, µmol/L	271.3 (48.4)	7.7% (4.7, 9.8)	0.79 (0.68, 0.87)	0.79 (0.67, 0.87)
Glycated albumin, %	16.4 (3.9)	8.7% (4.1, 11.5)	0.81 (0.71, 0.88)	0.90 (0.84, 0.94)
1,5-anhydroglucitol, µg/mL	13.5 (7.1)	20.7% (8.9, 27.8)	0.93 (0.89, 0.96)	0.93 (0.89, 0.96)

Abbreviations: CI, confidence interval; CV_w, within-person coefficient of variation; ICC, intraclass correlation coefficient; SD, standard deviation
*Overall mean, including both initial and repeat measurements
†CV_w was calculated as the square root of the within-person variance, divided by the mean squared.

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Epidemiology/ Genetics POSTERS

1670-P

Changes in Sex Hormone Binding Globulin and Incidence of Diabetes in the Diabetes Prevention Program

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Incident diabetes appears inversely related to plasma sex hormone binding globulin (SHBG) concentration in epidemiologic studies, but whether diabetes prevention interventions increase SHBG levels and if such an increase protects against diabetes onset is unknown. We examined effects of intensive lifestyle intervention (ILS) or metformin (MET) vs. placebo (PLB) on SHBG over the first year of the Diabetes Prevention Program (DPP), a randomized trial of people at high risk for diabetes. We also assessed whether treatment-related changes in SHBG levels at 1 year were associated with 3-year diabetes risk.

In multivariable linear regression models of changes in SHBG [mean (SHBG Year 1 - SHBG Baseline)], adjusted for several baseline variables, ILS resulted in greater 1-year changes in SHBG than PLB or MET in men, women, and postmenopausal women without hormone use (Table).

Table.

Variable	Males [M]		Premenopausal (no hormone use) [W]		Postmenopausal with no hormone use [PWN]		Postmenopausal with hormone use [PWH]	
	Beta Coefficient	p-value	Beta Coefficient	p-value	Beta Coefficient	p-value	Beta Coefficient	p-value
FPG	0.10	0.27	**0.40**	**0.04**	-0.09	0.55	-0.26	0.40
2-hr glucose	-0.01	0.77	-0.08	0.36	0.12	0.08	-0.03	0.80
Age	**-0.28**	**<.01**	**1.01**	**<.01**	0.19	0.14	0.26	0.42
Caucasian	2.34	0.12	-1.87	0.52	0.49	0.84	1.80	0.70
Smoking	0.18	0.95	1.96	0.72	1.01	0.83	-3.42	0.71
Alcohol	0.05	0.55	0.18	0.68	0.36	0.25	-0.58	0.18
Leisure activity	0.03	0.08	-0.03	0.72	-0.08	0.20	-0.11	0.31
Waist	-0.01	0.94	0.02	0.91	0.13	0.43	-0.35	0.27
BMI	-0.16	0.58	0.04	0.93	-0.49	0.15	0.49	0.44
1/Fasting Insulin	3.08	0.90	7.29	0.88	-24.28	0.50	-52.54	0.45
ILS vs. PLB	**3.93**	**0.02**	**11.53**	**<0.01**	**8.088**	**<0.01**	9.56	0.08
MET vs. PLB	-0.69	0.68	-1.30	0.71	-0.21	0.94	4.42	0.40
ILS vs. MET	**4.62**	**0.01**	**12.83**	**<0.01**	**8.30**	**<0.01**	5.14	0.32

These treatment effects did not produce consistent effects on diabetes incidence. Among M-PLB, each 10-unit increase in SHBG at 1 year was associated with a lower risk of diabetes at 3 years (HR 0.86, 95% CI 0.77, 0.97); SHBG changes were not associated with decreased diabetes risk in any other group.

In the DPP, ILS, but not MET, was associated with favorable changes in SHBG. SHBG changes were associated with reduced diabetes incidence in M-PLB only. Further study is needed to understand moderators of SHBG and effects of SHBG modification.

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1671-P

Difference in Contribution of Beta Cell Function and Sarcopenia in Developing Diabetes Mellitus between Old and Young Adults

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Although the prevalence of diabetes in the elderly population has been growing, very few have focused on clinical characteristics of elderly-onset diabetes mellitus. We aimed to investigate the difference in contributing factors in developing diabetes between old and young adults. We analyzed data from the 2008 - 2010 Korean National Health and Nutrition Examination Survey. In this nationwide survey, selected samples were weighted to represent the entire Korean population. We selected subjects with recent-onset diabetes (duration <5 years) and classified them according to age: elderly- (age ≥75 years), usual- (45 - 64 years), and early-onset group (25 - 39 years). The homeostasis model assessment of insulin resistance (HOMA-IR) and β-cell function (HOMA-β) were used to estimate insulin resistance and β-cell function, respectively. Sarcopenia was defined by appendicular skeletal mass/weight (%) less than 1 SD below the gender-specific mean for healthy young adults using dual-energy X-ray absorptiometry. Subjects with elderly-onset diabetes showed a significantly better HOMA-β [means (standard error) 82.4 (6.1)%] compared with those of the usual- [61.2 (2.9)%] and early-onset [63.1 (6.4)%] groups (P = 0.002). Elderly-onset group had significantly higher insulin resistance compared to the usual-onset group [HOMA-IR: means (standard error) 5.8 (0.7) vs. 4.4 (0.2), P = 0.017]. Prevalence of sarcopenia in each group was 66.0% in elderly-, 40.8% in usual- and 40.6% in young-age group. In the multivariate analysis, sarcopenia was significantly associated with the risk of diabetes in elderly-onset group (odds ratio 2.11, 95% confidence interval 1.18 - 3.76; P = 0.011) but not in the other age groups. Subjects with elderly-onset diabetes has significantly higher β-cell function compared to subjects with younger age-onset diabetes. Sarcopenia might be more important contributing factor in developing diabetes mellitus in old adults.

1672-P

Familial Clustering of Diabetes Predicts Type 2 Diabetes Risk More Strongly than Social Clustering of Obesity in the Framingham Offspring Study

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Obesity and family history of diabetes are the two strongest risk factors for type 2 diabetes (T2D). Prior work has shown that an individual's risk of obesity is influenced by his/her social contacts. We examined T2D clustering in a social network to estimate the influence of familial and non-familial social ties on T2D risk. We hypothesized that T2D risk is associated with social ties to people with T2D and with body mass index (BMI) of social contacts.

Administrative data identified interpersonal ties between Framingham Offspring Study participants at each of 8 exam visits from 1971 to 2008 (N=4837 participants). T2D status of each person (ego) and each social contact (alter) was defined as fasting glucose > 125 mg/dl or taking diabetes medications. We used generalized estimating equations clustered by ego to estimate associations between prevalent ego T2D and alter T2D or BMI across 8 exams, adjusting for ego's sex, age, BMI, self-reported T2D family history, count of 19 T2D common genetic variants, size of social network, and exam visit. Analyses were repeated in networks stratified by familial versus non-familial ties.

Ego T2D was associated with alter T2D (OR 1.43, p= .002) but not alter BMI (OR 1.01, p= .3). When stratified by ego-alter relationship, ego T2D was associated with familial alter T2D (OR 1.53, p= .02) but the effect was weaker

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for non-familial alter T2D (OR 1.32, p= .09). Adjusting for genetic risk attenuated the familial ego-alter T2D association (OR 1.40, p= .06) but marginally strengthened the non-familial ego-alter T2D association (OR 1.38, p= .05).

We found that T2D risk was shared across social ties, with a greater effect across familial than non-familial ties. Though obesity is known to be shared among social contacts, shared T2D risk was independent of shared obesity. Further analyses that account for ego education and interactions of genetic risk with relationship type are needed to fully characterize T2D risk in social networks.

1673-P

Risk for Type 2 Diabetes among Low Income Adults in the U.S. by Insurance Status

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The National Diabetes Prevention Program (NDPP) is an alliance of public and private organizations that aims to achieve wide-scale implementation and coordination of evidence-based lifestyle intervention programs to prevent type 2 diabetes in the United States. State health departments are working to increase the number of Medicaid enrollees participating in NDPP programs. Using data from 2,619 non-pregnant adults aged 20-64 years with family income ≤138% Federal Poverty Line who were not on Medicare in the 2007-2012 U.S. National Health and Nutrition Examination Surveys, we estimated the proportions of low income adults at high risk for type 2 diabetes by self-reported insurance status: those having Medicaid coverage, those currently uninsured persons who would be potentially eligible for Medicaid or subsidized private insurance under the Affordable Care Act (hereafter called "those eligibles"), and those having private insurance. At high risk for diabetes was defined as meeting the American Diabetes Association (ADA) criteria for screening for type 2 diabetes (persons age ≥45 years, or body mass index ≥25 kg/m^2 plus ≥1 additional risk factor). We also estimated prevalence of prediabetes in a fasting subsample (n=950), defined as those with fasting plasma glucose (FPG) level 100-125 mg/dl or elevated A1C level 5.7%-6.4%. Among adults on Medicaid (n=526), 47.2% (95% confidence interval 36.6 - 57.8%) had prediabetes and 72.8% (67.1-78.5) were at high risk for diabetes. Among eligibles (n=1,270), 37.8% (31.3-44.2) had prediabetes, and 67.0% (95% CI 63.9-70.1) were at high risk. Among privately-insured low-income adults (n=823), 28.7% (20.1-37.4) had prediabetes and 55.2% (45.5-65.0) were at high risk (p<0.05 compared with those on Medicaid and eligibles). Our results indicate that a large proportion of U.S. adults on Medicaid or potentially eligible for Medicaid or subsidized private insurance were at high risk for diabetes and could likely benefit from diabetes primary prevention efforts.

1674-P

The Rate of Growth in Diagnosed Diabetes Prevalence in U.S. Counties Slowed between 2004-2008 and 2008-2012

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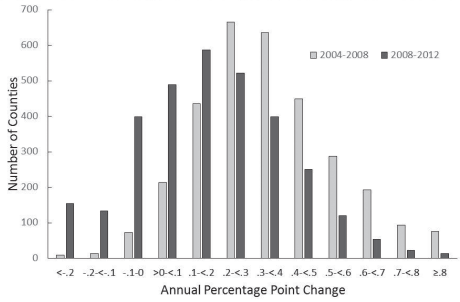
A recent study using nationally representative data suggested that the rate of increase in the prevalence of diagnosed diabetes in U.S. adults leveled off or slowed in 2008. We used publically available county estimates of diagnosed diabetes prevalence (based on state representative survey data of adults aged ≥ 18 years (*http://www.cdc.gov/diabetes/atlas/countydata/County_ListofIndicators.html*) to examine whether a slowing or leveling off is also evident across 3143 U.S. counties. For each county, we estimated the average annual percentage point change (APPC) in age-adjusted prevalence within two time periods - 2004-2008 and 2008-2012. To estimate APPC, we used multilevel regression that included random effects by county and year. Cubic splines were used to smooth the estimates over time. The distribution of county APPCs for 2008-2012 is to the left of the 2004-2008 distribution (Figure), indicating that the growth in prevalence was lower in 2008-2012 than in 2004-2008. The median APPC for counties in 2008-2012 (0.16) was half the median APPC in 2004-2012 (0.32). Southern and Appalachian counties which had high rates of diabetes and high APPCs in 2004-2008 tended to have low APPCs in 2008-2012. In summary, our county level data suggest a potential slowing in the diabetes epidemic which is particularly encouraging for counties known to be disproportionately burdened by diabetes.

Distribution of Annual Percentage Point Change, US Counties, 2004-2008 and 2008-2012



1675-P

Excess Risk of Dying from Infectious Causes in Those with Type 1 and Type 2 Diabetes

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To investigate infection-related mortality in individuals with type 1 and type 2 diabetes.

A total of 1,108,996 individuals with diabetes who were registered with the Australian Diabetes register between 2000 and 2010 were linked to National Death Index. Mortality outcomes were defined as infection-related$_{A-B}$ death (ICD 10 codes: A99-B99), pneumonia (J12-J189), septicemia (A40 & A41), and osteomyelitis (M86). Standardised mortality ratios (SMRs) and 95% confidence intervals (CI).

During a median follow-up of 6.7 years, there were 2,819, 2,164, 1,248 and 147 deaths from infection-related$_{A-B}$ causes, pneumonia, septicemia, or osteomyelitis, respectively. Crude mortality rates from infections$_{A-B}$ were 0.147 and 0.431 per 1000 person-years in type 1 and type 2 diabetes, respectively. For infection-related$_{A-B}$ mortality SMRs were 4.42 (95% CI: 3.68 - 5.34) and 1.47 (1.42 - 1.53) for type 1 and type 2 diabetes, respectively. For pneumonia in type 1 diabetes, SMRs were approximately 5 and 6 in males and females, respectively while the excess risk was around 20% for type 2 (both sexes). For septicemia, SMRs were approximately 10 and 2 for type 1 and type 2 diabetes, respectively, and similar by sex. For osteomyelitis in type 1 diabetes, SMRs were 16 and 58 in males and females, respectively, and around 3 for type 2 diabetes (both sexes).

Although death due to infection is rare, we confirm that diabetic patients have an increased mortality from a range of infections, compared to the general population, and that the increased risk appears to be greater for type 1 than type 2 diabetes.

1676-P

Assessing Current Glycemic Control in Newly Diagnosed Diabetes Patients in China

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NEW2D study was a prospective and longitudinal cohort study to investigate initial treatment pattern and treatment evolution during the course of the disease and clinical outcomes in newly diagnosed T2DM patients in China. Patients >20 years old and had T2DM diagnosis <6 months were recruited and followed up to 36 months. Physical examinations and lab tests information were obtained from patients' medical record. We report the one-year result of this study.

A total of 5985 patients from 81 hospitals nationwide were recruited in 2013. The patient proportion of reaching glycemic control measured by Hemoglobin A1c (HbA1c) <6.5% was 25.4% at baseline and 47.0% at 12 month. At the baseline, 39.5% patients received oral hypoglycemic agents (OHA) alone,17.9% received insulin alone or with OHA(s), and 42.6% received none. At 12 month, the patients received OHA(s) alone, insulin alone or with OHA(s), and none were 58.1%, 19.2% and 22.7%, respectively. Multivariate analyses showed that the proportions of reaching HbA1c target were significantly increased over-time (p<0.001). Meanwhile, patients were less likely to achieve HbA1c <6.5% if: Age ≥65y (p<0.05), body mass index ≥28 kg/m2 (p<0.001), current smoker (p<0.001) and no exercises (p<0.05). Patients receiving insulin alone (p<0.0001), or insulin with one OHA (p<0.0001) had lower possibility of reaching HbA1c target compared to no treatment.

Nearly half of newly diagnosed patients did not reach stringent HbA1c control target in this population after one-year treatment. The study demonstrates the gap between the guideline recommendations and the actual management. Lifestyle changes and medication optimizations need to be set as priority in newly diagnosed T2DM patients.

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1677-P

Association of Payment Source with Emergency Department Use by Patients with Diabetes in the United States

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Accurate population-based estimates of Emergency Department (ED) use by patients with diabetes is important for understanding the healthcare burden. We used data from the 2009 and 2010 National Ambulatory Medical Care Survey (NAMCS) and the National Hospital Ambulatory Medical Care Survey (NHAMCS) to examine the likelihood of ED visits by patients with diabetes according to payment source. We analyzed Patient Record Forms completed by trained surveyors that provided information on patient sociodemographic factors, diagnoses, and medical care from medical records. We selected patients ≥18 years of age with diabetes as ascertained by the question "Does the patient have diabetes?" Among 22,261 visits (15,010 from NAMCS and 7,251 from NHAMCS) made by patients with diabetes, we identified 5,700 ED visits in the surveys, esimating 21.8 million (S.E. 1.4 million) ED visits made by patients with diabetes in the U.S. over two years. Mean ages (±SD) were 59.0 (± 0.3) and 62.2 (±0.3) for patients making ED and non-ED visits, and 57% and 54% of the patients were female, respectively. Using a univariate logistic regression model, odds of ED visits among patients with self-pay was 6.9 times higher (95% CI: 5.2, 9.2) compared to those with private insurance. Similarly, odds of ED visits among those with Medicaid were 3.5 times (2.8, 4.2) and Medicare 1.7 times (1.5, 2.0) higher compared to those with private insurance. After adjusting for age, sex, race/ethnicity, income, education, region, and rural/urban status, the odds of ED visits for those with self-pay, Medicaid, and Medicare compared to those with private insurance remained significant: odds ratio 5.4 (4.7, 6.2), 2.5 (2.1, 2.8), and 1.8 (1.6, 2.0), respectively. In conclusion, payment source is a strong predictor of the likelihood of ED visits. Other research suggests that this effect is mediated by differences in access to or quality of outpatient care.

1678-P

Intensity of Glycemic Treatment among U.S. Adults with Diabetes, 1999-2012

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Recent guidelines for glycemic control emphasize individualized A1c targets. Life expectancy is a major factor to consider since the benefits of intensive glucose control emerge over decades. However, the effect of these new guidelines on treatment practices and A1c levels in the U.S. population is unknown. Cross-sectional data from the National Health and Nutrition Examination Study were used to determine the extent to which older adults are intensively treated to lower A1c levels and whether this practice has changed during 1999-2012. Participants were adults age ≥20 years who self-reported a physician diagnosis of diabetes (n=1,333, NHANES 1999-2004; n=1,128, NHANES 2005-2008; n=1,313, NHANES 2009-2012). The use of any diabetes medication and mean A1c were determined among adults with diabetes by age, a surrogate for life expectancy. In 2009-2012, 89.2% of adults with diabetes age ≥65 were taking any type of diabetes medication and 62.2% were taking insulin and/or sulfonylureas, compared to 77.3% and 44.5% of adults age 20-49, respectively (both $p<0.05$). The higher prevalence of medication use in older vs. younger adults was stronger in those achieving A1c<7.0%. More than half (52.0%) of adults age ≥65 with an A1c<7.0% were taking insulin and/or sulfonylureas compared to 20.6% with A1c<7.0% age 20-49. In addition, among adults taking insulin and/or sulfonylureas, mean A1c was lower (7.3%) for adults age ≥65 compared to those age 20-49 (8.3%, $p<0.001$). Insulin and/or sulfonylurea use decreased significantly over time among adults age 65-74, but not among the elderly as a whole (age ≥65). There were few differences over time in the prevalence of use of any medication, and none in mean A1c, regardless of age. National data on glycemic medication use and A1c levels do not align with current guidelines that focus on life expectancy as an important factor in setting glycemic targets. Physicians should carefully consider the risks/benefits of tight glycemic control and intensive medication use in older patients.

1679-P

Prevalence of Thyroid Dysfunctions in Prediabetes

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Using data from the recent adult population-based survey in Turkey (n=26,499, 63% female) we aimed to evaluate the thyroid status of individuals with different categories of prediabetes including Isolated IFG (n=3,123), Isolated IGT (n=1,663), Combined IFG+IGT (n=1,705), and High Risk A1C (n=6,696).

Although the mean (SEM) concentrations of FT4 and TSH did not differ across the groups, in the combined IFG+IGT group the mean Anti-TPO level was numerically, and Anti-Tg level was remarkably higher than the other groups (p=0.003). This was not changed when the data were adjusted for age, gender, BMI, lipids, and known thyroid diseases. Anti-Tg levels were positively correlated with OGTT-2hPG and negatively correlated with fasting insulin.

The prevalence of overt and subclinical hypo and hyperthyroidism, and positive Anti-TPO and Anti-Tg antibodies are shown in the Table.

Table.

Prediabetes Category	Prevalence of Thyroid Dysfunctions (%)					
	Hyperthyroidism		Hypothyroidism		Anti-TPO (+)	Anti-Tg (+)
	Overt	Subclinical	Overt	Subclinical		
Isolated IFG	0.5	0.5	0.9	3.4	11.7	13.5
Isolated IGT	0.8	0.6	1.4	3.1	11.8	13.8
Combined IFG+IGT	0.6	0.9	1.5	4.2	14.4	16.3
High Risk A1C	0.5	0.6	1.6	3.2	11.7	13.6

In terms of individual dysfunctions, there was no difference across the prediabetes categories except higher frequency of positive Anti-Tg in "IFG+IGT" ($p<0.001$). However, of the combined IFG+IGT group, 21.6% had at least one thyroid dysfunction, and this was significantly higher than in the other categories (Isolated IFG: 17, Isolated IGT: 17.7, and High Risk A1C Group: 17.6%, $p<0.001$).

In conclusion, thyroid diseases are common among persons with prediabetes. Anti-Tg but not Anti-TPO is associated with glucose metabolism. Combined IFG+IGT category may be the most vulnerable group.

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1680-P

Pregnancy-induced Hypertension and Postpartum Hypertension on the Risk of Diabetes among Gestational Diabetes Women

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Women with a history of pregnancy-induced hypertension or gestational diabetes mellitus (GDM) have a higher risk for postpartum diabetes. We aimed to examine the association of pregnancy-induced hypertension and postpartum blood pressure with postpartum diabetes risk among women with a history GDM. We conducted a population-based study among 1263 GDM women at 1-5 years after delivery in Tianjin, China. Logistic regression or Cox regression was used to assess the associations of pregnancy-induced hypertension and postpartum blood pressure with postpartum pre-diabetes and diabetes risks. GDM women who had a history of pregnancy-induced hypertension but did not use antihypertensive drugs during pregnancy had a 4.24-fold higher risk (95% CI: 2.13-8.47) of developing diabetes compared with those who were normotensive in index pregnancy. Compared with GDM women who had normal blood pressure at postpartum, hypertensive women at postpartum were 3.55 times (95% CI: 1.76-7.13) and 2.97 times (95% CI: 1.75-5.05) more likely to develop diabetes and prediabetes, respectively. The odds ratios of postpartum diabetes and prediabetes associated with each 10 mmHg increase in systolic blood pressure were 1.27 (95% CI: 1.06-1.54) and 1.20 (95% CI: 1.06-1.35). Each 10 mmHg increase in diastolic blood pressure contributed to a 1.52-fold higher risk (95% CI: 1.20-1.91) for postpartum diabetes and a 1.42-fold higher risk (95% CI: 1.22-1.65) for postpartum prediabetes. For women with prior GDM, hypertension during the index pregnancy and postpartum were risk factors for postpartum type 2 diabetes.

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For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1681-P

WITHDRAWN

1682-P

All-Cause and Diabetes-specific Hospital Readmissions among Adults with Diabetes, 2007-2012

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Hospital admissions and readmissions are common among patients with diabetes and incur substantial personal, societal, and economic burden. However, little is known about the causes of hospitalization among these patients, particularly for acute diabetes complications (ADCs). We used claims from Optum Labs Data Warehouse (OLDW), an administrative dataset of commercially insured and Medicare Advantage individuals across the U.S. Our study population included adults ≥18 years of age with established diabetes who were admitted to the hospital for any cause between January 1, 2007 and December 31, 2012. We examined the most common causes for hospital admissions and readmissions, including the proportion due to ADCs. We quantified unplanned readmission rates within 30 days of discharge; and used logistic regression to identify comorbidity-adjusted risk factors for these readmissions. During these 5 years, there were 471,196 index admissions among 295,806 patients; mean age on admission 66.5 years (SD, 12.7). ADCs accounted for 3.6% of admissions, ranking fourth after heart failure, coronary atherosclerosis, and osteoarthritis. All-cause readmission rate was 18.9%, and 3.4% of readmissions were for ADCs. All-cause readmission occurred after 26.3%, 16.4%, 10.6%, and 19.1% admissions for heart failure, coronary atherosclerosis, osteoarthritis, and ADCs, respectively. Higher comorbidity burden, type 1 diabetes, prior ADC hospitalization, and insulin use were all associated with increased odds of all-cause and ADC-specific readmission (all $p<0.001$). Thus, in this national cohort of adults with diabetes, nearly 20% of all admissions resulted in hospital readmission within 30 days of discharge. The vast majority of readmissions were not related to diabetes or to the cause of proximal admission. Multimodal strategies that do not focus exclusively on a single disease or risk factor are therefore needed to reduce admissions and readmissions in this high risk group.

1683-P

The Effect of IV Contrast on Renal Function in Patients on Metformin with Decreased eGFR

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Given the concern for acute kidney injury (AKI) with intravenous (IV) contrast and theoretical risk of lactic acidosis with metformin use in the setting of AKI, the Food and Drug Administration mandates that metformin be discontinued for two days post-contrast and kidney function retested prior to resuming metformin. However, little evidence supports this practice. We are conducting a retrospective cohort study of patients at the San Francisco Veterans Affairs Medical Center to determine if there is a change in kidney function in patients on metformin with estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73m^2 who receive IV contrast. Of the 35 patients identified thus far, mean age is 71±8 years, 31 (89%) are male, and 18 (51%) are Caucasian. Mean pre-contrast creatinine (Cr) was 1.29±0.13 mg/dL and post-contrast Cr was 1.25±0.14 mg/dL; p=0.14 (overall t-test). Mean pre-contrast eGFR was 54±6 ml/min/1.73m^2 and post-contrast eGFR was 59±19 ml/min/1.73m^2; p=0.04 (overall t-test). To assess whether IV contrast and pre-contrast Cr (or eGFR) were associated with a change in kidney function, generalized linear models were developed. Covariates included: age, sex, ethnicity, body mass index, diabetes duration, hemoglobin A1c; presence of albuminuria, hypertension, cardiovascular disease, heart failure, cirrhosis; and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and non-steroidal anti-inflammatory drugs. In fully-adjusted models, there was no significant change in Cr: β-coefficient -0.67 (95% confidence interval [CI] -1.37 to 0.02), p=0.06. And there was no significant change in eGFR: β-coefficient -0.67 (95% CI -1.73 to 0.40), p=0.22. Findings should be confirmed in larger studies. Our findings suggest that the current practice of holding metformin for two days after IV contrast should be re-evaluated as there was no significant change in kidney function even in a higher risk group of outpatients on metformin who received IV contrast.

1684-P

Antiplatelet Agents for Primary Prevention of Stroke and Myocardial Infarction in Japanese Diabetic Patients with Carotid Artery Plaque

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Low-dose aspirin is recommended for primary prevention of cardiovascular disease (CVD) in patients with diabetes mellitus (DM) who are considered at high risk in U.S. but not in Europe. Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) trial showed that aspirin was not effective for primary prevention of CVD in patients with DM in Japan. The use of aspirin therapy in DM patients for primary prevention of CVD remains controversial. Reports of the use of antiplatelet agents (APA) for primary prevention of CVD or stroke (S) in DM patients who have carotid artery plaques (CAP) are limited. We therefore retrospectively investigated the association between APA and myocardial infarction (MI) or S in DM patients with CAP.

We evaluated 246 Japanese DM patients (men 140, age 64±10 years) with at least one CAP detected by carotid artery ultrasound from 2007 to 2012. We excluded patients with a past history of CVD or S. The median follow-up period was 3.7 years. In patients on APA, there were no significant differences in the occurrence of MI and S, or either MI or S compared with patients who were not taking APA as determined by the Kaplan-Meier method. On the other hand, in patients with carotid arterial stenosis (CAS) of 40% or above, those on APA had a significantly lower incidence of S and either MI or S (log-rank p=0.046 and p=0.040, respectively). The follow-up period and family history of either MI or S were significantly associated with occurrence of either MI or S on univariate logistic regression analysis, and both remained significantly associated with either MI or S (follow-up months, p=0.006; family history, p=0.005) on multivariate logistic regression analysis. MI significantly correlated with maximum intima-media thickness (p=0.005) and HbA1c (p=0.007), and S significantly correlated with the follow-up period (p=0.031).

We conclude that APA is effective for primary prevention of S and MI in DM patients with CAS.

1685-P

Predictors of Remission of Type 2 Diabetes following a Short-Term Intensive Metabolic Intervention

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Recent evidence suggests that short-term intensive treatment with insulin or oral diabetes medications can induce remission of early type 2 diabetes. We analyzed predictors of diabetes remission following a short-term intensive metabolic intervention comprising lifestyle interventions, insulin glargine, metformin and acarbose.

Eighty three patients with type 2 diabetes diagnosed within 3 years prior to enrollment were randomized to (i) an 8-week intensive metabolic interven-

tion, (ii) a 16-week intensive metabolic intervention, or (iii) standard diabetes therapy, and followed for 28 weeks. After the short-term intensive intervention was completed, the diabetes medications in the intervention groups were discontinued and participants followed for hyperglycemia relapse. Diabetes remission was defined as HbA1C<6.5% off chronic diabetes drugs.

Twelve weeks after stopping diabetes medications, 21.4% of patients (RR 1.50, 95% CI 0.47-4.74) in the 8-week intervention group and 40.7% (RR 2.85, 95% CI 1.03-7.87) in the 16-week group were found to have diabetes remission compared to 14.3% in the control group. Shorter duration of diabetes (adjusted OR of remission 0.84, 95% CI 0.76-0.94 per 10-month increase), lower baseline fasting plasma glucose (OR 0.49, 95% CI 0.26-0.94 per 1 mmol/L increase) and percent weight loss from baseline at 16 weeks after randomization (OR 1.37, 95% CI 1.02-1.83 per 1% weight loss) were found to be significant independent predictors of remission.

This study demonstrates that shorter duration of diabetes, lower baseline fasting plasma glucose and percent weight loss from baseline are important independent predictors of diabetes remission following a short-term intensive metabolic intervention.

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1686-P

Missing Oral Antihyperglycemic Drug Data in Large Claims Databases

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Missing and misclassified data is an important limitation of claims databases. Missing prescription data has become an increasing concern since the inception of low-cost generic programs in 2006, as patients may obtain inexpensive prescriptions outside of their pharmacy benefit.

This study examined the potential for missing data in initiators of oral antihyperglycemic drugs in Marketscan claims data. Patients with type 2 diabetes Mellitus (T2DM) having apparent new prescriptions of thiazolidinedione (TZD) were compared to those with new prescriptions of metformin (MET) monotherapy. Unlike MET, TZDs are rarely used as monotherapy for T2DM and are not part of low-cost generic programs. Frequency of hemoglobin A1c (A1C) tests in the year prior to treatment initiation were summarized for new users of TZD monotherapy, TZD combination therapy, and MET monotherapy for the entire study period (2004-2012), and in 2004-2007 and 2008-2012. If new users of TZD monotherapy were true monotherapy users, we expected similar patterns of A1C testing between TZD and MET monotherapy groups.

We identified 208,436 new TZD users, aged 25-64, of whom 159,924 (76.7%) were monotherapy users; 644,407 new users of MET were identified. In the year prior to treatment initiation, 21.7%, 14.7%, and 11.9% of TZD monotherapy, combination therapy, and MET monotherapy, respectively, received 3 or more A1C tests. Time trends also show greater discrepancy between therapy groups in 2008-2012 (27.4%, 17.2%, and 12.4% for TZD monotherapy, TZD combination, and MET, respectively) compared with 2004-2007 (17.4%, 13.1%, and 10.8% for TZD monotherapy, TZD combination, and MET, respectively).

In conclusion, TZD monotherapy users consistently demonstrated more frequent A1C testing prior to initiation compared with TZD combination and MET monotherapy users, suggesting that some TZD monotherapy new users identified in claims data may have been on prior treatment for T2DM. This potential for misclassification needs to be further explored.

1687-P

Obstructive Sleep Apnea (OSA) in Asian Type 2 Diabetes Patients: Prevalence and Impact on Glycemic Control

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OSA is a risk factor of insulin resistance and type 2 diabetes. The prevalence in T2DM patients ranged from 58-86%, mostly in Western countries. OSA severity correlated with glycemic control in some studies. The data in Asian population are lacking. With a growing diabetes epidemic in Asia, we conducted a cross-sectional study to determine the prevalence of OSA and its impact on glycemic control in Asian T2DM patients.

Eighty-one patients were interviewed for their diabetes history. Medical records were reviewed for most recent HbA1c values, medication use, and history of retinopathy or nephropathy (eGFR<60 or albuminuria). OSA was screened using an overnight in-home monitoring device (Watch-PAT200).

