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## INVESTIGATING BLOOD PRESSURE DETERMINANTS USING GENETIC EPIDEMIOLOGY

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*Investigating blood pressure determinants using genetic epidemiology*

– Alice Giontella

PhD thesis

Verona, 14 November 2022

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# ABSTRACT

The heritability of blood pressure (BP) and hypertension is mainly due to a polygenic background. Thanks to the advance of Genome-wide association studies (GWAS, over the last two decades, more than 1,000 single nucleotide polymorphisms (SNPs) have been identified to be associated with BP traits. These, taken singularly, have a small effect on BP, but when grouped, they can explain 30-50% of the heritability of BP. Different strategies, classified under the field of genetic epidemiology, have evolved to exploit and interpret the genetic determinants of complex diseases. These include the construction of genetic risk scores (GRS), summing up all the risk alleles of the SNPs associated with a trait, and Mendelian Randomization (MR) to assess if an association between a modifiable exposure and an outcome is causal. In this thesis, I am presenting four works in which these approaches were used to investigate the genetic determinants of blood pressure and hypertension. In the first study, a GRS was constructed including more than 800 SNPs associated with either systolic BP (SBP) or diastolic BP (DBP) and we evaluated how it is associated with BP traits, hypertension, and cardiovascular disease (CVD) risk, in two Swedish cohorts, the Malmö Diet and Cancer (MDC) study and the Malmö Preventive Project (MPP). In the following three studies, we used MR methods to assess the causal association of different exposures, i) different adiposity traits in study II, ii) thyroid hormones in study III, iii) serum calcium and calciotropic hormones in study IV, with BP traits, hypertension, and CVD in MDC and MPP.

As a result, we found that the GRS built with more than 800 SNPs can discriminate clinically meaningful differences in mmHg between individuals classified as being low-risk versus high-risk based on their GRS. Moreover, the score was independently associated with hypertension risk and CVDs, and with the same order of magnitude as traditional non-genetic risk factors. In the first MR study, the four adiposity traits exhibited a different causal role on the risk of prevalence and incidence of hypertension. This result could reflect distinct pathological mechanisms linking obesity and hypertension. Then we found that low TSH is slightly inversely associated with SBP, while a strong association in

the same direction was reported with atrial fibrillation. Finally, serum calcium level showed a causal association with DBP while fibroblast growth factor 23 (FGF23) was inversely associated with SBP.

In conclusion, genetic epidemiology provides useful techniques that help in stratifying individuals based on their genetic risk and providing new insight into the pathophysiology of hypertension. Since genetic information is available from birth, it is possible to speculate that personalized prevention and intervention strategies could be developed in the future even early in life.

# INTRODUCTION

## Physiology of blood pressure

Blood pressure (BP) is the pressure generated by the blood flow against the large arteries of the systemic circulation. It consists of two components, one mostly representing the cardiac output (Systolic, SBP), and the other mostly the peripheral resistance (Diastolic, DBP). Indeed, systolic blood pressure is the pressure generated by the blood ejection after the ventricular contraction (systole); and diastolic blood pressure is the pressure present at ventricular relaxation (diastole).

In addition to cardiac contractility, multiple physiological mechanisms in the renal, vascular, and endocrine systems contribute to blood pressure regulation through short-term or long-term controls [1].

In case of a rapid change of blood pressure happening within seconds, different numbers of receptors and reflexes rapidly respond to activate/inactivate sympathetic and parasympathetic nerves which regulate cardiac output and peripheral vascular resistance. In the *medulla oblongata* the vasomotor center activates sympathetic nerves which can regulate blood pressure by stimulating heart rate and contractility, venoconstriction, and vasoconstriction through the release of catecholamines in arterioles and in adrenal medulla [2].

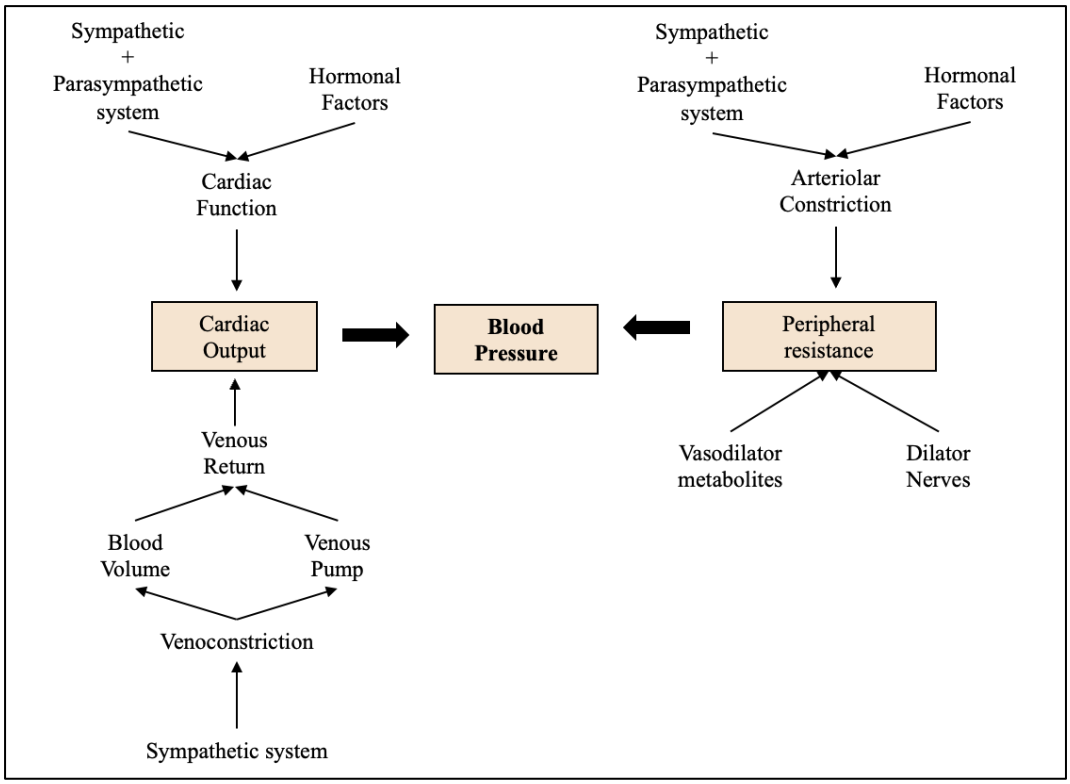
Parallel mechanisms responsible for the long-term regulation of blood pressure, act mainly on maintaining blood volume through different renal mechanisms that are hormonally controlled [3].

Kidneys are responsible for extracellular fluid volume (ECFV) homeostasis and peripheral vascular tone made possible by the regulation of water and sodium (Na+) – and its accompanied ions- excretion by hormonal mechanisms [3].

One of the main mechanisms is the Renin–Angiotensin–Aldosterone system (RAAS), a cascade reaction involving the production of angiotensin II passing by renin and angiotensin I. Angiotensin II contributes either to a rapid response, because it is a potent vasoconstrictor, and to long-term control, stimulating the release of aldosterone, which acts on blood volume regulation. It promotes renal

reabsorption of Na+ and water in the renal distal tubule mostly [3] through the upregulation of NA+/K+ pump in the basolateral membrane and the expression of the epithelial Na+ channel (ENaC) in the luminal membrane.
Another parallel regulatory system is represented by a hypothalamic hormone, the vasopressin, also known as antidiuretic hormone (ADH). It is stimulated by responses to blood pressure change, perceived by baroreceptors or sensor, and angiotensin II, and it increases water reabsorption with a consequent increase in plasma volume and arterial pressure. High concentration of vasopressin has been shown to contribute also to vasoconstriction, increased peripheral resistance, and arterial pressure [4]. In Figure 1, a simplified representation of the main blood pressure regulation processes is shown.

Figure 1 A summary of the main physiological control that regulate arterial blood pressure [2].



Blood pressure can be measured by a cuff wrapped around the arm and registered by a sphygmomanometer. Since blood pressure values vary a lot across the 24 hours, the guidelines recommend performing two/three measures interspersed by 5 minutes. [5]. According to the European Society of Hypertension guidelines (ESH) for management of hypertension in adults, the diagnosis should be performed using either office or out-of-office BP measurement, that is ambulatory blood pressure monitoring (ABPM), which allows monitoring of blood pressure over 24 or 48h period or home blood pressure monitoring (HBPM) [6].

According to the current guidelines of the European Society of Hypertension (ESH), normal office values for an adult are considered about 120 mmHg (SBP) over 80 mmHg (DBP), values at which the maintenance of such a normal range would allow the correct distribution of oxygen and nutrients to all body compartments [1]. Between 120/80 mmHg and 140/90 mmHg, the values can be considered high blood pressure, while blood pressure values consistently higher than 140mmHg for SBP and 90mmHg for DBP, are considered the thresholds that drive into the pathological condition called hypertension [7].

## Hypertension

The World Health Organization (WHO) in 2021 reported almost 1.3 billion individuals aged 30-79 are estimated to be affected by hypertension worldwide. Moreover, it is a leading cause of cardiovascular events and accounts for almost 10 million deaths annually [6]. Besides such a dramatic number, there is the fact that about 46% of these people are unaware of their condition and only 21% are treated. Thus hypertension, considered a “Silent Killer”, stands out as the first leading modifiable risk factor for morbidity and mortality [7].

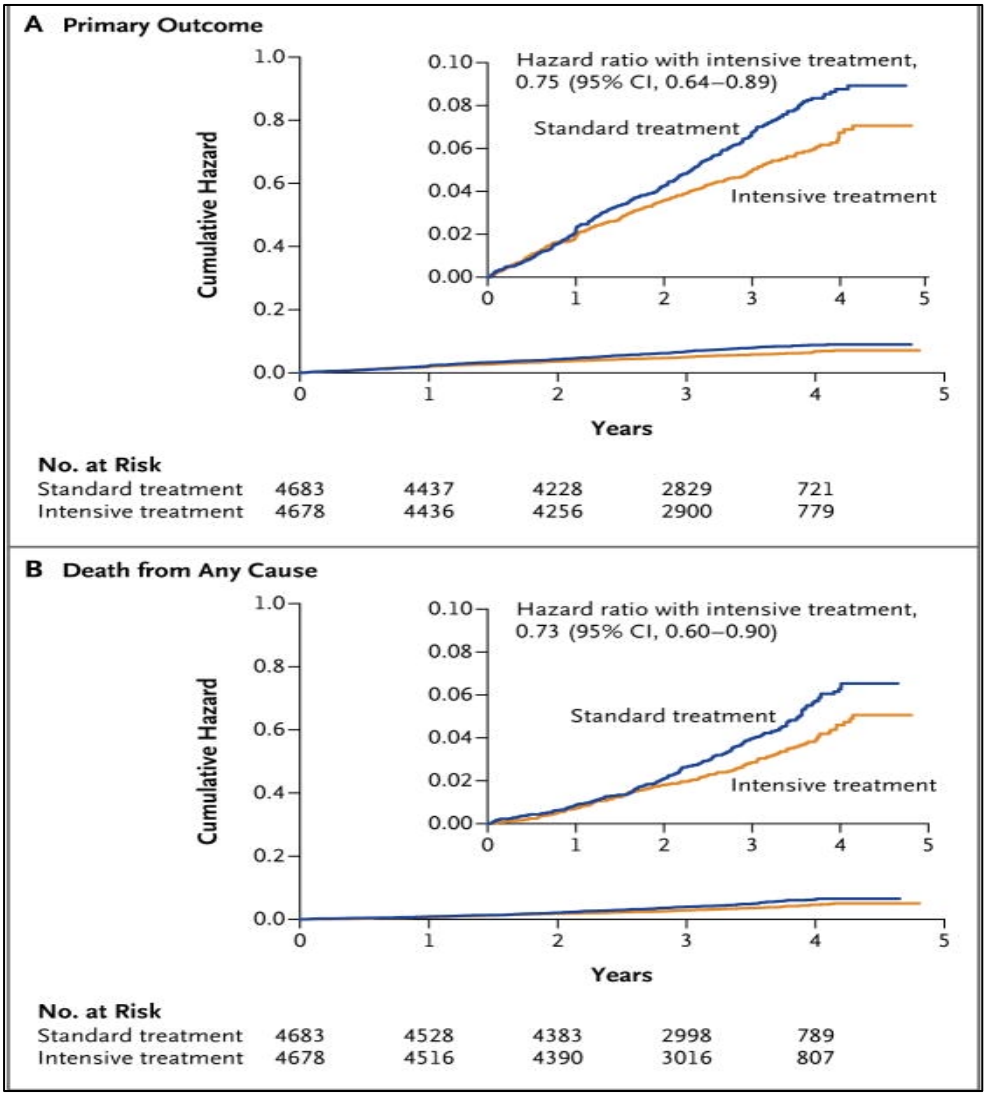
Both office and out-of-office blood pressure have been identified as independent risk factors for cardiovascular disease including myocardial infarction, heart failure, haemorrhagic stroke, peripheral artery disease and sudden death; atrial fibrillation and neurocognitive decline [6]. Hypertension often coexists in presence of comorbidities like dyslipidaemia, glucose intolerance, and chronic kidney disease (CKD) which increase the cardiovascular risk.

Long-term uncontrolled hypertension represents a risk for onset of complications, including organ damage, cardiovascular diseases (CVDs) and death [8].

The relevance of hypertension management on cardiovascular health has been largely shown by clinical trials [9,10]. Among these is the SPRINT (the Systolic Blood Pressure Intervention Trial), which has reported a reduction of 30% up to 64% in stroke, heart failure, myocardial infarction, and higher survival probability (Figure 2) in individuals who underwent intensive antihypertensive treatment targeting to lower systolic blood pressure <120mmHg, versus individuals in the arm targeting "normal" (135-139 mmHg) values.

The SPRINT was only one of the numerous randomized clinical trials (RCTs) aimed at identifying and quantifying the effect of blood pressure lowering on the reduction of CV events. A recent meta-analysis including 123 RCTs and 613,815 participants estimated a significant reduction of total CV diseases relative risk ([RR] 0.80, 95% CI 0.77-0.83), coronary heart disease (0.83, 0.78-0.88), stroke (0.73, 0.68-0.77), and heart failure (0.72, 0.67-0.78) every 10 mmHg of SBP reduction [11].

Figure 2 Estimated effect of antihypertensive treatment aimed at lowering SBP, evidenced in the SPRINT trial [9].




## Risk factors and mechanisms underlying hypertension

Hypertension is influenced by a complex and interconnected panel of risk factors, both physiological, genetic, and environmental [12]. Among the latter, the modifiable risk factors include diet, physical activity, and overweight/obesity. The effect on blood pressure of lifestyle intervention, aimed at improving dietary habits and physical activity has been largely reported [13,14]. A diet rich in fruits, vegetables, and low-fat dairy products; whole grains, poultry, fish, and nuts; and poor in red meat, sweets, sugar-containing beverages, total fat, saturated fat, and

cholesterol, previously defined as the DASH diet (Dietary Approach to Stop Hypertension), is recommended as a non-pharmacological management of hypertension [14]. From RCTs, it is known that intervening in following a DASH diet can contribute to a reduction of SBP and DBP by 5.2 mmHg and 2.6 mmHg respectively [14].

Physical activity intervention has also shown to have a beneficial effect on BP lowering, as suggested by some RCTs. A recent meta-analysis including more than 5,000 individuals reported a net improvement of both SBP and DBP after endurance training at a moderate or high intensity [15]. Same for weight reduction interventions, in which a 4.3% weight decrease corresponded to an average improvement in BP of 2.5 mmHg [16]. The pattern of blood pressure increases linearly with average body mass index (BMI), moreover obesity (BMI $\geq$30 kg/m$^2$) and hypertension share a metabolic pattern of insulin resistance with glucose intolerance, elevated plasma triglyceride and low high-density lipoprotein cholesterol levels [17]. Obesity and hypertension are two of the main causes of non-communicable diseases and mortality worldwide [6,18]. In the Framingham Heart Study, it has been estimated that 60-70% of hypertension is associated with obesity, and there is a 3-fold increased risk to develop hypertension in obese people [19].

A relevant factor in obesity and obesity-related hypertension is represented by fat distribution in which the adipose tissue acts as an active endocrine and paracrine organ secreting metabolic mediators which participate in different metabolic processes [20].

In conjunction with BMI, which is the most commonly used measure of general obesity, additional markers of adiposity could better indicate different fat compartments which are considered independent risk factors for hypertension and CVD [21,22]. These include Waist Circumference (WC) and Waist to Hip ratio (WHR), easily measurable proxies for abdominal obesity, or more accurate indices like body fat (BF) percentage and measure of visceral adiposity tissue (VAT) [22]. Impaired adipose tissue function could contribute to a proinflammatory, and atherogenic state and may be mechanistically linked to the development of obesity-associated disorders [23]. Different physiological mechanisms could

contribute to hypertension development in presence of obesity like alterations in the renin-angiotensin-aldosterone system, increased activation of the sympathetic nervous system, insulin resistance, leptin resistance, inflammation, and endothelial dysfunction [24]. However, even if it is well-known that adiposity itself is a risk factor for hypertension [24–26], how different measures of obesity influence BP is less clear.

Additional risk factors for hypertension include insulin resistance, diabetes, chronic kidney disease, aging, dyslipidaemia, high alcohol intake, stress [27]. Moreover, abnormalities in several systems are seen in hypertension including the central nervous system, hormonal systems, and inflammation, but some aspects of the mechanisms remain elusive [28].

Potentially, most of the disturbances affecting the intermediate phenotypes involved in the physiological pathways regulating peripheral resistance or cardiac output, could represent a risk factor for hypertension [29,30].

To give a clear example of that, and to introduce one of the research objects that will be covered in the following pages, the role of Calcium ($Ca^{2+}$) homeostasis and its regulatory hormones will be mentioned. The physiological axis of the calciotropic hormones which include Parathyroid hormone (PTH), 25(OH)2)D (the active form of Vitamin D), and Fibroblast growth factor 23 (FGF23) is involved in a tightly concerted regulation of serum $Ca^{2+}$ concentration across kidneys, intestine, and bones [31].

$Ca^{2+}$ plays a role in muscle stimulations, including vascular smooth cells, thus it can affect the vascular tone and mediate vasoconstriction, which can increase peripheral resistance and consequently BP [30]. Calciotropic hormones have been reported to regulate BP through mechanisms that can be dependent and independent from $Ca^{2+}$ [32–36].