Participants' mean age was 57.1±11.3 yr and mean BMI was 27.6±5.3 kg/m2. The prevalence of OSA [apnea-hypopnea index (AHI) ≥5] was found to be 77.8%, with 32.8%, 24.6%, and 14.8% had mild (AHI 5-<15), moderate (AHI 15-<30) and severe OSA (AHI≥30), respectively. The OSA group had a significantly higher BMI (29.0±4.8 vs. 25.8±4.3 kg/m2, p=0.01), longer diabetes duration (11.8±9.6 vs. 5.9±4.8yr, p<0.01) and poorer glycemic control [median HbA1c (IQR) 7.21 (6.74- 8.11) vs. 6.78 (6.23-7.43)%, p=0.05] than the no-OSA group, while there were no differences in age, sex, needs for insulin treatment, rates of retinopathy or nephropathy between the two groups.

After adjusting for age, sex, BMI, diabetes duration and insulin use, higher AHI independently predicted the chance of having a poor glycemic control (HbA1c ≥7%) (B 1.067, 95% CI 1.006-1.132, p=0.03). Each one point increase in AHI corresponds to a 6.7% increase in chance of having a HbA1c ≥7%. In addition, a robust regression analysis adjusting for the same covariates revealed that higher AHI was independently associated with higher HbA1c level (p=0.03).

In summary, OSA in Asian type 2 diabetes patients is highly prevalent, similar to that of the Western population. Severity of OSA is independently associated with poor glycemic control.

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1688-P

Nonalcoholic Fatty Liver Disease but Not Alcohol-associated Fatty Liver Disease Is a Significant Risk Factor for the Onset of Impaired Fasting glucose among Men

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Background: Fatty liver is associated with glucose intolerance and hepatic insulin resistance. The effect of alcohol consumption on the onset of glucose intolerance is controversial, and no previous studies have showed that fatty liver predicts the onset of glucose intolerance according to the amount of alcohol consumption. This study examines the potential relationship between fatty liver disease and the onset of impaired fasting glucose as stratified by the amount of baseline alcohol consumption.

Methods: We enrolled 6,403 persons (3,194 men and 3,209 women) between 18-80 years old who had >2 annual check-ups from 2003-2010. After excluding persons with fasting plasma glucose levels ≥110 mg/dl and those who were currently taking anti-diabetic agents, the remaining 5,924 subjects were classified into two groups based on alcohol consumption: less than 20 g/day (non-alcoholic group) and more than 20 g/day (alcohol-associated group). The onset of impaired fasting glucose was defined as fasting plasma glucose ≥110 mg/dl during the observation period. Fatty liver was identified by ultrasonography.

Results: In the non-alcoholic group and the alcohol-associated fatty liver disease group, 5.5% and 6.7% of the men, and 1.6% and 3% of the women developed impaired fasting glucose (IFG), respectively. Fatty liver was positively associated with the onset of IFG in males with non-alcoholic fatty liver disease (NAFLD) (adjusted hazard ratio, 2.255; 95% CI, 1.367-3.788, P = 0.001) after adjusting for previously reported risk factors for IFG. However, males with alcohol-associated fatty liver disease and females with either type of fatty liver disease did not show such an association.

Conclusions: NAFLD but not alcohol-associated fatty liver disease among men is a significant risk factor for the onset of impaired fasting glucose, suggesting the need to consider additional etiologies of fatty liver disease in clinical practice.

1689-P

Estimation of the Prevalence of Genetic and Acquired (non-HIV-associated) Lipodystrophies in the U.S. Using Electronic Medical Record (EMR) Data

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The prevalence of lipodystrophy (LD) in the general population is difficult to estimate due to its rarity, extensive genetic and phenotypic heterogeneity, and problems in recognizing some of its forms. As a result, prevalence must be estimated based on small numbers of patients identified in any given sample. Furthermore, calculated prevalence is expected to be sensitive to patient sampling methodologies, projection assumptions, and data source.

In the first analysis of its kind, a retrospective cohort study design was used to estimate the prevalence of genetic and acquired (non HIV associated) LD using EMR data and physician notes from a large national network of U.S. providers from 2000-2014. Diagnostic criteria including an ICD-9-CM code 272.6 for LD and text strings available in physician notes were used with expert clinical review to identify and classify diagnosed patients by types of LD.

For author disclosure information, see page A810.

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Of approximately 17 million patients in the EMR database, 1,606 had an ICD-9-CM diagnosis indicating LD and no evidence of HIV (prevalence: 94/1,000,000). Upon detailed review of physician notes by two clinical experts, 3 patients were classified as having congenital generalized LD, 41 were classified as familial partial LD, 5 as acquired partial LD, and the remainder as localized LD or unable to be classified due to non-specific physician notes. Among the 49 with congenital generalized or partial forms of LD (prevalence: <3/1,000,000), 72% had high triglyceride values (>200 mg/dL), and 69% had a diagnosis of type 2 diabetes.

Through a detailed review of EMR data and physician notes, over 80% of patients with a diagnosis indicating LD could not be classified due to non-specific physician notes. Efforts aimed at training physicians to recognize and properly document lipodystrophic syndromes and to standardize coding of these syndromes in EMR data would be beneficial to understanding the true prevalence of these unique syndromes.

1690-P

Metformin Use and Breast Cancer Stage At Diagnosis

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Metformin use may be associated with a reduction in breast cancer risk and mortality among women with diabetes. Some studies have suggested that metformin may also impact breast cancer stage and molecular subtypes, however results from these studies have been inconsistent and limited by small sample sizes and incomplete drug data. The objective of our study was to examine the association between metformin use and breast cancer stage in older women with diabetes. We used population-based data from Ontario, Canada to identify women over age 68 with diabetes who were diagnosed with breast cancer between 2007 and 2013. Using multivariate logistic regression models adjusting for demographic factors, comorbidity, and mammography, we explored the association between metformin within three years of breast cancer diagnosis with the likelihood of early (I-II) vs. late stage (III-IV) breast cancer. We also explored the association between metformin use and estrogen receptor (ER) status, tumour size and lymph node status. Among 3125 women with diabetes and breast cancer, mean age at breast cancer diagnosis was 77.2 (+/-6.4) and mean duration of diabetes was 8.8 (+/- 5.9) years. Prior to cancer diagnosis, 1519 were metformin users and 1606 were non-metformin users. There was no significant association between metformin use and stage of breast cancer (adjusted OR 0.96, 0.78-1.17), and this finding did not change for cumulative use of metformin. We also found no association between metformin use and likelihood of an ER+ tumour, presence of positive lymph nodes or larger tumour size.<br In conclusion, we did not find an association between metformin use and breast cancer stage or subtype among older women with diabetes. Our findings do not support a role for metformin use in reducing the growth or aggressivity of breast tumors before diagnosis in women with diabetes. However, these findings are limited to older women, and further research may be warranted to explore this association among younger women or those with shorter duration of diabetes.

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1691-P

Hospital Incidental Diagnosis of Diabetes: A Population Study

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Hyperglycemia and incidentally diagnosed diabetes (IDD) after hospital admission are known predictors of poor prognosis. Characterization of IDD as well as further associated risk of mortality are, however, still unclear. The present study was aimed at characterizing IDD and comparing the associated mortality risk with that of patients with known diabetes (KD). Diagnosis of IDD was retrospectively done by a new method, considering patients discharged by hospitals of Tuscany, a region of central Italy numbering about 3,700,000 inhabitants, in year 2011 (n=214,991) with no history of past discharges with main or secondary diagnosis of diabetes, no trace of previous glucose-lowering drugs (GLD) prescription, and who were given, after discharge, at least two GLD prescriptions: the first within 30 days and the second over the next 6 months. Two-year adjusted mortality risk, expressed as hazard ratio (HR), was tested by a Cox regression analysis, comparing IDD subjects alive on 1st January 2012 (n=863) and KD patients with at least one hospital admission in 2011 (n=31,710). IDD was diagnosed in 974 individuals with an age-and-sex standardized rate of 3.75 cases per 1,000 hospitalized subjects. Male sex, ageing, non-Italian citizenship (in 4.5% of total IDD), higher Charlson co-morbidity index in previous hospitalizations and non-adherence by family physicians to standardized guidelines in delivering diabetes care, were associated with higher IDD risk. Two-year mortality risk, adjusted for age, sex, co-morbidity index, and adherence by family physicians to standardized guidelines in care delivering, was about 20% higher in IDD than in patients with known diabetes (HR: 1.20; 95% CI: 1.01-1.41; p=0.033). In conclusion, in our population IDD was related to older age, male sex, history of previous more co-morbidities, non-Italian citizenship, and physicians' non adherence to shared common guidelines. Finally, as compared with matched KD individuals, IDD was associated with a significantly higher adjusted mortality risk.

1692-P

A Readmission Risk Prediction Model for Patients with Diabetes in a Rural Integrated Health System

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Hospital readmission within 30 days of discharge (early readmission, ER) is a high-priority quality measure and target for cost reduction. A method to predict ER risk of diabetic patients in a rural setting is lacking. We conducted a retrospective cohort study of adult patients with diabetes discharged from a hospital in a rural integrated health system between 1/1/2005 and 4/30/2013. Diabetes was defined by a primary or secondary discharge ICD-9-CM code of 249.xx, 250.xx or 357.2. Index discharges were excluded for patient age <18 years, transfer to another hospital, inpatient death, or discharge from an obstetric service. We constructed a predictive model for all-cause ER by multivariable logistic regression. Among 27,789 unique patients, there were 56,261 index discharges of which 8,741 (15.5%) were associated with ER. We considered a total of 56 variables across several domains (sociodemographics, laboratory results, medications, utilization, and medical conditions). The following predictors of ER were retained in the model ($p<0.05$): age at admission, history of heart failure, DKA/HHS, or drug abuse, number of outpatient visits in the past 180 days, whether or not the admission was the 30 day readmission of a prior discharge, prior ED admissions in the past 180 days, prior inpatient admissions in the past 180 days, admission source (emergency department, unplanned outpatient, scheduled or transfer), length of hospital stay, pre-admission insulin or steroid use, serum albumin, hemoglobin, sodium, and estimated glomerular filtration rate. C-statistic is 0.68. ER risk in the highest tertile was 25.6%, accounting for 54.6% of all ER. This model may predict ER risk of adult diabetic patients in a rural setting and may be useful to target discharge-support resources to those at higher risk. Prospective studies are needed to test the utility of this model in rural and other health care settings.

1693-P

Changes in the Lifetime Risk of Diabetes and Cancer, 1995-2012

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It is known that persons with diabetes have a higher risk of cancer then persons without; for all cancers about 20% higher incidence rates. This study quantifies the lifetime risk of diabetes and cancer in Denmark, and describes how these have changed in the last decades.

The Danish National Diabetes Register, Cancer Register and Central person register (for all deaths) were merged for the period 1995-2011. Incidence rates of diabetes and cancer as well as mortality rates, both for persons with and without diabetes and/or cancer were modelled using Poisson models with continuous effects of age and date of follow-up and date of birth. The estimated rates were used in a multistate Markov model to assess the lifetime risk of diabetes, cancer as well as both diseases jointly.

Incidence rates of diabetes increased 4% per year and cancer incidence rates 2% per year in the study period, whereas mortality rates decreased 4% per year, largely independent of disease status. The lifetime risk of diabetes increased from 20% (M:22.1,F:20.7) in 1995 to about 40% (M:42.9,F:38.9) i 2012, whereas the lifetime risk of cancer increased from 34% (M:32.7,F:35.2) to 55% (M:56.8,F:53.4). The lifetime risk for both diseases increased from 6% (M:5.8,F:5.4) to some 20% (M:22.2,K:17.8). The increase in incidence rates of diabetes and cancer plays a major role for the increase in lifetime risk, but the decrease in mortality may play an important role too, as the increasing number of survivors might be more susceptible both to diabetes and cancer. This phenomenon might be more pronounced among survivors with one of the two diseases, and may further contribute to the increasing lifetime risk.

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1694-P

Reductions in Hemoglobin and Packed Cell Volume over 3 Years in UKPDS Patients with Newly Diagnosed Type 2 Diabetes

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Diabetes increases the risk for developing anemia by 2-3 fold, compared to those without diabetes and similar renal function. We examined hemoglobin (Hb) and packed cell volume (PCV) changes over three years in UK Prospective Diabetes Study (UKPDS) patients with newly-diagnosed type 2 diabetes randomized to diet, sulfonylurea, metformin or insulin therapy.

Of 4209 patients, 2727 remained on monotherapy at three years and had the requisite data (Table 1). Paired t-tests were used to examine univariate changes from baseline for Hb & PCV. Multiple regression models, adjusting for baseline age, sex, ethnicity, HDL-cholesterol, triglyceride, urine albumin, eGFR and Hb or PCV values were also performed, with diet as the reference group.

Hb levels fell significantly by 1.5%, 2.4%, 4.8% & 1.7% with diet, sulfonylurea, metformin and insulin therapy respectively, as did PCV levels (1.8%, 2.7%, 5.0% & 2.2% respectively). After adjustment, a statistically greater fall in Hb was seen only with metformin, but falls in PCV remained statistically greater with sulfonylurea, metformin and insulin.

Hb and PCV levels fell over three years with diet, sulfonylurea, metformin and insulin therapies, but to the greatest extent with metformin. The extent to which these changes reflect time related reductions following diagnosis of diabetes, and possibly B12 associated impact with metformin, needs to be determined.

Table. Analyses by Treatment Group.

Treatment group	Hematological Variable	Baseline	Three year difference	95% Lower Confidence Interval	95% Upper Confidence Interval	P-value	Adjusted P-value
Diet (n=723)	Hb (g/dl)	15.08	-0.23	-0.32	-0.14	<0.0001	---
	PCV (%)	44.76	-0.81	-1.08	-0.54	<0.0001	---
Sulfonylurea (n=1002)	Hb (g/dl)	15.11	-0.37	-0.44	-0.31	<0.0001	n.s.
	PCV (%)	44.73	-1.21	-1.42	-1.00	<0.0001	0.0047
Metformin (n=246)	Hb (g/dl)	14.86	-0.71	-0.88	-0.54	<0.0001	<0.0001
	PCV (%)	44.19	-2.22	-2.65	-1.78	<0.0001	<0.0001
Insulin (n=756)	Hb (g/dl)	15.02	-0.26	-0.34	-0.18	<0.0001	n.s.
	PCV (%)	44.57	-0.96	-1.20	-0.72	<0.0001	<0.0001

1695-P

Potential Risk Factors Associated with the Presence and Severity of CKD in U.S. Adults with T2DM: NHANES (2007-2012)

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This study examined the presence, severity, and potential risk factors for chronic kidney disease (CKD) in individuals with type 2 diabetes (T2DM). Individuals ≥18 years of age with T2DM were identified from the NHANES 2007-2012 via self-reported diabetes or antidiabetic agent use. Those with type 1 diabetes, pregnancy, missing serum creatinine lab value, age, gender, or race were excluded. CKD severity was defined based on KDIGO 2012 guidelines using the CKD-Epi equation: mild =Stage 1-3a; moderate to severe = Stage 3b-5. Odds ratios were calculated via multivariable logistic regression with appropriate NHANES weights. Of 2006 T2DM individuals, 38.3% had CKD, primarily mild (77.5%). Increased odds of having CKD were associated with: older age, higher BMI, HbA1c, systolic blood pressure (SBP), being Black or Mexican American, having hypertension, retinopathy, stroke or congestive heart failure (CHF). Being female, low income, having retinopathy, coronary heart disease or CHF were associated with increased odds of having moderate to severe versus mild CKD. Our findings highlight risk factors for having CKD and predicting disease severity among T2DM patients which may improve disease management. These data suggest controlling factors beyond HbA1c and SBP may reduce CKD incidence, and proactive screening/treating for certain comorbid conditions in early stages of CKD may slow progression.

Table 1. Risk Factors of CKD Presence and Severity in T2DM.

eGFR calculated using CKD-EPI equation	CKD vs. No CKD (N = 811 vs. 1,051)		Moderate to Severe vs. Mild CKD (N=178 vs. 633)	
	Odds Ratio (95% CI)	*p*-value	Odds Ratio (95% CI)	*p*-value
Demographic Characteristics				
Age, years	1.05 (1.03-1.07)	<.0001	1.03 (0.98-1.07)	0.2229
Female (vs. Male)	0.77 (0.59-1.02)	0.0701	2.26 (1.49-3.43)	0.0001
Race (vs. Non-Hispanic White)				
Non-Hispanic Black	1.33 (1.02-1.73)	0.0346	1.05 (0.62-1.79)	0.8498
Mexican American	1.85 (1.17-2.91)	0.0082	0.75 (0.36-1.55)	0.4329
Other Hispanic	0.91 (0.64-1.28)	0.5779	0.99 (0.42-2.34)	0.9875
Other, including multiracial	1.31 (0.91-1.86)	0.1427	0.80 (0.37-1.73)	0.5678
Comorbid Conditions				
Hypertension	1.78 (1.20-2.64)	0.0044	2.68 (0.97-7.44)	0.0580
Retinopathy	1.69 (1.22-2.35)	0.0016	2.64 (1.75-3.99)	<.0001
Stroke	1.84 (1.21-2.79)	0.0044	1.35 (0.75-2.45)	0.3160
Coronary heart disease	1.05 (0.71-1.55)	0.8144	2.75 (1.41-5.39)	0.0032
Congestive heart failure	2.41 (1.45-4.01)	0.0007	2.21 (1.21-4.03)	0.0096
Lab Test Results				
HbA1c, %	1.18 (1.09-1.29)	0.0001	0.92 (0.77-1.10)	0.3515
Systolic blood pressure, mmHg (per 10 point increase)	1.22 (1.12-1.33)	<.0001	1.02 (0.90-1.15)	0.7534
BMI	1.03 (1.00-1.05)	0.0266	1.01 (0.97-1.04)	0.7944

BMI: Body Mass Index; CKD-EPI: The Chronic Kidney Disease Epidemiology Collaboration equation
Mild CKD: KDIGO Stage 1 to 3a; Moderate to severe CKD: KDIGO Stage 3b to 5
The model also controlled diabetes duration, education level, insurance type, diastolic blood pressure level, and survey cycle, which were insignificantly associated with presence of CKD.

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1696-P

Regional Differences in Diabetes Prevalence by Age and Urban/ Rural Setting

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The prevalence of diabetes has been increasing for many decades, along with increases in life expectancy and urbanization. In order to predict future diabetes prevalence, it is essential to closely examine the relationship between diabetes prevalence and urbanization.

As a component of the 2014 update of the IDF Diabetes Atlas 6th Edition, a literature search of studies reporting age-specific prevalence for type 1 and 2 diabetes was conducted and the Analytic Hierarchy Process used to systematically select studies for inclusion. Logistic regression was applied to generate smoothed age-specific prevalence estimates for adults 20-79 years which were then applied to UN population estimates for 2014. From the 173 studies that were used for the Atlas estimates, only 26 studies from 25 countries contained data for rural and urban territories reported separately. The age profiles of diabetes prevalence were compared for those countries with rural/urban data using with 95% confidence intervals.

There was a wide heterogeneity in the association between urbanization and diabetes prevalence. In 13 out of 25 countries assessed, there was no significant difference in diabetes prevalence between urban and rural settings by age (Fiji, Gambia, Greece, Guinea, Hungary, Iran, Jamaica, Malaysia, Mozambique, Pakistan, Republic of Korea, Romania, and Uzbekistan). In 7 countries assessed, there was significantly higher diabetes prevalence in urban settings, compared to rural settings, between the ages of 25 and 80 (India, Nepal, Philippines, Saudi Arabia, Sri Lanka, Thailand, and Tunisia). In 5 countries diabetes prevalence was significantly higher in urban environments between 40 and 70 years (Bangladesh, China, Oman, Samoa, and Turkey).

This analysis found that in 52% of the countries analysed, there was no significant difference in diabetes prevalence by age in urban and rural settings. In countries where a difference was found, the diabetes prevalence was higher in urban settings, compared to rural settings.

1697-P

Diabetes, Diabetes Treatments, and Lung Cancer Risk

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Lung cancer is a common disease and even a small, real increase in risk associated with diabetes would represent a significant problem for public health.

A meta-analysis on lung cancer risk in diabetic patients compared to healthy subjects was undertaken according to PRISMA guidelines. Random-effects meta-analyses were computed with tests for heterogeneity and publication bias.

There was no increased risk of lung cancer among diabetic patients (SRR=1.04 95% CI 0.96, 1.13; 32 studies). The risk remained non-significant in studies adjusting for smoking (SRR=0.98 95% CI 0.90, 1.06) and among stud-

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ies not adjusting for smoking (SRR=1.08 95% CI 0.95, 1.24). There was no significantly increased risk of lung cancer among diabetic patients in studies conducted in North America (SRR=1.02 95% CI 0.89, 1.18), Europe (SRR=1.01 95% CI 0.88, 1.17) or Asia (SRR=1.10 95% CI 0.93, 1.31).

22 studies investigated the association between diabetes treatments and lung cancer. The risk of lung cancer was increased among patients with diabetes treated with any type of insulin (SRR=1.20 95% CI 1.03, 1.41) and remained unchanged when the analysis was restricted to observational studies (SRR=1.20 95% 1.01, 1.43). The risk of lung cancer among glargine users, the focus of ten studies, was not increased (SRR=1.04 95% CI 0.91, 1.19) and this persisted when restricted to observational studies (SRR=1.02 95% CI 0.88, 1.18). Risk of lung cancer among patients prescribed non-glargine insulin had an increased risk of lung cancer (SRR=1.50 95% CI 1.10, 2.04). Risk of lung cancer was reduced among users of Thiazolidinediones (TZD) (SRR=0.67 95% CI 0.54, 0.85) but not metformin (SRR=0.94 95% CI 0.73, 1.22).

The risk of lung cancer is not increased among patients with diabetes compared to healthy subjects. Those diabetic patients prescribed glargine do not have an increased risk of lung cancer although users of other insulins have a significantly increased risk. TZD users have a decreased risk of lung cancer while there is no significant protection conferred by using metformin.

1698-P

Birth Weight and Subsequent Risk of Type 2 Diabetes and Hypertension across Two Generations in Chinese Females

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To compare the trans-generational associations of birth weight with subsequent risk of type 2 diabetes and hypertension, we conducted a cross-sectional survey among 10324 females from 3888 families in Shanghai, China, during the period of November 2012 and January 2013. Self-reported information on birth weight, birth length, gestational week, and diagnosis of type 2 diabetes and hypertension were obtained by in-person interviews using a structured questionnaire. A positive association was observed between maternal and daughters' birth weight, with 1 kg increase in maternal birth weight linked with an average of 0.335 kg (95% CI: 0.307-0.363) elevated birth weight in the female offspring. Maternal diabetes was also related with an average of 0.062 kg (95% CI: 0.019-0.104) increase in birth weight and a higher risk of subsequent type 2 diabetes in their daughters (OR: 3.173; 95% CI: 1.946-5.174). Maternal hypertension was not associated with birth weight of their daughters, but nearly quadrupled the subsequent risk of hypertension in their female offspring (OR: 3.769; 95% CI: 2.886-4.922). Although no significant association was observed between birth weight and prevalence of type 2 diabetes or hypertension in the subjects aged 20 years or above, path analysis and mediation analysis showed that offspring's birth weight, as a mediator of maternal and daughters' diabetes status, explained 2.8% of the association, but didn't mediate the association between maternal and daughters' hypertension status. Our findings suggest that different mechanisms may underlie the trans-generational associations of birth weight with subsequent risk of type 2 diabetes and hypertension in Chinese females.

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1699-P

Lifestyle Modification Is Equally Effective in Nonobese and Obese Asian Indians with Prediabetes in Reducing the Incidence of Type 2 Diabetes

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The effectiveness of lifestyle modification (LSM) in prevention of type 2 diabetes (T2DM) was mainly attributed to benefits of weight reduction in the western studies in which mostly obese particpants were included. In Asian Indians, with relatively lean body mass index (BMI) the effectiveness was independent of appreciable weight loss. The objective of this analysis was to assess whether baseline body mass index (BMI) influenced impact of LSM on incidence of diabetes among Asian Indians with impaired glucose tolerance (IGT). Data of two Indian Diabetes Prevention Programmes were combined for this analysis (2006 and 2013; n=709). Propotion of obese (BMI≥ 25 kg/m2) participants was more than that of no-obese (BMI< 25 kg/m2) individuals (410 (57.8%) vs. 299 (42.2%)). Incident diabetes was diagnosed in 227 out-of 709 participants during the total follow-up period; 88 and 139 in the intervention and control group respectively (relative risk reduction: 39% (HR: 0.61 [95% CI: 0.46-0.79]; P<0.0001). The effect of intervention on the incidence of diabetes was similar in each BMI stratum (BMI< 25: HR: 0.60 [95% CI: 0.39-0.91]; P=0.015; BMI≥ 25: HR: 0.61 [95% CI: 0.43-0.87]; P=0.006). Cox regression model showed that the lower beta cell compensation at baseline (HR: 0.990 [95% CI: 0.988-0.994]; P<0.0001 and intervention (HR: 0.56 [95% CI: 0.37-0.85]; P=0.007) significantly influenced the development of diabetes. Baseline BMI did not influence the outcome. To summarize, the mechanism of action of lifestyle intervention in Asian Indians is independent of baseline BMI.

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1700-P

Influenza and Pneumococcal Vaccination Rates among Greek Diabetes Patients between 2003-2013 and Its Influence on Their Morbidity and Hospitalization

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Diabetic patients are particularly susceptible to influenza and pneumococcal infection. The aim of this study was to estimate the vaccination rates in Greek diabetes patients between 2003 and 2013 along with its influence on morbidity, hospitalization, duration and outcome of hospitalization.

1098 type 2 diabetes mellitus patients (590 in 2003 and 508 in 2013) were eligible in this study. All patients answered a questionnaire about vaccination between October and December and two months after appropriate counsel on immunization. All respiratory infections and consequent hospital admissions were recorded by telephone interviews two months after the end of the vaccination period.

More patients had received the influenza vaccine in 2003 (62.1% vs. 52%, p=0.033) while more patients had received the pneumoccocal vaccine in 2013 (39.4 vs. 16.1%, p=0.012). In 2013 more patients had received both vaccines compared to patients in 2003 (23.6 vs. 14.7, p=0.028). The probabilities of respiratory infection were notably higher in the absence of influenza vaccination (OR=4.112, 95% CI: 1.931-8.037, p=0.001) and pneumoccocal vaccination (OR=2.870, 95% CI: 1.163-6.388, p=0.001) in 2013, significantly correlated only with the influenza vaccination in 2003 (OR=1.177, 95% CI: 1.071-2.965, p=0.033). The duration of hospitalization was longer in patients without any vaccination in 2013 (OR=2.874, 95% CI: 1.188-4.538, p<0.0001) while the presence of complications or death during hospitalization was correlated with the absence of any vaccination in 2013 (OR=2.458, 95% CI: 1.221-3.984, p<0.0001).

The rate of influenza vaccination among Greek diabetes patients has declined through time. Diabetes patients without any vaccination present higher morbidity and more hospital admissions while the duration and the outcome of hospitalization are correlated with the compliance to the vaccination programme.

1701-P

Effects of Telmisartan on Insulin Sensitivity in Hypertensive Patients: A Meta-analysis of Randomized Controlled Trials

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The angiotensin II type 1 receptor blocker (ARB), telmisartan has a possible effect on the activation of the peroxisome proliferator activated receptor gamma (PPAR-γ) that is an essential regulator of lipid and glucose metabolisms. Since a PPAR-γ agonist, thiazolidinedione, is an insulin sensitizer, we have evaluated the impact of telmisartan on insulin sensitivity by a meta-analysis in hypertensive patients. Studies were identified through electronic searches and included if they met the following inclusion criteria: (i) randomized controlled trials that compared telmisartan with a placebo or other antihypertensive agents in adults; (ii) reporting homeostatic model assessment of insulin resistance (HOMA-IR); (iii) having a trial duration of at least 12 weeks that assessed clinically relevant doses of 20 to 80 mg/dayas telmisartan. HOMA-IR was analyzed as weighted mean differences (WMD) under a random effects model. A total of 17 comparisons met inclusion criteria, which included 1,283 study participants, 644 treated with telmisartan and 639 treated with comparator drugs. In a meta-analysis, telmisartan significantly reduced HOMA-IR among all studies (WMD = -0.71, 95% confidence interval (CI), -1.16 to -0.26). HOMA-IR was also decreased significantly compared with calcium channel blockers (CCBs) (WMD = -0.70, 95% CI, -1.17 to -0.23), but not with other ARBs (WMD = -0.75, 95% CI, -1.66 to 0.15). Publication bias was not found in the analysis (P=0.87). In a meta-regression analysis, telmisartan has a greater efficacy on HOMA-IR in groups

with smaller mean values of baseline age (P<0.05), higher of base line fasting insulin levels (P<0.01) and longer duration of the telmisartan treatment (P<0.05). The present meta-analysis suggests that telmisartan can improve the insulin resistance index. Further molecular and biological studies are needed to elucidate these potentially beneficial effects of telmisartan on insulin resistance.

1702-P

Substance Use among Adolescents and Young Adults With and Without Diabetes

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Extant literature on whether substance use differs among youth with/without diabetes is mixed, and we lack nationally representative epidemiologic profiles of these behaviors during adolescence and young adulthood, periods of peak risk.

We analyzed national data from the Panel Study of Income Dynamics (Child Development & Transition to Adulthood Supplements) from 1997-2011 to investigate tobacco, alcohol, and marijuana use during the period of adolescence (12-18) and young adulthood (19-26). Our sample included 54 youth with type 1 or 2 diabetes, 1679 youth with other chronic conditions, and 411 youth with no conditions. Multivariable results adjusted for: age, gender, race/ethnicity, socioeconomic status, and psychological distress.

Prevalence of tobacco smoking was 39.1% for youth with diabetes, 51.8% for youth with other conditions, and 49.4% for youth with no conditions. Adolescents with diabetes were significantly less likely to report being ever (AOR=0.25, p=0.01) or regular smokers (AOR=0.08, p=0.03) than those with or without other conditions in adjusted analyses.

High levels of ever or binge drinking were reported by youth with diabetes (75.6% & 24.6%, respectively) and substantial levels of marijuana use were reported (53.3%) though these levels were not different than those of their peers. Youth with diabetes reported marijuana initiation at younger ages (14.1 years) compared to youth with or without other conditions (15.8 & 15.3 years, respectively), although differences did not persist after adjustment.

In a nationally representative cohort, substance use levels were substantial among youth with diabetes, although risks for smoking were lower and those for drinking and marijuana use no different than those among other youth. Youth with diabetes may initiate substance use comparatively early. Hence, improved assessment, monitoring, and intervention for risk behaviors among this group are warranted.

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1703-P

Dipeptidyl Peptidase-4 Inhibitor Use Is Not Associated with an Increased Risk of Acute Pancreatitis in High-risk Type 2 Diabetic Patients: A Nationwide Cohort Study

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Safety data about the risk of acute pancreatitis associated with dipeptidyl peptidase-4 (DPP-4) inhibitor use in high risk type 2 diabetic patients with prior history of pancreatitis or hypertriglyceridemia was limited. Here we conducted a retrospective cohort study analyzing Taiwan National Health Insurance claim database. The risk associated with sitagliptin was compared to that with acarbose, a second-line antidiabetic drug prescribed in patients with similar diabetes severity without known effect on pancreatitis. A total of 8,526 sitagliptin initiators and 8,055 acarbose initiators who had hypertriglyceridemia and received fibrates therapy or prior hospitalization history for acute pancreatitis were analyzed for the risk of hospitalization due to acute pancreatitis with adjustment for baseline propensity score.