Every perturbation of the components responsible to maintain calcium homeostasis, could conceivably differently affect BP and contribute to hypertension. However, contrasting results have been found in observational studies and meta-analyses, possibly due to the confounding factors that may interfere, and through mechanisms that are not completely understood [37].

There is nearly a 5-10% of patients with hypertension whose condition is attributable to a unique underlying pathological condition that is potentially recognizable and treatable. These are considered “secondary Hypertension”, as opposed to “essential Hypertension” that is a multifactorial disease in which the panel of all the risk factors that we have previously mentioned, act synergistically but with a different burden in different individuals [17].

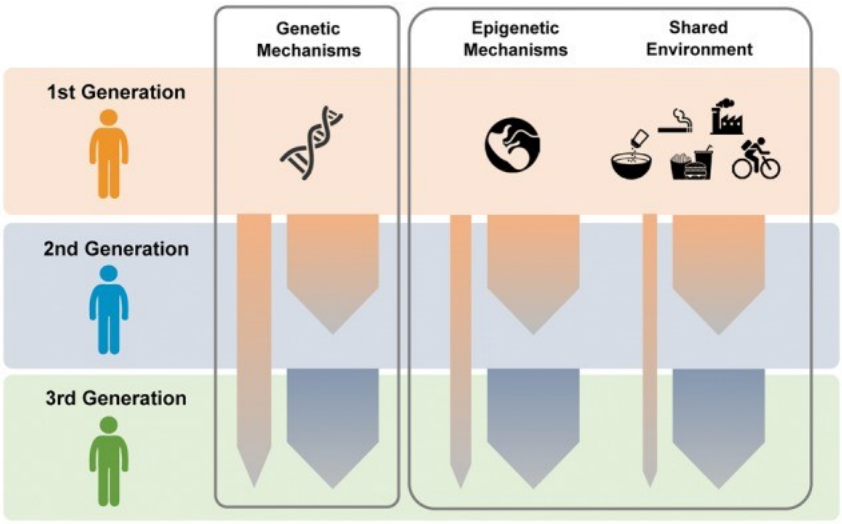
Secondary hypertension includes renal chronic diseases like renovascular and renoparenchimal hypertension; primary aldosteronism; coarctation of the aorta; pheocromocytoma; and thyroid dysfunction, including both hypothyroidism and hyperthyroidism [38].

## Genetics of blood pressure

Genetics is an important determinant of blood pressure regulation. Hypertension is a highly heritable trait and about 70% of the familial aggregation of blood pressure is due to shared genes and to a shared environment [17]. The familial risk of hypertension is transmitted across multiple generations, as shown by *Niiranen* and colleagues, which used data over 5 decades from three generations of the Framingham Heart Study (n=8,048), to investigate the role of heredity on hypertension risk. They showed that a high risk for hypertension is transmitted from grandparents to the child despite of environmental factors like salt intake, physical activity, or intergenerational differences (Figure *3*) [39].

As described from different studies in families, clinic BP shows a 15-40% of heritability while ambulatory BP rises even to 60% [1,39,40].

Figure 3 Schematic representation by Niiranen showing how genetic, epigenetic, and environmental factors are transmitted through the generations [39]




On the base of its genetic component, hypertension can be classified as monogenic and polygenic. Monogenic-hypertension, as suggested by the name, is attributable to a mutation in a single gene.

Currently, about 17 groups forms of monogenic forms of hypertension and hypotension attributable to mutations in more than 30 genes, have been identified (Table 1 Effects on BP of monogenic forms of Hypertension and Hypotension).

Among these, there are familiar forms of Hyperaldosteronism, such as type I Glucocorticoid Remediable Aldosteronism (GRA) and Familial hyperaldosteronism II, Liddle's syndrome, Apparent mineralocorticoid excess (AME), some Hydroxylase deficiencies featuring hypertension, while some others such as Bartter syndrome or Gitelman syndrome that are associated with increased natriuresis and hypotension [41].

Table 1 Effects on BP of monogenic forms of Hypertension and Hypotension

| Condition | Gene | Effect on BP |
|---|---|---|
| **11β-Hydroxylase deficiency** | CYP11B1 | ↑ |
| **17α-Hydroxylase deficiency** | CYP17A1 | ↑ |
| **21-Hydroxylase deficiency** | CYP21A2 | ↓ |
| **Apparent mineralocorticoid excess** | HSD11B2 | ↑ |
| **Bartter syndrome** | SLC12A1, CLCNKA, CLCNKB, KCNJ1, MAGED2 | ↓ |
| **Familial hyperaldosteronism type I** | Chimeric CYP11B1-CYP11B2 | ↑ |
| **Familial hyperaldosteronism type II** | CLCN2 | ↑ |
| **Familial hyperaldosteronism type III** | KCNJ5 | ↑ |
| **Gitelman syndrome** | SLC12A3, CLCNKB, | ↓ |
| **Hypertension and brachydactyly syndrome** | PDE3A | ↑ |
| **Hypertension exacerbation in pregnancy** | NR3C2 | ↑ |
| **Pseudohyperaldosteronism type 1 Liddle syndrome** | SCNN1B, SCNN1G | ↑ |
| **Multiple endocrine neoplasias, type IIA** | RET | ↑ |
| **Paragangliomas (1–5)** | SDHA, SDHAF2, SDHB, SDHC, SDHD | ↑ |
| **Pseudohypoaldosteronism type II (also known as Gordon syndrome)** | CUL3, KLHL3, WNK1, WNK4 | ↑ |
| **Sporadic aldosterone-producing adenoma or primary aldosteronism** | ATP1A1, ATP2B3, CACNA1D, KCNJ5 | ↑ |
| **Von Hippel–Lindau disease** | VHL | ↑ |

Most of the monogenic forms of hypertension are due to rare, defined as having a maximum allele frequency (AF) of <1%, pathogenic loss-of-function (LOF), or gain-of-function (GOF) variants which can affect mineralocorticoid, glucocorticoid, or sympathetic pathways [42,43].

LOF and GOF are missense single nucleotide variants, which cause a change in aminoacidic protein level causing a disruption in protein function and consequent loss or gain of the specific function of the protein, respectively [44]. They are usually responsible for conferring a several-fold increased risk of hypertension or hypotension and a change of 20mmHg-50mmHg from normal values in individuals carrying the risk allele [1,45]. Interestingly enough, even in cases of autosomal recessive (AR) hypertensive/hypotensive disease, i.e. Gitelman Syndrome, the presence of a mutated allele can influence BP even in heterozygous carriers [46].

The factor driving hypertension in these conditions is represented by a volume expansion consequent to either an increased sodium ($Na^+$) reabsorption in the distal nephron, or hyperstimulation or excess synthesis of mineralocorticoid receptors [42,43].

Patients affected by monogenic forms of hypertension often show electrolyte disturbances like metabolic alkalosis with hypokalaemia or metabolic acidosis with hyperkalaemia and, in most cases, a suppressed renin-angiotensin system [42]. The diagnosis of each syndrome is made possible by the valuation of clinical or laboratory characteristics in addition to genetic testing [47,48].

At the population level, the contribution of the monogenic forms on the public burden of hypertension is small, given their rarity, but their study helped to identify relevant pathways in blood pressure regulation [1].

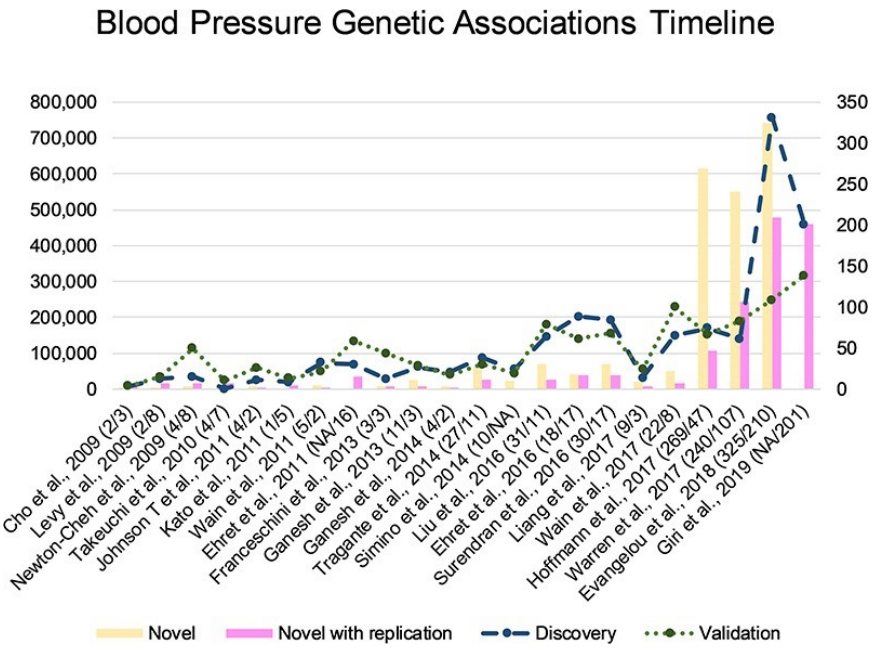
Except for the above-mentioned cases, the most common form of hypertension has a polygenic inheritance, which is not a surprise considering its multifactorial nature and the number of physiological mechanisms contributing to blood pressure control and raise. A polygenic trait is a continuous variable, normally distributed in the population, instead of occurring as a discrete alternative phenotype.

Differently from monogenic forms, polygenic components of BP comprise the cumulative information deriving from a lot of common genetic variants, also called single nucleotide polymorphisms (SNPs). A common variant is defined as having an allele frequency (AF) in the population greater than 1%. They are responsible for a small effect on the outcome, rarely exceeding effect estimates measured as an odds ratio (OR) above 1.5, contrary to the previously described monogenic mutation.

They are most of the time not considered "functional" because they do not alter the gene function [49]. Common variants associated with a quantitative phenotype or a complex disease, are mainly identified with genome-wide association studies (GWAS), a large-scale genotyping strategy testing for association between hundreds of thousands of genetic variants and an outcome [50].

Thus, they contributed to revealing new genetic loci and pathways associated with blood pressure. Up to 2015, only 64 loci had been identified, while the most recent GWASs performed on blood pressure traits, and including around 1 million individuals, identified more than 1400 SNPs associated with SBP or/and DBP. The graph in Figure 4 shows the number of identified loci from GWAS in a timeline of 10 years [51].

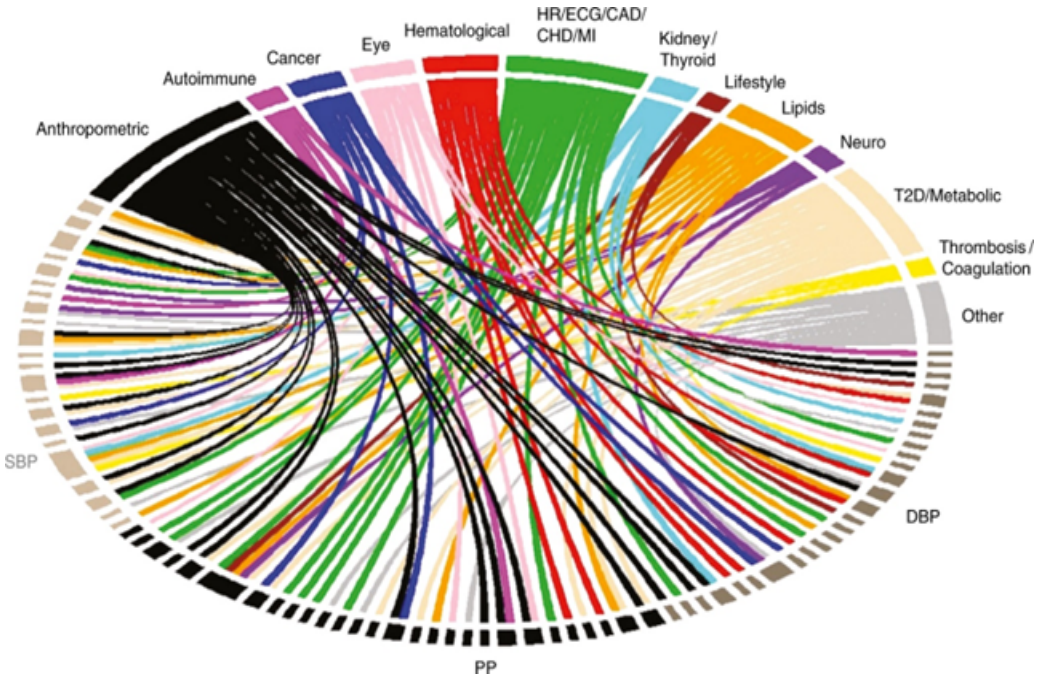
Figure 4 Discovery of genetic loci associated to BP, during a 10-years' timeline. Source: *Cabrera et al. (2019)* [51]




It has been estimated that SNPs can cumulatively explain around 27% of the 30-50% of estimated heritability of BP, when considering only the ones having a p-value below the genome-wide significance level of $p<5*10^{-8}$ [52–54].
Most of these variants are SNPs in non-coding regions and are highly pleiotropic, which means they are also correlated to other traits, making it difficult to infer causality [52].

In Figure 5, a nice graphical overview of pleiotropy in blood pressure-associated loci has been represented by one of the above-mentioned GWAS, by *Evangelou* and colleagues [52]. Functional analysis looking at tissue and DNase hypersensitivity highlighted and confirmed the relevant role of pathways involved in the vascular tone, sodium handling, ventricular remodelling, lipid metabolism, and adrenal secretion and development [52].

Figure 5 Graphical representation of pleiotropy of blood pressure associated genes. Source: *Evangelou et al* [52].



## Genetic Epidemiology

The discipline which studies the distribution of diseases in the population is epidemiology, whose aim is to study "which" factors are involved in the presence of a disorder in a population, and "how" they are contributing to it. Genetic factors represent a relevant determinant of diseases. Their understanding would help to clarify the basics of physiological pathways and individual genetic susceptibility [55]. Traditionally, the study of genetics included different study designs with different aims [56]:

- Familial aggregation to discover the actual presence of a genetic component for the disease
- Segregation to investigate the pattern of inheritance
- Linkage studies to identify which part of the chromosome is involved
- Association studies to find which gene allele is the one contributing to the disease.

The need to understand the role of genetics in the development of diseases contributed, starting from the latest 1960s, to join forces from epidemiology, medicine, and statistics to look at genetics from a public health point of view. The emerging field started to be called "genetic epidemiology" by Morton, Chung, and Mi in 1967. At the time it referred to the role of the genes in controlling familial aggregation, but it evolved and expanded through the years with the advance of population-based genetics studied (Figure 6) [57].
In 2010 DeWan, from Yale University, identified 5 milestones in the genetic epidemiology field [58]:

⇒ The Logarithm of Odds (LOD) score for computing the linkage in families, was defined first time by Morris in 1955.

⇒ The LIkelihoods in PEDigrees (LIPED) computer program was developed by Ott and was the first computer program to compute linkage in 1974.

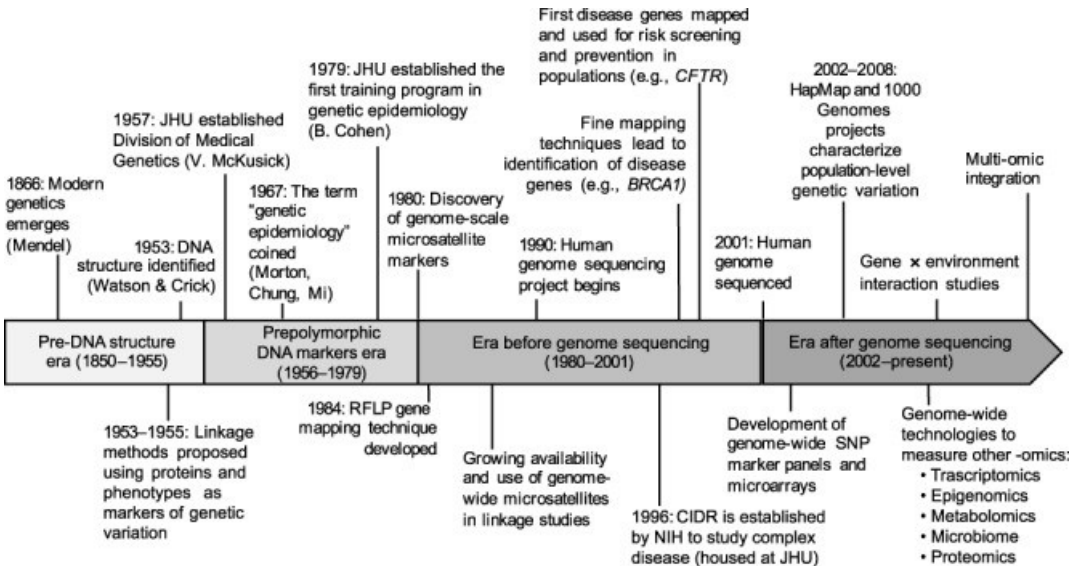
⇒ The first theoretic paper described how to apply association mapping to the genetics of complex diseases. Risch and Merikangas 1996 determine the theoretical shift from linkage analysis to association analysis when dealing with

complex diseases. They were the first to demonstrate that in the case of complex traits and loci having an allele frequency higher than 10, almost 50 times more families should be needed to detect a significant association with a Genotypic Risk Ratio (GRR) of 1.5, which was at the time, the maximum GRR observed at the observational studies, on complex traits [58].

⇒ The initial completion of the Human Genome Project, in 2001, (http://www.genome.gov/10001772). The project reported the first detailed map of the human genome and laid the foundation for the large-scale collaborations that are now a common standard for genetics studies [59]. The Human Genome Project 2001 reported the first detailed map of the human genome. Parallelly, the HapMap Project mapped almost 4 million common SNPs in the genome and showed that they exist in blocks of highly correlated variants (Linkage Disequilibrium, LD) [59].

⇒ The first publication of a Genome-Wide-Association study using SNP marker in 2002 by Ozaki for the investigation of a gene associated with myocardial infarction [60].

Figure 6 Representation of genetic epidemiology method evolution. Source *Duggal 2019* [57]



Since then, two decades have passed and DNA sequencing has become cheaper and more accurate in detecting variants.
Moreover, thanks to international collaborations involving hundreds of thousands of well-phenotyped individuals, it has been possible to detect always more variants associated with some traits and to reach a large sample size to obtain an efficient statistical power for the analysis [50]. Together with Human Genome Project and HapMap Project, GWAS method exploded and become the pre-eminent tool to discover polymorphic genes associated with diseases [61].