In the crude analysis, sitagliptin was associated with a decreased risk of acute pancreatitis (HR 0.74; 95% CI: 0.62-0.88) compared to acarbose in diabetic patients with prior pancreatitis hospitalization history or hypertriglyceridemia. The association was abolished after adjusting for propensity score quintiles (adjusted HR 0.95; 95% CI: 0.79-1.16). Similar results were found separately in either patients with prior hospitalization history of acute pancreatitis (adjusted HR 0.97; 95% CI: 0.76-1.24) or those with hypertriglyceridemia (adjusted HR 0.86; 95% CI: 0.65-1.13). No significant association was found with different duration or accumulative doses of sitagliptin. In the stratified analysis, no elevated risk was found for men or women, and for those aged ≥ or < 60 years.

We concluded that use of sitagliptin was not associated with an increased risk of acute pancreatitis in high-risk patients with hypertriglyceridemia or with past history of acute pancreatitis.

1704-P

Diabetes and Prediabetes in a Cohort of Korean Employees

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Asians tend to develop diabetes at younger ages and lower body mass index (BMI). Identifying individuals at high risk and provide interventions are imperative for prevention. We conducted a prospective study to characterize diabetes risk factors and examine the associations between the Korean diabetes screening score (ranged 0 to 11; validated and calculated using age, family history, hypertension, waist circumferences, smoking, and alcohol drinking) and incident diabetes and prediabetes in a cohort of 12,370 Korean employees aged ≥28 who joined in the Samsung Health Initiatives in 2002-3. Diabetes and prediabetes were defined by physician diagnosis and/or fasting glucose. At baseline, the mean age was 34.5 (3.9) years; 96.5% were men; 64.2% had BMI >=23 kg/m^2; 42.7% were current smokers; 33.3% had at least one drink per day; 15.6% had hypertension; and 48.6% had elevated diabetes risk scores (>=5 points). After 6 years of follow-up, 919 workers (7.4%) developed diabetes and 3,125 workers developed prediabetes (32.8%). Compared to employees with risk score<=4, the odds ratios of incident diabetes and prediabetes in employees with risk scores 5-7 and >=8 were significantly elevated. After adjustments for additional covariates, the associations attenuated but remained significant for incident prediabetes (Table 1). Health promotion including weight loss and smoking cessation is needed for this employee population.

Table 1. Odds Ratios of Incident Diabetes & Prediabetes.

	Model 1	Model 2	Model 3
Odds ratio of incident diabetes			
5-7 vs. <=4	1.66 (1.45-1.91)	1.34 (1.14-1.58)	1.26 (1.07-1.50)
>=8 vs. <=4	1.82 (1.27-2.61)	1.29 (0.88-1.90)	1.16 (0.79-1.71)
Odds ratio of incident prediabetes			
5-7 vs. <=4	1.28 (1.17-1.39)	1.29 (1.17-1.43)	1.24 (1.11-1.38)
5-7 vs. <=4	1.81 (1.39-2.37)	1.88 (1.41-2.49)	1.79 (1.34-2.38)

Model 1: Unadjusted, include risk score only; Model 2: Age and sex-adjusted; Model 3: Model 2 + dyslipidemia, education, employment duration, and job field and title.

1705-P

Clinical Differences in Patients Receiving Antidiabetic Drugs With and Without a Diagnosis of Diabetes in U.S. Electronic Health Records (EHR)

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Studies of antidiabetic drugs (AD) often rely on diagnostic codes to identify the study population, excluding patients with no recorded DM diagnosis. We examined clinical differences between treated patients with and without a diagnosis of DM among a random sample of 1,000,000 patients in the Humedica Research Database (2007-2013), a de-identified EHR database in the U.S. Among initiators of any AD, we identified DM diagnoses in the 12 months prior to drug initiation. Patients with other indications for AD therapy were removed. Of the 23,351 initiators, 64% had type 2 DM (T2D), 53% were female and 13% under 45. The most common drugs at initiation were insulin and metformin. Almost 30% had no DM diagnosis in the prior year (Table 1). This group was more likely to be pre-diabetic based on HbA1c levels.The baseline prevalence of comorbidities was lower for those with no DM diagnosis and those with type 1DM (T1D). Patients in all 4 categories were similar on common lab tests. On average, all groups except T1D had BMI scores in the obese range. Within 12 months after initiation, 24% of the "No Diagnosis" group received a DM diagnosis (94% for T2D). These results suggest a significant proportion of patients initiating AD with no diagnosis are pre-diabetic, younger, and have fewer comorbidities than T2D. This should be taken into account in the design and interpretation of studies of AD.

For author disclosure information, see page A810.

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Table. Select Characteristics for Categories of DM Diagnosis.

Baseline Characteristics	No Diagnosis N=6910 29.6%	T1D N=418 1.8%	T2D N=14,963 64.1%	T1D & T2D N=1060 4.5%
Age under 45	19.6%	52.0%	8.5%	20.3%
Female	58.2%	49.0%	50.0%	52.4%
Unspecified Essential Hypertension	23.6%	15.6%	48.3%	55.0%
Serum Creatinine mg/dl median (IQR)	0.9 (0.7-1.1)	0.9 (0.7-1.1)	0.9 (0.8-1.2)	1.0 (0.8-1.3)
Total Cholesterol mg/dl median (IQR)	177 (152-208)	173 (150-195)	166 (143-196)	163 (142-193)
BMI median (IQR)	30.2 (25.6-36.0)	26.8 (23.3-31.3)	32.5 (28.0-37.7)	31.5 (26.7-36.8)
HbA1C% median (IQR)	6.2 (5.7-6.9)	7.9 (7.0-9.0)	7.2 (6.5-8.2)	7.7 (6.8-8.9)

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1706-P

Association between Diabetes and Depressive Symptoms in Postmenopausal Women: Findings from the 2009 Taiwan National Health Interview Survey

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Previous research indicated that patients with diabetes have nearly twice the risk of comorbid depression as the general population. The changes in sex hormone profile associated with menopause may also increase the risk of depressive symptoms. Therefore, the aim of this study was to investigate the association between diabetes and depressive symptoms in postmenopausal Taiwanese women using data from a nationwide, population-based survey. Postmenopausal women aged 50 to 64.9 years were identified from the 2009 Taiwan National Health Interview Survey. Exclusion criteria included women who had hysterectomy or oophorectomy and those who had previously or currently received hormonal replacement therapy. The main outcome measure was depressive symptoms in the past week, which was evaluated using the Center for Epidemiologic Studies Short Depression Scale (CES-D 10). A cut off score of 10 or greater was considered depressed. The mean age of the 319 respondents was 56.9 years (standard deviation 3.7 years). Depressive symptoms were presence in 26 respondents (8.2%) and 31 respondents had diabetes (9.7%). Multivariate logistic regression analysis revealed that diabetes (adjusted odds ratio [AOR]=4.10, p=0.009), living alone (AOR=4.31, p=0.020), and lack of regular exercise (AOR=5.65, p=0.001) were independent and significant factors of depressive symptoms in postmenopausal women. In conclusion, findings from this study suggested that clinicians should be vigilant for depressive symptoms among their postmenopausal patients with diabetes.

1707-P

Characteristics and Medication Adherence of Patients with Type 2 Diabetes Mellitus (T2DM) Initiating Linagliptin and Other Diabetes Medications (Noninsulin) in Routine Care

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Linagliptin is a dipeptidyl peptidase-4 (DPP-4) inhibitor marketed for T2DM treatment. Limited information is available regarding the characteristics of patients initiating linagliptin and their adherence to treatment in routine care settings. Within a large, nationwide U.S. health insurance database (Optum Clinformatics), we identified T2DM patients initiating linagliptin or other diabetes medication (non-insulin) from May 2011 through June 2012. The patient characteristics at baseline are described in Table 1. The patients were followed for adherence measures for up to 12 months. Along with meglitinides, linagliptin initiators had the greatest burden of comorbidities (Table 1). Linagliptin and saxagliptin initiators had the highest proportion of days covered (PDC) at 77.5% and 75.8%, and greater persistence of therapy at 12 months (P12), 51.5% and 49.8%, respectively. The lowest adherence measures were observed among initiators of meglitinides (PDC 64%, P12 22.6%), glitazones (PDC 68.8% P12 28.4%) and GLP-1 receptor agonists (PDC 68.3%, P12 33.6%). These patterns of adherence were similar after propensity score matching and in another U.S. commercial health insurance database (MarketScan), suggesting the differences in adherence measures are not due to patient or health insurer characteristics.

Table 1.

Characteristic	Linagliptin (N=2820)	Sitagliptin (N=18491)	Saxagliptin (N=8100)	Metformin (N=72694)	Sulfonylureas (N=33868)	Glitazones (N=7203)	Meglitinides (N=1184)
Age, Mean (SD)	55.90(10.06)	54.40(10.16)	53.68(9.66)	52.57(10.56)	53.75(10.40)	53.67(9.99)	57.08(10.46)
Females, N (%)	1175(41.67)	7600(41.10)	3400(41.98)	32251(44.37)	13631(40.25)	2679(37.19)	505(42.65)
Charlson comorbidity index, Mean (SD)	1.68(1.29)	1.45(1.11)	1.40(0.98)	1.27(1.01)	1.44(1.21)	1.37(1.10)	1.79(1.53)
Ischemic heart disease, N (%)	129(4.57)	712(3.85)	276(3.41)	2434(3.35)	1410(4.16)	199(2.76)	79(6.67)
Congestive heart failure, N (%)	62(2.20)	260(1.41)	79(0.98)	718(0.99)	594(1.75)	54(0.75)	35(2.96)
Renal dysfunction, N (%)	335(11.88)	1259(6.81)	471(5.81)	2857(3.93)	2322(6.86)	492(6.83)	168(14.19)
Malignant neoplasms, N (%)	206(7.30)	1094(5.92)	408(5.04)	3720(5.12)	1959(5.78)	372(5.16)	103(8.70)

1708-P

The Predictability of Adipocytokines for Developing Prediabetes and Type 2 Diabetes

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Diabetes is a worldwide public health problem and its prevalence in Asia is rapidly growing. So it would be very important to find proper biomarker to predict future prediabetes and diabetes. We performed this study to find which adipokines could be strong predictor for future glucose alterations.

A total of 1,000 participants were recruited from the Ansung cohort (prospective, community-based rural cohort) in Korea. All subjects underwent a 75-g oral glucose tolerance test and eight kinds of adipokines (PAI-1, Resistin, IL-6, Leptin, MCP-1, TNF-α, RBP4, and Adiponectin) were measured by the Human serum Adipokines LINCOplex kit (Linco Research, St. Charles, MO, U.S.) at baseline examination. Excluding subjects who were diagnosed with type 2 diabetes (T2D) at baseline and were not followed up, 571 subjects were enrolled and regularly examined at every 2 years for 10 year-period.

At baselines, 241 participants were NGT and 330 participants were prediabetes. At 10 years, 120 in subjects with NGT have developed prediabetes (n = 38) and T2D (n = 82). And 228 in subjects with prediabetes have developed T2D. In multivariate logistic regression analysis, the NGT group with the highest tertile of PAI-1 levels were 4.27 times (95% CI 1.25–14.63, P=0.026) more likely to develop prediabetes than those in the lowest tertile. The subjects with lower tertile levels of adiponectin had more than threefold risk for development of prediabetes than those with the highest tertile. The NGT group with the highest tertile of RBP4 levels was 5.07 times (95% CI 1.70–15.09, P=0.004) more likely to develop T2D than those in the lowest tertile. The prediabetes groups with the highest tertile of RBP4 or Resistin levels were 1.87 and 2.85 times (95% CI 1.00–3.51, P = 0.051, and 95% CI 1.49–5.43, P = 0.001) more likely to develop T2D than those in the lowest tertile, respectively.

Increased serum PAI-1, RBP4, resistin or decreased adiponectin levels were independent risk factors for progression to prediabetes or T2D in the non-diabetic people.

1709-P

Diabetes and Cancer and Impact of Therapies: Analyses of 20 Meta-analyses in 2014

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Meta-analyses may generate conflicting findings depending on the selection criteria used and methodological rigor. All meta-analyses published during 2014 were assembled to compare their findings on the association of diabetes, diabetes therapies and cancer risk.

Twenty meta-analyses (reporting 66 estimates of risk) were identified which evaluated the association between diabetes and cancer. Forty risk estimates demonstrated a statistically significant increase in risk of cancer among subjects with diabetes and 16 showed a non-statistically significant increase in risk. Interestingly, 4 showed no difference in risk in those with or without diabetes, 2 showed a non-statistically significant decrease in risk and 4 showed significantly decreased risks. Consistency was found in all 7 analyses of colorectal cancer showing an increased risk among those with diabetes as did all 4 studies of pancreas cancer.

Insulin was the most frequent subject of meta-analyses of diabetes treatments and cancer risk (23 studies). Six studies of insulin and colorectal cancer demonstrated increased risk of which half were statistically significant. All 3 meta-analyses of sulfonylureas were non-statistically significant. Of 7 meta-analyses on TZDs, 3 demonstrated statistically significant increased

risks of bladder cancer. Of 16 meta-analyses of metformin, 11 demonstrated a significantly reduced risk of cancer (all cancers, breast, colorectal).

Meta-analyses published in 2014 have contributed to the understanding of the associations between diabetes, diabetes therapies and cancer risk but some have severe methodological deficiencies and their findings should be taken with caution. Nevertheless, the clearest association was between the increased risk of colorectal cancer in diabetes subjects and the increased risk of colorectal cancer among those prescribed insulin compared to other anti-diabetic medications.

1710-P

International Comparison of Smoking and Metabolic Control in Patients with Type 1 Diabetes (T1D)

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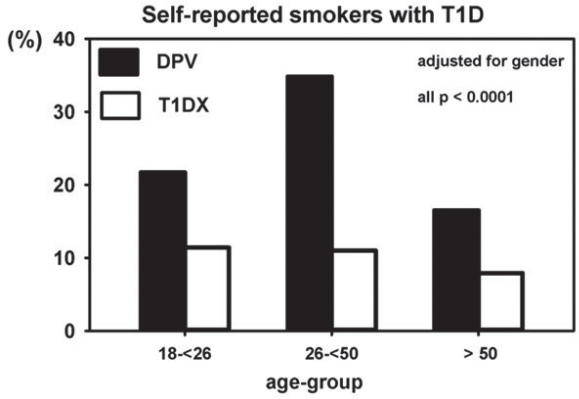
Smoking may potentiate the risk of micro- and macro-vascular complications in T1D. We assessed smoking status in patients with T1D ≥18 years with >1 year T1D duration in the T1D Exchange (T1DX) registry in the U.S. (n=10 589) and the DPV registry in Austria and Germany (n=9 826). Smoking status (current, former and non-smokers) and its relationship with metabolic outcomes were compared between and within each registry.

Current smoking status was defined by smoking at least one cigarette per day; former-smokers reported smoking in the past, while non-smokers never smoked. For sub analysis, age groups (gr. 1:18-<26 years, gr. 2: 26-<50 years and gr. 3: ≥50 years) were considered.

In DPV current smoking rates (adjusted for age and gender) were higher compared with the T1DX registry (24.1% vs. 9.7%), while the % of former smokers was lower (5.1% vs. 18.0%) although the % of non-smokers was equal (70%) in both registries. Current smokers were higher in DPV in all age groups. Previous smokers were similar in age group 1 and 2, but higher in the T1DX registry in gr. 3 (5.3% vs. 35.2%).

HbA1c was significantly higher in smokers in both registries (DPV 8.5% vs. 7.9%; T1DX 8.6% vs. 7.9%, (p<0.0001)).

In conclusion, patients with T1D who smoke had significantly higher HbA1c. The high number of smokers in DPV is a concern. Anti-smoking policy and smoking cessation programs established in the U.S. seem to be successful strategies to reduce smoking.



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1711-P

First-Line and Intensified Treatment with Glucose Lowering Drugs in 232,797 Swedish Type 2 Diabetes Patients

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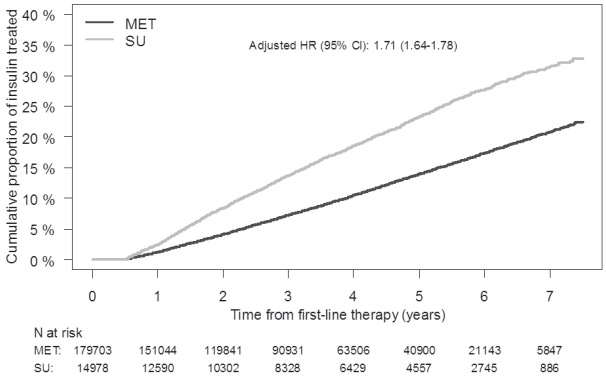
The aim was to investigate first-line and subsequent drug treatment for all type 2 diabetes (T2D) in Sweden. All individuals dispensed for the first time with any glucose lowering drug during 2006-2013, n=232,797, were identified in the national prescription registry. Patients with type 1 diabetes or gestational diabetes were excluded. Cox survival models adjusted for age and gender were used to estimate likelihood for treatment intensification during up to 7 years of follow-up. In 2013, annual incidence and prevalence of drug-treated T2D was 368/100,000 and 4.4%, respectively, i.e. suggesting that they are greater than reported by the Swedish National Diabetes Registry. T2D patients initiated medication with a single non-insulin antidiabetic drug (NIAD), insulin (alone or with NIAD) or dual NIAD (85.7%, 12.7% and 1.6% respectively). Among single NIAD; 90.0% was metformin; 7.5% sulfonylurea (SU) and 2.4% other. SU was associated with higher risk of second- and third-line and insulin initiation compared with metformin, hazard ratio (95% CI): 1.78 (1.73-1.83); 1.80 (1.68-1.92) and 1.71 (1.64-1.78) respectively.

The incidence and prevalence of drug treated T2D was higher than previously reported and prescribers in Sweden adhere to T2D medication guidelines. First line treatment with SU compared to metformin was associated with earlier treatment intensification and insulin start.

Figure: Risk for change to insulin treatment after first line treatment with metformin or SU.



Supported By: AstraZeneca

1712-P

Smoking Cessation before Diabetes Occurrence Reduces Liver Cancer Mortality in Men: A Prospective Cohort Study

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Limited evidence exists regarding diabetes and timing of smoking cessation for deaths from hepatocellular carcinoma (HCC). This research aimed to investigate the association between diabetes, smoking habits, and timing of smoking cessation relative to diabetes in a prospective cohort. We consecutively followed a total of 29,206 men (aged 40 to 94 years) receiving health screening from 1 January 1998 to 31 December 2008. Non-diabetic quitters were defined as quitters who had quitted smoking before having diagnosis of diabetes. There were 186 deaths from HCC ascertained by validated death certificates and the national death registry. Diabetes (adjusted hazard ratio [HR], 2.36; 95% confidence interval [CI], 1.53 to 3.64) was positively associated with deaths from HCC. Never-smokers had a lower adjusted risk of HCC deaths compared to current smokers (HR, 0.46; 95% CI, 0.32 to 0.66). Diabetic participants with anti-diabetic agents had a similar risk of deaths from HCC compared to diabetic participants without anti-diabetic agents. Among all ever-smokers with current or past smoking habits (n=14,514), non-diabetic quitters (HR, 0.41; 95% CI, 0.20 to 0.84) had decreased deaths from HCC compared with diabetic smokers. However, diabetic quitters (HR, 0.86; 95% CI, 0.31 to 2.34) and non-diabetic smokers (HR, 0.55; 95% CI, 0.29 to 1.06) were observed to have a similar risk of deaths from HCC to diabetic smokers. The reduced risk of HCC deaths in non-diabetic quitters versus diabetic smokers remained significant in lag-time sensitivity analyses, applied to check for reverse causation. In conclusion, diabetes was positively associated with deaths from male liver cancer independently of chronic hepatitis B. To be associated with reduced liver cancer mortality, men should keep never smoking or quit smoking preceding diagnosis of diabetes.

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1713-P

Serum Fatty Acid Proportions Are Related to Development of Metabolic Syndrome in Japanese Male Workers

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Serum fatty acids (FA), such as saturated FAs, are known to be responsible for the development of metabolic syndrome (MetS). However, most reports are from cross-sectional studies, which compared serum FA proportions between healthy subjects and subjects with MetS, and the role of serum FAs in the development of MetS remains unclear. In addition, available prospective cohort studies proving a causal association between serum FA proportions and MetS

For author disclosure information, see page A810.

are still limited. The aim of the present study was to investigate the causal association between serum FA proportions or FA ratios that reflect desaturase activity and the incidence of MetS in Japanese male workers.

We here report a prospective occupational-based cohort study, which has been conducted since 2008 in Japan. A total of 303 male workers without MetS and lipid components of MetS aged 20 to 60 years were followed up prospectively (mean follow-up period: 3.7 years). We evaluated serum FA proportions and ⊿5desaturase, ⊿6desaturase, ⊿9stearoyl-CoA desaturase (SCD)1 and ⊿9-SCD2, which reflect desaturation of FAs estimated from the FA product-to-precursor ratios.

The age-adjusted incidence of MetS significantly increased with increasing quartile of baseline serum oleic acid level (P for trend<0.01). In multivariate analysis after adjusting for age, BMI, smoking habit, alcohol intake, and regular exercise, the HR of MetS was 6.49 [95% CI: 1.44 to 29.25, P=0.02] in the highest quartile, compared with the lowest quartile. Interestingly, the age-adjusted incidence of MetS and the multivariate-adjusted HR of MetS also increased with increasing quartile of ⊿9-SCD2 (P for trend for both <0.01).

Our findings suggest that increased serum oleic acid proportion and ⊿9-SCD2 are risk factors for the incidence of MetS in Japanese male workers. These results imply the possibility that the desaturase that synthesizes monounsaturated FAs by insertion of a double bond into saturated FAs could be associated with the development of MetS.

1714-P

Alcohol and Marijuana use among Youth with Diabetes

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For youth with diabetes, alcohol and marijuana use may jeopardize health and self-care, yet knowledge and assessment of these behaviors are limited.

To inform care, we measured use of alcohol and marijuana by youth with diabetes and tested associations with knowledge and guidance. We collected cross-sectional data from consented youth aged 9 -18 years in care for type 1 diabetes (T1D) using a structured online assessment. Eligible youth had diabetes for ≥ 1 year and spoke English. We analyzed data in SAS using descriptive statistics and regression controlling for age, sex and race. The Boston Children's Hospital IRB approved the research.

Of 100 participants (66% response), 43% were female, mean age 16 years (± 2.08 years). Average age of alcohol/marijuana initiation was respectively 15.8/15.3 years. Older age was associated with use (p <0.01 for both). Among 83 high school (HS) youth: 36%/26% reported past year alcohol/marijuana use respectively; 24% reported using both. 23% of HS youth reported they drank in the past 90-days, of which 67% reported binge drinking. When asked if alcohol could interfere with their medications, 44.3% of HS youth answered "no" (incorrect) or "I don't know"; 54.6% answered thus when asked if alcohol could interfere with their labs. Among HS youth, 71% reported being asked by their care team in the past year about their drinking, while 53%, 49% and 41% reported being told that alcohol use was not healthy, could make their disease worse, and could interfere with their medications, respectively. Knowledge and guidance were not consistently related to use though answering incorrectly about alcohol/lab interactions was associated with binge drinking (p<.01). Among past year marijuana users: 35% reported substituting it for alcohol and perceiving alcohol as riskier; 24% perceived that marijuana helped their symptoms.

Alcohol and marijuana use are prevalent among youth with T1D. Knowledge about interactions between alcohol and medications/lab tests is poor. Education and screening are warranted to ameliorate risk.

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1715-P

The Association between Visit-to-Visit Variability of Fasting Plasma Glucose and All-Cause Mortality in Chinese Type 2 Diabetic Patients

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Diabetes is associated with long-term complications that include cardiovascular and kidney disease and is an important cause of mortality worldwide. The importance of visit-to-visit glycemic variability in diabetes remains unclear. This study aimed to assess the relationship between visit-to-visit variability in fasting plasma glucose (FPG) and all-cause mortality in Chinese type 2 diabetic patients.

From Jan 2007 to Dec 2007, 6,847 type 2 diabetic patients with at least four records of FPG in the first year during regular follow-up were included in this analysis. They were followed through Nov 2014. The data were obtained from Electric Health Recording (EHR) of Shanghai Minhang District of China. Glycemic variation were calculated using standard deviation and coefficient of variation of FPG (FPG-SD and FPG-CV respectively), and Cox proportional hazards regression model was applied to estimate the effect on all-cause mortality adjusting for other related risk factors.

11.94% (n=818) of the cohort died during an average of 6.2 years follow-up, resulting in a mortality rate of 19.43 per 1000 person-years. The mean FPG-SD was 0.91 mmol/L. After multivariate adjustment, hazard ratios for the second (0.37 to 0.66 mmol/L), third (0.66 to 1.15 mmol/L) and fourth (>1.15 mmol/L) versus first FPG-SD quartile (<0.37 mmol/L) were 0.90 (0.74, 1.11), 1.00 (0.84, 1.26) and 1.39 (1.15, 1.68), respectively (p=0.001). The mean FPG-CV was 0.12. Multivariable hazard ratios for the second (0.56 to 0.10), third (0.10 to 0.15) and fourth (>0.15) versus first FPG-CV quartile (<0.05) were 0.89 (0.73, 1.10), 1.06 (0.87, 1.30) and 1.36 (1.12, 1.64) (p=0.002).

High level of glycemic variability is associated with an increase of all-cause mortality, and both FPG-SD and FPG-CV may be independent predictors of all-cause mortality in Chinese type 2 diabetic patients.

Supported By: Shanghai Municipal Commission of Health and Family Planning

1716-P

Association of Plasma Vanadium with Impaired Glucose Regulation in Adults

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Vanadium compounds have shown beneficial effects on glucose metabolism in animal and clinical studies, but there are few epidemiologic evidences. Our previous study has recently shown that plasma vanadium levels declined in type 2 diabetes (T2D). The current study aimed to examine the association of plasma vanadium levels with impaired glucose regulation (IGR) and plasma heme oxygenase-1 (HO-1), a stress-responsive protein. A cross-sectional study was conducted involving 176 IGR and 824 normal glucose tolerance (NGT) individuals. An oral glucose tolerance test was performed to assess IGR. Plasma vanadium and HO-1 was measured by inductively coupled plasma mass spectrometry (ICP-MS) and ELISA, respectively. Plasma vanadium levels were lower in IGR group than in NGT group (P < 0.01). The odds ratios (95% confidence interval) for IGR across the increasing plasma vanadium quartiles were 1 (reference), 0.53 (0.28-1.00), 0.41 (0.21-0.81) and 0.07 (0.02-0.24), respectively, after multivariate adjustment including lifestyle factors, body mass index and family history of diabetes. Plasma HO-1 concentrations significantly decreased across quartiles of plasma vanadium levels (P < 0.01). In a linear regression model, a 1-unit increase in vanadium was associated with a decrease in HO-1 (β coefficient = - 0.21 ± 0.07, P = 0.005). Our results suggested that plasma vanadium concentrations were inversely associated with IGR and plasma HO-1 levels in Chinese adults.

1717-P

Integrating Structured and Unstructured Data in EHR for Stratification and Characterization of Diabetics

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The recent explosion of data from Electronic Health Records (EHR), have opened new paths for characterizing complex diseases and stratifying patients. Diabetes is such a disease where large efforts and resources are put into understanding its etiology and best treatments.

In this study we analyzed EHRs from a Danish diabetes center, which consisted of 14,018 T1D and T2D patients spanning 12 years and constituting almost 5.4M journal entries.

For both describing patients and mapping between unstructured (text) and structured (typed values) data we used ICD10 diagnosis codes. The codes from the unstructured data were found using an in-house developed text-mining pipeline, while the other codes were extracted directly from the structured data.

We stratified patients by implementing both a data-driven approach based on cosine similarities of the patients diagnosis codes vector, and a hypothesis approach based on sex and longitudinal HbA1c levels for characterizing well and unregulated diabetics.

By comparing ICD10 codes between the unstructured and structured data, we found only a small overlap. When investigating the differences we verified that the structured data lacked information that was not directly related to diabetes, but could be relevant when determining treatment strategies. For instance, no ICD10 codes for cancer were found in the structured data, and we thus propose a necessity for integrating both types of data when analyzing EHRs.

We were able to cluster patients into descriptive categories using ICD10 codes. We found a clear division of T1D and T2D patients, and when comparing the average HbA1C levels for patients in the clusters with the clusters found using HbA1C levels, we saw sub-groups with higher average HbA1C levels, indi-

cating a distinction of well and unregulated diabetics. The study shows, that by integrating all available data in EHRs it is possible to enhance the information on patients and stratify them into diagnosis and biochemical relevant clusters.

1718-P

The Association between the Level of Glycemic Control in Patients with Type 2 Diabetes and Diabetic Risk Factors among Their Household Members: A Study from Rural Uganda

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Early diagnosis is a key to the management of diabetes and prevention of co-morbidities. However, in Sub-Saharan Africa between 36-99% of people with diabetes are unaware of their disease status, which is partly due to limited access to diagnostic tools. Managing type 2 diabetes (T2D) involves adherence to dietary instructions and such instructions may also affect the diabetic risk factors in individuals with whom a patient with T2D shares daily life with. Thus, not achieving glycemic control could be associated with increased diabetic risk in individuals sharing household with the patient with T2D.

Therefore, to assess the association of glycemic control in patients with T2D and diabetic risk factors in their house mates, measurements of HbA1c, fasting plasma glucose (FPG), hypertension, anthropometry, dietary intake, smoking status and alcohol intake were obtained from 45 rural Ugandan patients with T2D and their 155 housemates.

Twenty-four patients (53.3%) did not reach their individual glycemic target according to ADA/EASD criteria. Compared to individuals from households with good glycemic control, individuals from households with a patient with poor glycemic control had higher levels of FPG and a higher weekly intake of staples (5.8 mmol/l vs. 5.5 mmol/l and 27.1 vs. 25.4, respectively. $p < 0.05$ for all tests). No differences were seen between the two groups of households in relation to HbA1c, hypertension, anthropometric measures, physical activity, oil intake, alcohol intake or smoking ($p > 0.05$ for all tests). All models were adjusted for sex, age, socio-economic status, education and patient time lived with T2D.

The results suggest that individuals sharing household with a patient not reaching glycemic control could be a target group for screening and prevention of T2D in settings with limited availability of diagnostic tools.

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1719-P

Metabolic Syndrome among Hispanics Living in a Midwestern City: Data from LILA (Latinos Living in Louisville Area) Study

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Metabolic syndrome (metS) is associated with increased risk of cardiovascular disease (CVD) and type 2 diabetes mellitus (DM). CVD is one of the leading causes of mortality in the Hispanic population, which is the largest and fastest growing ethnic minority in the U.S. We studied the prevalence of metS and attributes in 53 adult men and women aged 19 to 83 years who attended the Hispanic community health fair, Louisville, Kentucky. The updated 2006 International Diabetes Foundation (IDF) and ATP-III criteria were used to define metS. Mean age (± SD) was 49.8 ± 12.4 (range 19 to 83 years) and mean BMI was 31.2 ± 11.3 kg/m^2 (range 20 to 46). A high prevalence of metS (69.8%) and central obesity (85.2% with IDF criteria and 66.7% based on ATP-III criteria) was found as compared to NHANES data for the U.S. population (22.9%) and U.S. Hispanics (35%) from HCHS/SOL study. Frequencies of various components of metS in the study population are shown in the table.

Table. Frequencies of Components of Metabolic Syndrome in the Study Population.

	Total (n=53)	Women (n = 26)	Men (n =27)
MetS - IDF	37 (69.8%)	18 (69.2%)	19 (70.4%)
MetS - ATPIII	37 (69.8%)	17 (65.4%)	20 (74.1%)
Hypertension by history	11 (20.8%)	17 (65.4%)	20 (74.1%)
DM by history	6 (11.3%)	2 (7.7%)	4 (14.8%)
Hyperlipidemia by history	11 (20.8%)	6 (23.1%)	5 (18.5%)
*WC - IDF criteria	48 (90.6%)	25 (96.2%)	23 (85.2%)
*WC - ATP criteria	39 (73.6%)	21 (80.8%)	18 (66.7%)
Blood pressure criteria	24 (45.3%)	11 (42,3%)	13 (48.1%)
Fasting blood glucose criteria	24 (45.3%)	9 (34.6%)	15 (55.6%)
Triglycerides criteria	28 (52.8%)	16 (61.5%)	12 (44.4%)
HDL criteria	30 (56.6%)	14 (53.8%)	16 (59.3%)

*WC = Waist circumference.

Our study emphasizes the higher prevalence of cardiovascular risk factors in Hispanic women and men. Early screening and intervention in this at-risk and often indigent patient population using culture sensitive community based intervention may improve CV outcomes and reduce health care costs.

1720-P

Bidirectional Association between Diabetes and Gout: The Singapore Chinese Health Study

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Studies suggest that gout is associated with increased risk of type 2 diabetes (T2D), while T2D was inversely related to incident gout. However, no cohort study has investigated the T2D-gout bidirectional association simultaneously. We analyzed data from the Singapore Chinese Health Study (SCHS), a cohort of 63257 Chinese aged 45-74 years at recruitment (1993-1998). Self-reports of diagnosed diabetes and gout were enquired at follow-ups I (1999-2004) and II (2006-2010). We included participants free of cardiovascular disease or cancer at follow-up I and with complete data for both follow-ups. For the analysis of T2D to gout (analysis I), those with prevalent gout were further excluded (final n=31137). For the analysis of gout to T2D (analysis II), those with prevalent diabetes were also excluded (final n=28668). Cox regression models were used to estimate relative risks (RRs) with adjustment for demographic and lifestyle factors, including BMI and history of hypertension. Mean age at follow-up I was 60.5 (SD 7.3) years, and mean follow-up was 6.9 (SD 1.3) years. In the analysis I, diabetes was associated with a 23% lower risk of developing gout (682 incident cases; RR 0.77; 95% CI 0.60-0.97). No significant interaction was found with sex, BMI or hypertension status. In the analysis II, gout was associated with 35% increased risk of developing T2D (2223 incident cases; 1.35; 1.12-1.63), while the association disappeared after adjustment for hypertension and BMI (1.00; 0.83-1.21). Significant interaction was found with BMI (Pinteraction=0.04) and hypertension (Pinteraction=0.007), and the association was marginally significant in adults with BMI <24 kg/m2 (1.30; 0.95-1.76) and significant among non-hypertensive participants (1.37; 1.02-1.84), but not in their counterparts. Our results provide compelling evidence that diabetes is associated with a lower risk of incident gout, while gout was positively related to diabetes among normal weight and non-hypertensive adults.

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EPIDEMIOLOGY—TYPE 1 DIABETES

Guided Audio Tour: The Epidemiology of Type 1 Diabetes *(Posters: 1721-P to 1728-P), see page 15.*

1721-P

Elective Cesarean Section and Risk of Childhood Type 1 Diabetes—A Nationwide Cohort Study

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Delivery by elective cesarean section has been proposed to be a risk factor for childhood type 1 diabetes, but results from studies are diverging. Increasing rates of cesarean section, as well as expanding research indicating a serious influence of the gut microbiota on future health, emphasize the need for large-scale studies to evaluate the clinical consequences of delivery by cesarean section in the general population.

In this Danish Nationwide cohort study we followed all singletons born during 1982-2010 and assessed the risk of childhood type 1 diabetes with onset before the age of 15 years by Cox regression. Four nationwide registers provided information on mode of delivery, outcome and confounders.

A total of 1,760,336 singletons contributed 20,436,684 person-years, during which 4,400 were diagnosed with childhood type 1 diabetes. The risk of childhood type 1 diabetes was increased in children delivered by elective cesarean section compared with vaginal delivery when adjusted for year of birth, parity, sex, parental age and education and paternal type 1 diabetes diagnosed before childbirth (HR 1.17; 95% CI 1.04 to 1.32), but not when adjusted for maternal type 1 diabetes (HR 1.07; 95% CI 0.95 to 1.21). However, childhood type 1 diabetes tended to be more prevalent in offspring of mothers with type 1 diabetes when delivered by elective cesarean section (HR 1.62; 95% CI 0.99 to 2.66). Delivery by emergency cesarean section was not associated with childhood type 1 diabetes. Paternal type 1 diabetes was

For author disclosure information, see page A810.

a stronger risk-factor for childhood type 1 (HR 11.79; 95% CI 10.22 to 13.59) than maternal type 1 diabetes (HR 6.47; 95% CI 5.23 to 8.00).

In conclusion, delivery by elective cesarean section does not increase the risk of childhood type 1 diabetes in the general population, but may increase the risk in offspring of women with type 1 diabetes. The finding that paternal type 1 diabetes compared to maternal type 1 is a two-fold higher risk-factor for childhood type 1 diabetes needs further evaluation.

1722-P

Factors Involved in Predicting Time to Type 1 Diabetes in Antibody Positive TrialNet Subjects

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Relatives of subjects with type 1 diabetes (T1D) positive for islet autoantibodies (Ab) have a high risk of progression to diabetes; however, rate of progression varies significantly. In 1287 TrialNet subjects positive for >1 biochemical Ab (IAA, GADA, IA-2A, ZnT8A), we analyzed new electrochemiluminescence (ECL) assays (ECL-IAA and ECL-GADA) at their initial visit and metabolic markers at baseline; after a median follow-up of 33 months, 164 of these subjects developed T1D. Univariate analyses showed that biochemical Ab, ECL-IAA, ECL-GADA, age, number of positive Ab, presence of HLA DR3/4-DQ8 genotype, HbA1c and oral glucose tolerance test (OGTT) markers (area under the curve (AUC) glucose, fasting C-peptide, and AUC C-peptide) were all significantly associated with progression to T1D. Four multivariate Cox proportional hazards models were compared, with the base model including age, OGTT markers and number of positive biochemical Ab. The ability to predict time to T1D was improved by adding ECL (but not specific biochemical) Ab to the base model. The model with combined categorical ECL assays (defined as positive if > one ECL assay was positive) was the best and factors that remained significantly associated with time to T1D were AUC C-peptide, AUC glucose, number of positive biochemical Ab and ECL positivity (Table). In Ab positive subjects, ECL assays improve the ability to predict time to T1D.

Table.

Covariate	P-value	Hazard ratio (95% CI)
Age	0.199	0.99 (0.97-1.01)
AUC glucose	<.0001	1.02 (1.01-1.03)
Fasting glucose	0.202	1.15 (0.93-1.42)
AUC C-peptide	<.0001	0.75 (0.69-0.83)
Fasting C-peptide	0.094	1.29 (0.96-1.72)
# of positive biochemical Ab	<.0001	2 vs. 1: 2.59 (1.52-4.45); 3 vs. 1: 3.06 (1.84-5.10); 4 vs. 1: 3.80 (2.12-6.80)
ECL (GADA or IAA): pos/neg	0.0003	8.88 (2.74-28.8)

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1723-P

Determinants and Prognosis of Early- vs. Late-Onset Islet Autoimmunity

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While incidence of islet autoimmunity (IA) peaks in early childhood, little is known about determinants of late-onset IA or its prognosis for future type 1 diabetes (T1D).

This study explored demographic and genetic characteristics, autoantibody appearance and persistence and progression to T1D in early- versus late-onset IA. Diabetes Autoimmunity Study in the Young (DAISY) followed 2,542 high-risk children for a median of 11 years. IA was defined as persistence of autoantibodies to insulin, GAD, IA-2 or ZnT8. Early-onset IA (<8 years) developed in 142 subjects; late-onset IA was documented in 60. Children with late onset were more likely to be of non-white ethnicity and have no first-degree relatives with T1D. Frequencies of HLA-DR3/4,DQ8, PTPN22, INS, CTLA4, and IFIH1 genotypes did not differ between groups.

Late-onset IA presented less often with multiple antibodies. Autoantibodies were more likely to revert to negative and progression to T1D was less frequent. Although followed for shorter time from IA onset, Kaplan-Meier survival analysis with log rank test showed decreased risk of spread to more antibodies (p=.04) or progression to T1D (p=0.003). Late-onset IA may be more frequent than previously appreciated, especially in Hispanics, Blacks and general population families free of T1D. Further follow-up of both early- and late-onset IA subjects is needed to explore implications for development of adult T1D, GDM, LADA and T2D.

Table. Characteristics of Early- vs. Late-Onset Islet Autoimmunity (IA).

Characteristic	Early-Onset (IA < 8 y)	Late-Onset (IA ≥ 8 y)	p-value
Male	52%	45%	ns
Hispanic or Black	14%	35%	.001
1st degree relative proband	64%	52%	.10
Sibling proband	27%	12%	.03
>1 antibody at onset	32%	10%	.001
IAA first	49%	32%	.03
ZnT8A first	27%	15%	.07
GADA first	51%	52%	ns
IA-2A first	20%	15%	ns
Spreading to other antibodies	60%	47%	.08
Revert to no IA	35%	57%	.003
Progression to T1D	47%	13%	.0001
Median follow-up (from 1st antibody)	7.0 yr	4.3 yr	.003

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1724-P

Predictors of Slow Progression to Diabetes in Children with Multiple Islet Autoantibodies

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Approximately 80% of children with multiple islet autoantibodies (IA) progress to type 1 diabetes (T1D), although rate of progression is variable. The Diabetes Autoimmunity Study in the Young (DAISY) has followed for T1D 118 children with multiple IA. Here, we compare rapid progressors (N=39) who developed T1D in <5 yrs with slow progressors (N=27) who had a diabetes-free follow-up for >10 yrs (5 eventually developed T1D). Excluded were 25 children diagnosed with T1D within 5-10 yrs and 27 children diabetes-free followed for <10 yrs. Gender, ethnicity, family history of T1D and HLA DR3/4-DQ8 were not significantly different between the two groups. Slow progressors had later onset of IA (5.8 vs. 4.0 yrs, p=0.03) and fewer IA (mIAA, GAD, IA2, ZnT8, electrochemiluminescence (ECL) IAA, ECL-GAD) at the initial positive visit than rapid progressors (1.6 vs. 3.0, p=0.0002). Antibody levels (mean ± SD) were also lower in slow progressors (Table). Of 25 non-HLA SNPs associated with T1D and previously analyzed in DAISY, only rs1990760 minor allele G (IFIH1) was less frequent in the slow progressors (30% vs. 49%, p=0.04). In multivariate analyses including age at seroconversion, HLA DR3/4 and all mean antibody levels, lower mean ECL-IAA independently predicted slower progression to T1D (OR 0.66, p=0.027). In conclusion, later onset of IA and lower IA levels predicted slower progression to diabetes among children with multiple IA.

Table.

Variable	Rapid Progressors (N=39)	Slow Progressors (N=27)	P value
Initial ECL-IAA	0.09 ± 0.18	0.01 ± 0.02	0.02
Initial mIAA	0.15 ± 0.40	0.01 ± 0.02	0.04
Initial IA-2	0.17 ± 0.35	0.02 ± 0.07	0.02
Initial GAD65	0.12 ± 0.27	0.02 ± 0.08	0.03
Mean ECL-IAA	0.10 ± 0.17	0.01 ± 0.02	0.01
Mean mIAA	0.12 ± 0.18	0.01 ± 0.02	0.001
Mean ZnT8	0.16 ± 0.21	0.06 ± 0.10	0.01

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1725-P

Glycemic Control and Acute Diabetes Complications during Transition from Pediatric to Adult Care

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Transition from pediatric to adult diabetes care is a high risk period marked by increased rates of disengagement from care and diabetes-related complications. We conducted a population based cohort from 2007-2014 using

uniquely linked pediatric and adult electronic medical records. We determined the impact on glycemic control and acute diabetes-related complications in the three years prior and subsequent to the transition. Transition occurred at 18 years of age in a total of 147 patients. The majority of patients (98%) had type 1 diabetes and 77 (52.4%) were female, 14 (10%) had co-existing hypothyroidism. At the baseline visit (age 15 yrs), median duration of diabetes was 5 yrs (range 0-14), mean (SD) weight 66.4 (13.4) kg, BMI 23.5 (4.0 kg/m$^{2)}$, SBP 118.2 (13.6) mmHg and DBP 65.3 (8.8) mmHg. There were 45 (31%) patients on an insulin pump, 96 (65%) on multiple daily injections, 3 (2%) on premixed insulin and 3 (2%) on oral agents.

The mean A1C was 8.66% (95% CI 5.77-13.66) prior to transition and 8.89% (95% CI 5.65-16.9) following transition. A1C changed by a mean (SD) value of 0.30% (1.47) (p=0.014). There were 65 and 101 emergency department visits and/or hospitalizations for acute complications (hypoglycemia and hyperglycemia) respectively before and after transition. Diabetic ketoacidosis (DKA) admissions were 3 times higher after transition (OR 3.0, 95% CI 1.19-7.5) as compared to before transition. Assist- requiring hypoglycemia occurred in 12% of patients before and 8% of patients after transition (OR 0.42, 95% CI 0.12 to 1.27). Urine albumin creatinine ratio (ACR) testing decreased after transition: 47 patients had an ACR done at least once pre-transition versus 29 post-transition. The number of patients having at least one LDL-C test increased following transition (14 patients before to 82 patients after).

Our results suggest that transition of young adults with diabetes to adult care has a negative impact on glycemic control and is associated with a significant increase in risk for DKA.

Epidemiology/ Genetics **POSTERS**

1726-P

The Haptoglobin 2 Allele Is Associated with Increased Urinary 15-isoprostane F2t Concentrations Over Time among Adults with Type 1 Diabetes

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We have previously shown that the Haptoglobin (Hp) 2 allele is a significant predictor of coronary artery disease risk in type 1 diabetes, potentially due to the decreased antioxidative potential associated with Hp 2. We, thus, assessed whether urinary 15-isoprostane F2t (IsoP) concentrations, a biomarker of oxidative stress and lipid peroxidation, differ by Hp genotype in adults with type 1 diabetes.

Urinary IsoP were measured at three time points during 20 years of follow up in a cohort of childhood onset type 1 diabetes (n=454, baseline mean age 28 and diabetes duration 19 years). Analyses were first conducted to evaluate differences in IsoP levels at the first time point of measurements (considered the baseline for this analysis). Mixed models were further constructed to assess the association between the repeated measures of urinary IsoP and Hp, after adjustment for diabetes duration and univariately significant risk factors.

No significant differences across Hp genotypes were observed at baseline with the exception of a trend toward higher IsoP concentrations with the number of Hp 2 alleles (p=0.02). In multivariable regression analyses allowing for diabetes duration, gender, smoking status, HbA1c, pulse, HDL and non-HDL cholesterol, glomerular filtration rate, WBC count, fibrinogen, hsCRP, adiponectin and α-tocopherol, Hp 2-2 was associated with higher IsoP compared to Hp 1-1 (β=0.14, p=0.04). Non-significantly greater urinary IsoP concentrations were also observed in Hp 2-1 carriers (β=0.09, p=0.18). In multivariable mixed models, both Hp 2-1 (β=0.09, p=0.06) and Hp 2-2 (β=0.11, p=0.02) were associated with elevated IsoP concentrations over the 20 year follow-up compared to Hp 1-1 carriers.

In this study of adults with type 1 diabetes, the Hp 2 allele is associated with greater IsoP concentrations over 20 years of follow-up, providing further, novel, evidence that the antioxidative capacity of Hp 2 is inferior to that of the Hp 1 allele.

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1727-P

Dietary Patterns and Waist-to-Height Ratio in Youth with Type 1 Diabetes: SEARCH for Diabetes in Youth Nutrition Ancillary Study

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The associations of dietary patterns with central obesity are not clear in youth with type 1 diabetes (T1D).

T1D cases 10-19 years newly-diagnosed between 2002 and 2005 were included (N=766). Data from the SEARCH food frequency questionnaire was used to calculate Mediterranean diet score (mKIDMED; range from -1 to 10; using a modified KIDMED index) and DASH diet score (range from 16.4 to 65.8; using an established DASH score for youth). Waist-to-height ratio (WHtR) was used as a surrogate for central obesity. Cross-sectional multiple linear regression was used with sequential adjustment for demographic, behavioral and clinical variables. Results were stratified by gender due to significant effect modification (P<0.05).

The mKIDMED score was not significantly associated with WHtR in any analyses, however, better diet quality reflected by higher DASH diet score were associated with lower WHtR for T1D males, independent of demographic and diabetes characteristics, energy intake, physical activity and BMI. The lack of significant associations for mKIDMED may be related to its narrow range compared to DASH score. For DASH score, the non-significant associations in females may be due to the difference of fat distribution between genders.

These findings suggest that adherence to a DASH diet may be associated with lower rates of central obesity in T1D males.

Table. Regression Coefficients of the Association of Diet Scores with WHtR in Youth with T1D[1].

	mKIDMED Score (N=766)		DASH Score (N=766)	
	Female (N=363)	Male (N=403)	Female (N=363)	Male (N=403)
	$\beta \pm SE$	$\beta \pm SE$	$\beta \pm SE$	$\beta \pm SE$
Model 1[2]	-0.001 ± 0.002	-0.002 ± 0.002	-0.0001 ± 0.0004	-0.0001 ± 0.0004**
Model 2[3]	-0.001 ± 0.002	-0.001 ± 0.002	0.0001 ± 0.0004	-0.0008 ± 0.0004*
Model 3[4]	-0.001 ± 0.002	-0.0005 ± 0.0018	0.0001 ± 0.0004	-0.0010 ± 0.0004**
Model 4[5]	-0.001 ± 0.001	-0.002 ± 0.001	0.0001 ± 0.0003	-0.0006 ± 0.0002*

[1]N=766, mean age=13.7±2.5 years, T1D duration=11.1±6.2 months;
[2]Model 1: unadjusted model;
[3]Model 2: adjusted for age, sex, race/ethnicity, parental education, household income, clinic site, leisure-time physical activity and total energy intake;
[4]Model 3: Model 2 + diabetes duration, insulin regimen, insulin dose per kilogram and HbA1c;
[5]Model 4: Model 3 + BMI z-score; ** P<0.05; ** P<0.01.*

Supported By: China Scholarship Council; National Institutes of Health-National Institute of Diabetes and Digestive and Kidney Diseases

1728-P

Association of Continuous Subcutaneous Insulin Injection Pumps with Lower HbA1c and Mortality in Type 1 Diabetes of Chronic Duration

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Continuous subcutaneous insulin infusion pumps (CSII) may improve HbA1c and quality of life relative to the use of multiple daily injections (MDI) in individuals with type 1 diabetes (T1D), yet there is limited information about the relationship of CSII to mortality. The 50-Year Medalist Study provides a unique opportunity to investigate in 944 individuals with more than 50y of T1D (mean duration=53y, HbA1c=7.1%, age=65y, age at onset=11y, daily insulin dose=0.43 u/kg; 59% use CSII, 49% for 10y or longer). Medalists using CSII have lower HbA1c (7.1% vs. 7.3%, p<0.001), are less likely to have detectable serum C-peptide (29% vs. 42%, p<0.001), are younger (64y vs. 68y, p<0.001), have shorter duration of disease (54y vs. 56y, p<0.001), have less cardiovascular disease (CVD) (37% vs. 45%, p=0.01), have higher eGFR (71 vs. 67 ml/min/1.73m2, p<0.001), are more likely to use statins (72% vs. 66%, p<0.05) and aspirin (53% vs. 43%, p<0.01), and are similar in use of antihypertensives (65% vs. 64%, p=0.90). We investigated the influence of CSII on mortality by Cox proportional hazards regression. Since 2003, 94 (10%) participants have passed away, 32 (6%) in CSII and 62 (16%) in MDI; 44% from CVD, 10% from cancer, 7% from direct complications of diabetes, and 7% due to accidents. Mean age at death was 77y. CSII use was associated with reduced mortality (hazard ratio (HR)=0.42, 95% CI: 0.27, 0.65) during a mean follow-up of 5y. Models adjusted for baseline characteristics and stratified by CSII show hazard increases by 1.09 for each unit (%) change in HbA1c for MDI compared to 1.30 for CSII; among Medalists who use CSII HbA1c has a larger role in risk for mortality than among those who use MDI. For Medalists using MDI additional factors of C-peptide, antihypertensive use, and duration of disease influenced mortality risk. CSII may reduce HbA1c and mitigate other risk factors, reducing mortality among individuals with chronic duration of T1D.

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Guided Audio Tour poster ADA-Funded Research

1729-P

Hemoglobin A1c and Mortality in Adults with Type 1 Diabetes: Updated Analysis from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Cohort

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A recent report from Sweden has suggested that individuals with type 1 diabetes who have an updated (over, on average, the prior 8 years) mean HbA1c <7.0% or 7-7.8% have a 2.36- and 2.38-fold increase in mortality compared to the background population. The EDC study of childhood onset type 1 diabetes has previously reported a similar pattern of little association across the bottom 2 quintiles of updated (over 22 years) mean HbA1c (<7.8 and 7.8-8.4%). In the current analyses, in order to reflect more contemporary experience, we consider only recent data (from 1996 to 2011, N= 440; mean age=37 years, duration=29 years; 66 deaths) and compare mortality to the background (Allegheny County) population. Comparing those with HbA1c < 7.0 and 7.0-7.8% at baseline (1996-98), the age adjusted SMRs are 1.85 (95% CI 0.75, 3.85) and 1.80 (0.84, 3.42) respectively while for the updated mean HbA1c the corresponding SMRs are 1.98 (0.92, 3.76) and 1.54 (0.68, 3.06). However, if the same groupings are based on the most recent HbA1c, the age adjusted SMR for <7.0% is 1.12 (0.49, 2.23) while for 7.0-7.8% it is 2.84 (1.44, 5.06). While these results thus confirm the shallow gradient of mortality risk by mean HbA1c below 7.8% seen in Sweden, they also, albeit based on a small sample size, suggest that mortality may be comparable to that of the general population for those with a most recent HbA1c <7.0%. These findings should be examined in other cohorts.

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1730-P

Glycemic Control Is Worse in the U.S. Compared with Germany/Austria among 33,258 Pediatric Patients with Type 1 Diabetes

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In this report, we investigate whether there are differences in glycemic control between the U.S. T1D Exchange (T1DX) and German/Austrian DPV registries across 33,258 pediatric patients (pts).

Pt characteristics, treatment modalities, and clinical outcomes (HbA1c, severe hypoglycemia [SH], and diabetic ketoacidosis [DKA]) were compared using Wilcoxon test for continuous variables and chi-square test for categorical variables, for 3 age groups.

Pediatric pts in the T1DX and the DPV were similar for sex, T1D duration, and continuous glucose monitoring (CGM) use. Pts in the T1DX performed less self-monitoring of blood glucose per day compared to those in DPV (p<0.001, Table). Children and adolescents in the T1DX had higher HbA1c and a lower % meeting the goal of <7.5% compared to those in DPV (p<0.001). The proportion of pts having ≥1 SH event (resulting in seizure/coma) in the past yr was similar between the two registries, but pts in T1DX had more DKA (p<0.001). Pump use differed by registry for all age groups (p<0.001); pump use was lower in the T1DX for young children <6, but higher in the T1DX for pts aged 6-<18.

Pediatric pts of all ages in the DPV achieved better clinical outcomes compared with the T1DX, despite higher pump use among T1DX children aged 6-<18. Further research is needed to better understand where to target interventions in the U.S. in order to improve clinical outcomes.

Table.

	<6 years		6-<12 years		12-<18 years	
	T1DX (n=674)	DPV (n=1,948)	T1DX (n=4,238)	DPV (n=6,779)	T1DX (n=6,645)	DPV (n=12,974)
HbA1c, % (mmol/mol)	8.2% (66)	7.4% (58)	8.2% (66)	7.5% (59)	8.7% (71)	8.2% (66)
% A1c <7.5% (<58 mmol/mol)	22%	56%	24%	53%	20%	36%
% with ≥1 SH event (seizure/coma) in past year	3%	2%	2%	3%	2%	3%
% with ≥1 DKA event (hospitalization) in past year	6%	3%	6%	4%	8%	5%
Self-monitoring of blood glucose (SMBG)/day	7	8	7	7	5	6
% on pump therapy	50%	74%	57%	47%	56%	39%

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1731-P

GAD Autoantibody Remission Associated with Risk of Type 1 Diabetes: TEDDY Study

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Little is known about the effects of the variable presence of islet autoantibodies on the risk of type 1 diabetes (T1D); remissions may be true remission of autoimmunity, humoral markers only or just assay variability. This study assessed autoantibody expression to further clarify the natural progression of the disease and identify factors associated with different progression rates in The Environmental Determinants of Diabetes in the Young (TEDDY) Study of genetically high-risk children. Eligible subjects were ≤10 years of age screened more than once for mIAA, GADA, and IA-2A. Persistent autoantibody was defined as an autoantibody present on ≥2 consecutive visits and confirmed in two reference laboratories. Remission was defined as ≥2consecutive negative visits post persistence. There were 566/8503 (6.7%) children who developed a persistent autoantibody (405 mIAA, 424 GADA, and 247 IA-2A). Autoantibody remission <12 months, 12–24 months and >24 months post persistence was 27.7, 10.1, and 6.0 per 100 person-years for mIAA, 17.1, 6.3, and 1.7 person-years for GADA, and 3.3, 1.3, and 1.0 for IA-2A. Higher initial autoantibody levels decreased the risk of remission (mIAA: HR 0.85, 95%CI (0.77-0.94), p=0.002; GADA: HR 0.35, 95%CI (0.25-0.49), p<0.001; and, IA2A: HR 0.55, 95%CI (0.35-0.87), p=0.01), all per 1 standard deviation. Gender, family history of T1D, country and age at seroconversion did not predict GADA or IA-2A remission. However, mIAA were more likely to remit in children with HLA-DR3/3 compared to HLA-DR4/4 (HR 2.21, 95%CI (1.2-4.2), p=0.02). Of those that remitted, 25% mIAA, 15% GADA and 50% IA-2A reverted back to persistence. After adjusting for baseline level, GADA remission (HR 2.8, 95%CI (1.7-4.8), p=0.0001), but not mIAA (HR 0.9, 95%CI (0.6-1.4), p=0.55) or IA2A remission (HR 1.0, 95%CI (0.9-1.1), p=0.38) predicted T1D. The predictive value of remission on risk of T1D appears to vary by autoantibody.

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1732-P

Unexpected Stability of Type 1 Diabetes Incidence in a U.S. Cohort, 1994-2010

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Recent studies show that the incidence of type 1 diabetes (T1D) is increasing worldwide by 2-5%, making the epidemiology of T1D of particular research interest. Potential risk factors under study include age, gender, location, race, genetics and environmental factors. Location is of particular interest since the rate at which incidence is increasing varies with region. Although T1D incidence has been difficult to study in the U.S. due to lack of population databases, the SEARCH study showed increasing incidence in U.S. non-Hispanic whites.

Residents in a Midwestern county in the U.S. receive virtually all medical care in the county. Medical encounters are indexed and linked to medical records, allowing rigorous study of epidemiology of diseases. Residents with T1D were found by searching multiple databases and participation in prior studies. Initially, a broad search based on diagnosis codes was used to identify potential cases between 1994-2010. Clinical charts were reviewed to accurately capture all incident cases. Incidence rates were directly standardized against the 2010 U.S. white population, and trends in incidence for age, gender and calendar time were analyzed with Poisson regression. Charts were also reviewed for biopsy proven celiac disease diagnosis.

There were 233 new cases with an age and gender-adjusted annual incidence rate of 9.2 (95% CI, 8.0-10.4)/100,000 population. In reference to a younger population of age<30 years, the rate of T1D was 17.0 (95% CI, 14.5-19.5)/100,000 person-years, based on 177 cases. Average annual incidence rates were higher in males than females (10.5 vs. 7.7/100,000, across all ages; P=0.015) and decreased with older age (P<0.001). There was no significant linear trend in T1D incidence (P=0.45), as incidence appeared to increase from 1994-2002 and decrease after. Among 109 T1D cases tested for celiac disease, 12% had celiac disease, higher compared to prior reports.

In contrast to recent studies, we did not see an increased incidence of T1D in a Midwestern U.S. population.

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1733-P

Nuclear Magnetic Resonance-determined Lipoprotein Subclasses and Carotid Intima-Media Thickness in Type 1 Diabetes: A Prospective Study

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We investigated the prospective associations of nuclear magnetic resonance-determined lipoprotein subclass profiles (NMR-LSP) with carotid intima-media thickness (IMT) in type 1 diabetes.

NMR-LSP were measured in an available subset of Diabetes Control and Complications Trial (DCCT) participants (n=455; men=246; women=209) at study entry ("baseline", 1983-89), and were related to carotid IMT determined by ultrasonography during the observational follow-up of DCCT, the Epidemiology of Diabetes Interventions and Complications (EDIC) study, in EDIC year 1 (1994-96), year 6 (1998-2000), and year 12 (2004-2006). Associations between NMR-LSP and IMT were examined by multiple linear regression stratified by gender and following adjustment for weighted mean HbA1c, albumin excretion rate, DCCT randomization group, ultrasonography devices, and IMT reader.

In men, we observed significant positive associations of DCCT baseline NMR-based LDL subclasses (total and small LDL) with common and internal carotid IMT, at EDIC years 1, 6 & 12. Significant inverse associations of mean HDL diameter with common and internal carotid IMT were also observed in men at similar time points. Furthermore, associations of HDL-subclasses [large (negative), medium (negative) and small (positive)] with common and/or internal carotid IMT were noted at one or more EDIC time points. Finally, small VLDL particles were positively associated with common carotid IMT, but only at EDIC year 1 in men (all $p<0.05$). No significant associations were observed in women.

We observed associations of LDL-subclasses and HDL particle size with IMT that persisted throughout the EDIC observational phase. These data suggest that NMR-LSP can reveal some associations of lipoprotein characteristics with future disease with regard to common and internal carotid IMT in men.

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1734-P

Determinants of Change of sAF over 4 Years of Follow-up in Type 1 Diabetes

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Skin Autofluorescence (sAF) is a non-invasive marker of the long-term accumulation of Advanced Glycation End products (AGEs) in tissues, implicated in complications of diabetes. Our study aimed to identify factors associated with the progression of sAF during 4 years of follow-up of subjects with type 1 diabetes.

In this prospective study, 159 patients with type 1 diabetes underwent two measurements of sAF with AGE Reader (Diagnoptics): one at inclusion (T0, 2009) and one at follow-up 4 years later (T4). At these time points, the variables reported to influence the accumulation of AGEs in transversal studies was recorded: age, sex, smoking, duration and control (HbA1C) of diabetes, and renal function (estimated glomerular filtration rate eGFR by EPI-CKD equation). The associations between sAF at T4 as dependent variable and measurements at T0, mean and variance of the T0 and T4 measurements of HbA1c and eGFR were studied in multivariate linear regression analysis adjusted on age, sex, baseline sAF at T0, body mass index, smoking status, and duration of diabetes.

At inclusion, the 159 patients were 51±15 years old, 39.3% women, BMI 25.0±3.9, duration of diabetes 23±14 years, HbA1c 7.7 ±1.0%, eGFR 89.5±21.9 mL/min/1.73 m2. The mean initial sAF was 2.13±0.56 AU (Arbitrary Unit), it significantly increased (at T4: 2.48 ±0.68 ($p<0.0001$), whereas the mean HbA1c (7.6 ±0.8%) and eGFR (89.6±21.3 mL/min/1,73 m2) were stable at T4. In multivariate analyses sAF at T4 was associated with sAF at T0 (β =0.75; 95% CI = (0.55 , 0.95), $p<0.0001$), eGFR at T0 (β =-0.07; 95% CI = (-0.12 ; -0.02), p=0.007), mean eGFR (β =-0.07; 95% CI = (-0.13 ; -0.02), p=0.006), and to the variance of HbA1c (β =0.09; 95% CI = (0.03 , 0.15), p=0.006).

In our patients with type 1 diabetes, the baseline sAF, renal function, and glycemic variability were the main contributors to the increase of sAF 4 years later.