Summary statistics resulting from the GWASs, describing the effect size and the p-value of the association between an allele and the outcome of interest [62], have been made available to worldwide researchers in some public databases and repositories, like the "GWAS Catalog" (www.ebi.ac.uk/gwas/home) or "dbSNP" (https://www.ncbi.nlm.nih.gov/snp/) [63]. From data comes new possibilities, and different techniques have been developed to use GWAS results for different aims, including a) to quantify the genetic predisposition of individuals for disease risk stratification, as in the case of the construction of Genetic Risk Scores (also called Polygenic Risk Score); b) to assess a causal inference of a modifiable exposure on an outcome, taking advantage of the Mendelian Randomization approach [64].

## Genetic Risk Score

Concerning the first point, the quantification of the individual's genetic risk, a common strategy used in genetic epidemiology is to aggregate the information of single SNPs that, taken singularly, are associated with the outcome with only a small effect size and consequently explain only a small proportion of the trait [65]. The risk variants associated with a trait are summed up into a Genetic Risk Score (GRS, Equations 1, 2) which becomes a quantitative measure of the individual's overall genetic susceptibility for the trait of interest.
Here is an example of what the sum of variants looks like:

1) $$GRS = \sum_{i=1}^{n} SNP_i$$

2) $$wGRS = \sum_{i=1}^{n} \beta_i SNP_i$$

In the first equation a standard GRS made up of the sum of SNPs is shown, while in the second, a weighted GRS (wGRS) is represented. The variants in the latter case are multiplied by "β", the weight of the association retrieved from the original GWAS.

GRSs have aroused interest because it is a simple tool useful to in parallel evaluate i) the individual risk, and ii) the predictive performance captured by the genetic variants [66]. Moreover, since the genetic components are present from birth, the information contained in the GRS is defined before the influence of environmental factors, and it could have a potential clinical utility as the earliest measurable disease risk [49]. This ability would depend on the performance of the score, which is evaluated by measuring the area under the receiver operating characteristics (ROC) curve (AUC).

The predictive performance would be influenced on one side by the grade of heritability of the trait, and on the other side by the quantity of information contained in the genetic variants [66].

Together with the AUC, it is useful to integrate the analysis using different parameters, like the proportion of variance explained (R2) derived from the linear regression of the GRS with the trait or Nagelkerke´s R2. Another strategy is to divide the population into quartiles or deciles of the distribution of the GRS and compare the two extremes, to evaluate the risk stratification ability to discriminate between individuals at low and high risk.

Different methodological approaches have been developed, and it is still a matter of debate, over the years to improve the predictability of the score. An algorithm to construct a GRS should consider [67]:

- Variants selection is based on the level of significance threshold [68,69]. Typically, the significance level for GWAS is set up at p<5x10-8, that is the value of p

corrected for multiple testing, because of the high number of tested associations that are performed in GWAS. This could represent a threshold too much stringent for some highly polygenic traits in which the total heritability could be distributed over thousands of common SNPs [67,68]. On the contrary, including too many SNPs might result in the inclusion of noise and a less precise risk prediction. Consideration should be done based on the genetic architecture of the trait/disease and the sample size [68].

- Linkage disequilibrium (LD). LD is present when two alleles from nearby genetic variants are inherited together. In this case, the two alleles are not independent.

  LD is usually quantified using the r2 which is the squared correlation of genotypes between a pair of SNPs [70]. As a correlation coefficient, its values go from 0 to 1 in case of complete independency between the alleles or dependency, respectively. Another LD measure is represented by the D prime (D´), an indicator of allelic segregation for two genetic variants. As for the r2, values go from 0, indicating no linkage or 1, in the case of total linkage.

  Correlation between the SNPs should be always considered to avoid over-representation of some genetic regions.

  LD pruning or clumping are methods used to filter out correlated variants. The first one consists in randomly removing one SNP from a pair in high LD while the second is pruning and retaining the most significant among the SNP pair [68]. More complex methods like LDpred [71] or lassosum [72] have been developed, but the best predictive approach is still a matter of debate.

GRS has been shown to overcome the challenge to discriminate individuals at clinically significantly increased risk, with effects comparable to the ones conferred by monogenic mutations or family history [45,68,73]. This demonstrates that GRS might bring clinical independent information to the disease risk evaluation and their incorporation in predictions model at the side of the other risk factors could be insightful.

This has been shown for various diseases including coronary artery disease (CAD), breast cancer, type 1 and 2 diabetes, obesity, and Alzheimer's disease

[45,74–76]. In the case of CAD, it has been shown that its polygenic component, defined by more than one million SNPs combined into a GRS, improved risk prediction independently both from the monogenic component and the traditional risk factors. [45,68].

In hypertension research, GRS has been largely used through the years to evaluate its performance in predicting hypertension, but despite being independently associated with hypertension risk with respect to traditional risk factors, it did not bring clinically relevant information in improving risk classification [53,73,77,78]. Results based on UK Biobank data in approximately 360.000 individuals, clearly argued against such concerns by showing clinically meaningful differences in systolic BP (~13 mmHg) between the top and bottom deciles of GRS [52].
Before clinical implementation of these findings can be considered, they need to be replicated using individual level data in population-based settings outside the UK Biobank. Moreover, even if the GRS is unchanged throughout life, its value in the prospective setting is unknown, i.e. what does it add in predicting future hypertension among non-hypertensive individuals [52,54].

## Mendelian Randomization

As already mentioned, GWAS have contributed to identifying hundreds of common variants associated with a trait/outcome and revealed insights into complex diseases. They also highlighted the pleiotropic nature of many complex diseases, a condition in which the discrimination of causal associations becomes arduous.
All the amount of information produced by GWAS can be leveraged to identify causal relationships. The most widely implemented method for this purpose is Mendelian Randomization, which takes advantage of genetic data to assess and estimate the causal effects of modifiable exposures based on observational data [64,79]. In 2003 Davey Smith and Ebrahim coined the term “Mendelian Randomization” (MR) thinking about the two first-ever genetic laws of inheritance, proposed by Gregor Mendel in 1866. The first is the “law of segregation” which describes that during the process of meiosis the two alleles

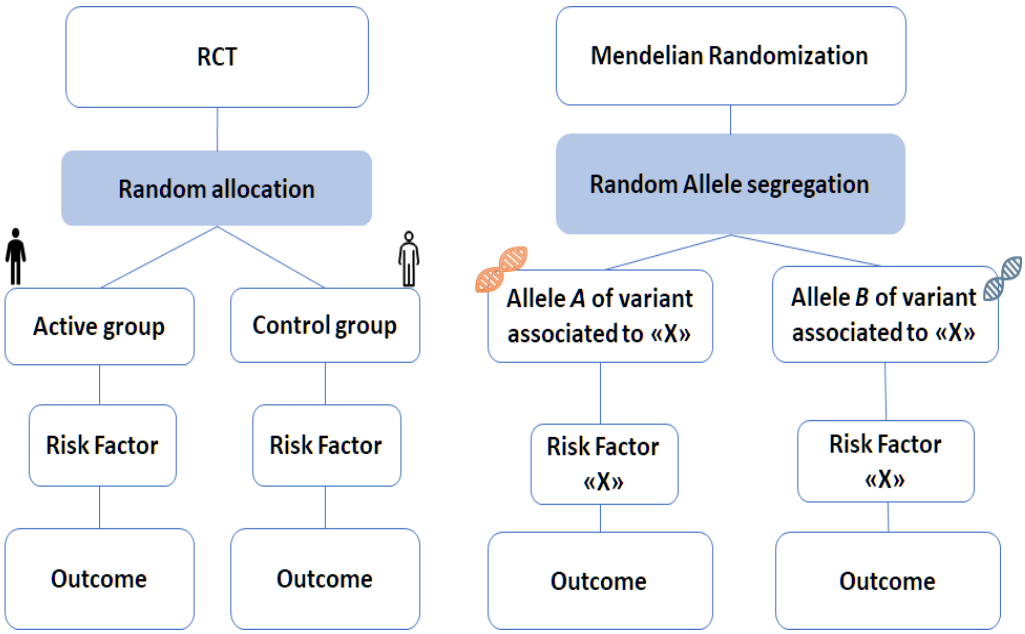
of each gene separate and each of them is distributed, randomly, in each of the two formed gametes. The second law, the "law of independent assortment", refers to the independent assortment of genes located on different pairs of homologous chromosomes, during meiosis.

This random assortment process, happening during segregation, was then elegantly integrated with the method of instrumental variables (IVs), well-known in economics and econometrics for evaluating a causal association in observational studies and avoiding confounders [80]. In the IV approach, the causal effect of exposure with an outcome is captured by a third variable, precisely the IV, which is associated with the exposure [80].

The gold standard to test causality for clinical hypotheses is represented by RCTs. Individuals are randomly assigned to either a treatment/intervention group or a control group. The effectiveness of the treatment/intervention is then evaluated by measuring what is the difference in the outcome between the two groups. The act of randomization balances the observed and unobserved characteristics of the individuals, making the RCT the rigorous tool able to evaluate the causality of a relationship in an unbiased context [81,82].

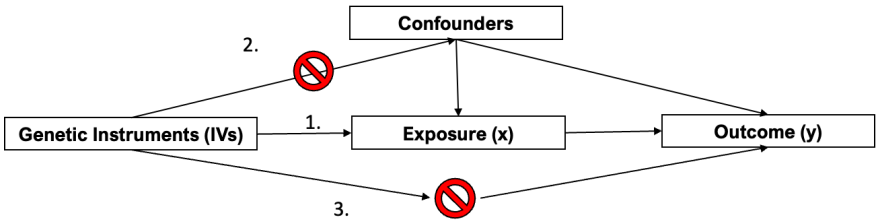
MR can provide an approach analogous to RCT, using as randomized factors the genetic alleles that randomly allocate individuals at conception in subgroups. The genetic variants are naturally proxies for the exposure/risk factor [82] (Figure 7). Using Mendelian Randomization, we can infer the causality of the relationship between an exposure and an outcome, potentially avoiding the effect of unobserved confounding factors or reverse causation, which is often the issue in conventional observational studies [37].

Figure 7. Representation of the analogy between randomized controlled trials (RCTs) and Mendelian Randomization




To be accurate, there are some differences between RCT and MR. The first is that it cannot be considered an entire randomization context because it is influenced by nature, indeed the alleles are transmitted from the parents and not by the random assignment by an investigator; for this reason, biological events are always characterized by the so-called quasi-randomization.
However, the random properties of genetic variants are represented by the random mating and the lack of selection effects on the variants. The second difference is what is evaluated at the end, that is not the effect of the genetic component on the outcome, but only the exposure on the outcome, differently from RCTs which evaluate the effect of the intervention/treatment [64]. Among MR´s strengths and advantages, there is the absence of reverse causality since the genetic background cannot be changed-, and the low cost and feasibility.
The fundamental of MR is represented by the relation between genetic instrument-exposure-outcome, as represented in the causal directed acyclic graph (DAG) in Figure 8.

Figure 8 Directed acyclic graph (DAG) representing the three assumptions at the base of Mendelian Randomization




In the graph, the conditions to be satisfied to perform an MR are shown, and they can be summarized in three assumptions [64,83]:

1. 'The relevance assumption': The variant is associated with the exposure
2. 'The exclusion restriction': The variant is not associated with the outcome via a confounding pathway. A confounder is a variable which is causally related to both exposure and outcome.
3. 'The exchangeability assumption': The variant does affect the outcome only by the exposure

An instrumental variable should also be evaluated for its strength. It is considered "weak" if it can explain a small amount of exposure variance. This can be assessed by an F statistic if the association of genetic variants-exposure is smaller than 10 [84].

Once the instrumental variable choice has been done according to the above-mentioned principles, it is possible to proceed with the estimate of the causal effect. Several MR methods exist to assess the causality and can be chosen on the base of the type of data, individual-level or summary statistics, and the kind of phenotype examined, binary or continuous.

### *Individual-level data*

Individual-level data refers to performing the analysis in a one-sample set in which the genotype, exposure and outcome data are available.

The simplest model for estimating the causal effect is represented by the Ratio of coefficients method represented in equations 3 and 4 for the continuous and

dichotomous outcomes, respectively. In the first case, the change in the outcome for a unit increase in the exposure is equal to the change in the outcome for a unit increase in the IVs scaled by the change in the exposure for a unit increase in the IVs [85]. In the second estimation, a log-linear or logistic regression model is used, and the estimate represents the change in probability of an event for a unit change in the exposure [85]. The term $\overline{y_1}$ in equation (4) refers to the log of the probability of an event and $\overline{x1} - \overline{x0}$ and $\overline{y1} - \overline{y0}$ is the average difference in the exposure/outcome between the two subgroups 0 or 1.

$$3)\ \text{Ratio, continuous outcome} = \frac{\hat{\beta}_{Y|Z}}{\hat{\beta}_{X|Z}}$$

$$4)\ \text{Ratio, dichotomous outcome} = \frac{\overline{y1} - \overline{y0}}{\overline{x1} - \overline{x0}}$$

Confidence intervals for the ratio method can be computed using 'Normal approximation' or 'Filler's theorem'.

When more IVs are used, a Two-stage method, known as Two-Step-Least-Squares (2SLS) is performed. It is a weighted mean of the ratio estimates for each of the IV. As the name suggests, it consists of two steps, in the first the exposure is regressed over IVs to obtain the fitted values of the exposure; in the second stage, the outcome is regressed on the fitted values previously computed [82]. 2SLS can be applied both to continuous and binary outcomes, but for the latter, a logistic regression should be used in the second step, and the adjustment for the residuals of the first stage is advised [85].
In individual-level setting, it is possible to combine multiple variants into a GRS to increase instrument strength.

### *Summarized data*

When summary results are available from the GWAS, the estimate (β), the standard error (SE), the significance (p-value) as well as information of the

SNPs, including chromosome position, effect allele and other allele, are reported. When only one IV is used, the ratio method, previously described, can be adopted. Whereas, in presence of multiple IVs, the ratio estimates of each of them are combined into a single estimate as in a meta-analysis, using the inverse-variance weighted (IVW) method. IVW is a weighted mean of the ratio estimates, and it is equal to estimates of 2SLS [86]. It is liable to bias if only one IVs doesn't satisfy IVs assumption and in presence of pleiotropy [87].
In the IWV method the association between the genetic instruments and the outcome is divided by the association of the genetic instruments with the exposure [88].
IWV is usually accompanied by another estimate, the weighted median, similar to IVW except for the use of a weighted median instead of a weighted mean, and it is consistent with up to 50% invalid instruments [87].
Other meta-analysis approaches should be considered when dealing with summary-level data, for example, heterogeneity evaluation. Visual plotting including scatterplots, funnel plots or radial plots are nice tools to visualise outliers and, in combination with Cochran´s Q statistic, help identify the presence of heterogeneity [64].

Pleiotropy assessment is also a crucial point to be considered when performing MR studies. Pleiotropy exists when a genetic variant is associated with both the exposure and outcome through a different pathway, which theoretically means violating the third assumption for the choice of instrumental variants. This could be easily evaluated in case the exposure is a single biomarker and the variants are near the coding genes but, for polygenic traits, like hypertension, pleiotropy is somehow expected [89]. In this case, posterior evaluations have been developed to tackle the problem. MR-Egger is a method that provides unbalanced estimates in the case of a balanced pleiotropy [90] and it is commonly used as a sensitivity analysis in MR to assess the plausibility of the causal estimates. The MR-Egger allows to estimate the causal effect according to the Instrument Strength Independent of Direct Effect (InSIDE) assumption, which states that the

pleiotropic associations of genetic variants must be uncorrelated with the genetic variant–exposure association [87].

MR-PRESSO is also part of the sensitivity analyses class and is used to detect outliers [89].
These evaluations are crucial for the correct interpretation of the results obtained with MR.

The use of MR has increased rapidly in the last decades, from 2003 when PubMed (https://pubmed.ncbi.nlm.nih.gov/) had only 1 article to 2021, which accounts for more than 1,200 manuscripts. This is encouraged by the presence of a large quantity of freely available summary statistics resulting from large consortia, and by the existence of tools, like the online app "MRBase" or packages developed in R software including "MendelianRandomization", "TwoSampleMR" or "MR-PRESSO". Moreover, MR has gained even more interest after defining its role, in determining causal links in cardiovascular diseases [91].
Unfortunately, many MR studies are inadequately reported and show incomplete evaluations of the causal effects. This led to recently redact some guidelines called Strengthening the Reporting of Observational Studies in Epidemiology applied to MR (STROBE-MR) providing a checklist of recommended items to be included in the study [92].

## Aim

In this work, I am presenting four studies, in which by using genetic variants (SNPs) identified through genome-wide association studies (GWASs), we aimed at:

Study I. We constructed a new GRS for blood pressure including 858 SNPs (BP-GRS858) associated with systolic or diastolic blood pressure traits. We then aimed at investigating the association of the BP-GRS858 with BP traits, hypertension prevalence, in two Swedish cohorts and at testing its performance as a predictive tool, also in comparison with other well-known risk factors. Finally, we wanted to estimate how much variance of cross-sectional BP the BP-GRS858 could contribute, on top of a previously reported GRS including the 29 top SNPs for BP (BP-GRS29) [73,93].

Study II. Study II is an individual-level MR, in which we aimed to compare the causal association of different adiposity measures (BMI, WHR, VAT ad BF) with blood pressure and hypertension in the MDC or MPP [94].

Study III. To date, there are no clear data about the causal association between thyroid function and blood pressure traits or adverse cardiovascular events. [95].

Study IV. Altered levels of calcium per se or through the effect of its regulatory hormones could affect blood pressure (BP), but the exact mechanisms remain unclear. We tested whether a causal relationship exists between serum calcium level and/or the regulatory hormones involved in its homeostasis (PTH, Vit-D, and FGF23) and high BP in the MDC, using a Two-Sample Mendelian Randomization (MR) study [96].