1735-P

The Incidence of Type 1 Diabetes Mellitus in Romanian Children Aged 0-14 Years Increased Constantly

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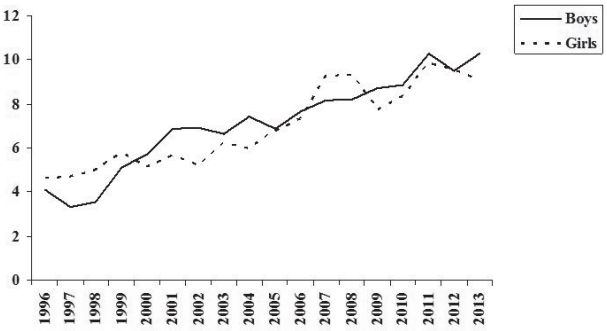
The aim of this work was to analyze the evolution of the incidence of type 1 diabetes mellitus (T1DM) in children aged 0-14 years from Romania, starting year 1996.

The primary source for incident cases was the Romanian Childhood Diabetes Register. The secondary source was represented by the medical records from "Cristian Serban" Medical Center from Buzias, a reference center for pediatric diabetes. The incidence was calculated in the age groups 0-4, 5-9, 10-14, and 0-14 years.

A number of 4,546 new cases of T1DM (2,346 - 51.6% boys, and 2,200 - 48.4% girls), aged less than 15 years, were found by both sources. The overall level of ascertainment was 96.8%. The estimated average incidence of T1DM during the studied interval was 7.06/100,000/year (95% CI 6.34 - 7.78). It was similar in boys (7.13/100,000/year, 95% CI 6.43 - 7.83) and in girls (6.99/100,000/year, 95% CI 6.25 - 7.73). The incidence in children aged 0-14 years raised extremely significant ($p<0.0001$) during the studied interval, being more than double in 2013 (9.71/100,000/year) than in 1996 (4.37/100,000/year), with a mean annual increase of 7.2% (Figure). This trend was noticed for all the age subgroups.

Romania is a country with an intermediate incidence of T1DM in children that showed a continuous increase over the studied interval.



1736-P

A Comparison of Diabetes Type 1 in South Asian and Caucasian Patients in the UK: The Type 1 in Minority Ethnic Populations (TIME) Study

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Diabetes type 2 (T2D) is up to six times more common in people of South Asian origin than in white Caucasians in the UK. Furthermore, onset is earlier with higher morbidity and mortality. Diabetes type 1 (T1D) has not previously been characterised in this group, despite South Asians comprising over 7% of the UK population. Recent reports suggest the prevalence of T1D is similar across South Asian and white Caucasian ethnicities. The aim of the TIME study was to characterise and compare T1D between South Asian and background white Caucasian populations.

We performed a case controlled analysis of 417 patients across two centres in the West Midlands, UK (a region in the UK with one of the highest South Asian populations) matching for age and gender (one South Asian patient matched to two white Caucasian). Data for 177 patients was analysed from the Queen Elizabeth Hospital (QEH) and 240 patients from New Cross Hospital (NCH).

The results are shown in Table 1. Values are median (interquartile range) with * indicating a p value <0.05.

In conclusion, we found that South Asians with T1D presented at a later age, and had more significant macrovascular risk factors than white Caucasians. Interestingly, there was no difference in glycaemic control or prevalence of microvascular complications. As for T2D, these findings have important implications for service delivery and personalized healthcare.

For author disclosure information, see page A810.

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Table 1. A Comparison of Diabetes Type 1 in South Asian and Caucasian Patients in the UK.

Characteristic (Number of Patients)	NCH South Asian (80)	NCH Caucasian (160)	QE South Asian (59)	QE Caucasian (118)
Age (yrs)	33.5 (23.75-45)	34 (23.75-45)	36 (28-44.5)	36 (28 – 44.75)
Age at diagnosis (yrs)	16 (9.75-24)*	12 (8-18)*	17.5 (10.75-26)	15 (10-22)
HbA1c (mmol/mol)	75 (61.5-88.5)	76 (63-91)	66.1 (55.25-81.75)	70.5 (61-83.6)
Systolic / Diastolic BP (mmHg)	121 (113-132)	125 (115-132)	130 (120.5-141.5)/ 86 (80.5-90)*	131.5 (120.3-144) / 82 (77.25-88.75)*
Weight (kg)	72.4 (58.9-82.35)	73.6 (64-90)	74 (58.65-85.75)	76.5 (66.2-88)
Total cholesterol (mmol/L)	4.7 (3.9 – 5.45)	4.6 (4-5.3)	4.45 (3.8-5.45)	4.1 (3.7-4.95)
HDL (mmol/L)	1.3 (1.0 – 1.6)*	1.4 (1.2-1.65)*	–	–

1737-P

Ecological Study between the Incidence of Type 1 Diabetes and Geochemical Data in Sardinia: Negative Correlation with Zinc and Copper

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Sardinia has the second highest T1D incidence rate (45/100.000, 0-14 years, 1989-2009) in the world, with the annual increase of 2.2%. The aim of this study was to explore the possibility that exposure to environmental elements (As, Be, Cd, Co, Cr, Cu, Mn, Ni, Pb, Sb, Se, Sn, Th, Tl, U, V, Zn) could explain previously reported geographical clustering of T1D in Sardinia. The measurements were mainly derived from stream sediment samples of the Geochemical Strategic Prospecting of Sardinia. Lithological formation threshold values were determined for each element. The formations covered by sufficient data were individually considered, while the others were pooled with formations of the same age and lithology. Sampling units included lithologically homogeneous municipal territories. T1D incidence data for 1989-2009 normalized for the size of each municipality were used. T1D and geochemical data were geo-referenced with a Geographic Information System (GIS) and analysed using correlation matrices. Significant negative correlations were found between T1D incidence and Cu (r=-0.35, p=0.0002) and Zn (r=-0.31, p=0.001), but not the other elements.

These preliminary data may suggest a protective role of environmental exposure to Cu and Zn and development of T1D. It is biologically plausible given the role of Zn in regulation of insulin secretion and in cellular processes of homeostasis and signalling. This ecological study must be validated in a prospective study including individual assessment of zinc and copper content in foods of children developing T1D.

1738-P

Pulmonary Function and Glycemic Control

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Reduced pulmonary function has been consistently observed in individuals with type 1 diabetes (T1D) and the mechanism is likely complex. Hyperglycemia has been shown to be associated with reduced pulmonary function but it is not clear whether this reduction is progressive across the range of HbA1c. We examined the association between Hba1c and pulmonary function derived through spirometry.

We performed spirometry on participants in the Coronary Artery Calcification in type 1 diabetes (CACTI) study and calculated the Forced Expiratory Volume at 1 second % predicted (FEV1pp) and the Forced Vital Capacity % predicted (FVCpp), adjusted for age, sex, body habitus and race. Glycemic control was measured using HbA1c, cigarette use was assessed as ever versus never smoking (SMOKE). We observed no overlap in HbA1c between controls and those with T1D so models were stratified. Two control participants with type 2 diabetes were excluded. General Linear Models were used to assess the relationship between HbA1c and the outcomes adjusting for SMOKE in all models and diabetes duration in the T1D adults.

121 participants completed spirometry; 47 T1D and 74 Controls. Participants did not differ by sex, asthma or smoking status but differed in HbA1c (T1D 7.7 ± 0.9, Control 5.5 ± 0.4) and race (p=0.01). Participants with T1D had lower FEV1pp (86%; 95%CI 83-90% vs. 98%; 95-100%, p<0.0001) and lower FVCpp (89%; 86-92% vs. 98%; 95-101%, p<0.0001) compared to controls. HbA1c was associated with reduced FVCpp in controls; 14% reduction for every 1% increase in HbA1c (p=0.006) but not with FEV1pp (p=0.06). In T1D participants HbA1c was not associated with FVCpp (p=0.3) or FEV1pp (0.9).

HbA1c is associated with reduced pulmonary function in control subjects but not in those with T1D suggesting that glycemic control may play a role across the non-diabetic range of HbA1c but not at levels of HbA1c typical seen in participants with T1D. This small, cross sectional study suggests that further work into the mechanisms linking glycemic control and pulmonary function is warranted.

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1739-P

Insulin Pumps: The Patient Perspective

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Limited research exists for describing opportunities and challenges associated with insulin pump therapy from the patient perspective. This study recruited current pump users, former pump users, and multiple daily injection (MDI; no history of pump use) users to complete an online survey designed to identify attributes of insulin pumps and integrated technology that create barriers to, or enhance, a person's ability to manage type 1 diabetes (T1D).

Two hundred fifty current pump users, 31 former pump users, and 69 MDI users were recruited from T1D Exchange's online patient community, Glu (myGlu.org). All participants were ≥ 18 years old with self-reported T1D. Survey questions focused on technology use and perceptions of how selection of insulin delivery method influences diabetes management.

A subset of our findings is summarized in Table 1. In this population, pump use was associated with higher income and the use of CGMS and diabetes-related web applications; however, insulin delivery method was not significantly related to recent HbA1c (Spearman's r=-.006, p=.917). Insulin delivery is rapidly evolving and it will be important to provide evidence-based information to patients, caregivers, and healthcare providers on the relative merit of different approaches. Online communities such as Glu may provide an effective path for collecting this information.

Table 1. Participant Characteristics.

	Current Pump Users [n=250]	Former Pump Users [n=31]	MDI Users [n=69]
Mean age [T1D duration]	43.1 [24]	41.6 [22.5]	45 [17.6]
Gender	M: 31% F: 69%	M: 19% F: 81%	M: 45% F: 55%
Household income > $75,000 (%)	51%	43%	44%
Recent HbA1c less than 7%	57%	32%	67%
Regular use of CGMS [% who found CGMS useful]	66% [89%]	27% [90%]	33% [87%]
Regular use of diabetes-related phone apps [% who found phone apps useful]	9% [21%]	22% [45%]	14% [31%]
Regular use of diabetes-related web apps [% who found web apps useful]	6% [24%]	0% [0%]	3% [5%]

Supported By: Eli Lilly and Company

1740-P

Comparison of Comorbidities and Resource Use between Pramlintide Users and General Type 1 Diabetes Mellitus Population Initiated on Mealtime Insulin

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Baseline comorbidity burden and resource use in type 1 diabetes mellitus (T1DM) were compared between patients identified as Pramlintide users and those who were not using Pramlintide.

Patients with T1DM aged ≥ 18 years of age were identified between January 2010 and September 2013 in MarketScan national claims database. The index date was the date of the first pramlintide prescription claim or, for non-users, the date of the first mealtime insulin prescription. Patients were required to have continuous enrolment during the 12 months before the index date ("pre-index period"). Severity and comorbidity burden were defined by diabetes related comorbidities, Charlson Comorbidity Index, Psychiatric Diagnostic Groupings, and Diabetes Complication Severity Index. Resource use included hospitalizations, emergency room and outpatient visits and related costs (all-cause and DM related). Resource use and disease burden in the pre-index period were compared between the cohorts.

Pramlintide patients with T1DM were older than mealtime insulin initiated T1DM patients (48% vs. 25% above 45 years for T1DM). Pramlintide users had a higher rate of DM related complications (37% vs. 10%). Pramlintide users had more DM related outpatient visits (99% vs. 73%). Mean pre-index DM related total cost was 2.5 times higher in Pramlintide -users than non-users ($8,767 vs. $3,489). Among pramlintide users, there was greater pre-index presence of depression (10% vs. 5%), hypoglycemia (16% vs. 6%),

renal impairment (11% vs. 5%) and obesity (8% vs. 2%). The statistical significance of all results was at p<0.0001.

Patients with pramlintide use had greater resource use and comorbidities in the 12-month period before pramlintide use compared to the year before mealtime insulin use in the T1DM population.

GENETICS—TYPE 1 DIABETES

Guided Audio Tour: Clinical Translation of Novel Genetic Findings *(Posters: 1741-P to 1748-P), see page 15.*

1741-P

Clinical and Genetic Predictors of Residual Insulin Secretion in New-Onset Type 1 Diabetes

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Type 1 diabetes (T1D) patients experience variable rates of loss of residual endogenous insulin secretion after diagnosis but determinants remain poorly defined. Since several studies have described the impact of variants in beta cell genes on insulin secretion in control populations, we sought to mathematically model both genetic and clinical data to determine factors important to rate of loss of insulin secretion in new onset T1D patients.

A total of 167 patients with T1D within 100 days of diagnosis (age 16.86 ± 8.77y) who had participated in the placebo arms of several intervention trials conducted by the Type 1 Diabetes TrialNet consortium from 2006-2011 were genotyped for ~200,000 single nucleotide polymorphisms (SNPs) related to metabolic and cardiovascular disease using the Illumina Cardio-MetaboChip. All patients had longitudinal insulin secretion assessed with mixed meal tolerance tests. A total of 344 variants were selected based on their pathway association with insulin secretion and beta cell development. Linear models were constructed to test the effect of these variants on insulin secretion patterns while accounting for clinical parameters such as sex, age, baseline BMI, and baseline HbA1c. All results were corrected for multiple comparisons using the Bonferroni method to determine significance.

No genetic variant or clinical parameter significantly influenced baseline AUC C-peptide. However, both age and genotype of RBPJ rs3109841 (A/C), a gene involved in beta cell differentiation, were significantly associated with rates of decline in insulin secretion (defined as the change in AUC C-peptide between month 0 and month 6). The addition of each dominant allele (C) significantly reduced the rate of decline in insulin secretion over the first 6 months after diagnosis (p=1.49x10-4). This data defines novel parameters important for determining early insulin secretion loss in T1D patients.

Supported By: Hellman Fellows Fund

1742-P

Meta-GWAS Identifies a Second Locus Associated with Skin Intrinsic Fluorescence

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Skin intrinsic fluorescence (SIF) is a non-invasive marker of advanced glycation end products (AGEs) and an indicator of long-term diabetic complications. *NAT2* has been identified as a major locus influencing SIF. Here, we aim to identify additional genetic loci influencing SIF in type 1 diabetes (T1D) subjects.

We performed meta-analyses of 2 GWAS in T1D subjects; Epidemiology of Diabetes Interventions and Complications (EDIC) and Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (n=1081 and 278, respectively). Ungenotyped SNPs were imputed using 1000 Genomes data (v3). Autosomal SNPs with minor allele frequency > 0.01 and high imputation quality (Info > 0.80) were included in meta-analyses. SIF was measured using the SCOUT DS device (VeraLight, Inc., Albuquerque, NM) at different excitation/emission (ex/em) levels. We tested the association of SNPs with SIFs by linear regression adjusting for age, sex, smoking status, skin tone, renal function and the *NAT2* SNP.

Two SNPs on chromosome 1 (r^2=1), rs7533564 (β (SE)=0.138 (0.023), p=1.88E-9) and rs7533823 (β (SE)=0.134 (0.023), p=9.31E-9), were associated with SIF1 (ex: 375nm, em: 435-655nm) exceeding the genome-wide significant threshold (p < 5E-8). These associations remained strongly significant after further adjustment for time-weighted HbA1c levels (p= 1.65E-8 and 8.85E-8, respectively). The SNPs were associated with SIF at the other ex/em levels (ex: 405-456, em: 440-655) with higher p-values; but not with mean HbA1c over time (p=0.099), nor with diabetic complications (cardiovascular, retinopathy, nephropathy and neuropathy) in EDIC. rs7533564 was associated with total glucose bound to collagen defined as fructose-lysine plus glucosepane, 2 AGEs measured by skin biopsy in a subsample in EDIC (β=0.226, p=0.039, n=170).

We identified a new locus on chromosome 1 associated with SIF in T1D subjects. Studies with larger sample sizes are required to investigate the association of identified SNPs with diabetic complications.

1743-P

Whole Exome Sequencing in a Family with Multiple Cases of Type 1 Diabetes Reveals a Candidate Susceptibility Mutation

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Familial aggregation of diabetes is frequently observed, however the disease-causing genetic variants in numerous families remain obscure. The aim of this study was to investigate the genetic background of a family with multiple cases of type 1 diabetes (T1D) using whole exome sequencing (WES). Identification of a disease-causing mutation would provide insights into the pathogenesis of rare monogenic diabetes as well as common polygenic diabetes.

The Japanese family contained 9 members and 4 of them had been diagnosed with T1D. The 4 affected members had been diagnosed with diabetes at between the age of 15 and 55, all of them had absolute insulin deficiency (fasting serum C-peptide < 0.1nmol/l). We performed WES in the 4 affected members as well as 2 unaffected family members using the Agilent SureSelect Human All Exon V5 kit and an Illumina Hiseq sequencer.

We predicted the familial aggregation of diabetes was caused by a rare non-synonymous variant. WES identified 439 non-synonymous variants present in all 4 affected members and absent in 2 unaffected members. After excluding common variants with minor allele frequency (MAF) of >1% in the 1000 genomes project or in a Japanese exome database, we selected 18 candidate variants that are predicted to be "disease mutations" by MutationTaster. Then we genotyped all family members and 105 Japanese normoglycemic controls for the 18 variants using Taqman method, and 16 of the candidate variants were rare (MAF <1%) in the controls. Among them 2 mutations (p.R608H in ARHGEF11, p.R355I in USH1C) were confirmed in all affected members and were absent in all 5 unaffected family members. The ARHGEF11 gene has been implicated to be involved in glucose metabolism in genetic association studies.

Accordingly, the R608H mutation in the ARHGEF11 gene might be a mutation for susceptibility to T1D. Family-based comprehensive WES is a promising strategy to elucidate the complex genetic background of diabetes.

1744-P

Can Genomic Information Aid in Establishing Aetiology of Young Adult Onset Diabetes?

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Establishing aetiology in young adult onset diabetes can be a challenge. We assessed if individual genetic risks using known type 1 (T1D) and type 2 diabetes (T2D) risk variants offer useful diagnostic discrimination between major diabetes subtypes.

North European subjects (n=715) with diabetes onset <45 years were provisionally classified as T1D (n=293), T2D (n=370) and LADA (n=52), based on pancreatic antibodies, time to insulin use from diagnosis, and c-peptide level. We used common risk variants for T1D (47 variants) and T2D (65 variants), plus high risk and protective variants for T1D in the MHC (23 variants) to calculate weighted Genetic Risk Scores (GRS) for T1D (T1DGRS) and T2D (T2DGRS). Differences in GRS between clinical parameters or diabetes subtypes were estimated with ANOVA or Wilcoxon signed rank test. The area under the receiver operator curve (AUC) was calculated for discriminating T1D and T2D using T1DGRS and T2DGRS.

Higher T1DGRS was associated with diagnosis <18 years ($p=2x10^{-13}$), undetectable c-peptide ($p=2x10^{-9}$) and insulin as initial or current treatment vs. tablets (both $p<10^{-22}$). Lower T2DGRS was observed with insulin therapy at diagnosis vs. diet (p=0.002) or tablet use (p=0.04) and with current oral therapy (p=0.0002). The difference in T1DGRS and T2DGRS between T1D vs. T2D cases was highly significant (both $p<10^{-22}$), as was the difference between T2D vs. LADA subjects ($p<10^{-22}$ and p=0.0001 respectively). Non-T1D cases starting insulin within 1 year of diagnosis had higher T1DGRS compared to the remainder (p=0.0004), thus estimating T1DGRS at diagnosis could aid in tailoring management. The AUC for clinically defined T1D and T2D patients using the T1DGRS and T2DGRS were 79.9% and 63.8%, respectively.

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

Genetic Risk Scores correlate with traditional diabetes classification parameters and differ between clinically defined diabetes subtypes. Genomic information could be a useful adjunct in the differential diagnosis and management of young adult onset diabetes from diagnosis.

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1745-P

A Novel, Inexpensive Test Can Discriminate between Type 1 and Type 2 Diabetes

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Background: Rising obesity rates make it more difficult to distinguish between type 1 and type 2 diabetes in young adults. Autoantibodies are positive in <80% of T1D and diminish over time. There is strong genetic predisposition for T1D that can be measured by Single Nucleotide Polymorphism (SNP) genotyping which is rapid, inexpensive, and stable over time.

Aim: To determine whether a genetic risk score (GRS) generated from common T1D risk SNPs could be used to predict insulin deficiency.

Methods: We developed a GRS from published T1D associated SNPs. We tested the ability of the score to distinguish clinically defined T1D and T2D in the Wellcome Trust Case Control Consortium (WTCCC, n=3887), and to identify progression to insulin deficiency (C-peptide negative > 3yrs post-diagnosis) in a cohort of 198 individuals diagnosed between 20-40 years where diagnostic uncertainty is common.

Results: The GRS was highly discriminative of T1D and T2D in the WTCCC (ROC-AUC=0.87, P<0.0001). A low score was indicative of T2D (GRS>0.28, 95% specific, 41% sensitive). A high score was indicative of T1D (GRS>0.33 95% specificity, 50% sensitivity). The GRS predicted progression to absolute insulin deficiency (AUC=0.89, P<0.0001). Of the 36 patients with C-peptide <600pmol/l only 1 had GRS<0.28. Of the 167 patients with a C-peptide >600pmol/l only 7 had GRS>0.33. GRS and auto-antibody status were independent and additive predictors (combined AUC=0.94).

Conclusion: A T1D GRS can accurately identify young adult patients who will require insulin treatment. This will be an important addition to correctly classifying individuals with diabetes when clinical features and autoimmune markers are equivocal.

Supported By: Diabetes UK

1746-P

Type 1 Diabetes Genetic Risk Score—A Novel Tool to Differentiate Monogenic Diabetes from T1D

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Identifying novel monogenic causes of young-onset diabetes is greatly facilitated if patients with polygenic type 1 diabetes (T1D) can be robustly excluded. We aimed to assess whether T1D genetic susceptibility can be used to differentiate patients with monogenic diabetes from T1D. Genetic susceptibility was captured using weighted genetic risk score (GRS) based on 33 T1D associated common genetic risk variants. The GRS was validated in known monogenic MODY (n=843) and T1D (n=1963) patients where it showed excellent discrimination (mean score ±SD, 0.23±0.03 vs. 0.28±0.03, ROC AUC 0.87, p<00001). 50% T1D and only 6% MODY patients had score >0.28 whereas 52% MODY and only 5% T1D patients had score <0.23. Odds Ratio for monogenic cause with a score <0.23, 0.24-0.27 and >0.28 was 83, 7 and 1 respectively.

We next compared the utility of GRS against a genetic test for all 23 causative genes in neonatal diabetes patients diagnosed <6 months (n=599). Genetic test confirmed monogenic etiology in 90% (241/267) patients with a score <0.23, 85% (222/261) with a score 0.24-0.27 and only 40% (29/71) with a score >0.28. Only 6% confirmed monogenic patients had a score >0.28.

These results suggest that 42/107 patients with score >0.28 and negative genetic test were likely to have T1D rather than a novel genetic cause. In keeping with this, these patients presented older (13 vs. 6 wk, p<0.0001), had higher birth weight (2.8 vs. 2.5 kg, p<0.0001), higher autoimmune disease (9.5% vs. 0.4%, p<0.0001), less syndromic presentation (14% vs. 35%, p=0.004) and less consanguineous parents (9.5% vs. 25%, p=0.03) compared to confirmed monogenic diabetes patients. Conversely, 65/107 patients with score <0.28 and negative genetic test were similar to monogenic patients.

In conclusion, GRS is a useful tool to differentiate monogenic diabetes from T1D. Using it identified 7% neonatal diabetes patients <6months with very early onset T1D that should be excluded from further in-depth genetic analysis to identify novel monogenic cause of diabetes.

1747-P

Monogenic Diabetes in Slovakia—Results of the Slovak Nationwide Survey Carried Out over the Years 2004-2014

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Maturity Onset Diabetes of the Young (MODY) is a heterogeneous group of monogenic diabetes with early onset, familiar appearance, and autosomal dominant inheritance. The aim of this study was to identify the etiology of the Slovakian families with the clinical suspicion on the monogenic diabetes by the DNA analysis of the known MODY genes.

Methods: 933 patients from 409 families were recruited from the diabetes outpatient clinics throughout Slovakia during the last decade (2004-2014). Relevant genes responsible for monogenic diabetes (GCK, HNF1A, HNF1B, HNF4A, NEUROD1, KCNJ11, insulin, and ABCC8) were sequenced and MLPA analyzed. The m.3243A>G mutation responsible for MIDD (maternally inherited diabetes and deafness) syndrome was analyzed using real-time PCR.

Results: patients from 119 families had a mutation in one of the target genes: 72 probands and their 105 family relatives had mutation in the GCK gene, 32 probands and their 40 family relatives had a mutation in the HNF1A gene; 4 probands and 2 family relatives had a mutation in the HNF4A gene, one proband had a mutation in the insulin gene, 2 probands had a HNF1B whole gene deletion and 8 probands with 10 relatives were carriers of m.3243A>G mutation. No KCNJ11, ABCC8 and NEUROD1 gene mutation carriers were found.

Conclusions: Out of 933 patients from 409 families with clinical suspicion for monogenic diabetes, the diagnosis was confirmed in 276 patients from 119 families, which represents 29% from referred probands. 69 different mutations (from which 25 are novel) were found in 4 out of 8 analyzed genes. The minimal prevalence for MODY is estimated to be 55 cases per million of inhabitants and represents 0.08% of all diabetic patients. The most prevalent MODY subtype in Slovakia is GCK-MODY representing 63% of all MODY. This is consistent with data from Poland, Germany and Czech Republic, where predominantly the pediatric population is analyzed. Opposite exists in UK, where the recruitment of rather adult patients is taking place.

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1748-P

Differential Expression of microRNA in MODY

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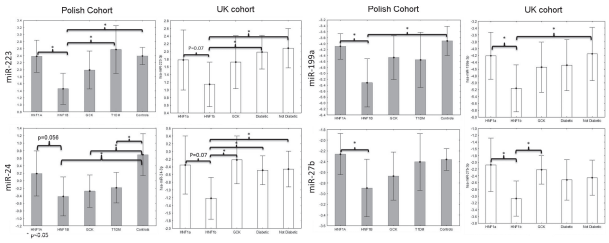
Transcriptional regulation of miRNAs coded by non-intronic genomic sequences is unclear and we hypothesized that transcription factors may be implicated in this process. This may result in altered profiles of serum miRNAs in forms of MODY caused by mutations of transcription factor genes.

The study was performed on two groups of subjects. The Polish cohort (N=60) consisted of 11 patients with HNF1B-MODY, 17 with HNF1A-MODY, 11 with GCK-MODY, an HbA1c-matched type 1 diabetes (T1DM) group (n=9) and 10 healthy controls. As a validation group, 61 clinically matched British patients were used mirroring the groups in the Polish one. The Polish group underwent miRNA serum levels profiling with qPCR arrays (Exiqon, Denmark) to identify differentially-expressed miRNAs. Validation was performed using qPCR. To determine whether serum expression reflects alterations at cellular level, we quantified miRNA levels in HepG2 cells with si-RNA knockdowns of HNF1A or HNF1B.

Significant differences (adjusted p<0.05) were noted for 11 miRNA. Six of them differed between HNF1A-MODY3 and HNF1B-MODY, and further 4 (miR-24, miR-27b, miR-223, and miR-199a) were confirmed in the validation group (Fig. 1). Pattern of miRNA hepatic expression was consistent with their serum levels as they all were significantly higher in HNF1A- than in HNF1B-deficient cells.

In summary, we identified 4 miRNAs that seem to be specifically dependent on HNF1B-transcriptional control.



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1749-P

Unmasking Genes Controlling How CD4+ T-Cells Pathogenically Activate Type 1 Diabetes-inducing CD8+ T-Cells

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Most beta-cell destruction in type 1 diabetes (T1D) is due to the cytotoxic effects of autoreactive $CD8^+$ T-cells that rely on $CD4^+$ T-cell help for their activation. Here we report that this process is in part controlled by our previously described T1D susceptibility locus on distal chromosome 11 (Idd32), discovered through a first-backcross between diabetes-susceptible NOD mice and diabetes-resistant C57BL/6 (B6) mice congenic for the NOD-derived $H2^{g7}$ MHC haplotype ($B6.H2^{g7}$). In adoptive transfer studies we found that lymphopenic recipients injected with $CD8^+$ T-cells transgenically expressing the diabetogenic AI4 TCR were completely resistant and susceptible to T1D when co-injected with $CD4^+$ T-cells from donors respectively expressing heterozygous ($Idd32^{NOD/B6}$) or homozygous ($Idd32^{B6/B6}$) B6 alleles at Idd32. Diabetogenic $Idd32^{B6/B6}$ $CD4^+$ T-cells required CD40-CD40L interactions to pathogenically activate AI4 T-cells. Surprisingly, protective $Idd32^{NOD/B6}$ $CD4^+$ T-cells inhibited AI4 T-cell activation through a mechanism that requires interferon-γ (IFNγ), generally considered a pro-inflammatory cytokine. In support that our findings are clinically significant, pre-activation with IFNγ reduced the cytotoxicity of human diabetogenic $CD8^+$ T-cells used in a cell-mediated lympholysis assay. Our results are important for addressing how $CD4^+$ T-cells control when tissue-specific $CD8^+$ T-cells, which harmlessly circulate in most individuals, sometimes become pathogenically activated. They are also important for interventions to block this disease-critical process.

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1750-P

Immunological Characteristics of Patients with Type 1 Diabetes (T1D) from Sao Paulo City in South America

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Genetic factors influence autoimmune manifestations of T1D. T1D incidence is low in South America where few data are known. To analyze the autoimmune manifestations of 865 T1D patients and 787 health controls attended in a city with high ethnic admixture, islet and extra-pancreatic autoantibodies (Abs) were analysed: glutamic acid decarboxylase (GAD65), tyrosine phosphatase (IA2), 21-hydroxylase, thyroid peroxidase (TPO), thyroglobulin (TG), liver/kidney microsomal type 1 (LKM1), smooth muscle, rheumatoid factor (RF) , TSH receptor, nuclear Ab (ANA). Except for LKM1 and RF, all the other Abs were more frequent in T1D patients than in controls (p<0.001). Islet were the most frequent in T1D, followed by thyroid and ANA Abs. Islet Abs frequencies were high and similar at the first year of diagnosis: IA2 Ab (67.8%), GAD65 Ab (69.4%) and ZnT8 Ab (72.6%), confirming T1D diagnosis of 92.2% cases. Despite a high frequency of females (60.3%) in our T1D population, only two Abs prevailed in females: gastric parietal cell (PCA) Ab (12.3% vs. 2.6%, p=0.03) and GAD65 Ab (during the first 2 years of disease: 74.7% x 60.5%; p=0.04). The GAD65 Ab titres were also greater in female (12.0±23.9 x 6.8±14.9 IU/mL, p=0.03) and in European descents than non European descents (10.6±22.2 x 6.4±12.6 IU/mL; p=0.014). HLA-DR4 alleles were associated with higher frequency of TPO Ab (p< 0.02); DR3 with ANA (p=0.01)); CTLA4 (+49A/G) with TPO Ab (p <0.03) and ZnT8 Ab (p=0.023); PTPN22 1858T with anti-GAD (26.5 x 15.9%, p = 0.03) and CD226 rs763361 with anti-GAD (31.9% vs. 24.5%) and with low C peptide levels. Only CD226 rs763361 prevailed in women with T1D compared to men (35.1x21.9%, p=0.0012). INS-VNTR alleles did not influence autoimmune manifestations of T1D patients. Unlike other autoimmune diseases and despite a higher frequency of females in our T1D population, the frequency of pancreatic and extra-pancreatic Abs was similar in both sexes, except by gastric parietal cell and GAD65 Abs, more frequent in females.

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1751-P

Association of AFF3 rs10865035 Polymorphisms with the Risk of Type 1 Diabetes Mellitus and Autoimmune Thyroid Disease in a Chinese Population

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AF4/FMR2 family, member 3 (AFF3) encodes a tissue-restricted nuclear transcriptional activator that may function in lymphoid development, and thus influence immunologic response. There were several studies reported AFF3 gene associated with the incidence of type 1 diabetes mellitus (T1DM) in Caucasian, and we hypothesize that single-nucleotide polymorphisms (SNPs) within AFF3 may also be some autoimmune diseases susceptibility loci. So the aim of this study was to investigate the association of rs10865035 polymorphisms with the two autoimmune diseases - type 1 diabetes mellitus (T1DM), autoimmune thyroid disease (AITD) susceptibility in Chinese population. We enrolled 246 children and adolescents with T1DM, 135 patients with AITD and 252 healthy individuals of China origin. The AFF3 gene polymorphisms was genotyped by PCR-direct sequencing, and the serum levels of glutamic acid decarboxylase 65 antibody (GADA), insulinoma associated protein-2 antibody (IA-2A), insulin autoantibody (IAA) and zinc transporter 8 antibody (ZnT8A) were detected by radio - immune precipitation assay (RIPA). The results indicated that the distribution of allele and genotype frequencies of AFF3 gene polymorphisms did not exhibit significant difference between AITD patients and healthy controls (p>0.05). However the distribution of alleles rs10865035 in AFF3 differed between T1DM and healthy controls (p=0.034). We also found that the results of the allele G and genotypes GG/AG of SNP rs10865035 revealed an association with T1DM risk (p<0.05). Furthermore, AFF3 rs10865035 polymorphisms allele frequency of T1DM patients was related with the positive rate of any islet autoantibodies (≥1Ab) ($\chi 2$=4.332,p=0.037). In conclusion, AFF3 polymorphisms may influence T1DM developing, but do not seem to be associated with AITD in Chinese population.

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1752-P

Epidemiological and Genetic Data of Type 1 Diabetes (T1D) Patients from São Paulo—A City with Large Ethnic Admixture

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Geographic region and ethnicity contribute to T1D risk. T1D incidence is low in South America and few data are known. Some differences with Caucasians were observed after comparing epidemiological and genetic data of 862 T1D patients and 791 controls.T1D prevailed in female (60.3%) and 18.9% were self reported as non Caucasian. HLA-DR and DQ alleles related to T1D risk were similar to those observed in Caucasians, but at a lower frequency. Only 84.7% of patients carried DR3 or DR4 alleles (OR=8.3) (p<0.0001) with similar frequency in European descents (85.3%) and from other ethnical origin (mainly African and Native American descents-81.2%; p=0.24). The HLA-DR*1 allele was protective only in non European descents and HLA-BRB1*0401/*0402/*0403/*0404/*0407 alleles have no effect on T1D predisposition in our cohort. PTPN22-1858T allele predisposed to T1D at lower frequency (18,7%; OR=1.9) and only in those with European ancestry. Further, T1D risk conferred by VNTR-INS class I alleles (60,4%; OR=3.4) and by CD226 rs763361 (33.5%; OR=1.5) was also lower than in Caucasians. CTLA4 alleles (-318 and +49 A/G) did not predispose to T1D. Age at diagnosis (12.1±8.1y) was related only to HLA-DR6 and DQB1*0201 alleles-respectively higher and lower age (p=0.02). T1D patients were divided into 5 groups according to birth date: <1960, 61-70, 71-80, 81-90, 90-2008. Females (54-64%) and European descents (76- 94%) prevaile in all periods. A progressive decrease of age at diagnosis was observed in the years 1970-2008, p< 0.0001. Except by an increase in HLA-DR9 frequency in recent years (p=0.03), the T1D risk determined by the other genes did not change. Epidemiological data of our T1D population differ from those of Caucasians, possibly due to our ethnic admixture and different environmental factors. A progressive decrease of age at diagnosis of patients born in the decade 1970 until the present days and a higher prevalence of T1D in females was observed.

Supported By: Fundação de Amparo à Pesquisa do Estado de São Paulo

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1753-P

Epigenomic Profiling of Primary Human T Cells Reveals Enhancers Associated with Type 1 Diabetes Susceptibility

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Genome-wide association studies have so far revealed more than 90 genomic regions that are associated with an increased risk of type 1 diabetes (T1D). But very few successful findings of actual etiologic SNPs are reported. The noncoding region represents 98.5% of the genome. Given the abundance of functional non-coding sequences in the genome, many SNPs, if they contribute to disease, likely act by impacting the noncoding genome and being involved in a regulatory function. Here, we present an integrative approach to rapidly and systematically screen candidate causal SNPs that reside in gene-distal enhancers. Using ChIP-Seq and primary T lymphocytes from subjects with T1D and healthy controls, we have generated genome-wide location maps of three histone modification marks, H3K4me1, H3K4me3, and H3K27Ac. We identified many genomic loci with altered epigenetic modification states between T1D subjects and healthy controls. Using histone modification signature, we identified a large compendium of transcriptional enhancers in both cell types. The enhancer compendium is enriched for GWAS SNPs associated with T1D and other autoimmune diseases. By linking enhancers and their target genes using our published algorithm, we were able to construct and compare the transcriptional regulatory networks (TRNs) in T1D patients and healthy controls. Using the disease-specific TRNs, we prioritized multiple GWAS SNPs that are high-confident causal variants associated with T1D. Our study also led to new insights into how genetic and epigenetic factors work together to modulate enhancer activities and how environmental factors influence the pathogenesis of T1D.

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1753A-P

STAT3 Signaling, But Not Fast-acting Neurotransmitter Release, Is Required For Leptin Action On Euglycemic Restoration In Type 1 Diabetes

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Abundant evidence demonstrated that central leptin administration is sufficient for normalizing blood glucose in insulin-deficient type 1 diabetes mellitus (T1DM). Yet, due to the wide distribution of leptin receptor-expressing (LepR) neurons, where and how leptin action in the brain underlies the hyperglycemia reversal effects remain largely unknown. To address this elusiveness, different mouse models with streptozotocin (STZ)-induced T1DM were treated with intracerebroventricular (i.c.v.) leptin infusion by using osmotic pumps. Despite being required for normal body weight regulation, release of fast-acting neurotransmitter GABA, glutamate or GABA and glutamate from LepR neurons was not required for mediating leptin's action on euglycemia restoration in STZ-induced diabetic mice. Concurrent with full reversal of hyperglycemia, normalization of both plasma glucagon levels and food intake was induced by i.c.v. leptin treatment in T1DM mice with specific disruption of GABA, glutamate, or GABA and glutamate release from LepR neurons. Interestingly, specific inactivation of signal transducer and activator of transcription-3 (STAT3) signaling in LepR neurons prevented the euglycemia restoration by i.c.v. leptin treatment in T1DM mice, but had no effects on normalization of food intake that was normally associated with euglycemia restoration. We conclude that, in the absence of insulin, functional STAT3 signaling but not release of fast-acting neurotransmitter of LepR neurons, is required for mediating leptin's antidiabetic action.

Supported By: JDRF

GENETICS—TYPE 2 DIABETES

Guided Audio Tour: Genome-Wide Association Studies and Their Follow-up *(Posters: 1754-P to 1761-P), see page 13.*

1754-P

Trans-Ethnic Genome-Wide Association Meta-analysis for Glycated Haemoglobin Levels in 159,940 Individuals of European, African American, South and East Asian Ancestry

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Glycated haemoglobin (A1C) is widely used to monitor glucose control and for type 2 diabetes diagnosis. So far, ethnic specific meta-analyses in exclusively European or East-Asian populations have revealed 17 loci associated with A1C. We investigated genetic determinants of A1C in individuals from four ethnic backgrounds.

We combined genome-wide (GW) and Metabochip (Mc) array data available in up to 159,940 non-diabetic participants from cohorts of European (EA: 28 GW, 20 Mc), African American (AA: 9 GW), East Asian (EAA: 12 GW, 1 Mc) and South Asian (SAA: 5 GW, 1 Mc) ancestry in an overall trans-ethnic and in ethnic specific meta-analyses. Each cohort performed quality control and imputation according to common standards. GW and Mc results were combined within each ancestry group using a fixed-effects meta-analysis in METAL. We used MANTRA to combine meta-analysis results from all four ancestries. We considered genome-wide level significance when p-value<2x10-8 in AA or <5x10-8 in other ancestries in METAL or Bayes factor>6 in MANTRA.

We found 42 novel loci associated with A1C: 38 loci in our trans-ethic MANTRA analysis, 3 in EA-only, 1 in EAA-only. We also confirmed the 17 known loci and found independent secondary signals at 5 of these loci. Functional enrichment analyses of A1C loci found significant enrichments in blood cell types, as well as fetal development of muscle and intestines. Cross trait look-ups revealed that many A1C loci were associated with glycemic traits, others with erythrocytic traits, while some are associated with neither, suggesting that biologic determinants other than glucose and erythrocytes contribute to A1C variation.

The novel loci identified expand our understanding of genetic and biologic determinants of A1C variation. The ability to examine interethnic differences in the allelic architecture of A1C is particularly relevant to the use of A1C as a global diagnostic test for diabetes.

1755-P

Association of Genetic Determinants of Fasting Glucose and Insulin with Other Metabolic Traits in the African-American Glucose and Insulin Genetic Epidemiology (AAGILE) Consortium

NISA M. MARUTHUR, MAGGIE C. NG, MAN LI, CHING-TI LIU, EDWARD KABAGAMBE, SRIDHARAN RAGHAVAN, STEPHEN RICH, Y-D IDA CHEN, JAMES B. MEIGS, ASSOCIATION OF GENETIC DETERMINANTS OF FASTING GLUCOSE AND INSULIN WITH OTHER METABOLIC TRAITS IN THE AFRICAN-AMERICAN GLUCOSE AND INSULIN GENETIC EPIDEMIOLOGY (AAGILE) CONSORTIUM, *Baltimore, MD, Winston-Salem, NC, Boston, MA, Nashville, TN, Charlottesville, VA, Los Angeles, CA*

Understanding the genetics of diabetes-related traits in populations of African ancestry (AA) may help elucidate biology contributing to ethnic differences in diabetes outcomes. We evaluated whether SNPs associated with fasting glucose (FG) and BMI-adjusted fasting insulin (FIB) are also associated with other metabolic traits in a multi-ethnic consortium [European ancestry (EA), N=58,074 (FG) and 51,950 (FI); AA, N=20,209 (FG) and 17,873 (FI)]. We tested cross-trait associations with 30 SNPs: 1) 4 SNPs (1 FG, 3 FIB) with Bayes' Factor ≥6 from discovery/replication using Meta-ANalysis of Trans-ethnic Association studies (MANTRA) and 2) 26 SNPs transferable to AA in our sample (plocus <0.05) selected from established EA loci (15 FG, 11 FIB). In AA subjects from additional cohorts (N=19,052 to 39,144), 14/30 SNPs were associated with ≥1 metabolic trait [type 2 diabetes (T2D), BMI, BMI-adjusted waist-hip ratio (bWHR), systolic (SBP) and diastolic blood pressure (DBP), hypertension (HTN), and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol] with the direction of association consistent with that of FG or FIB. T2D (n=6), HDL (n=4), and bWHR (n=3) had the greatest number of associations with FG and FIB SNPs while LDL and HTN exhibited no significant associations. A FIB SNP, rs6450057 (PELO), discovered in AAGILE using MANTRA, was associated with HDL. Two known FIB SNPs were associated with ≥2 metabolic traits: rs6717858 (COBLL1-GRB14) was associated with T2D, bWHR, and HDL; rs17811863 (PDGFC) was associated with SBP and DBP. We present evidence suggestive of pleiotropic effects of FIB SNPs in AA subjects. Our results confirm the association of rs6717858 with adiposity-related traits and suggest loci to inform the pathophysiology, including insulin resistance, of metabolic disease in persons of African ancestry.

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1756-P

Trans-ethnic Fine-Mapping Implicates Regulatory Variation at Glycemic Quantitative Trait Loci: The African-American Glucose and Insulin Genetic Epidemiology (AAGILE) Consortium

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Genome-wide association studies (GWAS) have identified 56 loci associated with fasting glucose (FG) or BMI-adjusted fasting insulin (FIB) in individ-

uals of European ancestry (EA). The causal transcripts and variants at many of these loci remain unresolved. We fine-mapped causal variation underlying these traits by trans-ethnic analysis of the GWAS-identified loci.

Sixteen cohorts with participants of African ancestry (AA) (N=11526 to 20209) contributed to a GWAS meta-analysis for FG and FIB (AAGILE). We used the Meta-ANalysis of TRansethnic Association studies (MANTRA) software to fine-map 56 GWAS-identified FG and FIB loci using summary statistics from EA individuals alone and in combination with results from AAGILE cohorts. We generated "credible sets" of SNPs for each locus, predicted with greater than 99% posterior probability to contain the causal variant at that locus, assuming a single causal variant in the region that was included in the analysis. At loci for which the credible set size was reduced by ≥ 25% when AA and EA results were combined, we examined regulatory annotation for each SNP (from regulomedb.org) as well as the positional description of pancreatic islet enhancers, promoters, and transcription factor binding sites (TFBS) (from isletregulome.org).

Credible set sizes at 15 of 56 loci (9 FG and 6 FIB) were reduced by ≥ 25%. At 5 of 9 FG and 4 of 6 FIB loci, the credible set contained at least one variant overlapping an eQTL or TFBS. At 3 FG and 2 FIB loci, the SNP with strong regulatory annotation also was strongly associated with the respective trait. Focusing on pancreatic islets, using the Islet Regulome Browser, the credible set contained a pancreatic islet promoter, enhancer, or TFBS at all 9 FG loci and 5 of 6 FIB loci.

Trans-ethnic fine-mapping combined with regulatory annotation data provides insights on putative causal regulatory mechanisms underlying glycemic quantitative traits.

1757-P

Genome-Wide Association Studies of Renal Diabetes Complications in Patients with Type 2 Diabetes

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Diabetes is associated with many chronic complications including diabetic kidney disease (DKD), a leading cause of end-stage renal disease (ESRD), however to date few robustly associated genetic factors have been identified.

Genome-wide association studies (GWAS) were performed on 7 case control phenotypes, based on the severity of diabetic nephropathy as characterized by micro-/ macro-albuminuria, or end stage renal disease (ESRD), or chronic kidney disease (CKD; eGFR <60 ml/min) and 1 continuous phenotype, eGFR, in 4 European studies comprising 5,717 patients with type 2 diabetes (T2D).

We analyzed 9,213,894 single nucleotide polymorphisms, imputed based on the 1000 Genomes (March 2012) reference panel, using EMMAX, adjusting for sex, age at onset, duration of diabetes and kinship matrix. Meta-analyses were performed using a fixed effects model and identified 139 SNPs with $p<5x10^{-6}$ from any of the binary phenotypes which were taken forward for *in silico* replication in 2 European cohorts with up to 3,356 samples.

After joint analysis of the discovery and replication cohorts no loci reached genome wide significance ($p<5x10^{-8}$). However a number showed modest replication, e.g. rs4977388 (T2D ESRD vs. all other phenotypes, $p = 2.25x10^{-7}$, near *MLLT3*), rs7916840 (DN, $p = 6.2x10^{-7}$ intronic to *GP158*) and rs2206136, (CKD, $p=5.42x10^{-7}$, intronic to *PLCB4*).

We also performed a joint analysis of eGFR with three European T1D studies comprising 3,961 patients analyzed using similar methods and phenotype definitions. A locus near *PHOSPHO2* showed genome wide significant association (rs1974990, $p=4.8x10^{-8}$).

We plan to further increase our power with additional *de novo* genotyping of these suggestive signals as part of the ongoing effort to investigate the biology of DKD. These include a joint analysis of T1D and T2D DKD as well as rare-variant analysis through exome sequencing in T1D DKD patients. By combining and comparing these different analyses we hope to gain a broader picture of the biology of DKD.

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1758-P

Transcriptional Profiles of Adipose and Muscle Tissue Are Associated with Insulin Sensitivity and Influenced by Genetic Variation in African Americans

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African Americans (AAs) are more insulin resistant with a higher insulin secretion response to glucose, when compared to age, sex, and BMI matched European Americans. Mechanisms explaining these unique features of AAs are unknown. Transcriptional profiling (Illumina HT12-V4) was performed on subcutaneous adipose and skeletal muscle from 256 fasting non-diabetic AAs (age 18-60 yrs; BMI 19-42 kg/m^2) to identify mechanisms associated with insulin sensitivity (S_I, evaluated by FSIVGT) and glucose homeostasis-related phenotypes. Regression analysis (age, sex and admixture-adjusted) identified positive (1169) and negative (1043) associations of adipose transcripts with S_I (FDR<1%). Compared to adipose, fewer transcripts in muscle were positively (56) and negatively (89) associated with S_I. Genes positively associated with S_I were enriched for eIF2, eIF4 - p70S6K, and mTOR signaling ($p=0.013\text{-}2x10^{-14}$) in both tissues. Adipose transcripts positively associated with S_I were enriched for isoleucine and valine degradation ($p\leq0.0002$); while negatively associated transcripts were enriched for leukocyte extravasation and toll-like receptor signaling ($p\leq0.002$). S_I associated transcripts were enriched ($p=2.5x10^{-6}\text{-}2x10^{-12}$) for oxidative phosphorylation, with expression in adipose positively associated with S_I (41 genes) and muscle negatively associated (9 genes). S_I associated co-expressed transcript modules were also enriched for these pathways. Integration of genotype data (Illumina Omni5+Exome) identified *cis*-regulatory SNPs (FDR<1%) for 363 and 42 S_I associated transcripts in adipose and muscle, respectively. The *TINP1* gene ($p=3x10^{-67}$) in adipose and the *SEC61G* gene ($p=2x10^{-25}$) in muscle were the strongest *cis*-eQTLs among S_I associated transcripts. This study identified genetic regulatory mechanisms of insulin sensitivity that may explain distinctive physiologic features of glucose homeostasis in AAs.

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1759-P

Histone Acetyltransferase (HAT) p300 Regulates Expression of Thioredoxin-Interacting Protein (TXNIP) and thereby Potentially Contributes to Glucotoxicity in Beta Cells

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Glucotoxicicity plays a key role in the deterioration of beta-cell function after glucose concentrations have reached diabetic levels and TXNIP has been demonstrated to be an important link between glucotoxicity and beta cell apoptosis. Using chromatin immunoprecipitation and qPCR in insulin-producing INS1 832/13 cells, we found that high glucose (25 mM) stimulated TXNIP mRNA expression in association with elevated acetylation at H3 lysine 9 (H3K9ace). The direct involvement of histone acetylation in glucose-stimulated TXNIP expression was confirmed by reversing or enhancing acetylation using HAT p300 inhibitor C646 and histone deacetylase 1 inhibitor CI994. C646 significantly inhibited TXNIP expression at both 5 mM (by ~40%) and 25 mM glucose (by ~75%), while CI994 greatly stimulated TXNIP expression at 5 mM (36-fold) and 25 mM glucose (3-fold). C646 also suppressed H3K9ace at the first coding region of TXNIP at low glucose by ~70% but not at high glucose, suggesting that glucose induced hyperacetylation at H3K9 may involve acetylation elevated by a spectrum of HATs and cannot be inhibited solely by C646. We also applied CRISPR with sequence-specific guide RNA to target mutate p300 in INS1 832/13 cells; our preliminary data showed that mutation of p300 abolished TXNIP expression at low glucose, which can be partially reversed by high glucose. Furthermore, exposure to high glucose (25 mM) or C646 for 24 hrs stimulated insulin secretion, and the cells continued to have elevated insulin secretion even 6 days after the first exposure to glucose, whereas the combination of high glucose and C646 had no further additive effect, suggesting that this process also involved histone acetylation. In conclusion, epigenetic mechanisms involving histone acetylation may be important future targets for treatment aiming at reversing the deleterious effects of glucose on beta-cell function.

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For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1760-P

KLF14, a Susceptibility Gene of Type 2 Diabetes, Is an Age-related Epigenetic Biomarker in Human and Mice

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It has been well known that DNA methylation is functionally relevant modification of the genome, which does not involve a change in the nucleotide sequence and allows dynamic changes of biological phenomena by controlling gene expression. Previously, we identified statistically significant gene where DNA methylation levels are correlated with chronological age by epigenome-wide scan using the Illumina Human Methylation 450 BeadChip and whole blood DNA from 480 general population subjects of different ages. These include Kruppel-Like Factor 14 (KLF14) gene, which appears to be a master regulator of gene expression in adipose tissue and have previously been associated with type 2 diabetes (T2D) in large GWAS analyses. To extend our knowledge on the mechanisms that are increasing risk of developing T2D by aging, we investigated reproducibility and organ specificity of methylation change on db/db and db/- mouse KLF14 promoter region (0.25kb upstream) that showed significance change in human population samples. Mice were dissected at the age of 4 weeks (young) or 50 weeks (aged), and various organ specimens including the cerebrum, the cerebellum, the heart, the lung, the liver, the pancreas, the spleen, the colon, the kidney, the testis (or the ovary) and the tail were prepared. Then, we carried out the bisulfite pyrosequencing on promoter region corresponding to that of human KLF14. We found that DNA methylation levels of these sites were increased with aging in the particular organ including spleen. Furthermore db/db mouse was observed more significant methylation change than db/- mouse. Our results suggested that change of methylation levels correlated with age on KLF14 is physiologically important because this change was conserved between humans and mouse. Considering the organ specificity, it is possible that KLF14 is not only susceptibility gene of T2D but also epigenetic biomarker of T2D in the hematological tissues.

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1761-P

Gene Editing of the Key Genomic Element within TCF7L2 Using the CRISPR/Cas9 System Reveals an Impact on Gene Expression and Splice Isoform Repertoire

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The single nucleotide polymorphism, rs7903146, within the gene encoding transcription factor 7-like 2 (*TCF7L2*) is considered the strongest associated variant with type 2 diabetes risk reported to date; furthermore, this variant is widely presumed to be the causal lesion at this locus. We elected to utilize the CRISPR/Cas9 system to conduct precise gene editing in HCT116 cells in order to study the role of this key genomic element within an intron of *TCF7L2* in an otherwise homogenous genetic background. Indeed, it has been shown that TCF7L2 is abundantly expressed in HCT116 cells, plus it has been previously shown that cardiometabolic-related pathways are regulated by TCF7L2 in this setting.

We designed constructs through the leveraging of short guide RNAs targeting flanking sites located both 700bp upstream and downstream of rs7903146, which successfully removed a 1.4kb genomic fragment.

We subsequently compared gene expression levels between the wild type and targeted cells homozygous for the deletion using real time PCR and observed that *TCF7L2* expression was significantly reduced ($P < 0.01$); in addition, the corresponding protein level was also found to be lower by Western blot analysis. We also observed that expression influenced by this deletion varied between exons, with exon 5 yielding the largest expression change, suggesting that this genomic region influences *TCF7L2* splicing. Furthermore, given that it has been hypothesized that *TCF7L2* exerts its effect via the enteroendocrine system, we also observed a significant decrease in the gene expression of dipeptidyl peptidase-4 (*DPP4*; $P < 0.01$), a key factor involved in glucose metabolism.

As such, our gene editing data suggests that this genomic element within an intronic region of *TCF7L2* influences type 2 diabetes risk by serving as an enhancer that influences both expression and the splice isoform repertoire of this key gene.

1762-P

Whole-Exome Sequencing in Multiplex Families Identifies NLRP9 as a Novel Gene for Type 2 Diabetes

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Type 2 diabetes (T2D) is results from the interaction of genetic and environmental factors. Despite the high heritability (30-70%) of T2D, genome-wide association study (GWAS) loci explain less than 10% of the genetic variance of T2D. Moreover, most of the GWAS loci in T2D are non-coding SNPs which make designing experiments for functional validation challenging. Family-based studies facilitate discovery of loci that segregate in multi-generational pedigrees with multiple affected individuals, and whole exome sequencing (WES) approaches are important to identify protein coding variants that may be validated with functional experiments and geared to clinical translation. In the present study we take advantage of these strengths of linkage studies and WES to identify coding variants of deleterious effect using 15 multi-generational African ancestry pedigrees with multiple T2D affected members. A total of 63 individuals with T2D and 26 controls from the 15 pedigrees were genotyped on the Illumina Omni 2.5M array for linkage analysis. In addition, 41 out of the 63 T2D individuals across the 15 pedigrees, and 10 unrelated controls were whole exome sequenced. Genomic regions showing linkage peaks, and screening criteria including deleteriousness, conservation, absence in controls, rareness in human population samples, and presence in at least two T2D affected pedigrees were used to prioritize variants. We found a total of 13 linkage peaks (LOD >=1.5), of which one overlaps with a shared missense coding variant chr19:60941404 C>T in the *NLRP9* gene that shows segregation with T2D in two pedigrees. Two FLNB variants (chr3:58055718 G>C and chr3:58064830 G>C) segregated with T2D in two pedigrees. NLRP9 is a member of the inflammasome complex and is located near a cluster of zinc finger protein genes. In conclusion, our finding suggests that the NLRP9 inflammasome is involved in T2D through detection of metabolic stress and release of proinflammatory cytokines leading to insulin resistance.

1763-P

Genetic Variant (R27S) in Insulin-like Peptide 5 Is Associated with Increased Insulin Sensitivity

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INSL5 is an orexigenic peptide secreted by L-cells in the colon. Furthermore, the *Rxfp4*-null mouse, which lacks a receptor for Insl5, exhibits a lean phenotype. To investigate the peptide's role in human biology, we searched for genetic variants in the *INSL5* gene. Using an exome chip to assess genotypes, we identified a nonsynonous SNP (R27S; rs146856578) in the *INSL5* gene with a minor allele frequency of 0.12 in the Old Order Amish, representing a 30- to 1000-fold enrichment relative to non-Amish European populations. A positively charged, basic amino acid (R or K) is evolutionarily conserved at position 27, the 5th amino acid in the B-chain of INSL5. The R27S substitution is predicted to damage protein function, based on *in silico* predictions by SIFT and GERP++. The S27-allele is associated with decreased fasting insulin levels (7.8±1.2 for S27-homozygotes, 9.9±0.3 for S27/R27-heterozygotes, and 10.7±0.2 mU/L for R27-homozygotes; p=0.004). In addition, there is a progressive decrease of ~1.2 cm in height for each copy of the S27-allele (p=0.00046), and a trend toward decreased body weight (p=0.08), with S27-homozygotes (N=19) weighing on average 8.2 kg less than heterozygotes (N=351) and 9.4 kg less than R27-homozygotes (N=1273). [Statistical analyses for insulin levels and height were carried out using an additive model with corrections for age, gender, and family structure. Data on body weight were analyzed using a recessive model.] These data are consistent with what one would predict for a loss-of-function mutation in an orexigenic peptide. This experiment of nature supports the hypothesis that INSL5 has a physiologically relevant role in regulating food intake in humans. Studies are underway to replicate the observed phenotype-genotype association findings, and also to synthesize the S27-INSL5 peptide to confirm whether the nonconservative S27-substitution alters peptide function.

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1764-P

Genetics of Fructosamine and Glycated Albumin in Adults without Known Diabetes

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Fructosamine (FA) and glycated albumin (GA) reflect average blood glucose over 2-4 weeks. We evaluated genetic determinants of these markers to 1) identify loci unrelated to glucose that may impact their interpretation and 2) to further characterize previously-identified HbA1c and fasting glucose (FG) loci from GWAS in European ancestry (EA) populations in African Americans (AA). For 1), we conducted genome-wide association analyses of serum FA and GA% in 7,655 participants of European ancestry (EA) without diabetes in the Atherosclerosis Risk in Communities Study. For 2), we evaluated whether prior HbA1c and FG SNPs were associated with glycemic markers in our sample of EA (n=7655) and AA (n=2117) subjects. 1) Intronic rs10419198 in RCN3 was significantly associated with FA (p=9.6E-10), and nominally associated with GA% (p=4.1E-06, with lower FA and GA% per copy of the minor T allele; Table). 2) Rs1402837 (G6PC2) was associated at study-wide significance with GA% and nominally with FA in the EA sample (Table). Variation in RCN3 was previously associated with serum total protein and albumin in East Asian populations. Neither of these loci was previously known to be associated with FA or GA% in EA or AA. While the genome-wide significant association of FA with RCN3 likely is due to a non-glycemic effect, the association between G6PC2 and GA% likely represents a glycemic locus, consistent with prior HbA1c findings in EA.

Table. Associations of rs10419198 and rs1402837 with glycemic markers.

	rs10419198[a]	rs1402837[b]
Gene	*RCN3*	*G6PC2*
Minor (A1)/major allele – European ancestry	T/C	T/C
A1 frequency – European ancestry	0.28	0.22
A1 frequency – African ancestry	0.78	0.31
β for ln(fructosamine); p value		
European ancestry	-0.13; 9.6E-10	0.058; 3.1E-03
African ancestry	0.08; 1.2E-01	0.0071; 8.4E-01
β for ln(glycated albumin); p value		
European ancestry	-0.05; 4.1E-06	0.082; 2.9E-05
African ancestry	0.063; 1.9E-01	0.039; 2.5E-01
β for ln(hemoglobin A1c); p value		
European ancestry	0.02; 3.2E-01	0.011; 1.7E-10
β for ln(fasting glucose)		
European ancestry	0.017; 4.2E-01	0.067; 1.5E-12

[a] Finding from GWAS in EA (p<5E-08 significant).
[b] Study-wide significant (p<7E-04) finding from evaluation of prior hemoglobin A1c and fasting glucose SNPs.

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1765-P

miR-192 and miR-200 Help to Diagnose Pancreatic Cancer among Diabetic Patients

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New-onset diabetes mellitus (DM) may be in the middle and older aged people an early symptom of pancreatic cancer (PC). This pancreatogenic diabetes can hardly be distinguished from type 2 DM. Unfortunately, sensitive markers for PC are still missing. MicroRNAs (miRNAs) seem to be promising markers that could improve early diagnosis and poor prognosis of PC.

Total of 35 patients with PC (25/10, with/without diabetes), 30 type 2 diabetic patients and 18 healthy controls were enrolled in our study. After isolation of miRNAs from serum using Exiqon kit, reverse transcription and RT-PCR were performed with expression assessment of 16 miRNAs that we had selected in a prior pilot study (miR-9, 16, 21, 30, 103, 126, 133, 146, 155, 191, 192, 196, 200, 375, 423, 454). ExpressionSuite software helped to capture the raw data. Using Biogazelle qbase+ software and its application GeNorm finder, we set miR-191 and miR-454 as reference genes for the next analysis. ANOVA test was performed for statistical evaluation.

Expressions of 12 miRNAs were significantly changed within the groups. The most significant difference was found in miR-192 and miR-200, which were comparably elevated in PC group versus DM and healthy controls: 3.3 (1.7-6.4) vs. 0.5 (0.4-0.6) and 0.4 (0.3-0.6) arbitrary units, p<0.00001. No significant difference of both miRNAs was observed between DM and healthy controls. No difference in miR-192 and miR-200 was found between diabetic and non-diabetic patients in the PC group. In addition, the lowest expression of miR-21 was observed in DM patients and the difference compared to other groups was significant (p <0.0001). The differences in other miRNAs were less expressed among the groups.

Our data demonstrates that miR-192 and miR-200 could be used as new markers of pancreatic cancer in patients with DM. A further prospective study enrolling patients with newly diagnosed diabetes is necessary to verify if both miRNAs could be used as early markers of PC in these patients without any symptoms of malignancy.

1766-P

Completing the Picture: Capturing the Genetic Basis of Untoward Glucose Metabolism through Plieotropic Analyses of Glucose-related Traits in a Population from Starr County, Texas

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Efforts to understand the genetic basis of the effects of untoward glucose metabolism have focused largely on independent clinical characteristics of disease. In Starr County, Texas, where trends in the rates of type 2 diabetes and obesity have stayed approximately 30 years ahead of rest of the country, we have utilized the results of decades of collection of hundreds of phenotypic measurements to perform massive single trait and pleiotropic analyses of single variant and gene-based burden tests of clinical and subclinical characteristics related to glucose metabolism.