# METHODS

## Populations

### *Malmö Diet and Cancer, MDC*

Cross-sectional BP, hypertension prevalence and incidence of cardiovascular events were studied in the MDC, a large-scale urban population-based cohort consisting of 30,447 individuals (58±7.6 yrs) from Malmö, Sweden. Of these, 29,386 were genotyped for GWAS. Men aged 46-73 and women aged 45-73 included between 1991 and 1996 were included [97,98]. At the baseline exam, BP was measured once in the supine position after 5 minutes of rest. Cardiovascular diseases (CVD: the sum of coronary artery diseases and stroke), stroke, coronary /artery disease (consisting of coronary events, coronary artery bypass graft [CABG] or percutaneous coronary intervention [PCI]), heart failure (HF), atrial fibrillation (AF), and total mortality were used as endpoints in the survival analysis. Endpoints referred to a follow-up time until 31 December 2016. The mean follow-up time across the population was 19.7±5.6 years. The general characteristics of the population are presented in Table 2.

Ethical permission for the MDCS was attained from The Ethical Committee at Lund University (LU 51–90 and DNR 652/2005) and all participants provided written informed consent.

### *Malmö Preventive Project, MPP*

MPP is an urban-based prospective study including BP measurement both at a baseline exam of Malmö citizens between 1974 to 1992 and at a re-examination between 2002 to 2006 in 18,240 individuals [73]. Of those, 9367 had undergone GWAS genotyping and are also part of MDC.

In MPP at baseline BP was measured after 1-minute rest in the supine position followed by another measurement after 1 minute in an upright standing position. This procedure was repeated also after 10 minutes of resting. BP values were averaged and used for the analysis for those subjects with a least three valid measurements. At reinvestigation, two measures in the supine position were

recorded. For those subjects with at least 2 valid measures, we used the averaged BP values.

In this population hypertension prevalence and incidence after a mean follow-up of 23.0±4.7 years were used as outcomes in Study I and II. The general characteristics of this population are presented in Table 2.

The ethics committee of Lund University approved the study protocols DNR 2009/633) and all participants provided written informed consent.

## Anthropometric and metabolic measures

Laboratory analyses were performed according to standard methods. Whole blood glucose and lipids were determined after an overnight fast and analyzed at the Department of Clinical Chemistry, Malmö University Hospital. Glomerular filtration rate (GFR) was computed applying the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation for creatinine in mg/dL. Information about medical history, anthropometric data, lifestyle and socio-economic factors, and family history of hypertension in first-degree relatives was derived from the baseline questionnaire. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters (kg/m2). BMI categories were defined depending on BMI values<18.5 kg/m2 or BMI>18.5 kg/m2 <25 kg/m2 or BMI>25<30 or BMI>30 kg/m2.

Waist circumference (cm) was measured between the lowest rib margin and the iliac crest and the hip circumference (cm) as the largest circumference between the waist and thighs. Waist to hip ratio (WHR) was computed. In the MDC, the percentage of body fat (BF) was estimated with Bioelectrical Impedance Analyzers (BIA) according to the manufacturers' algorithm (BIA 103, JRL systems, single-frequency analyzer, Detroit, USA) [94].

## Definition of hypertension

In both cohorts, hypertension was defined as either being on treatment with antihypertensive drugs or having either SBP ≥140 mmHg or DBP ≥90 mmHg

according to current European guidelines [6]. In the cross-sectional BP analyses in MDC, BP was adjusted using a stepped addition method that took into account the number of antihypertensive drugs as previously described [73,99], i.e. 8/4, 14/10, 20/16, and 26/22 mmHg were added to SBP/DBP when individuals were treated by one, two, three and four drugs respectively. In the MPP, since the number of antihypertensive drugs was not available, we adjusted SBP/DBP respectively for 15mmHg and 10mmHg in presence of antihypertensive therapy [93].

## Definition of Cardiovascular events (CVD) in MDC

Coronary artery diseases included fatal or nonfatal myocardial infarction, death from ischemic heart disease, and the treatment procedures coronary artery bypass graft surgery (CABG) and percutaneous coronary intervention (PCI), whichever of these events came first. Death due to ischemic heart disease was defined based on the International Classification of Diseases ninth and tenth revisions (ICD-9 and ICD-10) codes 412 and 414 (ICD-9) or I22–I23 and I25 (ICD-10). Further on, myocardial infarction was defined by the codes 410 and I21 (ICD-9 and ICD-10, respectively). CABG was identified from national Swedish classification systems of surgical procedures, the KKÅ system from 1963 until 1989 and the Op6 system since then. CABG was defined as a procedure code of 3065, 3066, 3068,3080, 3092, 3105, 3127, 3158 (Op6) or FN (KKÅ97) [93]. The definition of PCI was made based on the operation codes FNG05 and FNG02. Stroke (fatal or nonfatal) was defined using codes 430, 431, 434 and 436 (ICD-9) and I60, I61, I63 and I64 (ICD-10). Cardiovascular events were used in Study I, in survival analysis, and in Study IV in the Two-sample MR.

## Genotyping

Genotyping of both cohorts was performed using the Illumina GWAS chip (GSA v1 array). Genotype was performed by Regeneron Genetic Centre using an Illumina GWAS chip (GSA array v1) according to the manufacturer's

standard protocols. Imputation was performed in three 10k-sample batches (n=9,299) for third batch), phasing to reference panel "hr1.1.2016" for European population (software used: eagle v2.3). Before imputation, autosomal SNPs with Minor Allele frequency (MAF) greater than 1%, with less than 1% missingness, with a Hardy-Weinberg equilibrium (HWE) less than $1x10^{-15}$ passed the quality control, resulting in a total number of 39,127,700 markers. Individuals with more than 10% of missing genotype data as well as blacklisted and duplicated ones were excluded [93].

## Genetic Risk Score

In Study I, a weighted genetic risk score, BP-GRS858, was constructed by adding up all risk alleles of the SNPs, that resulted to be GWAS-significantly (p-value<$5x10^{-8}$) associated with hypertension, systolic and diastolic BP in previous GWAS studies [52,54]. Beta-coefficients used for individual variant weighting and the effect-alleles were derived from the same meta-analyses [52,54].

We first computed two trait-specific GRSs that were averaged to obtain BP-GRS858 including 858 variants. We derived at first, a systolic blood pressure (SBP) GRS including 474 independent variants, then a diastolic blood pressure (DBP) score including 384 variants. Twenty-eight SNPs were included in both scores because associated with both traits. Independency among variants was tested using pairwise linkage disequilibrium (LD) statistics. LD matrix was computed using PLINK version 1.90b5.2 *(--ld)* and a threshold of r2=0.1 was used. Among pairs of SNPs that were above threshold of r2, and thus considered not independent, we retained the SNP with the lowest reported p-value. For variants that were not available in our dataset, we looked for LD-proxies ($r_2$>0.8), using the web-based application LDLink 3.7.2 (module: Ldproxy, available at https://ldlink.nci.nih.gov/?tab=ldproxy) provided by National Cancer Institute [93]. The list of variants, the weights and the effect allele used to derive the score are provided in the Appendix I.

BP-GRS858 was standardized to Z-Score, to have a mean of 0 and 1 unit variance. The BP-GRS858 was then categorized into quartiles and deciles based on its distribution in the population.

## Statistics

### Overview of the main statistical models used in the studies

In all the studies continuous variables are presented as mean±SD and as percentage for categorical variables. Two-way ANOVA was used to test whether a variable changes across different groups. Multiple linear regression was used to explore the relationship between a group of independent explanatory variables and a dependent variable. The method seeks the best fitting curve that minimize the sum of squared error terms. In case of a binary dependent variable, indicating whether an event occurred or not, we modeled the probability of the occurrence of the event, using a logistic regression function. A Measure of good fitness of a model was obtained by calculating the r-squared ($r^2$) which represents the percentage of dependent variable variation in the model. The larger it is, the better the model fits the observation.

A logistic regression´s goal is to find the best fitting which maximize the log likelihood function. The results can be interpreted in terms of odd ratio (OR): the ratio between the odd that an outcome would exist given an event, on the odd that an outcome would exist in absence of the event.

For time-to-event data, the probability that an event had occurred given a set of predictors, after a certain period of time, was assessed with the hazard function of Cox Regression Analysis. A value of Hazard Ratio (HR) was obtained as result.

Statistical analyses were performed by SPSS software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 22.0. Armonk, NY: IBM Corp.), *R software* (R Core Team, 2018, v 3.5.1, packages "*ivpack*", "*MendelianRandomization*", "*TwoSampleMR*") [100–102], or *Plink 1.9* [103].

The significance level was set at $p < 0.05$ and all tests were two-sided.

Additional statistical details, specific to each study, will be presented in the next few pages.

### Study I

In the MDC, a linear regression model was used to test the association of the score with cross-sectional BP-related traits. Two adjustement models were tested for the analysis: model A) adjusting for age, sex, and body mass index (BMI); model B) model A plus adjustment for the BP-GRS we previously constructed including 29 SNPs (BP-GRS29) [73,93] to evaluate the improvement added by the BP-GRS858 with respect to the BP-GRS29. The r-squared ($r^2$) and the partial $r^2$ for each model are presented to allow a comparison of the effect size of different risk factors.

### Hypertension prevalence and incidence

A logistic regression model was used to assess the association of the BP-GRS858 with the prevalence of hypertension at baseline in both cohorts and with hypertension incidence at reinvestigation in the MPP, evaluated after a mean follow-up time of 23.0±4.7 years. For the analysis of the prevalence of hypertension in MPP 9,156 among the 9,367 had data sufficient for a correct classification both at baseline and at re-investigation. For the analysis of hypertension incidence, among the 9,156 subjects, 3,135 who were already hypertensive at baseline were excluded, leaving 6,021 individuals for the analysis. In the MDC cohort, among the 29,292 who have complete data for BP classification at baseline, 11,325 were normotensive [93].

Since different covariates were available for the two cohorts, different adjustment models were adopted. For MDC the following models were constructed: A) age, sex, $age^2$, age x sex; B) as model 1 plus obesity, diabetes, apolipoprotein A (APOA), apolipoprotein B (APOB), smoking status; C) model 2 plus systolic or diastolic BP.

For the MPP we used the following three models: A) age, sex, age x sex, $age^2$, heart rate; B) as in model 1 plus BMI, diabetes (fasting blood glucose≥6.1 mmol/L), hypercholesterolemia (total serum cholesterol >5.17 mmol/L or specific treatment), hypertriglyceridemia (serum tryglicerydes≥1.7mmol/L), High-Density Lipoprotein (HDL)-cholesterol, smoking status, family history of hypertension ($1^{st}$ relative); C) as in model 2 plus systolic BP, glomerular filtration rate (GFR), physical activity level and civil status. Unfortunately, due to the difference in the

panel of exposures that was available in the two cohorts, we couldn't make the two models more harmonized that in the above-described way. Follow-up time from baseline was also added as a covariate to the models in the longitudinal analyses. The area under the curve (AUC) was evaluated before and after adding the BP-GRS858 to model C.

### *Incidence of cardiovascular endpoints in MDC*

Survival analysis using COX proportional hazard models was used to evaluate the role of the BP-GRS858 in the incidence of cardiovascular endpoints in MDC. All subjects that already encountered cardiovascular events before baseline evaluation were excluded from the analysis. Three models were used for adjustment. Covariates in the models were respectively: A) age and sex, B) as in model 1 plus obesity, diabetes mellitus, APOA, APOB, smoking, C) as in model 2 plus hypertension. Both continuous and quartiles of GRS were analyzed both in longitudinal and survival analysis. Heart failure and mortality endpoints were also adjusted for prevalence of cardiovascular disease and coronary artery disease.

## Study II

## Mendelian Randomization

### Instrumental variables

A genetic risk score for BMI (GRS-BMI565), a GRS for WHR (GRS-WHR324), a GRS for predicted visceral adiposity (GRS-VAT208) and one for body fat distribution (GRS-BF81) were constructed by including respectively 565, 324, 208 and 81 independent SNPs retrieved from the most recent meta-analyses [104–106]. The scores were weighted for the beta coefficients reported in the primary studies [104–106].

The four GRS (GRS-BMI565, GRS-WHR324, GRS-VAT208, GRS-BF81) were used as instrumental variables (IVs) in the Mendelian Randomization analysis [94].

## Association with Exposure

The association with the exposure traits and the GRSs is presented in Table 9. Since not all the traits specific for their corresponding GRS were available, we had to use one of the other adiposity traits as proxy.
In Table 9 a summary of the sources of GWAS summary statistics is presented.

## Causal estimate in the individual-level data setting

For continuous outcome (SBP, DBP at baseline, and at reinvestigation) two steps least square (2SLS) regression was used to assess the causal association of the four GRSs. For binary outcomes (hypertension prevalence and incidence) we used the analog of 2SLS consisting of two sequential regressions with the difference that the second step consists of logistic regression of the fitted values from the first step on the outcome [107].
The exposure traits (BMI, WHR, BF) and the outcomes (SBP, DBP) have been used as standardized residuals resulting after adjustment for age, sex, age$^2$, age*sex. These models were used accordingly to our previous studies investigating the same outcome [93,108] . Age squared and age*sex transformation terms were included in the models to consider the non-linear behavior of the age.

## Sensitivity analysis

When dealing with multiple instrumental variables, an alternative approach to the aggregation in a GRS is to use the estimates from each of the instrumental variables using summarized data analysis, as in a meta-analysis [86]. With the increasing number of variants used in MR investigations, it is increasingly unlikely that all variants are valid IVs [87].
Inverse-variance weighted (IVW) method, MR-Egger, and weighted median were used as sensitivity analyses in the MDC cohort to assess the robustness of any casual finding of the multiple genetic variants involved in the construction of the four adiposity-trait GRSs, to avoid the violation of IVs assumption [109].

## Study III

### *Mendelian Randomization*

#### Instrumental variables and association with exposure

Single nucleotide polymorphisms (SNPs) and summary statistics associated with TSH, FT4, hypothyroidism, hyperthyroidism, and TPOAb were selected from the latest GWAS studies [110,111] to be used as instrumental variables for the two-sample MR analysis,

Only uncorrelated SNPs ($r2 < 0.01$) that were associated with the traits at the GWAS significance level ($p < 5 \times 10^{-8}$) were included in the analysis. SNPs with palindromic alleles and with intermediate allele frequencies were excluded.

#### Association with the Outcomes

The association of the genetic instruments with the outcomes was evaluated using genotypes from MDC Study [97], using as outcome blood pressure values and cardiovascular events.

Linear and logistic regression models were used to compute the association of the genetic variants with continuous traits (age, sex, and AHT-adjusted systolic and diastolic blood pressure) and with dichotomized events (cardiovascular diseases), respectively. Potential causality was evaluated using the inverse variance weighted (IVW) method, and the weighted median and MR-Egger methods were used in sensitivity analyses to explore bias introduced by the presence of pleiotropy. Cochran's Q test was used to infer the presence of heterogeneity, with $p < 0.05$ suggestive of the presence of heterogeneity among the MR estimates generated by the individual instrumental variables. The presence of outliers was tested using MR-PRESSO [112] and a leave-one-out analysis was used to verify if the causal effect would rely on a single variant [113].

## Study IV

### *Mendelian Randomization*

A two-sample MR study was performed in which the summary statistics of the association of the genetic variants with the exposure and the outcomes come from two separate GWASs.

### Instruments and association with exposure

We selected SNPs and their summary statistics information, that were GWAS significantly associated ($p<5X10-8$) with serum levels of calcium, Vit-D, PTH, and FGF23 from the most recent GWAS meta-analyses [114–117], and used instrumental variables for the MR analysis. Selected SNPs were then clumped based on linkage disequilibrium using a stringent threshold ($r2>0.001$) and SNPs with palindromic and intermediate allele frequencies were excluded from the analysis.

The selected studies included respectively 305,349 (calcium), 417,580 (Vit-D); 29,155 (PTH); and 16,624 (FGF23) individuals [114–117], for more details it is possible to consult Table *17*.

### Association with the outcome

The summary statistics for the association of the SNPs with BP traits were obtained from genetic data in the Malmö Diet and Cancer (MDC) study (n=29,298) [97,118].

### Causal estimates

As for study III, Inverse Weighted Median (IVW) and weighted median were used to combine the estimates, and assess the causal relationship between genetically predicted calcium, PTH, and FGF23 and blood pressure traits. Heterogeneity was evaluated by Cochrane's Q heterogeneity test. Palindromic SNPs with intermediate allele frequency were removed from the analysis. As a sensitivity analysis, we used MR-Egger to evaluate the presence of pleiotropy, leave-one-out analysis, and MR-PRESSO to detect outliers.

# RESULTS

## Study I. Results

### Genetic Risk Score

Eight hundred fifty-eight SNPs were included in the BP-GRS858. The list of genetic variants, effect alleles, and weights used to construct the BP-GRS858 are reported in the Appendix 1 (Tables A1, A2).

### Cross-sectional association of BP-GRS858 to BP in MDC

In the MDC, the BP-GRS858 (model A) was highly significantly associated with all tested BP traits, as shown in Table 3. One standard deviation (SD) increase in the BP-GRS858 corresponded to an increment of 3.3 mmHg of SBP (Beta, 95%CI: 3.3, 3.1-3.5; $P=7.46x10^{-200}$) and 1.7 mmHg of DBP (Beta, 95%CI: 1.7, 1.6-1.9; $P=5.07x10^{-206}$). The results remained significant also after adjustment for the BP-GRS29 [73] both for SBP (Beta, 95%CI: 3.1, 2.9-3.4; $P=2.4 \times 10^{-195}$) and for DBP (Beta, 95%CI: 1.7, 1.5-1.8; $P=1.8 \times 10^{-147}$) as also shown in the Table 3 (model B). Similar findings were found in the analogous analyses replicated in the MPP and are presented in Table 4.
When comparing the top versus the bottom quartiles and deciles of BP-GRS858, respectively, we found a difference of 9.0/11.2 mmHg for SBP (Figure *9* a, c)) and 4.8/6.0 mmHg for DBP (Figure *9* b, d)).

### Prevalence of Hypertension in MDC and MPP

Analyzing the prevalence of hypertension in the MDC we found that a single SD increase in the BP-GRS858 was significantly associated with the prevalence of hypertension (OR [95%CI]: 1.45 [1.41-1.49]; $P= 1.1 \times 10^{-171}$ for model 1). When comparing the highest vs. the lowest quartiles of the BP-GRS858, we found an odds ratio of 2.7 (OR [95%CI]: 2.78 [2.56-3.01], $P= 1.1 \times 10^{-138}$) that increased to 3.7 when comparing extreme deciles (3.71 (3.32-4.14), $P= 4.22 \times 10^{-118}$), in model A. The association was significant also in the MPP where the BP-GRS858 was associated with the prevalence of hypertension, either when using the continuous

standardized score (OR [95%CI]: 1.35 [1.29-1.41], P= 1.410-$^{37}$), or described as categorical variable of extreme quartiles (2.14 [1.88-2.44], P= 3.22x10-30) or deciles (2.95 [2.39-3.64], P= 7.50x10-24). The effect size of the associations was attenuated but remained significant when adjusting for other covariates in different models (see Table 5).