Together, these capture a more complete picture of type 2 diabetes. These measures, spanning from subclinical to a broad spectrum of untoward effects of impaired glucose control, include characteristics of cardiovascular, ocular, metabolic, sleep, and obesity-related health, and range from uncorrelated to highly intertwined (Pearson's correlation: 0-0.98, median = .11). In addition to identification of genome-wide significant associations of genes and variants with single traits, e.g. top signals for galectin-3, a biomarker of cardiovascular health, include rs74769851 (p value, 1x10-9) and LGAL3 (<10-20), we identified genes that contribute most across these domains of comorbity. Top findings include CNTN4, (associated with traits related to hemoglobin, sleep, weight, and insulin) and SORCS2 (sleep, infectious disease, and anthropometrics). In addition, we have identified gene-based pathways significantly enriched for diverse pleiotropic effects including insulin stimulated glucose transport, and insulin exocytosis.

By simultaneously considering the diverse traits of the spectrum of effects within the axis of comorbidity of diabetes, we are able to learn new things about the genes and pathways that are contributing to adverse health in Starr County, a community undergoing an epidemic of obesity and diabetes.

1767-P

Extensive Targeted Next Generation Sequencing Yields a High Diagnosis Rate in Monogenic Diabetes

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Background: Monogenic diabetes represents a heterogeneous group of metabolic disorders resulting from defects in single genes. Defects are categorized primarily into two groups: disruption of beta cell function or a reduction in the number of beta cells. Monogenic diabetes remains undiagnosed in over 90% of subjects, mainly because the access to genetic testing is not available. The aim of our study was to screen a cohort of individuals with suspected monogenic diabetes.

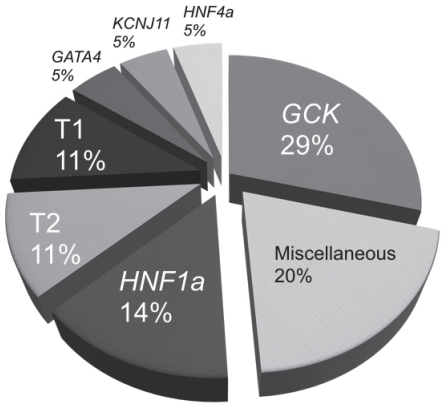
Methods: The selection criteria for testing were the following: neonatal diabetes, syndromic diabetes with extra-pancreatic features, auto-antibody negative type 1 diabetes, type 2 diabetes diagnosed before the age of 30 years or before the age of 40 years without metabolic features. Genetic analysis was performed by high throughput sequencing (all coding and splicing regions of 323 potential diabetes genes). The most prominent variants were confirmed by Sanger sequencing.

Results: We have analyzed 95 diabetic individuals with suspected monogenic diabetes and found variants in 72% of the subjects, in 21% no variants could be detected, in 7% the sequencing has to be repeated. The different genetic results are depicted in Fig. 1.

Conclusions: This testing approach shows a high yield of positive results and could possibly be used as a diagnostic test. Some of the variants have not been published so far and need functional validation.

For author disclosure information, see page A810.

Fig.1



Genetic results from next generation sequencing: T1: variants in genes associated with T1 diabetes, T2: variants in genes associated with type 2 diabetes, *GCK*: glucokinase, *HNF1a*: hepatocyte nuclear factor 1a, *HNF4a*: hepatocyte nuclear factor 4a, *GATA4*: gata-binding protein 4, *KCNJ11*: potassium channel, inwardly rectifying subfamily J, member 11.

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1768-P

The Study to Understand the Genetics of the Acute Response to Metformin and Glipizide in Humans (SUGAR-MGH): Genetic Risk Scores (GRS) to Predict the Response to Type 2 Diabetes Medications

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There has been a recent explosion of published genetic associations with glycemic traits. For most of these discoveries, however, the biochemical, functional and clinical relevance are unknown. SUGAR-MGH perturbs different arms of the glucose homeostasis system in humans to uncover the physiology of genetic variants for which no mechanism is known, and also aims to explore if there is a genetically determined response to glipizide or metformin.

Participants (n=667) not taking anti-diabetic medications undergo a sulfonylurea challenge, where they receive glipizide 5 mg in the fasting state and have blood drawn at regular time intervals. They then take a total of 2000 mg of metformin over the course of 2 days and return for blood draws and an OGTT.

We genotyped variants previously associated with glycemic traits, and constructed 3 GRSs: for fasting glucose (FG), fasting insulin (FI) and β-cell function (HOMA-B). The GRS for each trait was constructed by assigning 0, 1 or 2 at each locus according to the number of trait-raising alleles present at the locus, and summed to provide the overall genetic risk for each diabetes-related phenotype.

The median (range) for FG, FI and HOMA-B GRS was 33 (24-49), 23 (12-33), and 23 (15-30), respectively. The 3 GRSs showed the expected associations with their respective baseline traits. During the glipizide challenge, the FG GRS was significantly associated with glucose trough (β=0.4163, SE=0.1151, P=0.0003), and remained significant after adjusting for age, sex, BMI, race/ethnicity and baseline FG (β=0.2219, SE=0.1033, P=0.03). The FI and HOMA-B GRSs were not significantly associated with selected pharmacogenetic endpoints. None of the GRSs was significantly associated with metformin response.

In this interim analysis, SUGAR-MGH shows there is a genetically determined response to glipizide beyond FG levels, which might help predict hypoglycemia to a sulfonylurea.

1769-P

Population-based Linkage Analysis Reveals a Major Locus for Triglycerides in a Founder Population at High Risk for Type 2 Diabetes

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Population-based linkage study offers an efficient way to identify quantitative trait loci (QTL) in founder populations, including loci with multiple and/or rare variants that are harder to detect in association studies. We used this method to identify QTLs for lipid measures in Pima Indians, who are at high risk for type 2 diabetes (T2D). Measures of total cholesterol, HDL-C, and triglycerides (TG) were obtained from 1,024 Pima Indians (mean age=42.1±12.7yrs, 55% females, and 46% with T2D) with genome-wide SNP data. The percentage of identical by descent allele sharing (%IBD) for all ~800,000 pairs of subjects was estimated based on ~400,000 SNPs with Beagle.

We conducted genome-wide linkage analyses, adjusting for age, sex, T2D status and a population stratification estimate from our GWAS. We identified 2 linkage signals with LOD > 3 (LOD=9.3 for TG on chr. 11q and 4.1 for HDL-C on chr. 1p) explaining 10.8% and 7.9% of total trait variance respectively. Power analyses indicated 80% power to detect a QTL accounting for 10% of variance; thus, we focused on TG for subsequent analyses. Conditional measured genotype analyses identified 3 independent variants that explained nearly the entire linkage signal for TG. The SNP with the strongest association (rs147210663, p=1.5*10E-13) reduced the LOD from 9.3 to 2.2, and explained 6.9% of variance in TG. This SNP predicts a functional AI-a43Thr in APOA3; the Thr allele is rare in most global populations but occurs in >5% of Pimas. The association of this SNP with TG was replicated in a second sample of 1,863 Pimas (p=2.7*10E-17, and p=7.9*10E-39 for 2 samples combined). Carriers of the Thr allele had, on average, a >40% reduction in TG levels compared to non-carriers (85.7±59.2 vs. 149.2±116.5mg/dl) with no interaction with T2D (p=0.90). In summary, we identified two major QTLs for lipids in Pima Indians. One mapped to APOC3 and functional variation at this locus may reduce TG levels in diabetic and nondiabetic individuals.

1770-P

Fine-mapping and Identification of Two Novel Susceptibility Loci for Type 2 Diabetes through 1000 Genomes and UK10K Imputation in 13,201 Cases and 59,656 Controls

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Despite the clear contribution of Genome-Wide Association Studies (GWAS) to the understanding of the genetics of type 2 diabetes (T2D), the known associated loci published to date only explain a small fraction of the estimated T2D heritability. Genotype imputation consists in predicting unobserved variants using a dense reference panel of haplotypes to increase the statistical power of GWAS. The emergence of novel and large reference panels, such as the 1000 Genomes Project (1KG), and the UK10K (http://www.uk10k.org/), based on low-coverage whole genome sequencing data, constitute a unique opportunity to perform a more accurate fine-mapping of known associated regions and to identify new markers associated to T2D by re-analysing existing GWAS datasets available in public repositories.

We have performed genome-wide imputation and association testing with 1KG and UK10K reference panels in 6 T2D GWAS datasets available in dbGaP and EGA repositories comprising 72,857 subjects (13,201 cases and 59,656 controls). For this purpose, we have used GWImp-COMPSs, an application developed in our group to perform fast and accurate genome-wide genotype imputation and association testing that requires minimal user intervention. Through integration of 1KG and UK10K reference panels, we were able to impute a total of 11,329,230 (11,3 M), with minor allele frequency (MAF) higher than 0.001. Using this approach we were able to discover two novel GWAS loci and replicate 13 of the known loci for T2D. Interestingly, fine mapping of one of the known regions showed that it was driven by a single haplotype harbouring three missense variants. Additionally, through conditional analysis, we identified for the first time a secondary signal for well known CDKN2A-CDKN2B region. These results demonstrate the value of re-analysing publicly available data using novel and denser reference panels in order to better define the architecture for T2D.

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1771-P

Genome-Wide Analysis and Trans-ethnic Fine Mapping of Type 2 Diabetes Loci in Africans

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The genomics of type 2 diabetes remains largely understudied in sub-Saharan Africa (SSA). We conducted the first genome-wide association study (GWAS) for type 2 diabetes using both a conventional tag SNP GWAS array and an exome array in 1,808 Africans enrolled in the Africa America Diabe-

tes Mellitus (AADM) Study. Single variant association analysis of ~15 million genotyped and imputed SNPs based on the GWAS array revealed genome-wide significant loci at the *TCF7L2* intronic SNP rs7903146 ($p=1.11 \times 10^{-8}$) and the *TIMP3/SYN3* intronic SNP rs4608622 ($p=4.85 \times 10^{-8}$). Meta-analysis with the MEDIA consortium of type 2 diabetes GWAS in African Americans (24,351 individuals) revealed an additional genome-wide significant locus in *INS-IGF2* (rs3842770, $p=1.18X10^{-8}$, polymorphic only in 1000 Genomes African ancestry samples) and strengthened the evidence for association with rs7903146 ($p=2.81 \times 10^{-32}$). Seventeen of the 65 best established type 2 diabetes loci in Europeans were replicated ($p < 0.05$, same direction of effect) and fine-mapping improved the resolution of most of these loci. Exome array analysis did not find any additional significant single variants but found suggestive evidence for three gene sets - *TRIM67, TRMT10A* and *CTTNBP2*. Our findings indicate that the genetic architecture of type 2 diabetes in SSA is characterized by several risk loci shared with non-African ancestral populations and novel loci that may be shared only among African ancestry populations. The study provides an important resource for meta-analysis of African ancestry populations and for transferability of novel loci in future studies.

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1772-P

Genetic Variants in the Lanosterol Synthase Gene Are Associated with Type 2 Diabetes

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Based on the results of genome-wide linkage analysis of T2DM in Japanese and fine mapping of the candidate region on chromosome 21q (Diabetes 52:209, 2003), we identified a statistically significant association between the single nucleotide polymorphism rs2075906 in the lanosterol synthase (LSS) gene and T2DM which was further replicated in Koreans (combined P value=1.3 × 10-8, odds ratio=1.21, 95% CI: 1.14-1.30). In Europeans, the T allele of rs7282352 which is in perfect LD with rs2075906 was showed no significant association with T2DM. However, the DIAGRAM investigators did find a weak association signal (rs2839128: P=4.9 x 10-4), located 30 kb downstream from LSS in C21orf56; replication of this association was not observed in Japanese (control genotypes 2,659/456/30; cases, 2,212/393/31, Pallele=0.41, OR=1.06). The most significant SNP, rs2075906 in Asians, was located in the YY1 motif of the LSS protein, and the risk genotype was associated with increased LSS expression in mononuclear cells in healthy individuals. In conclusion, we identified a novel T2DM susceptibility gene, LSS, in Asian populations and increased expression of this gene increased risk of T2DM.

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1773-P

Functional Investigations of the Monogenic Diabetes Gene HNF1a Identify Rare Variants as Risk Factors for Type 2 Diabetes in a General Population

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The role of rare genetic variants in common disease is currently not well known. In a previous study, we found that a significant fraction of individuals from the Framingham and Jackson Heart Studies carry rare protein damaging variants in one of seven monogenic diabetes genes although most individuals were euglycemic. To investigate whether functional characterization of such variants can improve disease risk prediction, we studied all non-synonymous coding variants inthe most common of the seven monogenic diabetes genes, *HNF1A*, identified among 4,003 individuals in the Framingham and Jackson Heart Studies. Of 27 rare *HNF1A* variants, *in silico* prediction tools reported four variants as putative pathogenic but noborderline association with diabetes was detected. All variants were functionally investigated focusing on effect on HNF-1A transcriptional activity (luciferase reporter assay in HeLa cells), DNA binding (Electrophoretic Mobility Assay) and subcellular localization (immunofluoresence). By functional investigation, eight variants were characterizedas functionally damaging based on the mutant proteins demonstrating impaired HNF-1A function (reduced DNA binding and/ortranscriptional activity <50%, or reduced nuclear translocation). Moreover, the clinical phenotype of carriers with functionally affected variants was significantly associated with diabetes ($p=8.1 \times 10^{-5}$, OR=6.33; CI 2.22-18.1). Thus, functional verification of variant effect in individuals carrying rare*HNF1A* variantsis neededto estimaterisk of developing type 2 diabetes.

1774-P

WITHDRAWN

1775-P

Polymorphisms in the ESR1 and ESR2 Genes Are Associated with Type 2 Diabetes in Females of Mexican-American Families

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Increasing evidence suggests a potential role of two estrogen receptors (ERα and ERβ) in the causative web of type 2 diabetes (T2D). We probed whether single nucleotide polymorphisms (SNPs) within 100 kb of the ESR1 and ESR2 genes (which encode ERα and ERβ, respectively) are associated with T2D in females.

We used the rich data from the San Antonio Family Heart Study of Mexican Americans. We included 327 and 165 SNPs around the ESR1 and ESR2 genes, respectively. Analysis was done in three steps: i) measured genotype analyses (MGA) implemented in SOLAR software for T2D as a discrete trait; ii) construction of gene-specific propensity scores using the allele dosages and the regression coefficients from MGA; and iii) testing association of the propensity scores with T2D. All models were adjusted for age, baseline waist circumference, serum triglycerides, systolic and diastolic blood pressure, top four principal components reflecting population ancestry and use of anti-hypertensive and lipid lowering drugs. Clinical utility was evaluated with integrated discrimination improvement (IDI) and net reclassification improvement (NRI).

We studied 827 women, 211 of whom had T2D (131 had T2D at baseline and 80 developed T2D during 6,897 person-years of follow-up). Thirty two (9.8%) and 12 (7.2%) SNPs in ESR1 and ESR2 were significantly associated with T2D. Propensity scores for both ESR1 and ESR2 were significantly associated with T2D (p=2.7x10-10 and 3.6x10-7, respectively). The IDI and NRI values for ESR1-specific score were 0.0503 and 0.4584 (p=5.4x10-10 and 1.2x10-8), respectively while those for ESR2-specific score were 0.0363 and 0.4197 (p=1.7x10-5 and 1.8x10-7), respectively.

Thus, strong evidence for the association of ESR1 and ESR2 with T2D in Mexican American females was found. Additional studies using gene expression, hormonal levels and their interactions are warranted. If substantiated, our results provide new drug targets for T2D treatment in females.

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1776-P

Identification of Novel Genes Contributing to Autosomal Dominant Diabetes by Whole-Exome Sequencing

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A total of 13 genes for maturity-onset diabetes of the young (MODY) have been identified to date. However, additional causative genes still remain unknown for >15% of MODY cases and for almost all of the other forms of autosomal dominant diabetes presenting at an older age than MODY. To identify these genes, we conducted a whole exome sequencing (WES) study in 52 multigenerational families with autosomal dominant diabetes and without evidence of mutations in known MODY genes. The mean age at diagnosis was <25, 25-35, and >35 years in 15, 26, and 11 of the families, respectively. After applying QC and frequency filters, candidate causative mutations (i.e., rare variants segregating with diabetes and predicted to have a functional impact) were identified in a total of 82 genes. Among these were mutations in 3 genes that had an established role in β-cell function and/or had been previously implicated in neonatal diabetes. These included G182E in HGF (Hepatocyte Growth Factor), P877fs in RFX6 (Regulatory Factor X 6), and K355Q in SLC19A2 (Solute Carrier Family 19 [Thiamine Transporter Member 2]). HGF is a growth factor promoting β-cell proliferation. Based on in silico modeling, the G182E mutation creates new H-bonds with surrounding amino acids, potentially altering HGF conformation. RFX6 and SLC19A2 were recently described as the causes of syndromic forms of neonatal diabetes - the Mitchell-Riley and the

For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

thiamine-responsive megaloblastic anemia (TRMA) syndromes, respectively. This preliminary WES analysis points to mutations in HGF, RFX6, and SLC19A2 as contributing to the etiology of autosomal dominant diabetes not due to known MODY genes. In vitro experiments are in progress to determine the functional impact of these mutations as well as those identified by WES in genes with less obvious links to glucose homeostasis.

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1777-P

Variants Associated with HDL-C Levels: Assessment for Association with Type 2 Diabetes in American Indians

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Previous epidemiological studies in Pima Indians have identified a protective role for higher HDL-C against the onset of T2D in women. In this study, we analyzed 35 SNPs from established HDL-C loci for association with HDL-C, T2D and related traits. Genotyping and analysis of these SNPs in 2,717 full-heritage Pima Indians informative for T2D status and lipid levels identified a significant association (P<0.05) for 14 SNPs with HDL-C. An un-weighted multialleleic genetic risk score analysis (GRS) including the 35 SNPs was significantly associated with HDL-C (P=3.6×10^{-6}), however the 21 SNPs not associated with HDL-C did not had any effect on HDL-C levels even in combination (GRS [21 SNPs], P=0.08). Therefore, only 14 SNPs were further genotyped in 4,993 American Indian samples informative for T2D (2,777 informative for lipid levels) and analyzed for association with HDL-C, T2D and related traits in the combined sample. In this analysis, 6 of the 14 SNPs at the *CETP, DOCK6, PPP1R3B, ABCA1* and *APOA1-C3-A4-A5* loci reached genome wide significance (P<4.9×10^{-7}) for HDL-C association. The GRS analysis including the 14 loci in the combined samples negatively correlated with HDL-C levels (β= -0.92mg/dL, P=3.1x10^{-48}) and had a strong positive correlation with insulin resistance as estimated by homeostasis assessment (HOMA-IR, P=8.6x10^{-5}, β (SD units) = 0.015). The GRS correlated positively with T2D (P=0.007, OR=1.03), but there was no interaction with gender (P=0.74). When analyzed individually, SNPs at the *CETP, HNF4A* and *KLF14* loci significantly associated with type 2 diabetes only in female subjects (3.2×10^{-4} - 7.7×10^{-5}), such that the HDL-C lowering allele increased the risk for T2D. The T2D risk alleles for the SNPs at the *CETP* and *KLF14* loci were associated with increased insulin resistance in female subjects as estimated by HOMA-IR (P<0.05). In conclusion, our studies suggest a modest effect of the genetic predisposition for lower HDL-C on the risk for T2D in American Indians.

1778-P

Genetic Architecture of Fasting Plasma Glucose in Pregnancy

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Pregnancy is characterized by metabolic adaptations that include a decline in fasting plasma glucose (FPG) in the setting of increasing insulin resistance. In non-gravid populations, FPG is heritable and associated with more than 50 gene loci. Whether the genetic architecture of maternal FPG is similar or different than the non-gravid state is unknown. To address this, we examined the heritability of maternal FPG and 50 gene regions associated with FPG in non-gravid populations in mothers who participated in the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. FPG was determined at ~28 weeks gestation in 1367 European ancestry (EU), 1178 Thai (TH), 1075 Afro-Caribbean (AC) and 817 Mexican-American (MA) mothers. Genome-wide SNP data were obtained using Illumina chips and imputation to ~2 million SNPS using HapMap3 reference panels. Heritability of FPG was estimated separately in each of the 4 populations using genome-wide complex trait analysis (GCTA). In a meta-analysis across the 4 populations, heritability was 60 + 17% (p = 5.9E-06), similar to what has been demonstrated in non-gravid populations. For each of the previously-reported 50 genetic loci associated with FPG, we examined association of the lead literature SNP and SNPs in linkage disequilibrium (r2 > 0.8) with maternal FPG within each ancestry group using linear regression analyses with an additive genotype variable, adjusting for population substructure and other covariates. Meta-analysis was conducted across ancestry groups under a fixed-effects model. To adjust for testing 50 LD blocks, p < 0.001 was considered significant. Five gene regions (PCSK1, MTNR1B, PPP1R3B, G6PC2, GCKR) were associated with FPG in the meta-analysis. In addition to the above gene regions, in ancestry group-specific analyses, IGF2BP2 was associated with FPG in AC mothers. These data demonstrate that FPG is heritable during pregnancy with both overlap and, possibly, differences in gene regions that account for the heritability compared to non-gravid populations.

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1779-P

Rs10401670 was Identified as a Possible Functional Variant Affecting Circulating Resistin by a Genome-Wide Search in Japanese

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Resistin is a cytokine causing insulin resistance. We reported that G/G genotype of single nucleotide polymorphism (SNP) at -420 (rs1862513) in the human resistin gene (*RETN*) increased susceptibility to type 2 diabetes. SNP-358 (rs3219175) as well as SNP-420, both located in the promoter of *RETN*, was tightly correlated with circulating resistin *via* a *cis*-acting effect. Circulating resistin was also affected by tag SNPs around the human decorin gene, identified as a possible resistin receptor, *via* a *trans*-acting effect.

To identify major quantitative trait loci for circulating resistin, we performed a genome-wide association study of 5708071 SNPs directly genotyped or imputed using references from the 1000 Genome Project in 448 general Japanese subjects.

The peak of -log P was found on the chromosome 19 where *RETN* was located. Precisely, the top SNP was SNP-358, followed by rs1423096, SNP-420, and rs10401670 (P<10^{-46}, <10^{-21}, <10^{-15}, and <10^{-14}, respectively). Rs1423096 and rs10401670 were located at 5 kb and 8.5 kb, respectively, downstream from the translation initiation site of *RETN*, and were in the same linkage disequilibrium block. The associations between circulating resistin and these 4 SNPs were replicated in other 2 general Japanese populations (both n=~2,000) and meta-analysis (SNP-358, P<10^{-857}; SNP-420, P<10^{-287}; rs1423096, P<10^{-208}; rs10401670, P<10^{-126}). The analysis of haplotypes showed circulating resistin was associated with rs10401670 independent of SNP-358 and SNP-420, although SNP-420 G/SNP-358 A haplotype had the strongest effect. Functionally, nuclear proteins specifically recognized T but not C at rs10401670 in electrophoretic mobility shift assay. The promoter with T at rs10401670 showed lower luciferase activity than that with C in THP-1 cells.

Therefore, rs10401670 was identified as a possible functional variant affecting circulating resistin by a genome-wide search in Japanese.

1780-P

Application of Two-Point Linkage and Association Analysis to Elucidate Genetic Signals of Glucose Homeostasis

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Combining two-point linkage and association analysis provides multi-dimensional support for the relationship of a single variant to a trait of interest, even when the variant does not yield striking results from either analytical method alone. This has been applied to sophisticated measures of glucose homeostasis from the Insulin Resistance Atherosclerosis Family Study using genetic data from the Illumina OmniExpress and HumanExome arrays. Genetic contributors to acute insulin response (AIR), insulin sensitivity index (S_I), disposition index (DI) and metabolic clearance rate of insulin (MCRI) were evaluated by two-point linkage and association analysis performed for each trait across 750,317 variants in a sample of 1034 Hispanic Americans (88 families). Overall, there were 8200 variants with LOD>1 and P<0.05 and 36 variants with LOD>2 and P<0.001. Of the 36, half were contributed by AIR association and linkage from at least 13 independent loci. DI and S_I each contributed eight variants representing 6 and 5 loci, respectively. Some signals of note include *MTNR1B* (AIR; P=7E06 and LOD 2.05), *CACNA1C* (DI; P=5E04 and LOD=2.05), *PDE1C* (DI; P=2E05, LOD=2.02), and *ESRP1* (AIR; P=2E05, LOD=3.15). CACNA1C is a calcium channel involved in insulin release, while PDE1C is a calcium-sensitive phosphodiesterase involved in aural insulin signaling. Several previously implicated diabetes-related loci were represented among those with nominal linkage and association evidence (P<0.05 and LOD>1). Namely, *JAZF1* was represented by 5 SNPs with LODs up to 3.38 and p-values as low as 1E04, and *CDKAL1* with LOD scores of up to 2.78 and p-values of 6E05. Other known loci represented include *PTPRD, KCNQ1, ADAMTS9, ARL15, GLIS3, ST6GAL1, WWOX, CACNA1D, LINGO2,* and *HMGA2,* among others. These novel and known signals demonstrate that incorporating two-point linkage analysis can identify meaningful signals that impact glucose homeostasis traits, often in the absence of striking association alone.

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1781-P

Polygenic Risk Scores in Type 2 Diabetes and Depression

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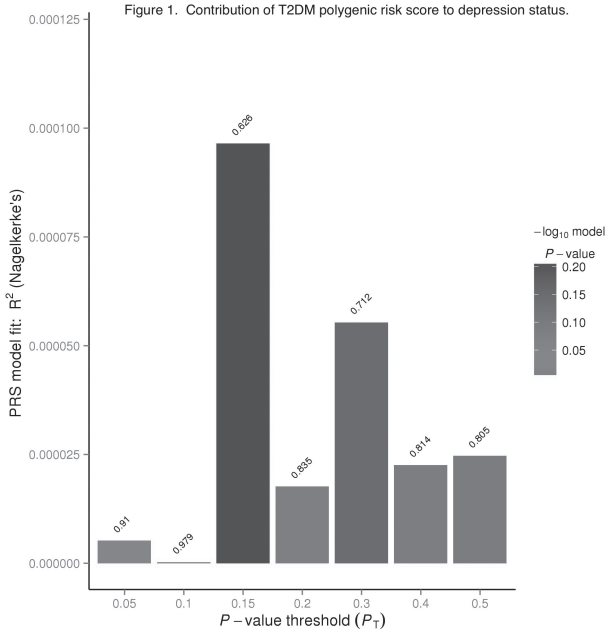
The underlying pathogenesis of the link between type 2 diabetes (T2DM) and depression is complex and likely to arise from interactions between genetic and environmental factors. Both T2DM and depression are considered polygenic traits and genome-wide association studies (GWAS) allow us to examine overlap in their genetic underpinnings. Polygenic risk scores can be calculated from single nucleotides polymorphisms that each captures modest effects of a trait. The aim of this study is to test whether genetic susceptibility to T2DM is significantly associated with depression status using polygenic risk scores. T2DM polygenic risk scores were derived from the association summary statistics of Diabetes Genetic Replication And Meta-analysis Consortium (34,840 cases and 114,981 controls), at various thresholds of association p-values. Logistic regression was used to test for association between T2DM polygenic score and depression status in the RADIANT-UK study (1,624 cases and 1,588 controls) using PRSice software (http://prsice.info). T2DM polygenic risk scores were not significantly associated with depression status (p=0.63; Figure 1). The sample size of RADIANT-UK (n=3,212) may be underpowered to detect true effect. In conclusion, T2DM polygenic risk scores may not be a major contribution to depression genetic susceptibility in this cohort.

Figure 1. Contribution of T2DM polygenic risk score to depression status.



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1782-P

Identification of a New Signal for Type 2 Diabetes in the Previously Established GLIS3 Gene

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The Kruppel-like zinc finger protein Gli-similar (*GLIS)3* plays a crucial role in pancreatic β-cell development, and loss-of function mutations in this gene cause neonatal diabetes. Common variation in *GLIS3* has been reported to be associated with both type 1 and type 2 diabetes (T2D) in prior genome-wide association studies. Therefore *GLIS3* was analyzed as a candidate gene for T2D in Pima Indians who have a high prevalence of this disease. 280 SNPs that tagged common variation (minor allele frequency ≥0.05; r^2≥0.85) across ~576 kb spanning *GLIS3* (Chr9:3774128-4350035 which covers ~50kb each side of the gene) were genotyped using an Affymetrix Axiom Custom array in a population-based sample of 3494 full-heritage Pima Indians. Genotypes were analyzed for associations with early-onset T2D (onset age<25 years) in a case/control sample (n=606), T2D (onset at any age; n=3494), and acute insulin response to an intravenous glucose bolus in individuals with normal glucose tolerance (n=298). Two intronic tag SNPs, rs7850128 and rs7035478 which were in high linkage disequilibrium (D'= 0.99, r^2=0.83) with risk allele frequencies (RAFs) of 0.53 and 0.58, respectively, were associated with early-onset T2D and T2D, but not acute insulin secretion. Conditional analysis showed that both SNPs contributed to the same signal. The association of rs7850128 with early onset T2D was OR=1.45 (1.17-1.81), p=9.7 x 10^{-4}; while the association with T2D (onset any age) was OR=1.22 (1.08-1.37), p=8.7 x 10^{-4}. Notably, rs7041847 which is the established T2D variant in *GLIS3* previously reported in East Asians, was not associated with T2D in Pima Indians [RAF=0.65, OR=1.07 (0.95-1.22), p=0.27]. The linkage disequilibrium between the Pima signal (rs7850128) and East Asian signal (rs7041847) was low (D'=0.53, r^2=0.22), and conditional analysis indicated that the SNP identified in Pima Indians represents a new diabetes signal in *GLIS3*.

1783-P

Charting Mediterranean Populations by Autosomal SNPs Represents an Anthropological Base for GWAS of Metabolic Syndrome with a New MEDISCOPE GeneChip

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The definitive success of GWAS (genome wide association studies) is pending on the ability to control population stratification. The MEDIGENE program was launched among Mediterranean countries for the study of metabolic syndrome (MetS) with the aim to find new population models. Among 6050 DNA samples, 475 samples from lean normal individuals were geographically located by birthplace 2 generations upstream, genotyped with 650,963 SNPs (EUR Chip) and analyzed by Principal Component Analysis (PCA) with SMARTPCA program. A MEDISCOPE micro-array chip was designed containing besides EUR SNPs 107,260 additional SNPs for MetS, including 40 prioritized genes at 1000 genome or HapMap density while 3898 SNPs were dedicated to anthropological features, including Neanderthal genome. Genotyping with EUR SNPs revealed an extraordinary correlation between of the geographic coordinates for birthplace and PCA eigenvectors. On West side, the most distant were Basque while on the East side the Turkish populations (closed to Turkic-speaking Karachays, Kumyks ϖand Balkars in Russia). Lithuanians and North Africans defined other clusters. While hundreds of SNPs differentiated these clusters, top 10 SNPs were defined for comparative pairs. Between French and Romanians 4 genes were different, including interleukin receptor (IL23R). French were also different from Catalans (Spain) by 8 genes, including protein kinase C theta (PRKCQ) while another 9 genes differentiate from North African Tunisians and Algerians, including tumor protein p63 (TP63). These data showed a sufficient genetic distance in Southern Europe and a strong genetic barrier over the Mediterranean Sea to propose new models for GWAS, not only based on autosomal SNPs but also taking the advantage of 1000 times more density. We conclude that considering anthropological markers GWAS will enter in a new era of an extraordinary opportunity to unravel culprit genes in complex disorders.