## Incidence of Hypertension in the MPP

The BP-GRS858 was significantly associated with the incidence of hypertension in the MPP cohort (Table 6) in all the tested models. In the first model, subjects in the top quartile and top decile of BP-GRS858 showed a more than doubled incidence of hypertension with respect to the ones in the bottom quartile or decile (OR [95%CI]: 2.05, [1.75-2.39] P=1.4x10$^{-21}$); 2.13, [1.67-2.71] P=2.2x10$^{-8}$) respectively (Table 6). In the statistical model including all covariates except the BP-GRS858 for the prediction of hypertension incidence, the AUC was 0.71 (0.69-0.72), which had a non-statistically significant increase to 0.72 (0.70-0.73) when adding the BP-GRS858 (Figure *10*).

### Comparison with BMI and other traditional risk factors

In Table 7, the contribution of each covariate included in model C for incident hypertension in the MPP is shown. Stratification in quartiles of other important factors traditionally associated with hypertension such as either BMI or baseline BP and the BP-GRS858, allows the comparison of the effect size in the fully adjusted model. In the MPP the contribution of the BP-GRS858 is fairly like that of the other well-known factors (see Table 7). We also evaluated the AUC after the addition of either BMI or diabetes to the fully adjusted model (without BP-GRS858), and we obtain no increment in AUC: 0.71 (0.70-0.72) before and after adding BMI or diabetes, respectively.

## Cardiovascular endpoints in the MDC

We found that the BP-GRS858 was significantly associated with the risk of CVD, stroke, coronary artery disease, heart failure, atrial fibrillation, and total mortality in the MDC (Table 8). The risk of cardiovascular events was

significantly higher comparing the top and the bottom quartile or decile of BP-GRS858 as shown in Table 8. Most of the associations were maintained also in the models adjusted for traditional risk factors. In particular, in the model A and B (Table 8), the BP-GRS858 remained associated to all events, while in the third model, after adjustment for hypertension, the association with heart failure, atrial fibrillation and with total mortality were no longer statistically significant (Table 8).

## Study II. Results

### Association of GRSs with exposures

In Table 10 the association of each of the four GRSs used as instrumental variables (IV), with their related exposure traits, is presented. The contribution to the model in terms of R-squared and the F statistic is also reported.

### Association of IVs with the outcomes

In Table 11 the results from the Mendelian randomization analysis of the four adiposity GRSs with the continuous traits SBP/DBP at baseline are shown for MPP (part 1.) and MDC (part 2.). In the MPP (Table 11, part 1. and Figure 11), all the GRSs except for the GRS-BF81 identify significant associations with baseline SBP and DBP. In the MDC (Table 11, part b. and Figure 12) the associations with baseline measurements were in line with the results in the MPP. In both studies, the GRS-WHR324 shows the strongest association, in particular with DBP. At the MPP follow-up, only the GRS-BMI565 remains significantly associated with the BP-related traits (Figure 11)

In table 12, the associations of the four GRSs the prevalence of hypertension and its incidence are reported. A higher Odd Ratio is found with GRS-WHR324 as compared to other adiposity-GRSs for both MPP (Table 12 and Figure 13) and MDC (Table 12 and Figure 14).

Regarding hypertension incidence in MPP, after the exclusion of participants already hypertensive at baseline, only the GRS-BMI565 remained significantly associated with incident hypertension (Figure 13).

Results from sensitivity analysis are presented in Table 13. As expected, the inverse-variance weighted method (IVW), reflects the results obtained by the 2SLS regression of the GRSs on the traits (Table 13). The latter shows significant associations for all the scores with both traits except for the GRS-BF81. Among the four scores, the only one that showed a significant association using the MR Egger method is the GRS-WHR324 both for SBP and DBP (Table 13).

## Study III. Results

### Association of IVs with the exposures

We selected 52 SNPs for TSH, 29 for FT4, 8 for hypothyroidism and hyperthyroidism, and 4 for TPOAb as instrumental variables for the analysis. More details about the GWAS are summarized in Study III

Table *14*.

A list of the variants is shown in the Appendix, in table A3.

### Association of IVs with the outcomes

A genetically increased level of TSH was found to be significantly associated with a decrease in systolic blood pressure (IVW, beta: −0.83; SE: 0.38; p: 0.03) in inverse variance weighted analysis. No other exposure showed an association with blood pressure (Table 15). The causal association was supported in the leave-one-out analysis, but it did not result in being significant at the Bonferroni threshold. In the evaluation of the association with cardiovascular events, genetically predicted TSH was inversely associated with atrial fibrillation (IVW, beta: −0.204; SE: 0.07; p: 0.004). The association was consistent across all three estimators, IVW, MR-Egger (beta: −0.455; SE: 0.169; p: 0.009), and weighted median (beta: −0.295; SE: 0.087; p: 0.001), as shown in Table 16 and was also maintained in the leave-one-out sensitivity analysis, even if a moderate instrumental heterogeneity was found (IVW, Q = 78.7, df = 51, p = 0.008; S4). Genetically predicted TPOAb showed an association with atrial fibrillation too but only using the IVW method (IWV, Beta: −1.48; SE: 0.67; p: 0.03). MR-PRESSO did not identify any outliers in the identified analysis. From the evaluation of the MR-Egger intercept, there was no clear evidence of pleiotropy, as suggested by the p-values greater than 0.05.

## Study IV. Results

### Association of IVs with the exposures

119 SNPs were used as proxies for serum calcium level, 78 for Vit-D, 5 for PTH, and 5 for FGF23. The list of the genetics instruments used is shown in Appendix, Table A4.

### Association of IVs with the outcomes

Genetically predicted serum calcium level was found to be associated to SBP (IWV: beta=0.07, SE=0.04, p=0.04) and DBP (IWV: beta=0.10, SE=0.04, p=0.007) as shown in Table 1. FGF23 resulted to be associated to lower SBP (IWV: beta=-0.11, SE=0.04, P=0.01), while genetically determined Vit-D and PTH did not show any association with BP (Table 18).

Only the association between calcium level and DBP remained significant in MR-Egger (beta(se)=0.19(0.07) p=0.003), although the other significant associations (Calcium vs SBP; FGF23 vs SBP) showed an effect size that is consistent with the one identified with IWV, not contradicting the causal effect identified by the main MR analysis [119].

In the sensitivity leave-one-out analysis, the results have been confirmed for all the significant findings. After having detected 3 outliers with MR-PRESSO test for calcium vs DBP association, as well as the presence of heterogeneity (Qp=0.0001), the analysis was repeated excluding them. Using the updated dataset, no large changes were found in comparison with the previous analysis (IWV: beta(se)=0.1(0.03); p=0.004). No outliers or heterogeneity (Qp=0.08) were detected for FGF23 vs SBP.

# DISCUSSION

We have presented four studies in which firstly we constructed an extended GRS for BP including 858 SNPs and evaluated its predictive performance in our Swedish cohorts, then we used different MR approaches to evaluate whether a causal association exists between some among the traditional risk factors including adiposity traits or hormonal factors with hypertension.

The rapid advance of Genome-Wide Association Studies (GWAS) in the last decades allowed the identification of a multitude of common genetic variants (or single nucleotide polymorphisms, SNPs) associated with phenotypes and diseases [59].

Summary statistics resulting from GWAS include information on the effect size and significance of the association of the effect allele with the trait of interest and are made available in public repositories. These are used in genetic epidemiology to improve the quantitative assessment of genetic influences on the disease [120]. Different methods have been implemented, including the construction of Genetic Risk Scores summing up the SNPs associated with a trait, and inferring the causality of an association using Mendelian Randomization (MR).

Using data from two urban-based Swedish cohorts, the Malmö Preventive Project (MPP) and the Malmö Diet and Cancer (MDC), and summary statistics from GWAS, we took advantage of these techniques to study the genetic determinants of blood pressure traits, and their role in the development of hypertension.

## Study I

In the first study, we constructed a new GRS for BP (BP-GRS858) including 858 SNPs associated with BP traits, from the most recent published meta-analyses [52,54]. We then tested the association of the BP-GRS858 with BP phenotypes and the incidence of hypertension and cardiovascular endpoints in the MPP and in the MDC. We evaluated its performance with respect to the previous score including 29 SNPs that we tested in the same cohorts in previous

work [73,99]. The BP-GRS858, as expected, was highly significantly associated with BP traits and one SD increase in age- and sex-adjusted BP-GRS858 corresponded to an increase of 3.3 mmHg for SBP and 1.7 mmHg for DBP in MDC. These associations are almost three times higher than the ones found using our previous score in which one SD increase of BP-GRS29 corresponded to 1 mmHg and 0.7 mmHg for SBP and DBP respectively [73,93]. We then investigated the role of BP-GRS858 on hypertension incidence, information not available in previous studies. Individuals in the top quartile of BP-GRS858 were two times more likely to become hypertensive with respect to those in the bottom one, independently from the other main risk factors of hypertension such as family history of hypertension, baseline BP, obesity, and diabetes. Indeed, the effect size is even higher than the one showed by BMI. This shows that BP-GRS858 could add additional predictive information regarding future risk of hypertension respect to more established clinically-used risk factors for the prediction of hypertension, including BMI and family history.

However, it has to be taken into account that the effect of BMI refers to a one time point measure, thus it could be underestimated.

Regarding family history of hypertension, it is generally true that offspring of hypertensive parents show higher risk of having high blood pressure, but not all hypertensives have a positive family history [121]. This is due to the highly polygenic architecture of hypertension. Thus, family history of hypertension could represent an incomplete or imprecise measure of the possible development of hypertension [68,122]. Indeed, it considers only the actual disease state and could not detect those individuals being at risk with no family history of the disease [68]. However, the combination of the family history with the polygenic risk evaluation could improve risk prediction [123].

Finally, in the MDC, we tested the effect of the BP-GRS858 on cardiovascular endpoints and found an association of the BP-GRS858 with total cardiovascular events, stroke, coronary artery disease, heart failure, atrial fibrillation, and total mortality, as shown also in previous studies [52].

Our results are in line with previous studies: the Airwave cohort, showed a difference of 6.0/9.3 mmHg for systolic BP between highest and lowest quintile

of a BP-GRS (267 variants) in individuals of younger than 50/older than 50 years respectively, and 3.7 and 4.6 mmHg for diastolic BP [124]. Evangelou and colleagues reported a difference of 10.4/12.9 mmHg of SBP and a difference of 6/7.5 mmHg when comparing the top and bottom quintile/decile of a sex-adjusted GRS, made up by 901 SNPs [52]. The difference in the number of included SNPs could be due to different inclusion criteria adopted during the selection of SNPs, for instance a different r^2 during the clumping stage, or during the searching for proxies SNPs. Indeed, for some SNPs we couldn't find any proxies SNPs satisfying our criteria of inclusion.

In the Airwave cohort, individuals in the top quintile of quintile of sex-adjusted BP-GRS267 showed a double risk for hypertension prevalence [124]; while in the UK Biobank (UKB) the risk of hypertension was 3.3 higher (OR 3.34; 95% CI: 3.24 to 3.45; $P < 1 \times 10^{-300}$) in the top decile compare to the bottom one [52]. We previously mentioned that alternative strategies comprise the inclusion in the score of all genotyped (and imputed) SNPs regardless of their significant association with the trait, as performed in the Finnish FinnGen study [125]. Here, a GRS of about 1 million variants was tested against BP and hypertension risk showing a difference of 14 mmHg in SBP and almost 2 times higher hypertension risk, in individuals between the top and bottom decile of the score [125].

Our findings confirm that adding novel genetic variants into a BP-GRS, despite each individual variants have a very low effect size, can explain a meaningful variation in terms of mmHg. This is relevant since is demonstrated that even a reduction of about 1-5 mmHg is associated to lower cardiovascular events [126,127]. Based on our results, we can affirm that the newer BP-GRS858 shows a relevant ability to predict individual risk. In particular, the score could be important in identifying those individuals that have a higher risk to become hypertensive and more likely to develop CVD due to their genetic predisposition [93]. Those individuals could potentially benefit from early identification of the risk, even during young adulthood or adolescence, by implementing screening and healthy behavior [93]. However, the translation into a clinical context should take into consideration ethical and social concerns [93,128,129].

### Strengths and limitations

One of the strengths of the present work is the population-based cohort data, in which we could explore different outcomes including time-varying one after a quite long follow-up time. This also extends to the possibility we had to adjust for various cofounders and to evaluate the effect of the GRS in relation to other risk factors. Another strength is that we included in the score SNPs and weights reported by the largest meta-analysis available.

Our study has limitations: the generalizability to other ethnicities or age groups except Swedish middle-aged individuals is not known. We could use only APOA and APOB plasma levels as substitutes for LDL and HDL-cholesterol in the risk models. We used a GRS based on a GWAS-significant p-value threshold, so it is likely that other SNPs associated to BP related traits could have been included using different p-values thresholds or rare variants (<1% MAF), regardless even of the specific association with BP/hypertension could give even better results, as shown in other studies [45,125].

## Study II

The main finding of study II is that genetically proxied measures of adiposity, condensed in GRSs, are associated with BP-related traits but with different magnitude. In particular, the GRS-BMI565 and the GRS-WHR324 were potentially causally associated with all BP-related traits measured at baseline but the WHR showed a higher estimate size. At follow-up, the genetically predicted association of WHR with BP tends to be attenuated and is no longer significant, contrary to BMI [94]. About more complex measures of adiposity such as body fat and visceral fat, their genetic component seems to be more limited in determining BP but still significant when hypertension prevalence is evaluated, at least in the MDC [94].

It is a fact that some of these discrepancies can be due to the relative weakness of the instrumental variables that have been used, making some GRS being

stronger than others. However, it is likely that our study can give some clues to understanding more deeply the biology of the well-known influence of body fat on BP. In fact, our data may indicate that the effect of BMI is important but with low magnitude throughout midlife to old age (the average age in the MPP was 45±7.4 yrs and in the MDC is 58±7.6 yrs) but also in older ones (the average age in MPP at reinvestigation is 68±5.8 yrs) [94]. Instead, the contribution to high BP of genetically proxied abdominal fat, represented by WHR, could seem much higher in midlife, overcoming BMI, than later. A stratification analysis according to age in the MDC, showed the GRS-WHR324 to be associated more strongly with prevalence of hypertension in older individuals than in the younger ones. This could suggest a survival bias for the analysis in MPP where participants with especially deleterious GRS-WHR324 could have died before the examination (see also Figure 11) [94].

Our results are in line with two recent studies but with some differences [130,131]. In a MR analysis in the UKB, including ~400,000 individuals, a GRS-BMI was associated to BP (beta [95%CI]: 0.19 [0.18,0.21] for SBP and 0.27 [0.26,0.29] for DBP) and to hypertension prevalence (OR [95%CI]: 1.10 [1.07,1.12]) of the same order of magnitude of the results we found in the MDC [130]. Also, the association of the genetic component of body fat and VAT with hypertension, that we found in the MDC, is consistent with a previous MR performed in UK Biobank [105,131]; despite we used BMI instead of VAT as an exposure trait [94.]

Even if the association of the instrumental variable GRS-WHR with BP and hypertension is reported in a previous study[130], the magnitude of the association is much higher in our samples [94].

The reason for such a difference in magnitude is not clear, it could be due to differences in ages between the two cohorts (slightly lower in the UKB than in the MDC), ethnicity (more homogeneous in the MDC), distribution of sex (higher prevalence of females in the MDC), and adiposity and BP traits (obesity is more prevalent in the UKB but hypertension is more prevalent in the MDC) [94].

The debate of which adiposity measure could be a better predictor of blood pressure or hypertension is still open, even in nongenetic studies. Several studies compare BMI, waist, WHR, waist-to-height ratio (another proxy for central

obesity), and VAT showing waist-to-height and waist circumference better predicting CV events and hypertension respect to BMI [132,133]. Others [134–136] show that BMI is more strongly associated with incidence of hypertension with respect to WHR [94]. Then, a study in young adults (18-36 years) shows that BMI has an equal or better ability to predict adult hypertension respect to WHR and other adiposity measures [94,137]. Other well-powered analyses showed that either VAT or BF are strongly associated with BP traits [138] and future risk of hypertension [139,140]. One issue when studying adiposity measures, is that they are highly correlated with each other, and they associate with different levels of measurement error. This could affect the strength of the observed associations [94,138].

Pathophysiological mechanisms potentially linking obesity to high BP include arterial stiffness (especially in older age), metabolic factors, endothelial and vascular dysfunction, the hyperactivation of the sympathetic nervous and the renin-angiotensin-aldosterone systems, sodium retention with a shift of the well-known pressure-natriuresis curve toward higher BP levels, and/or other renal dysfunctions [94,141,142]. VAT seems to be a pivotal player, as being detected as a site becoming resistant to insulin and leptin and to altered molucoles and hormones secretion including adiponectin, leptin, resistin, TNF-a, and IL-6 [94,143,144].

From our results, we could speculate that adipokines produced in visceral fat and insulin resistance could be more relevant in affecting BP and for the development of hypertension in midlife, while the total fat is important through the entire life and remain determinant when arterial stiffness becomes prominent [94].

In previous MR studies, BMI was causally linked to insulin and inflammation markers, such as IL-6 that could be on turn associated with hypertension development [145].

Recently, it was shown that SNPs related to VAT are strongly associated also with hypertension, in line with our study[94] , suggesting a relevant role of visceral fat in high BP [94].

## Strengths and limitations

Among the strengths of this study, the fact that we used the more recent validated GRSs associated with adiposity traits, the use of MR design that can avoid confounding and reverse causality; and the results were supported in sensitivity analyses that are more robust to the presence of variants with pleiotropic associations [37,94,146].

Our study has some limitations. i) There is overlap between the MDC and MPP samples so that, even if the two studies had their own examinations at different time points, they cannot be considered as a real replication. ii) Some GRSs were weaker instrumental variables than others, especially when we used proxy traits as exposure[94]. Thus, some of the differences in the associations we found between adiposity-related GRSs and BP could be due to the fact that the GRS-BMI565 and the GRS-WHR324 were better instrumental variables than the GRS-BF81 and the GRS-VAT208 [94]. Indeed the GRS-BF81 and GRS-VAT208 were regressed on BMI in the MPP study, necessarily dampening their predictive value[94]. iii) we have different statistical power for hypertension prevalence and incidence in the two cohort. iv) concerning the hypertension incidence analysis, this is restricted to people not having hypertension at baseline and could be then less prone to develop hypertension [94].

v) pleiotropy could be present among the included variants, making hard to identify a clear dissection between all the observed adiposity-related traits. Since the aim of the present study was to evaluate the causal effect of the adiposity traits described by all available genetic variants, which could serve as best proxies for the exposures, we decided to not include any sensitivity analysis selecting only those variants that could be associated with more than one adiposity traits. However, this could indeed be included in future studies to exploit deeply the findings from the present work. All the above-mentioned points, that in some ways could be considered an intrinsic limitation of the usage of genetic variants as instrumental variable [147], contribute to reducing the strength of the causal inference of our analysis [94].

## Study III

In this two-sample summary-level MR study, we evaluated the causal association of thyroid function with blood pressure traits and cardiovascular diseases. SNPs associated with TSH, FT4, hyperthyroidism, hypothyroidism, and TPOAb identified from most recent GWAS studies [110,111] were used as instrumental variables. Genetically predicted TSH showed an inverse causal relationship with systolic BP. The link between a decreased level of TSH, of which a decrease to under the normal range is usually associated with hyperthyroidism, and high systolic BP has been largely reported in clinical studies that have found systolic, but not diastolic BP to be higher in patients with hyperthyroidism [95,148]. This is also demonstrated by the beneficial effects that pharmacological or surgical treatment of hyperthyroidism has on systolic blood pressure. It has been shown that after the normalization of the thyroid hormones a decrease up to almost 5 mmHg is observed [149,150]. In a two-sample MR study, which used the same instrumental variables we used in our study, an association with genetically determined TSH levels and pulse pressure was identified, as well as with systolic BP, but after excluding a set of genetic variants [95,151]. Despite the consistency of the results with the one shown in the literature, our association remained significant only at IVW analysis, and was not significant at Bonferroni multiple testing correction. We found a nonsignificant MR-Egger causal estimate and an intercept which differed from zero, even if it was not significant, (beta: −0.05; p: 0.39), thus it can be suggestive of pleiotropy [95,152]. Genetically predicted hyperthyroidism, despite not reaching statistical significance, showed a significant association with SBP for a SNP, *rs12138950* in the *CAPZB* gene that is in high linkage disequilibrium (LD, r2 > 0.9) with a SNP among those used in the TSH instrumental variables (*rs10917469*) [94]. CAPZB is mapped in chromosome 1 and encodes for capping actin protein of muscle Z-line subunit beta which is linked to the response to elevated platelet cytosolic Ca2+ and MAPK-ERK pathways (GeneCards identifier: GC01M019339). We found the associations between TSH and TPOAb and the presence of atrial fibrillation to be statistically significant for all the MR estimators (IVW, MR-Egger and weighted median). This is of clinical relevance since the link between atrial fibrillation and thyroid function has been

largely described. Indeed, it was reported that atrial fibrillation is reverted in 60% to 75% of patients after they receive antithyroid treatment [94,153]. A large number of Mendelian randomization studies, involving large-scale genetic consortia [154–156] and longitudinal studies [153,157,158], reported the associations between TSH or hyperthyroidism with atrial fibrillation. A low TSH level could affect atrial fibrillation by increasing left ventricular mass and diastolic dysfunction [95,155,159]. Genetically approximated TPOAb levels were linked to a decreased risk of atrial fibrillation. Among the four SNPs included in the analysis, rs2010099 was the one showing a clearer association with the outcome. It is located in the proximity of the gene KALRN (chromosome 3q21.2) that encodes for Kalirin, a guanine nucleotide exchange factor (GEF) in the Rho guanosine triphosphatase (GTPase) signalling pathway, involved in smooth muscle cell signalling and migration [95,160]. It has been reported being highly expressed in the left atrium, mitral valve, right atrium and ventricle, and the tricuspid valve and aorta (ENSG00000160145) [95]. This gene was found to be associated with megakaryopoiesis and platelet formation and has also been identified as a target gene for coronary artery disease, diabetes mellitus, coronary calcification, and neointimal hyperplasia [95,111,160–162].

### Strengths and Limitations

A strength of this work is the use of the MR method to infer the causal role of thyroid function on the cardiovascular outcome, which minimize the effect of confounding factors. Moreover, the use of a two-sample MR, in which genetic instrument–exposure and genetic instrument–outcome associations are evaluated in two independent cohorts, minimize the bias introduced by weak instruments [95,163]. Secondly, using summary estimations from large-scale genomic consortia, it is possible to avoid power limitations. Another strength is the use of genetic variants associated with specific thyroid hormones could shed light on how each affects specific outcomes.

Among the limitations of this work there is the possible presence of horizontal pleiotropy, due to the association of SNPs with parallel pathways, as suggested from the sensitivity analysis (MR-Egger). Further analyses, including multivariable Mendelian randomization, would be needed to clarify which other

phenotypes interact in the associations [95]. These could be clarified if even other factors, for example height, can be implied in the causal association [95,164].

## Study IV

The present work investigated whether a causal relationship exists between calcium, vitamin D (Vit-D), parathyroid hormone (PTH), and fibroblast growth factor 23 (FGF23) plasma concentration with BP using a Two-Sample MR approach. Vit-D, PTH and FGF23 are calciotropic hormones involved in maintaining calcium (and phosphate) homeostasis, through the regulation of uptake and retention of serum calcium concentration, through the kidneys, gut, and bones [96,165].

Genetically-predicted serum calcium level was associated with increased SBP and DBP. These results are in line with several observational studies [35,166–168]. Serum calcium could affect BP by acting via i) stimulation of the renin-angiotensin system; ii) the influence of the vascular smooth cell contractility and consequently the peripheral vascular resistance; IV) sympathetic stimulation of the heart, kidneys, and blood vessels [35,96,168].

There are no previous MR studies investigating the causal relationship between serum calcium and BP. A recent Phenome-Wide (PheWas) based Mendelian Randomization showed a direct association of calcium with hypertension in the UKB [169]. Moreover, high calcium has been linked to different cardiometabolic and neurological outcomes, in MR studies [96,170].

Genetically predicted Vit-D did not show a significant association with BP. The same null finding was found in a two-sample MR that used the same SNPs as in our work [115]. Another MR, including four SNPs, reported a protective effect on BP, while *Kunutsor and colleagues*, using the same SNPs, could not detect any clear effect [96,171,172]. In the same study a pooled meta-analysis of RCTs was performed, which evaluated the effect of vitamin D intervention on BP and no evidence of a significant effect was found. However, a reduction in DBP was detected in participants with pre-existing cardiometabolic disease [171]. An umbrella review summarized the effect of vitamin D supplementation in RCT

and genetically predicted vitamin D levels, estimated in MR, on different health outcomes[96]. A beneficial effect of vitamin D intervention on many cardiometabolic outcomes was reported but hypertension was not among them[173]. The evaluation of a causal role of vitamin D on cardiometabolic outcomes encounter some difficulties, due to variability and the non-linearity nature of the association between vitamin D and the outcomes [173]. Additionally, recent MR studies demonstrated a central role of obesity as a mediator in vitamin D associations [96,174].

No association was found even between genetically predicted PTH and the explored outcomes. We cannot compare with other results, since this is, to our knowledge, the first MR exploring this relationship. From the literature, there is a wide consensus that elevated PTH is associated with higher BP levels [36,175,176], but the causal link, and the independency of PTH from calcium level are not clarified [96,176–178].

A genetically predicted lower level of FGF23 was found to be associated with increased systolic BP, but it was not significant at MR-Egger analysis. Hoever this shown a direction and a magnitude of the effect size consistent with the IVW. From the literature the role of FGF23 in BP rising is not. Physiologically FGF23 could act on hypertension through the activation of the renin-angiotensin-aldosterone system (RAAS) directly, or indirectly mediated by mineral concentrations of phosphate and calcium [96,179].

Longitudinal and observational studies have shown a higher level of FGF23 associated with a higher risk of hypertension incidence [32,180] or have reported higher FGF23 concentration in hypertensive individuals [181]. However, it is not clear whether this association could be mediated by unmeasured metabolic cofounders for example the ones involved in the RAAS system like serum renin, aldosterone, or urine sodium levels [96,182]. Only one MR study performed the same analysis we did in our study, and it reported neither an association with BP nor with markers of renal function. The difference in the results because we used BP values after adjustment for age, sex, and antihypertensive medications, moreover we included an additional SNP[96]. In the same study, the authors

showed FGF23 to be inversely associated with coronary artery disease (CAD) and myocardial infarction, a direction consistent with our results [96,183].
There are numerous studies reporting an association between high level of FGF23 with adverse outcomes in patients with chronic kidney disease (CKD) and end-stage renal disease (ESRD) [184], supporting a central role of FGF23 in the regulation of phosphate levels. FGF23 is then considered a potential early biomarker for the disease, in which an increased level in response to a decrease in glomerular filtration rate (GFR) has been associated with vascular calcification and cardiovascular diseases [96,179]. However, is not clear whether it should be considered a cause or a consequence of the increased level of phosphate in renal disease [179]. A low level of FGF23 could result in high phosphate and calcium level, as also suggested by $FGF23^{-/-}$ knock-out models [185], and could represent a risk factor for hypertension and cardiovascular disease [96].

## Strengths and limitations

Among the strengths of the present study is the use of the MR approach, which allows inferring causality of an association, minimizing the effect of confounding factors. The use of a Two-Sample MR setting could be an advantage in the evaluation of a causal relation, as explained previously in the text. Moreover, this is the first MR which investigates the role of serum calcium and PTH in BP traits.
There are some limitations. First, we used genetic instruments which can explain only a small amount of the variation of the exposures: 5.8% for calcium; 5.7% for Vit-D, 4.2% for PTH; 3% for FGF23. This could cause a false-negative result. In the future could be useful to update the analysis whenever more genetic variants are reported in GWAS. As previously mentioned, the Two-Sample MR has limitations, for example, some population characteristics that could be different between the two groups. Thirdly, we could not provide a triangulation of causal inference with observational data using the same sample.
Finally, pleiotropy could be present since we are dealing with correlated metabolites. The present study should be followed by further investigation

including focusing on target genes that could have clinical relevance, using a bi-directional MR, rare genetic variants or focusing on drug target genes .

## Final Remarks

Throughout this thesis, I have explored how the polygenetic component of blood pressure, defined by a multitude of single nucleotide polymorphisms, can be used by different genetic epidemiologic strategies to identify individuals at high risk to develop hypertension and to validate some possible causal associations with known or less known risk factors. The GRS-858 was strongly associated with BP traits, hypertension, and CVD, independently and with comparable effect sizes as compared to traditional risk factors. This would render the score potentially useful for clinical practice since the genetic information is available since childhood and the test could be taken once at a relatively low cost. However, before this can be applicable, technical, and ethical issues should be solved and the relative benefit through the life span should be demonstrated by ad hoc randomized controlled trials (180).

Then, I showed how MR can be relevant in pinpointing some relevant associations that could provide a deeper understanding of the specific pathways and genes involved in these causal links.

These works are open to future investigation to fill some gaps in the field.

The information derived from the common variants included in the score could be integrated with rare variants detected through Whole Exome or Genome Sequencing, to improve knowledge of penetrance of high-risk variants; or combined with gene-environmental interaction, in which traditional risk factors are not considered independent [186].

There are also several extensions to MR that could be adopted, including multivariable, network, non-linear, or drug-target genes MR [187,188].

In conclusion, the genetic association produced by genetic epidemiology serves as precious information to elucidate complex trait pathways and networks of pathophysiological mechanisms. Since the genetic background is available since birth, it could contribute to predicting individual risk and identifying new druggable targets and will promote progression towards a personalized prevention and treatment approach.

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# TABLES

Table *2* General Characteristic of the populations, MPP and MDC [93]

| | MPP (n=9,367) | MDC (n=29,295) |
|---|---|---|
| | *Mean±SD/%* | *Mean±SD/%* |
| Age, yrs | 46.8±6.28 | 58.0±7.61 |
| Sex, % Male | 55.4 | 39.7 |
| BMI, kg/m$^2$ | 24.3±3.4 | 25.8±4.0 |
| Waist to Hip Ratio | 0.92±0.09 | 0.86±0.15 |
| BodyFat, % | - | 26.8±7.0 |
| SBP, mmHg | 126.5±14.2 | 141.1±20.0 |
| DBP, mmHg | 85.2±8.7 | 85.6±10.4 |
| Follow-up SBP, mmHg | 144.9±20.0 | - |
| Follow-up DBP, mmHg | 83.6±10.5 | - |
| Heart rate, bpm | 68.2±9.4 | - |
| Diabetes at baseline, % | 3.8 | 4.4 |
| Smoke, % smokers | 32.7 | 26.5 |
| Hypercholesterolemia, % over 200 mg/dl | 66.3 | - |
| HDL cholesterol, mmoL/L | 1.4±0.43 | - |
| Hypertensive, % | 34.2 | 61.3 |
| Follow-up Hypertensive | 63.3 | - |
| Civil state, % Married/cohabiting | 32.7 | 61.1 |
| Physical Activity, % Prevalent sedentary habits | 32.2 | - |
| GFR, mL/min/1.73m$^2$ | 85.3±17.4 | - |
| Apo A, mg/dl | - | 56.8±28.2 |
| Apo B, mg/dl | - | 107.1±26.1 |

*Legend: APO A: apolipoprotein A; APO B: apolipoprotein B; BMI: body mass index; DBP: diastolic blood pressure; GFR: estimate glomerular filtration rate; HDL: high density lipoprotein; MDC: Malmö Diet and Cancer; MPP: Malmö Preventive Project; SBP: systolic blood pressure; SD: standard deviation*

Table *3* Association of BP-GRS858 and BP traits in MDC [93]

| ***SBP,mmHg*** | | | | ***DBP, mmHg*** | | |
|---|---|---|---|---|---|---|
| *Model A ($r^2$=0.24)** | | | | *Model A ($r^2$=0.14)** | | |
| | *Beta (95%CI)* | *p-value* | *partial $r^2$* | *Beta (95%CI)* | *p-value* | *partial $r^2$* |
| **Age, ys** | 1.05 (1.02-1.08) | $1.00x10^{-300}$ | 0.41 | 0.17 (0.16-0.19) | $7.02x10^{-109}$ | 0.14 |
| **Sex** | -2.51 (-2.94-(-2.07)) | $1.19x10^{-29}$ | -0.07 | -3.43 (-3.68-(-3.21) | $2.39x10^{-176}$ | -0.02 |
| **BMI†** | 3.44 (3.22-3.66) | $1.30x10^{-209}$ | 0.19 | 0.22 (2.19-2.41) | $1.00x10^{-300}$ | 0.23 |
| **BP-GRS858†** | 3.26 (3.05-3.47) | $7.46x10^{-200}$ | 0.18 | 1.74 (1.63-1.86) | $5.07x10^{-206}$ | 0.18 |
| *Model B ($r^2$=0.24)** | | | | *Model B ($r^2$=0.15)** | | |
| | *Beta (95%CI)* | *p-value* | *partial $r^2$* | *Beta (95%CI)* | *p-value* | *partial $r^2$* |
| **Age, ys** | 0.17 (0.16-0.19) | $7.02x10^{-109}$ | 0.14 | 0.17 (0.16-0.19) | $7.02x10^{-109}$ | 0.14 |
| **Sex** | -3.44 (-3.68-(-3.21) | $2.39x10^{-176}$ | -0.18 | -3.44 (-3.68-(-3.21) | $2.39x10^{-176}$ | -0.18 |
| **BMI†** | 2.32 (2.20-2.43) | $1.00x10^{-300}$ | 0.23 | 2.32 (2.20-2.43) | $1.00x10^{-300}$ | 0.23 |
| **BP-GRS29†** | 0.24 (0.12-0.37) | $8.44x10^{-5}$ | 0.02 | 0.24 (0.12-0.37) | $8.44x10^{-5}$ | 0.02 |
| **BP-GRS858†** | 1.65 (1.53-1.77) | $1.91x10^{-154}$ | 0.16 | 1.65 (1.53-1.77) | $1.91x10^{-154}$ | 0.16 |

*Model A: age, sex, BMI; model B: as model A plus BP-GRS$_{29}$. †Expressed for standard deviation unit increment. Legend: BMI: body mass index; BP-GRS$_{29}$: blood pressure genetic risk score made up by 29 SNPs; BP-GRS$_{858}$: blood pressure genetic risk score made up by 858 SNPS; DBP: diastolic blood pressure; $r^2$: r-squared SBP; systolic blood pressure.*

Table 4. Association of BP-GRS858 and BP traits in MPP [93]

| ***SBP, mmHg*** | | | | ***DBP, mmHg*** | | |
|---|---|---|---|---|---|---|
| *Model A ($r^2$=0.15)** | | | | *Model A ($r^2$=0.15)** | | |
| | *Beta (95%CI)* | *p-value* | *partial $r^2$* | *Beta (95%CI)* | *p-value* | *partial $r^2$* |
| **Age, ys** | 0.48 (0.42-0.54) | $1.25x10^{-88}$ | 0.21 | 0.229 (0.196-0.262) | $8.80x10^{-42}$ | 0.14 |
| **Sex** | 3.26 (2.59-3.92) | $6.38x10^{-16}$ | 0.08 | 3.62 (3.21-4.04) | $7.23x10^{-64}$ | 0.18 |
| **BMI†** | 1.24 (1.15-1.33) | $2.75x10^{-144}$ | 0.26 | 0.74 (0.68-0.80) | $1.60x10^{-145}$ | 0.26 |
| **BP-GRS858†** | 2.61 (2.33-2.90) | $1.14x10^{-68}$ | 0.18 | 1.72 (1.54-1.90) | $6.76x10^{-77}$ | 0.19 |
| *Model B ($r^2$=0.15)** | | | | *Model B ($r^2$=0.15)** | | |
| | *Beta (95%CI)* | *p-value* | *partial $r^2$* | *Beta (95%CI)* | *p-value* | *partial $r^2$* |
| **Age, ys** | 0.55 (0.50-0.61) | $6.28x10^{-89}$ | 0.21 | 0.230 (0.20-0.26) | $5.25x10^{-42}$ | 0.14 |
| **Sex** | 2.79 (2.11-3.47) | $8.94x10^{-16}$ | 0.08 | 3.61 (3.20-4.03) | $1.47x10^{-63}$ | 0.18 |
| **BMI†** | 1.20 (1.11-1.29) | $2.54x10^{-144}$ | 0.26 | 0.74 (0.68-0.79) | $1.41x10^{-145}$ | 0.26 |
| **BP-GRS29†** | 0.42 (0.11-0.72) | 0.01 | 0.03 | 0.29 (0.10-0.47) | 0.003 | 0.03 |
| **BP-GRS858†** | 2.53 (2.23-2.84) | $5.36x10^{-60}$ | 0.17 | 1.65 (1.46-1.83) | $6.52x10^{-67}$ | 0.18 |