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1784-P

A Variant of PSMD6 Is Associated with the Therapeutic Efficacy of Oral Antidiabetic Drugs in Chinese Type 2 Diabetes Patients

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The PSMD6 variant rs831571 has been identified as a susceptibility locus for type 2 diabetes mellitus (T2DM). This study aimed to investigate the association of this variant with therapeutic effect of oral antidiabetic drugs in Chinese T2DM patients. 209 newly diagnosed T2DM patients were randomly assigned to treatment with repaglinide or rosiglitazone for 48 weeks, and therapeutic effects were compared. In the rosiglitazone cohort, rs831571 showed significant associations with decreased 2-h glucose after 24 weeks of treatment (P=0.0364) and reduced HbA1c levels after 24 or 48 weeks of treatment (P=0.0247 and 0.0460, respectively). The C allele was significantly associated with reduced fasting plasma glucose (FPG) at 24 and 32 weeks (P=0.0172 and 0.0257, respectively). Survival analyses showed that CC homozygotes were more likely to attain a standard FPG level (P=0.0654). In the repaglinide cohort, rs831571 was significantly associated with decreased 2-h glucose after 48 weeks of treatment (P=0.0371) and reduced HbA1c levels after 24 or 48 weeks of treatment (P=0.0096 and 0.0101, respectively). In addition, rs831571 also showed significant associations with HOMA-IR after 48 weeks of treatment with repaglinide (P=0.0235). In conclusion, the PSMD6 variant rs831571 was associated with the therapeutic effect of rosiglitazone and repaglinide in Chinese T2DM patients.

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For author disclosure information, see page A810.

Guided Audio Tour poster ADA-Funded Research

1785-P

WITHDRAWN

1786-P

Searching for New Mutations by Mitochondrial Genome-Wide Screen in Patients with Early-Onset Type 2 Diabetes in Chinese Han Population

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Objective: To investigate the prevalence of 3243 A to G mutation of the mitochondrial DNA and search for novel mutations by mitochondrial genome-wide screen in patients with early onset type 2 diabetes in Chinese Han.

Methods: We collected 177 patients diagnosed with type 2 diabetes before 40 years old in Peking University People's Hospital from January, 2011 to June, 2014. Firstly, the mt3243 A to G mutation was screened by PCR-RFLP technique. Secondly, 70 maternally inherited diabetic patients among 177 patients were sequenced to look for more patients with mt3243 A to G by Sanger. Finally, 40 patients with maternally inherited diabetes and without mutation of mt3243 A to G were screened for the mutations across the whole mitochondrial genome by DNA directly sequencing.

Results: Two diabetic patients with mt3243 A to G mutation were detected in 177 patients by PCR-RFLP, and another two patients with mt3243 A to G mutation were detected by Sanger sequencing from 70 patients with maternally inherited diabetes. These 4 patients had lower body mass index, impaired hearing, maternal inheritance, and insulin-dependent treatment. We also identified one patient simultaneously carried 3337 G to A, 11903 G to A and 16325 T to C mutations by sequencing of the entire mitochondrial genome, and did not found mt3337 G to A mutation in 100 subjects with normal oral glucose tolerance.

Conclusion: The prevalence of mt3243 A to G is 2.3% in the patients with early onset type 2 diabetes in Chinese Han. The accuracy of Sanger sequencing was much higher than that of PCR-RFLP. From the sequencing of the entire mitochondrial genome, we found the mt3337 G to A mutation, which potentially contribute to diabetes. It is possible that the prevalence of mitochondrial diabetes is underestimated by traditional methods.

1787-P

Casual Gene Prediction at Type 2 Diabetes Loci through Integration of Genetic Association and Functional Annotation

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GWAS studies have identified nearly 100 loci influencing type 2 diabetes (T2D) risk. However, as most associated variants are non-coding, the genes through which causal variants act are largely unknown. We aimed to identify genes through which risk variants at T2D loci act and protein interaction networks in which these genes reside through integration of large-scale genetic and genomic annotation data.

We developed a scheme to assign causal "candidacy" scores to genes and applied it to all 1,511 genes within 500kb of 93 known T2D signals. In brief, this scheme integrated data from (a) fine-mapped localization of causal variants using Bayesian credible sets, (b) regulatory annotations from ENCODE and T2D-relevant tissues (e.g. pancreatic islets, adipose), (c) annotations linking regulatory elements to target genes (e.g. *cis* eQTLs), (d) coding variant T2D associations from exome sequence and array data and (e) biological annotations of gene function. We then normalized the resulting scores across all genes at each locus. This approach generated high candidacy scores for many established causal genes (e.g. *SLC30A8, MTNR1B),* and highlighted novel candidates at others (e.g. *NKX6-3* at *ANK1* locus).

We then used scores as seeds to build an interaction network of proteins (from InWeb), using a weighted prize-collecting Steiner tree, consisting of 255 seed and 210 non-seed proteins. Non-seed proteins in the resulting network were significantly enriched for T2D association in HapMap GWAS data from DIAGRAM (VEGAS, Fisher p=.001). The most inter-connected proteins in the network were non-seed proteins, YWHAZ and TRAF6, which both have independent molecular evidence for a role in T2D-relevant processes.

These results suggest a high degree of functional inter-connectivity among causal genes influencing T2D. Further, they provide a resource for experimental validation of causal gene targets at established loci and discovery of novel risk genes in disease-relevant networks.

1788-P

A Genetic Risk Score of 96 Variants Linked with Type 2 Diabetes and Cardiometabolic Risk Traits Is Associated with Cardiovascular Mortality in 29-Years Follow-up of the Framingham Heart Study (FHS)

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Cardiovascular diseases (CVD) are a major cause of death and are often associated with type 2 diabetes (T2D). Genome-wide studies (GWAS) identified loci associated with T2D, CVD and traits leading to early death. We investigated whether these loci in aggregate carry a higher risk of all-cause and CVD mortality in the FHS. We computed an unweighted genetic risk score (GRS) of 96 variants selected by effect-size within respective GWAS to represent the top 25% of GWAS variants for the following traits: T2D, coronary artery disease, myocardial infarction (MI), stroke, sudden cardiac death, heart rate, long QT-interval, heavy smoking and 15-years all-cause mortality. We used pooled logistic regressions with genetic-only (GRS adjusted for sex) and full CVD risk factors adjusted models (sex, age, smoking, prevalent non-fatal CVD) to test the association of 96-GRS with all-cause and MI/stroke mortality in 3,426 FHS participants across 29 years follow-up (p<0.025 (p=0.05/2) for significance). Prevalence of non-fatal CVD, T2D and smoking was 7.5, 6.1 and 26.4% at baseline and 18.5, 15.9 and 13.2%, respectively, at the beginning of the last period considered. Cumulative incidence of fatal MI/stroke and all-cause mortality was 5.1 and 22.5%, respectively. The 96-GRS was associated with MI/stroke mortality in both genetic-only (OR[95% CI]: 1.04[1.0-1.1], p=0.006) and fully adjusted model (1.04[1-1.1], p=0.009). Association with all-cause mortality did not reach our statistical significance criteria (1.01[1-1.03], p=0.029, genetic-only; 1.02[1-1.03], p=0.034, fully adjusted). An aggregate burden of 96 GWAS variants with the largest effect size on cardiometabolic traits is predictor of MI/stroke death in longitudinal analysis of a large population of European ancestry. Further studies need to specify the impact of cardiometabolic disease genetics on current mortality prediction models.

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1789-P

Prediction of Incident Type 2 Diabetes with Genetic and Nongenetic Risk Factors in Multiple African-American Populations

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The prevalence of type 2 diabetes (T2D) in African Americans (AA) is twice that of European-Americans. Impaired glucose homeostasis is influenced by beta-cell dysfunction (BCD) and insulin resistance (IR). The relationship between genetic risk variants associated with glucose homeostasis and T2D risk has yet to be fully explored in AA populations. We hypothesized that genetic variants in the pathways involved in β-cell dysfunction, insulin resistance or both may improve predictive ability beyond the established demographic and clinical risk factors, and that this relationship is modified by obesity (defined as ≥30kg/m2). To test our hypotheses we pooled data from four population-based, prospective studies (n=5,488 AA) free of T2D at baseline. There were 821 incident T2D cases for a cumulative incidence of 5.9% over 25 years. The BCD GRS and the BCD/IR GRS were significantly associated with increased T2D risk; each risk allele increased T2D risk by 3.7% [HR=1.037, 95% CI: 1.006, 1.070] and 2.9% [HR=1.029, 95% CI: 1.002,

1.057], respectively. However, no improvement in model C statistics or Net Reclassification Index (NRI) was observed when comparing models with and without the GRSs and stratification by obesity status did not change results significantly. The observed increased T2D risk with the beta-cell dysfunction GRS but not the insulin resistance GRS suggests that genetic risk variants related to beta-cell dysfunction may play an important role in T2D risk prediction among African Americans.

1790-P

Comprehensive Second Generation Genetic Diagnosis of Maturity Onset Diabetes of the Young

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Maturity Onset Diabetes of the Young (MODY) is a monogenic disorder, caused due to a mutation in one of the 13 MODY genes which are primarily involved in β cell development and functioning. Utilizing our previously established cost-effective Second Generation Genetic Diagnosis of MODY (2GD-MODY) protocol with the 10 gene panel, a wide spectrum of mutations were identified in 19% of the clinically diagnosed MODY subjects. In the present study we aimed to further develop the 2GDMODY protocol to screen all the known 13 MODY genes. We utilized our improvised 14 multiplex PCRs for gene enrichment followed by sequencing on Ion Torrent Personal Genome Machine (PGM). The 59Kb target was sequenced at mean coverage depth of at least 200x and 99% of the target bases were sequenced with a minimum coverage of 20x. We identified mutations in 21% (13/60) of the young onset diabetes subjects screened (mutation Table). These finding were confirmed by Sanger sequencing and the novel mutations were absent in 100 control subjects. This is a first report of a novel KLF11 gene mutation and also two novel digenic mutations involving HNF4A, HNF1A and ABCC8 genes from India. The 2GDMODY protocol on Ion Torrent PGM is a flexible, scalable, cost effective, sensitive and specific genetic screening approach in a heterogeneous disorder like MODY.

Table.

SNO	Sex	Age	AD	BMI	Acanthosis	DKA	GAD	ADFH	GENE	DNA Change	Amino acid Change
1	F	38	26	28.4	AB	AB		3G	*HNF1A *HNF4A	c.1047C>A c.782T>C	p.H349Q p.M261T
2	M	33	27	23.1	AB	P	AB	3G	*ABCC8 *HNF4A	c.2781C>G c.445G>A	p.W927C p.G149R
3	F	31	29	27.1	AB	AB	AB	2G	*HNF1A	c.985G>A	p.E329K
4	M	28	27	24.6	AB	AB		3G	PDX1	c.725C>T	p.P242L
5	M	32	28	28.2	AB	AB	AB	3G	PDX1	c.670C>A	p.E224K
6	F	27	25	34	P	AB		3G	PDX1	c.670C>A	p.E224K
7	F	26	26	32.8	P	AB	AB	3G	*HNF1B	c.578T>C	p.M193T
8	F	33	30	21.3	AB	AB		2G	NEUROD1	c.723C>G	p.H241Q
9	M	17	17	28.4	AB	AB	AB	AB	*NEUROD1	c.751C>A	p.A251S
10	F	29	28	21.4	AB	AB		3G	*KLF11	c.529C>T	p.R177X
11	F	29	28	23.1	AB	AB	AB	3G	PAX4	c.92C>A	p.R31L
12	M	10 M 6 M			AB	P	AB	AB	INS	c.265G>A	p.R89C
13	M	35	35	23.8	AB	AB	AB	2G	*ABCC8	c.379T>C	p.I127V

*Novel mutation, AB- Absent, P- Present, ADFH- Autosomal dominant family history, G-Generation.

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1791-P

Familial Renal Glucosuria in a Family with Impaired Glucose Control

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Background and Aims: Renal glycosuria is a condition where glucose is excreted in the urine despite normal blood glucose levels. A majority of the familial renal glycosuria cases are caused by deleterious mutations in SLC5A2, a gene coding for the SGLT2 transporter responsible for 90% of the glucose reuptake in the kidney. We aim to characterize the underlying genetic cause of glycosuria in a family with renal glycosuria and impaired fasting glucose/impaired glucose tolerance (IGT/IGT) or diabetes and to explore whether glycosuria protects from deterioration of glucose tolerance.

Materials and Methods: We performed exome sequencing of 23 family members, 8 with renal glycosuria. Of the 8 affected individuals, 5 were diagnosed with IFG/IGT or diabetes. Change in glucose tolerance was tested as change in area under the glucose curve (AUCOGTT).

Results: A total of 5 variants were found in the sequenced region of SLC5A2, 4 SNVs and one 6 bp deletion. Both snpEff and SIFT ranked the deletion as highly detrimental. The 6 bp deletion removes 4 coding and 2 intronic bases which causes a frame shift and splice site mutation in the third exon with a high probability of functional consequences on the protein. The deletion was seen in 9 individuals, 6 with glycosuria and 3 without, and significantly associated with glycosuria (p=0.023). Of the nine carriers of the deletion, five had IFG/IGT/diabetes; 3 of them also had glycosuria. There was no significant difference in change in AUCOGTT over time between carriers and non-carriers of the deletion.

Conclusion: Glycosuria in this family is most likely caused by a deletion in the SLC5A2 gene. The data do not provide any support for the view that increasing glucose excretion in the urine would protect from diabetes.

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1792-P

Investigation of Novel Type 2 Diabetes QTL in an NZO x DBA/2J Backcross

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The New Zealand Obese (NZO) mouse, a model of human obesity and type 2 diabetes (T2D), was used in the past to identify various quantitative trait loci (QTL) and subsequently pathogenic genes, eg. Ifi202b and Tbc1d1. By backcrossing the NZO mouse with the lean and diabetes-susceptible DBA/2J we aim to identify novel T2D genes.

Several metabolic traits of an NZO x DBA/2J backcross (N2) population were characterized on a high-fat diet (45% fat) and QTL were identified by linkage analysis. Gene expression as well as sequencing data of parental NZO and DBA mice were overlayed with QTL. Recombinant congenic strains (RCS) have been generated through repeated backcrossing of DBA x NZO progeny with selected genotypes to NZO. N4 RCS have been extensively phenotyped by weekly blood glucose and body weight measurements, oral glucose tolerance tests, computed tomography and metabolomics profiling. Pancreata have been additionally analyzed by immunohistochemistry.

Diabetogenic QTL were identified on chr. 1, 2, 4, 6, 9, 11, 13, 17, 18 and 19. Our data revealed that the strongest T2D QTL (Nidd/DBA) with a LOD score of 9 was on chr.4. N2 mice containing Nidd/DBA developed a more severe hyperglycemia, accompanied with hypoinsulinemia and a loss of adipose tissue. Ongoing analysis of RCS has revealed two interesting loci between 88 - 93 and 107 - 141 Mbp on chr. 4. Through transcriptomics we could determine that in the more proximal locus DBA confers 26 unique missense variants, including 3 frameshift and 4 stop-codon mutations. Additionally, 16 genes contain regulatory region variants that correspond to a differential mRNA expression in peripheral tissues and/or pancreatic islets. Within the distal locus, 90 missense variants are conferred by DBA including 8 frameshift and 7 stop-codon mutations. 175 genes contain regulatory region variants that correspond with differential gene expression. By repeated backcrossing and characterization of RCS we aspire to narrow down these loci and discover novel T2D susceptibility variants.

1793-P

Large-Scale Evaluation of 59 GWAS-Identified Type 2 Diabetes Risk Variants in Adult Chinese

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Few studies have examined the effects of known T2D risk variants, either individually or collectively using genetic risk scores (GRS), on T2D risk in the Chinese population. We addressed this using data from 82,477 unrelated genotyped participants in the prospective China Kadoorie Biobank (CKB) of 0.5 million adults (http://www.ckbiobank.org) that recoded 4,998 prevalent T2D cases at baseline and 1,412 incident T2D cases over ~7 years of follow-up. Since both impaired β-cell function and insulin resistance (IR) contribute to T2D etiology, we also explored their genetic effects separately by constructing GRS for β-cell dysfunction (GRS_{β}) and IR (GRS_{IR}).

Of the 59 known T2D risk variants (as genotyped in CKB by Oct 2012), 55 variants showed directionally consistent associations with combined (prevalent + incident) T2D, 36 of them nominally significant (P<0.05). Our study confirmed for the first time the association of *ADCY5*-rs11708067 with T2D in East Asians (P=0.0046) showing a higher effect size (OR [95% CI]: 1.78 [1.19-2.64] vs. 1.12 [1.09–1.15], P for difference 0.02) in Chinese than Europeans (MAFs, 0.003 [Chinese] vs. 0.226 [European]). Variants at 7 loci

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(*THADA, MAEA, CDKAL1, CDKN2A/B, TCF7L2, KCNQ1*-rs2237892, *DUSP9*) were associated with incident T2D (P<0.05).

An overall T2D-GRS constructed from 53 variants (GRS_{t53}) genotyped in the majority of subjects (>80% of subjects) was strongly associated with combined T2D (OR 1.07[1.06–1.08], P=1.3×10^{-95}). The GRS_{β} (25 variants) had a stronger effect than GRS_{IR} (6 variants): (OR 1.09 [1.08–1.10] vs. 1.05 [1.03–1.08], P for difference 0.01). Moreover, both GRS_{t53} and GRS_{β} were strongly associated with incident T2D (HR 1.04 [1.02–1.05], P=2.1×10^{-8}; HR 1.05 [1.04-1.07], P=5.9×10^{-9} respectively).

In summary, our results not only confirmed the associations of most of the previously GWAS-identified loci with T2D but also provided insights into the value of T2D-related GRS with respect to risk stratification in the Chinese population.

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1794-P

Next Generation Sequencing Methylation Profiling Interactions with Genetic Variation from Lean and Obese Subjects

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Obesity has become a critical health concern. Insulin resistance is an underlying metabolic consequence of obesity and type 2 diabetes. The development of insulin resistance has both genetic and environmental components. The role of epigenetics factors, such as DNA methylation, which is the addition or removal of a methyl group on cytosine, is not well understood. A single nucleotide polymorphism (SNP) is a single base change in the DNA sequence and can cause variations in the genome. When SNPs are present, they can alter the methylation status of the genome, and potentially could alter gene expression and protein function. Vastus lateralis muscle biopsies were taken in the postabsorptive state, and next-generation sequencing reduced representation bisulfite treatment was performed on the DNA isolated from obese (n=10; BMI=32.9±0.7 kg/m2) and lean (n=12; BMI=23.4±0.7 kg/m2) subjects. From sequencing analysis, over a million methylation sites were captured and of these sites, 1,015 were associated with a SNP. DNA methylation was significantly different (A/A 0±0, A/G 0.37±0.2, G/G 0.96±0.05; P<0.01) at a known site of genetic variance (rs3749166) for calpain 10 (CAPN10), which has previously been associated with susceptibility to type 2 diabetes. SNP genotyping was performed for CAPN10 on all subjects, which resulted in lean genotypes 2-A/A, 5-A/G, 5-G/G, and obese genotypes 5-A/A and 5-A/G. The A allele was associated with increased blood pressure (A/A 125/78, A/G 123/76, G/G 114/69 mm/Hg; P<0.05) and trended towards an association with BMI (A/A 30.2±5, A/G 28.3±5, G/G 23.0±3 kg/m2; P=0.06); however, larger cohort studies are necessary to capture all possible associations. This study provides evidence that SNP sites that create an available cytosine allow methylation, and that the SNP rs3749166 may be associated with metabolic disease. This interaction may be the link for further understanding how SNPs act as biomarkers for susceptibility for certain diseases.

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1795-P

The DNA Methylation of Single Nucleotide Polymorphism (SNP)-420 in RETN Affects Plasma Resistin in Addition to Its Genotype

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We previously reported that SNP-420 (rs1862513) in the promoter region of the human resistin gene (*RETN*) was associated with type 2 diabetes (T2D) (Am J Hum Genet 2004). Plasma resistin was highest in G/G genotype, followed by C/G, and C/C (Diabetes Care 2007). A cytosine-phosphate-guanine dinucleotide "CpG" is a possible methylation site of DNA. SNPs affecting CpG sequences could affect gene expression. SNP-420 is expected to be this type of CpG SNP. The aim of this study is to examine whether methylation at -420 affects plasma resistin.

We analyzed plasma resistin and methylation at -420 in *RETN* in 2,078 Japanese subjects. The methylation at -420 was highest in C/C genotype, followed by C/G, and G/G. Multiple regression analyses were performed involving plasma resistin as a dependent variable, and age, sex, BMI and hsCRP as independent variables in each of SNP-420 genotype. Methylation at -420 was inversely associated with plasma resistin in C/C and C/G genotype (standardized regression coefficient (β)=-0.24499, P< 0.0001; and β=-0.1247, P< 0.0001, respectively). No association was found in G/G genotype. The multiple regression analyses involving methylation at -420 as a dependent variable and age, sex, BMI, SNP-1093, SNP-537, SNP-420, SNP-358, SNP+157, SNP+299, and SNP+1263 as independent variables revealed that SNP-420 and SNP+1263 were responsible for the methylation. The C-C haplotype defined by SNP-420 C>G and SNP+1263 C>G conferred lower methylation than the reference C-G haplotype, (-0.78%, P=0.00021) suggesting that in addition to SNP-420, SNP+1263 was responsible for the methylation at -420.

In conclusion, whereas plasma resistin was mainly determined by the SNP-420 genotype itself, methylation at -420 could have an additional effect. SNP+1263 also could have the effect on methylation at -420.

1796-P

Genome-Wide Gene-Gene Interaction with Insulin Secretion Loci Reveals Novel Loci Contributing to Type 2 Diabetes Etiology in African Americans

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Type 2 diabetes is the result of metabolic defects in insulin secretion and insulin sensitivity, yet most of the ~70 genetic loci associated with T2D risk map to insulin secretion/beta cell biology. We hypothesized that insulin resistance loci contribute to T2D risk through interaction with insulin secretion loci. To test this hypothesis SNPs associated with acute insulin response to glucose (AIR), a dynamic measure of first-phase insulin secretion, in African Americans (AfA) from the IRAS Family Study (n=492 subjects) were tested for genome-wide interaction in the ARIC, CARDIA, JHS, MESA, and WFU cohorts (n=7,000 AfA T2D patients and controls). Analyses were performed selecting SNPs from established T2D loci with documented insulin secretion defects in GWAS studies (T2D-IS SNPs; n=5) or novel AIR loci (AIR P<5E-4; n=5) from IRASFS. Individual SNPs were tested for interaction with GWAS SNPs in each cohort using logistic regression modeling T2D as the outcome followed by meta-analysis of interaction effects. Although no SNPs reached genome-wide significance for interaction, tests with T2D-IS SNPs exhibited a signature of signals previously associated with cardiovascular disease. Interaction tests with novel AIR SNPs exhibited a signature of signals from loci previously associated with obesity-related traits. Nominally significant (P<1E-5) interactions were observed at several interesting loci including CDKAL1 (rs843319, P=7.44E-06), LYPLAL1 (rs10746381, P=4.43E-06), DGKB (rs978989, P=2.72E-06), and CXCL12 (rs7921850, P=2.52E-06). BMI adjustment resulted in loss of association in the novel AIR interaction tests, while top signals in the established T2D interaction tests were robust against this adjustment (-log(P) mean difference = 2.45 vs. 0.48). Overall the biology of loci interacting with the test SNPs were consistent with their being good candidates for further analysis of their relationship with insulin resistance.

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1797-P

Renal Risk Genotype in APOL1 Protects against Diabetes and Diabetic Nephropathy

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In individuals with African ancestry, the recessive genotype GG at rs73885319 and the homozygous deletion at rs71785313 in the gene APOL1 confer increased risk for chronic kidney disease (CKD) and several forms of end-stage kidney disease, but not diabetic nephropathy. We conducted a study to determine why APOL1 risk variants for end-stage kidney disease do not associate with diabetic nephropathy. Study samples include African Americans enrolled in the Howard University Family Study (HUFS) - a cross-sectional population-based study (n=988); the Atherosclerosis Risk in Communities Study (ARIC) - a prospective population-based study (n=2,523); the Natural History of APOL1-associated Nephropathy Study (NHANS) - a prospective study of first-degree relatives of patients with non-diabetic end-stage kidney disease (n=865); and West Africans enrolled in the Africa America Diabetes Mellitus Study (AADM) - a cross-sectional case-control study of type 2 diabetes (T2D; n=1,011). We found that the GG genotype was associated with protection against T2D (odds ratio of 0.591,) whereas the homozygous deletion was not associated with T2D (odds ratio of 1.002). Among individuals with the GG genotype, we observed significant but incomplete protection against

CKD in T2D cases compared to controls (0% vs. 9.5%). In contrast, among heterozygotes and non-carriers, the prevalence of CKD was higher among T2D cases compared to controls (15.8% vs. 6.4%). Furthermore, the GG genotype was associated with a 40.2% reduction of fasting insulin levels (p = 1.15×10-6) in T2D cases. In conclusion, the recessive genotype at rs73885319 but not at rs71785313 in APOL1 is associated with protection against T2D. Among those with T2D, the same recessive genotype at rs73885319 is associated with protection against CKD and lower fasting insulin levels. Protection from diabetic nephropathy may be due in part to a modulating effect of the APOL1 renal risk genotype (GG) on insulin secretion and/or clearance.

1798-P

Insights from Functional Analysis of the TCF7L2 locus: PARP-1 Inhibition Rescues Glucose-induced Shortened Lifespan in Caenorhabditis elegans

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TCF7L2 is one of the most strongly associated type 2 diabetes loci reported to date, although the pathophysiologic mechanism by which variation within this gene modulates risk remains poorly understood. It was previously reported that the most abundant specific protein factor to bind across the presumed causal lesion at this locus, rs7903146, was poly [ADP-ribose] polymerase type 1 (PARP-1). This finding was suggestive that PARP-1 activity may influence glucose regulation. Here, we investigated whether targeted PARP-1 inhibition with Olaparib could restore animal health in the setting of hyperglycemia.

High glucose concentrations progressively shorten the lifespan of the nematode, *C. elegans*, in part by altering insulin signaling pathways that are well-conserved from *C. elegans* to mammals. We evaluated the lifespan of wild-type (N2 Bristol) animals grown in 16mM or 25mM glucose, levels that would correspond to an estimated HbA1c of 11.7% or 17.3% in human patients, respectively, either alone or in the presence of 100uM Olaparib. Interestingly, significant rescue from glucose-induced short lifespan was achieved with Olaparib. In contrast, Olaparib had no beneficial effect on rescuing animal lifespan in hyperglycemic conditions in a knock-out strain harboring a deletion of the PARP-1 homolog, *pme-1*.

In summary, these data show that direct PARP-1 inhibition specifically rescues longevity under hyperglycemic stress in *C. elegans*. These findings are suggestive that PARP-1 modulation offers a novel therapeutic approach in the treatment of type 2 diabetes.

1799-P

Assessing Pathophysiologic Effects of Genetic Variants Associated with Type 2 Diabetes and Related Traits by Leveraging Compartmental Modeling

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Little is known about how loci underlying type 2 diabetes (T2D) risk or variation in related traits influence T2D pathogenesis. We used a compartmental model-based (CM) approach to dissect the biology underlying genotype-phenotype relationships and interpret their pathogenic effects. The CM links validated models of glucose (GLU) and insulin kinetics into a single construct able to simulate GLU and insulin profiles from clinical protocols, e.g., oral glucose tolerance test (OGTT). Each parameter in the CM denotes a specific biologic function, thus one or more "genes" can be assigned to one or more model parameters, and simulations performed to assess genetic effects on glucoregulation. Simulations were performed in which the PPARG P12A variant was imposed on a parameter (p3) determining insulin signaling transduction. Genotype-specific p3 values were drawn from a literature-derived population distribution, constrained by gene frequencies, and assuming an additive genetic model. 1000 OGTTs were simulated by randomly selecting a p3 value from the population distribution. Resultant OGTT GLU profiles for the AA genotype tightly clustered in the normal range while GLU profiles for PA and PP genotypes show considerable variability; 3% of PA and 11% of PP genotypes having 2-hour GLU >140 mg/dl. Power analysis based on 3000 replicates of 1000 OGTTs showed 60 min GLU having maximum power to detect association with P12A. We validated the CM-based simulation results by testing the association between P12A and OGTT GLU, adjusting for covariates, in 1621 related individuals from the BetaGene study. OGTT 60 min GLU showed strongest evidence for association with P12A (p=0.036), compared to fasting (p=0.55), 30 (p=0.10), 90 (p=0.06) or 120 min (p=0.39), consistent with the model-based power analysis. This study demonstrates that a physiologically-based CM can be used to better understand the pathophysiologic implications of genetic variation.

For author disclosure information, see page A810.

1800-P

Genetic and Nongenetic Studies of Type 2 Diabetes in Three Susceptible Asian Populations: Malay, Chinese, and Indian

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Both classical and genetic risk factors have been reported to contribute to the pathogenesis of type 2 diabetes. Although numerous epidemiological studies have been conducted in diverse populations, the Malaysian population remains unstudied to date, despite its high, and increasing, prevalence of type 2 diabetes. We studied the effect of known genetic and classical type 2 diabetes risk factors in Malaysian subjects of Malay, Chinese and Indian ancestry from the Malaysian Cohort project. Using the MetaboChip array, we genotyped 1,604 Malays (722 cases, 882 controls), 1,654 Chinese (819 cases, 835 controls) and 1,728 Indians (851 cases, 877 controls). We assessed association of 62 individual candidate single nucleotide polymorphisms (SNPs) previously associated with type 2 diabetes as well as a genetic risk score (GRS) aggregated across all SNPs. Using the same samples, we also estimated the population attributable risk percent (PAR%) for a number of classical risk factors for type 2 diabetes. After Bonferroni correction, 7 individual SNPs were associated with type 2 diabetes in the combined Malaysian sample, with many more showing nominal association. The GRS was strongly associated with type 2 diabetes in all three Malaysian ancestral groups, but explained only 1.0 to 1.7% of total risk variance. Thus while known genetic risk alleles appear to overlap between Malaysian and other populations, these seem unlikely to explain the rapidly escalating disease prevalence in Malaysia. In contrast, four classical risk factors accounted for a large proportion of type 2 diabetes risk variation in the Malaysian samples: age, gender, waist circumference and physical inactivity. Thus, modifiable risk factors including diet, obesity and physical inactivity may be major contributors to the type 2 diabetes epidemic in Malaysia. Strategies targeting these factors may significantly reduce the incidence of type 2 diabetes in the Malaysian population.

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IMMUNOLOGY

Guided Audio Tour: Progress in the Treatment of Type 1 Diabetes *(Posters: 1801-P to 1807-P), see page 13.*

1801-P

Heterogeneity in Type 1 Diabetics Is Defined by Contrasting C-Peptide Declines, Autoreactive T Cell Burdens, and Metabolomic Differences

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Immunointervention trials have proven difficult in type 1 diabetes (T1D). The answer could lie in heterogeneity in T1D etiology. Four recent human studies show loss of insulin secretion, measured through C-peptide, is highly correlated with the age of onset of T1D. Subjects with early onset of disease (< 20 years of age) lose remaining insulin secretion at a faster rate compared to patients who become diabetic during adulthood (> 20 years of age). Here we expand these studies of possible subject heterogeneity by examining autoreactive T cells and metabolite patterns in subjects with either rapid or slow decline in insulin secretory capacity.

We first confirmed significantly different rates of C-peptide loss in early and late onset diabetics ($p < 0.0001$). C-peptide in early onset diabetics (n=290) became undetectable within a few years of onset. In contrast, low levels of C-peptide were detected in late onset diabetics (n=200), even decades after onset.

Flow cytometry studies then demonstrated a surprising difference in abundance of autoreactive T cells (p=0.0002). While such cells were undetectable in most early onset patients even when C-peptide was still present (n=43), many of the late onset patients (n=200) maintained detectable autoreactive T cells even with long-standing disease and with no detectable C-peptide.

We analyzed blood serum of 25 early and 25 late onset diabetics on a metabolomics GC/HPLC/MS platform for distinct metabolic fingerprints of contrasting disease etiology based on age of onset and rate of C-peptide decline. We uncovered significant differences ($p < 0.05$, $q < 0.05$) in 32 of 690 detected metabolites between the two T1D groups.