*Model A: age, sex, BMI; model B: as model A plus $BP\text{-}GRS_{29}$. †Expressed for standard deviation unit increment. Legend: BMI: body mass index; $BP\text{-}GRS_{29}$: blood pressure genetic risk score made up by 29 SNPs; $BP\text{-}GRS_{858}$: blood pressure genetic risk score made up by 858 SNPS; DBP: diastolic blood pressure; $r^2$: r-squared SBP; systolic blood pressure.*

Table 5. Association of BP-GRS858 with Hypertension prevalence in MPP and MDC [93]

| **Prevalence of Hypertension in MPP** | | | | | | |
|---|---|---|---|---|---|---|
| | **Model A* (n=9,156)** | | **Model B* (n=8,804)** | | **Model C* (n=8,625)** | |
| | *OR (95% CI)* | *p-value for trend* | *OR (95% CI)* | *p-value for trend* | *OR (95% CI)* | *p-value for trend* |
| **BP-GRS858** For 1 SD increase | 1.35 (1.29-1.41) | **$1.28x10^{-37}$** | 1.36 (1.30-1.43) | **$5.03x10^{-34}$** | 1.21 (1.13-1.29) | **$1.64x10^{-8}$** |
| **BP-GRS858** $4^{th}$ vs $1^{st}$ quartile | 2.14 (1.88-2.44) | **$1.91x10^{-31}$** | 2.21 (1.92-2.54) | **$6.63x10^{-30}$** | 1.58 (1.32-1.90) | **$5.20x10^{-7}$** |
| **BP-GRS858** $10^{th}$ vs $1^{st}$ decile | 2.95 (2.39-3.64) | **$1.04x10^{-32}$** | 2.90 (2.31-3.63) | **$1.48x10^{-29}$** | 1.81 (1.35-2.42) | **$6.72x10^{-6}$** |
| **Prevalence of hypertension MDC** | | | | | | |
| | **Model A* (n= 29,262)** | | **Model B* (n= 26,578)** | | **Model C* (n= 26,562)** | |
| | *OR (95% CI)* | *p-value for trend* | *OR (95% CI)* | *p-value for trend* | *OR (95% CI)* | *p-value for trend* |
| **BP-GRS858** For 1 SD increase | 1.45 (1.41-1.49) | **$1.2x10^{-171}$** | 1.47 (1.43-1.52) | **$3.2x10^{-151}$** | 1.14 (1.09-1.19) | **$1.0x10^{-7}$** |
| **BP-GRS858** $4^{th}$ vs $1^{st}$ quartile | 2.78 (2.56-3.01) | **$6.4x10^{-150}$** | 2.88 (2.64-3.14) | **$1.55x10^{-138}$** | 1.42 (1.22-1.64) | **$2.47x10^{-5}$** |
| **BP-GRS858** $10^{th}$ vs $1^{st}$ decile | 3.72 (3.32-4.14) | **$4.2x10^{-143}$** | 3.89 (3.45-4.39) | **$3.27x10^{-145}$** | 1.67 (1.36-2.04) | **$2.50x10^{-5}$** |

** Model A: age, sex, age2, age x sex, heart rate, follow-up time; Model B: as model 1 plus body mass index (BMI), diabetes, hypercholesterolemia, hypertriglyceridemia. Model C: as model 2 plus systolic or diastolic blood pressure, glomerular filtration rate (GFR), physical activity level and civil status*
*Legend: BP-GRS29: blood pressure genetic risk score made up by 29 SNPs; BP-GRS858: blood pressure genetic risk score made up by 858 SNPS; OR: Odd Ratio*

Table 6 Association of BP-GRS858 with the incidence of hypertension in MPP [93]

| **Incidence of hypertension** | | | | | | |
|---|---|---|---|---|---|---|
| | Model A* (n=5,971) | | Model B* (n=5,819) | | Model C* (n=5,639) | |
| | OR (95% CI) | p-value† | OR (95% CI) | p-value† | OR (95% CI) | p-value† |
| BP-GRS858‡ | 1.31 (1.24-1.38) | 3.7x10-22 | 1.32 (1.25-1.40) | 3.14x10-22 | 1.26 (1.19-1.34) | 1.09x10-14 |
| 4th vs 1st quartile (68.8% vs 53.1% HT) | 2.05 (1.75-2.39) | 1.4x10-21 | 2.09 (1.78-2.46) | 2.24x10-21 | 1.90 (1.60-2.25) | 1.36x10-14 |
| 10th vs 1st decile (68.6 vs 52.1% HT) | 2.13 (1.67-2.71) | 2.2x10-18 | 2.19- (1.71-2.81) | 3.84x10-18 | 1.83 (1.40-2.38) | 1.63x10-11 |

** Model A: age, sex, age2, age x sex, heart rate, follow-up time; Model B: as model 1 plus body mass index (BMI), diabetes, hypercholesterolemia, hypertriglyceridemia, high density lipoprotein (HDL), smoking status, family history of hypertension; Model C: as model 2 plus systolic or diastolic blood pressure, glomerular filtration rate (GFR), physical activity level and civil status. †p-value for trend. ‡BP-GRS858 is expressed as continuous variable for standard deviation increment. Legend: OR: Odd Ratio*

Table 7 Contribution that each variable included in model C gives to the incidence of hypertension in the MPP [93]

| | **OR** | **95%CI** | **p-value** |
|---|---|---|---|
| Age, ys | 1.15 | 1.02-1.29 | 0.022 |
| Sex | 8.97 | 2.91-27.68 | 0.0001 |
| BP-GRS858 | | | |
| 2nd vs 1st quartile | 1.28 | 1.10-1.50 | 0.001 |
| 3rd vs 1st quartile | 1.67 | 1.42-1.96 | 3.75x10-10 |
| 4th vs 1st quartile | 1.94 | 1.64-2.29 | 1.07x10-14 |
| BMI | | | |
| 2nd vs 1st quartile | 1.31 | 1.13-1.53 | 0.001 |
| 3rd vs 1st quartile | 1.38 | 1.17-1.82 | 0.0001 |
| 4th vs 1st quartile | 1.51 | 1.25-1.82 | 1.32x10-5 |
| SBP, mmHg | | | |
| 2nd vs 1st quartile | 1.90 | 1.67-2.18 | 2.55x10-21 |
| 3rd vs 1st quartile | 3.28 | 2.78-3.88 | 1.61x10-44 |
| 4th vs 1st quartile | 5.68 | 3.76-8.58 | 1.71x10-16 |
| Diabetes | 1.63 | 1.06-2.51 | 0.03 |
| Family history of hypertension | 1.19 | 1.05-1.36 | 0.01 |
| Smoking status | 1.66 | 1.46-1.88 | 6.01x10-15 |
| Heart rate, bpm | 1.01 | 1.00-1.02 | 0.02 |
| Follow-up time | 1.12 | 1.10-1.15 | 5.04x10-19 |
| Hypercholesterolemia | 1.07 | .94-1.21 | n.s. |
| Hypertrygliceridemia | 1.02 | .84-1.23 | n.s. |
| GFR, mL/min/1.73m2 | 1.00 | 1.00-1.00 | n.s. |
| HDL cholesterol, mmoL/L | 0.69 | 0.59-0.80 | 6.16x10-7 |
| Level of physical activity | 1.04 | 0.90-1.19 | 0.62 |
| Civil State | 0.97 | 0.85-1.11 | n.s. |

*Legend: BMI: body mass index; BP-GRS858: Genetic risk score for blood pressure traits made up by 858 SNPs; GFR: estimate glomerular filtration rate; HDL: high density lipoprotein; OR: Odd Ratio; SBP: systolic blood*

Table 8 Association of BP-GRS858 with cardiovascular endpoints. [93]

| | Model A | | Model B | | Model C | |
|---|---|---|---|---|---|---|
| | *HR (95%CI)* | *p-value** | *HR; 95%CI* | *p-value** | *HR; 95%CI* | *p-value** |
| **$BP\text{-}GRS_{858}$ (for 1 SD increase)** | | | | | | |
| CVD | 1.12 (1.10-1.15) | **$1.9x10^{-18}$** | 1.11 (1.08-1.14) | **$6.6x10^{-14}$** | 1.08 (1.05-1.11) | **$1.0x10^{-7}$** |
| Stroke | 1.14 (1.10-1.19) | **$7.5x10^{-14}$** | 1.13 (1.09-1.18) | **$3.3x10^{-11}$** | 1.10 (1.061.14) | **$1.2x10^{-6}$** |
| Coronary Artery Disease | 1.13 (1.10-1.17) | **$2.3x10^{-15}$** | 1.12 (1.08-1.15) | **$3.2x10^{-11}$** | 1.09 (1.05-1.12) | **$7.6x10^{-7}$** |
| Heart Failure | 1.13 (1.08-1.19) | **$3.2x10^{-5}$** | 1.13 (1.08-1.19) | **$4.1x10^{-7}$** | 1.09 (1.04-1.15) | **0.0005** |
| Atrial Fibrillation | 1.06 (1.03-1.09) | **$3.2x10^{-5}$** | 1.06 (1.03-1.09) | **0.0001** | 1.03 (1.003-1.065) | **0.03** |
| Total mortality | 1.05 (1.03-1.07) | **$4.0E^{-6}$** | 1.04 (1.02-1.07) | **$7.8E^{-5}$** | 1.02 (1.00-1.04) | **0.046** |
| **$4^{th}$ vs $1^{st}$ quartile of $BP\text{-}GRS_{858}$** | | | | | | |
| CVD | 1.42 (1.31-1.54) | **$2.0x10^{-16}$** | 1.38 (1.27-1.50) | **$2.8x10^{-12}$** | 1.27 (1.17-1.39) | **$5.2x10^{-7}$** |
| Stroke | 1.44 (1.29-1.60) | **$1.1x10^{-9}$** | 1.41 (1.26-1.58) | **$3.0x10^{-9}$** | 1.29 (1.15-1.45) | **$1.4x10^{-5}$** |
| Coronary Artery Disease | 1.46 (1.33-1.60) | **$2.0x10^{-13}$** | 1.40 (1.27-1.54) | **$3.5x10^{-11}$** | 1.30 (1.17-1.43) | **$3.5x10^{-7}$** |
| Heart Failure | 1.37 (1.19-1.57) | **$1.1x10^{-5}$** | 1.37 (1.19-1.59) | **0.0002** | 1.24 (1.070-1.44) | **0.031** |
| Atrial Fibrillation | 1.15 (1.05-1.25) | **0.002** | 1.13 (1.04-1.24) | **0.006** | 1.06 (0.968-1.16) | **n.s** |
| Total mortality | 1.12 (1.06-1.19) | **0.0002** | 1.10 (1.03-1.17) | **0.007** | 1.04 (0.978-1.11) | **ns** |
| **$10^{th}$ vs $1^{st}$ quartile of $BP\text{-}GRS_{858}$** | | | | | | |
| CVD | 1.48 (1.33-1.65) | **$1.3x10^{-13}$** | 1.41 (1.26-1.59) | **$3.6x10^{-10}$** | 1.28 (1.14-1.44) | **$1.8x10^{-5}$** |
| Stroke | 1.57 (1.36-1.82) | **$3.2x10^{-8}$** | 1.52 (1.30-1.77) | **$1.8x10^{-7}$** | 1.35 (1.16-1.58) | **0.0002** |
| Coronary Artery Disease | 1.56 (1.369-1.77) | **$1.3x10^{-11}$** | 1.48 (1.30-1.70) | **$1.1x10^{-8}$** | 1.35 (1.18-1.54) | **$1.6x10^{-5}$** |
| Heart Failure | 1.53 (1.27-1.86) | **0.002** | 1.57 (1.28-1.92) | **0.006** | 1.38 (1.12-1.69) | **n.s** |
| Atrial Fibrillation | 1.21 (1.08-1.37) | **0.001** | 1.23 (1.09-1.39) | **0.018** | 1.14 (1.04-1.28) | **n.s.** |
| Total mortality | 1.13 (1.37-1.22) | **0.005** | 1.10 (1.01-1.20) | **0.034** | 1.02 (0.94-1.12) | **n.s.** |

*Legend: *:p-value for trend. CVD: cardiovascular diseases; CI: confidence interval; HR: hazard ratio*

## Study II

Table 9 Studies from which the summary statistics of adiposity traits were retrieved. [94]

| ***GRS*** | ***TRAIT*** | ***STUDY*** | ***SAMPLE SIZE*** | ***ETHNIC GROUP*** |
|---|---|---|---|---|
| GRS-$BMI_{565}$ | Body mass index | Pulit et al 2019 | n= 694,649 (UKBiobank: n=484,563, GIANT: n=210,086) | European |
| GRS-$WHR_{324}$ | Waist to hip ratio | Pulit et al 2019 | 694,649 (UKBiobank, n=484,563+ GIANT, n=210,086) | European |
| GRS-$VAT_{208}$ | Predicted visceral adiposity trait (VAT) | Karlsson et al 2019 | UKBiobank, n=325,153 | White and British ancestry |
| GRS-$BF_{81}$ | Body fat mass; measured with bio-electrical impedance (BIA) and dual energy X-ray absorptiometry (DXA | Rask-Andersen et al 2019 | UKBiobank, n= 362,499 | White and British ancestry of UKBB |

*Legend: BF, Body Fat; BMI, Body Mass Index; GRS-$VAT_{208}$, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-$BF_{81}$, Genetic risk score for Body Fat based on 81 SNPs; GRS-$WHR_{324}$ Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-$BMI_{565}$, Genetic Risk Score for Body Mass Index based on 565 SNPs; WHR, Waist Hip Ratio*

Table 10 Association of IVs with exposures [93]

| | MPP | | | | MDC | | | |
|---|---|---|---|---|---|---|---|---|
| | *Beta (95%CI)* | *p-value* | $R^2$ | *F* | *Beta (95%CI)* | *p-value* | $R^2$ | *F* |
| | BMI | | | | BMI | | | |
| **GRS-BMI$_{565}$** | 0.201 (0.179,0.218) | $8.0E^{-86}$ | 0.005 | 393 | 0.200 (0.189,0.211) | $3.4E^{-263}$ | 0.04 | 1,226 |
| | WHR | | | | WHR | | | |
| **GRS-WHR$_{324}$** | 0.086 (0.065,0.107) | $4.8E^{-16}$ | 0.007 | 66 | 0.046 (0.034,0.057) | $4.7E^{-15}$ | 0.002 | 61 |
| | BMI | | | | % body fat | | | |
| **GRS-BF$_{81}$** | 0.063 (0.043,0.083) | $9.5E^{-10}$ | 0.004 | 37 | 0.045 (0.034,0.057) | $1.5E^{-14}$ | 0.002 | 59 |
| | BMI | | | | BMI | | | |
| **GRS-VAT$_{208}$** | 0.128 (0.107,0.147) | $1.19E^{-35}$ | 0.016 | 156 | 0.136 (0.125,0.147) | $1.12E^{-121}$ | 0.02 | 555 |

*Legend: BF, Body Fat; BMI, Body Mass Index; F, F statistics; GRS-VAT$_{208,}$ Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF$_{81,}$ Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR$_{324}$ Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI$_{565}$, Genetic Risk Score for Body Mass Index based on 565 SNPs; MPP, Malmö Preventive Project; MDC, Malmö Diet and Cancer; $R^2$, r-squared; WHR, Waist Hip Ratio*

Table 11. Causal association of the four GRSs with BP traits, estimated with 2SLS regression, in the two cohorts [94]

| ***1) MPP*** | ***SBP AT BASELINE (N=9,140)*** | | | | ***DBP AT BASELINE (N=9,140)*** | | | |
|---|---|---|---|---|---|---|---|---|
| | ***Model 1*** | | ***Model 2*** | | ***Model 1*** | | ***Model 2*** | |
| | *Beta (95%CI)* | *p-value* | *Beta (95%CI)* | *p-value* | *Beta (95%CI)* | *p-value* | *Beta (95%CI)* | *p-value* |
| $GRS\text{-}BMI_{565}$ | 0.231 (0.131,0.331) | $3.4E^{-6}$ | 0.233 (0.133,0.333) | $4.2E^{-6}$ | 0.251 (0.153,0.349) | $4.0E^{-7}$ | 0.257 (0.157,0.357) | $3.0E^{-7}$ |
| $GRS\text{-}WHR_{324}$ | 0.426 (0.175,0.677) | 0.001 | 0.288 (0.123,0.453) | 0.001 | 0.529 (0.286,0.772) | $3.24E^{-5}$ | 0.367 (0.202,0.532) | $1.4E^{-5}$ |
| $GRS\text{-}BF_{81}$ | 0.247 (-0.07,0.563) | 0.125 | 0.241 (-0.07,0.552) | 0.130 | 0.275 (-0.036,0.586) | 0.084 | 0.269 (-0.017,0.576) | 0.087 |
| $GRS\text{-}VAT_{208}$ | 0.326 (0.173,0.479) | $3.1E^{-5}$ | 0.336 (0.187,0.485) | $9.7E^{-6}$ | 0.270 (0.162,0.378) | 0.001 | 0.296 (0.149,0.443) | $8.3E^{-5}$ |
| | **SBP AT FOLLOW-UP (N=9,041)** | | | | **DBP AT FOLLOW-UP (N=9,041)** | | | |
| $GRS\text{-}BMI_{565}$ | 0.163 (0.060,0.260) | 0.002 | 0.158 (0.058,0.258) | 0.002 | 0.178 (0.078,0.278) | 0.001 | 0.172 (0.072,0.272) | 0.001 |
| $GRS\text{-}WHR_{324}$ | 0.083 (-0.146,0.312) | 0.475 | 0.048 (-0.050,0.196) | 0.053 | 0.061 (-0.089,0.211) | 0.431 | 0.055 (-0.098,0.208) | 0.477 |
| $GRS\text{-}BF_{81}$ | -0.166 (-0.497,0.165) | 0.327 | -0.161 (-0.482,0.160) | 0.325 | -0.034 (-0.353,0.285) | 0.834 | -0.033 (-0.343,0.277) | 0.834 |
| $GRS\text{-}VAT_{208}$ | 0.128 (-0.029,0.285) | 0.110 | 0.122 (-0.042,0.286) | 0.111 | 0.200 (0.043,0.357) | 0.012 | 0.190 (0.04,0.339) | 0.012 |
| ***2) MDC*** | ***SBP AT BASELINE (N=29,247)*** | | | | ***DBP AT BASELINE (N=29,247)*** | | | |
| $GRS\text{-}BMI_{565}$ | 0.166 (0.104,0.222) | $4.0E^{-8}$ | 0.205 (0.145,0.265) | $8.3E^{-12}$ | 0.239 (0.18,0.298) | $4.4E^{-16}$ | 0.248 (0.188,0.308) | $6.8E^{-17}$ |
| $GRS\text{-}WHR_{324}$ | 0.620 (0.336,0.940) | $2.0E^{-5}$ | 0.546 (0.311,0.781) | $5.7E^{-6}$ | 0.767 (0.477,1.057) | $2.5E^{-7}$ | 0.676 (0.431,0.921) | $6.0E^{-8}$ |
| $GRS\text{-}BF_{81}$ | 0.129 (0.094,0.164) | 0.310 | 0.142 (-0.038,0.322) | 0.305 | 0.311 (0.274,0.348) | 0.02 | 0.267 (0.089,0.445) | 0.003 |
| $GRS\text{-}VAT_{208}$ | 0.182 (0.096,0.268) | $3.3E^{-5}$ | 0.226 (0.142,0.310) | $1.6E^{-7}$ | 0.267(0.183,0.351) | $7.6E^{-10}$ | 0.284 (0.200,0.368) | $3.1E^{-11}$ |

*Legend: DBP: Diastolic Blood Pressure;-$GRS\text{-}BMI_{565}$, Genetic Risk Score for Body Mass Index based on 565 SNPs; $GRS\text{-}BF_{81}$, Genetic risk score for Body Fat based on 81 SNPs; $GRS\text{-}VAT_{208}$, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; $GRS\text{-}WHR_{324}$ Genetic Risk Score for Waist Hip Ratio based on 324 SNPs. SBP: Systolic Blood Pressure. Model 1: raw association (without adjustment); Model 2: the exposure trait was used as the residual from linear regression with age, sex, $age^2$, age*sex.*

Table 12 Causal estimates of the association of exposures with hypertension prevalence and incidence in the MPP [94]

| MPP | Hypertension Prevalence n=9,137 | | | | Hypertension Incidence n=5,971 | | | |
|---|---|---|---|---|---|---|---|---|
| | **Model 1** | | **Model 2** | | **Model 1** | | **Model 2** | |
| | *OR (95%CI)* | *p-value* | *OR (95%CI)* | *p-value* | *OR (95%CI)* | *p-value* | *OR (95%CI)* | *p-value* |
| GRS-$BMI_{565}$ | 1.51 (1.21, 1.88) | 0.0003 | 1.48 (1.19,1.83) | 0.0003 | 1.34 (1.03,1.74) | 0.029 | 1.33(1.03,1.72) | 0.03 |
| GRS-$WHR_{324}$ | 2.46 (1.46,4.14) | 0.001 | 1.85 (1.33,2.58) | 0.0003 | 1.07 (0.58,1.98) | 0.820 | 1.05 (0.70,1.57) | 0.820 |
| GRS-$BF_{81}$ | 1.46 (0.71,2.99) | 0.274 | 1.45 (0.74,2.83) | 0.274 | 0.48 (0.21,1.11) | 0.079 | 0.49 (0.22,1.09) | 0.079 |
| GRS-$VAT_{208}$ | 2.01 (1.43,2.83) | $6.2E^{-5}$ | 1.95 (1.41,2.70) | $6.2E^{-5}$ | 1.28 (0.85,1.94) | 0.235 | 1.27 (0.86,1.89) | 0.235 |

*Legend: GRS-$BMI_{565}$, Genetic Risk Score for Body Mass Index based on 565 SNPs; GRS-$BF_{81}$, Genetic risk score for Body Fat based on 81 SNPs; GRS-$VAT_{208}$, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-$WHR_{324}$ Genetic Risk Score for Waist Hip Ratio based on 324 SNPs. Model 1: raw association (without adjustment); Model 2: the exposure trait was used as the residual from linear regression with age, sex, $age^2$, age*sex.*

Table 13. Summary level estimates of the association with BP traits[94]

| | | ***SBP*** | | ***DBP*** | |
|---|---|---|---|---|---|
| | *Method* | *Estimate(95%CI)* | *p-value* | *Estimate(95%CI)* | *p-value* |
| | Weighted median | 1.90(0.09,3.71) | 0.04 | 2.05(1.15,2.95) | <0.0001 |
| **GRS-BMI$_{565}$** | IVW | 2.75(1.66,3.85) | <0.0001 | 2.00(1.45,2.55) | <0.0001 |
| | MR Egger | 1.79(-1.15,4.73) | n.s. | 1.32(-0.15,2.81) | n.s. |
| | Weighted median | 4.67(2.57,7.08) | <0.0001 | 2.44(1.23,3.65) | <0.0001 |
| **GRS-WHR$_{324}$** | IVW | 3.18(1.68,4.67) | <0.0001 | 1.95(1.19,2.71) | <0.0001 |
| | MR Egger | 4.25(1.68,4.67) | 0.03 | 2.51(0.54,4.47) | 0.012 |
| | Weighted median | 0.19(-0.02,0.40) | n.s. | 0.18(-0.04,0.39) | n.s. |
| **GRS-BF$_{81}$** | IVW | 0.08(-0.10,0.25) | n.s. | 0.19(-0.01,0.38) | n.s. |
| | MR Egger | 0.13(-0.11,0.37) | n.s. | 0.12(-0.14,0.38) | n.s. |
| | Weighted median | 0.15(0.05,0.24) | 0.003 | 0.18(0.08,0.28) | <0.0001 |
| **GRS-VAT$_{208}$** | IVW | 0.13(0.06,0.20) | <0.0001 | 0.19(0.12,0.26) | <0.0001 |
| | MR Egger | 0.13(-0.10,0.36) | n.s. | 0.21(-0.03,0.44) | n.s. |

*Legend: DBP: Diastolic Blood Pressure; GRS-BMI$_{565}$, Genetic Risk Score for Body Mass Index based on 565 SNPs; GRS-BF$_{81,}$ Genetic risk score for Body Fat based on 81 SNPs; GRS-VAT$_{208,}$ Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-WHR$_{324}$ Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; IWV: inverse weighted median; SBP: Systolic Blood Pressure.*

## Study III

Table 14 GWAS from which summary statistics were retrieved. [95]

| Trait | Study (PMID) | n cohorts | n individuals | n cases |
|---|---|---|---|---|
| TSH | 30367059 | 22 | 54,288 | - |
| FT4 | 30367059 | 19 | 49,269 | - |
| Hypothyroidism | 30367059 | 19 | 53,423 | 3440 |
| Hyperthyroidism | 30367059 | 19 | 51,823 | 1840 |
| TPOAb | 24586183 | 11 | 18,297 | - |

*Legend: FT4, free tetraiodothyronine; TPOAb, anti-thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone*

Table 15 Causal estimates of the association of exposures with BP traits. [95]

| | **IVW** | | | **MR Egger** | | | **Weighted Median** | | |
|---|---|---|---|---|---|---|---|---|---|
| **TSH** | | | | | | | | | |
| | **β** | **SE** | ***p*** | **β** | **SE** | ***p*** | **β** | **SE** | ***p*** |
| SBP | −0.83 | 0.38 | 0.03 | −1.37 | 0.92 | 0.14 | −0.74 | 0.62 | 0.23 |
| DBP | −0.08 | 0.51 | 0.88 | −0.12 | 0.30 | 0.69 | −0.07 | 0.21 | 0.74 |
| **FT4** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| SBP | 0.18 | 0.31 | 0.56 | −0.22 | 0.68 | 0.75 | 0.12 | 0.41 | 0.77 |
| DBP | 0.29 | 0.30 | 0.33 | −0.42 | 0.66 | 0.53 | 0.19 | 0.40 | 0.63 |
| **Hypothyroidism** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| SBP | −0.56 | 0.49 | 0.25 | −1.91 | 2.12 | 0.40 | −0.41 | 0.47 | 0.38 |
| DBP | 0.11 | 0.23 | 0.62 | 0.16 | 1.02 | 0.88 | −0.04 | 0.24 | 0.86 |
| **Hyperthyroidism** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| SBP | 0.49 | 0.25 | 0.05 | 0.83 | 1.27 | 0.54 | 0.33 | 0.033 | 0.32 |
| DBP | 0.10 | 0.13 | 0.50 | −0.39 | 0.68 | 0.59 | 0.03 | 0.17 | 0.84 |
| **TPOAb** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| SBP | 3.25 | 5.9 | 0.59 | −38.6 | 33.2 | 0.37 | −0.64 | 6.2 | 0.37 |
| DBP | 1.29 | 3.84 | 0.74 | −34.4 | 14.6 | 0.14 | −1.9 | 3.2 | 0.56 |

*Legend: DBP: Diastolic Blood Pressure; FT4, free tetraiodothyronine; SBP: Systolic Blood Pressure; TPOAb, anti-thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.*

Table 16 Causal estimates of the association between exposures and cardiovascular events. [95]

| | IVW | | | MR Egger | | | Weighted Median | | |
|---|---|---|---|---|---|---|---|---|---|
| **TSH** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| CVD | 0.03 | 0.06 | 0.56 | 0.11 | 0.16 | 0.48 | −0.10 | 0.08 | 0.89 |
| Atrial fibrillation | −0.204 | 0.07 | 0.004 | −0.455 | 0.169 | 0.009 | −0.295 | 0.087 | 0.001 |
| Stroke | 0.06 | 0.07 | 0.40 | 0.03 | 0.19 | 0.89 | −0.01 | 0.10 | 0.92 |
| **FT4** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| CVD | −0.01 | 0.08 | 0.87 | −0.002 | 0.18 | 0.99 | −0.02 | 0.10 | 0.81 |
| Atrial fibrillation | −0.06 | 0.09 | 0.53 | −0.17 | 0.20 | 0.40 | −0.19 | 0.12 | 0.10 |
| Stroke | −0.14 | 0.09 | 0.11 | −0.20 | 0.20 | 0.31 | −0.23 | 0.13 | 0.08 |
| **Hypothyroidism** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| CVD | 0.02 | 0.05 | 0.71 | 0.03 | 0.209 | 0.89 | −0.001 | 0.005 | 0.98 |
| Atrial fibrillation | −0.56 | 0.49 | 0.25 | −1.91 | 2.12 | 0.4 | −0.4 | 0.48 | 0.39 |
| Stroke | −0.04 | 0.07 | 0.54 | −0.01 | 0.32 | 0.97 | −0.07 | 0.08 | 0.37 |
| **Hyperthyroidism** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| CVD | −0.01 | 0.05 | 0.75 | 0.06 | 0.26 | 0.81 | 0.007 | 0.05 | 0.88 |
| Atrial fibrillation | 0.11 | 0.06 | 0.08 | 0.44 | 0.30 | 0.19 | 0.11 | 0.05 | 0.03 |
| Stroke | −0.04 | 0.05 | 0.45 | −0.27 | 0.297 | 0.40 | −0.02 | 0.07 | 0.72 |
| **TPOAb** | | | | | | | | | |
| | β | SE | *p* | β | SE | *p* | β | SE | *p* |
| CVD | 0.40 | 0.93 | 0.66 | −7.95 | 3.79 | 0.17 | −0.07 | 0.82 | 0.94 |
| Atrial fibrillation | −1.48 | 0.67 | 0.03 | −6.75 | 4.09 | 0.24 | −1.16 | 0.88 | 0.19 |
| Stroke | −0.06 | 0.79 | 0.94 | 0.72 | 4.86 | 0.89 | −0.14 | 0.94 | 0.88 |

*CVD: Cardiovascular Disease; FT4, free tetraiodothyronine;IVW; inverse variance weighted; TPOAb, anti-thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone.*

## Study IV

Table 17 Information about the GWAS from where summary statistics were obtained. [96]

| Trait | Study (PMID) | n cohorts | Cohort | n |
|---|---|---|---|---|
| Calcium | 33887147 | 1 | UKBiobank | 305349 |
| Vit-D | 32242144 | 1 | UKBiobank | 417580 |
| PTH | 34381493 | 13 | | 29155 |
| FGF23 | 30217807 | 7 | ARIC (8594); CHS (1988); Indiana (1128); MESA (2163); MrOS GBG (937); MrOS Malmö (894); OPRA (920) | 16624 |

*Legend: FGF23: Fibroblast Growth Factor 23; PTH: serum Parathyroid concentration; Vit-D: vitamin D*

Table 18 Effect estimates of Calcium, Parathyroid hormone, and FGHF23, versus BP traits. [96]

| | | *SBP, mmHg* | | *DBP, mmHg* | |
|---|---|---|---|---|---|
| | n SNPs | Beta (SE) | P | Beta (SE) | P |
| **Calcium** | | | | | |
| IWV | 119 | 0.07 (0.04) | 0.04 | 0.10 (0.04) | 0.007 |
| Weighted median | 119 | 0.04 (0.06) | 0.50 | 0.11 (0.06) | 0.077 |
| MR Egger | 119 | 0.11 (0.06) | 0.10 | 0.19 (0.07) | 0.003 |
| **Vit-D** | | | | | |
| IWV | 78 | 0.06 (0.03) | 0.07 | 0.03 (0.04) | 0.05 |
| Weighted median | 78 | 0.08 (0.04) | 0.06 | 0.04 (0.04) | 0.04 |
| MR Egger | 78 | 0.07 (0.04) | 0.07 | 0.06 (0.04) | 0.21 |
| **PTH** | | | | | |
| IWV | 5 | 0.01 (0.07) | 0.9 | -0.01 (0.09) | 0.9 |
| Weighted median | 5 | 0.01 (0.04) | 0.8 | -0.05 (0.04) | 0.2 |
| MR Egger | 5 | -0.06 (0.11) | 0.6 | -0.08 (0.12) | 0.5 |
| **FGF23** | | | | | |
| IWV | 5 | -0.11 (0.04) | 0.01 | -0.08 (0.04) | 0.06 |
| Weighted median | 5 | -0.10 (0.05) | 0.06 | -0.08 (0.05) | 0.1 |
| MR Egger | 5 | -0.08 (0.24) | 0.8 | 0.22 (0.23) | 0.4 |

*Legend:DBP: Diastolic Blood Pressure; FGF23: Fibroblast Growth Factor 23;IWV: Inverse Weighted Median; PTH: serum Parathyroid concentration; SBP: systolic Blood Pressure Vit-D: vitamin D*

# FIGURES

## Study I

Figure 9 Difference in mmHg of SBP (a, c) and DBP (b, d) between quartiles and deciles of the BP-GRS858.
Legend: SBP, systolic blood pressure; DBP, Diastolic Blood pressure [93]

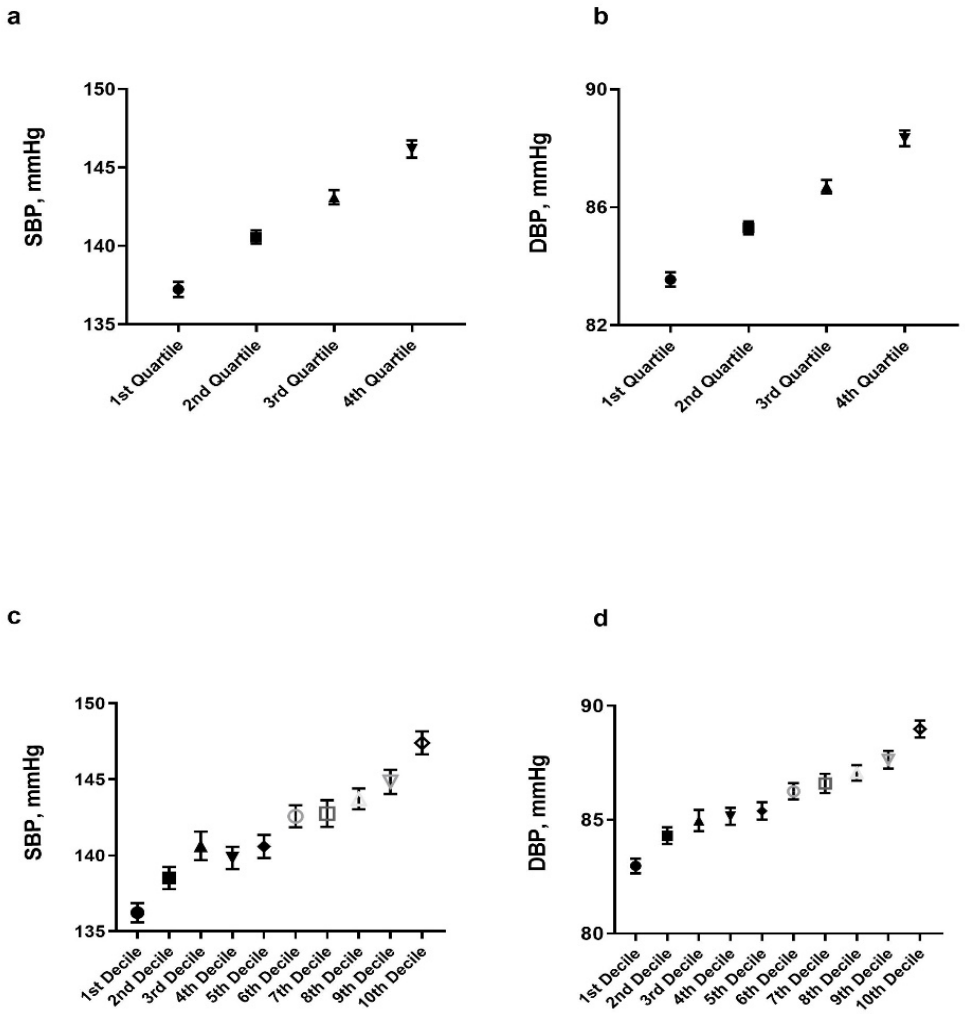
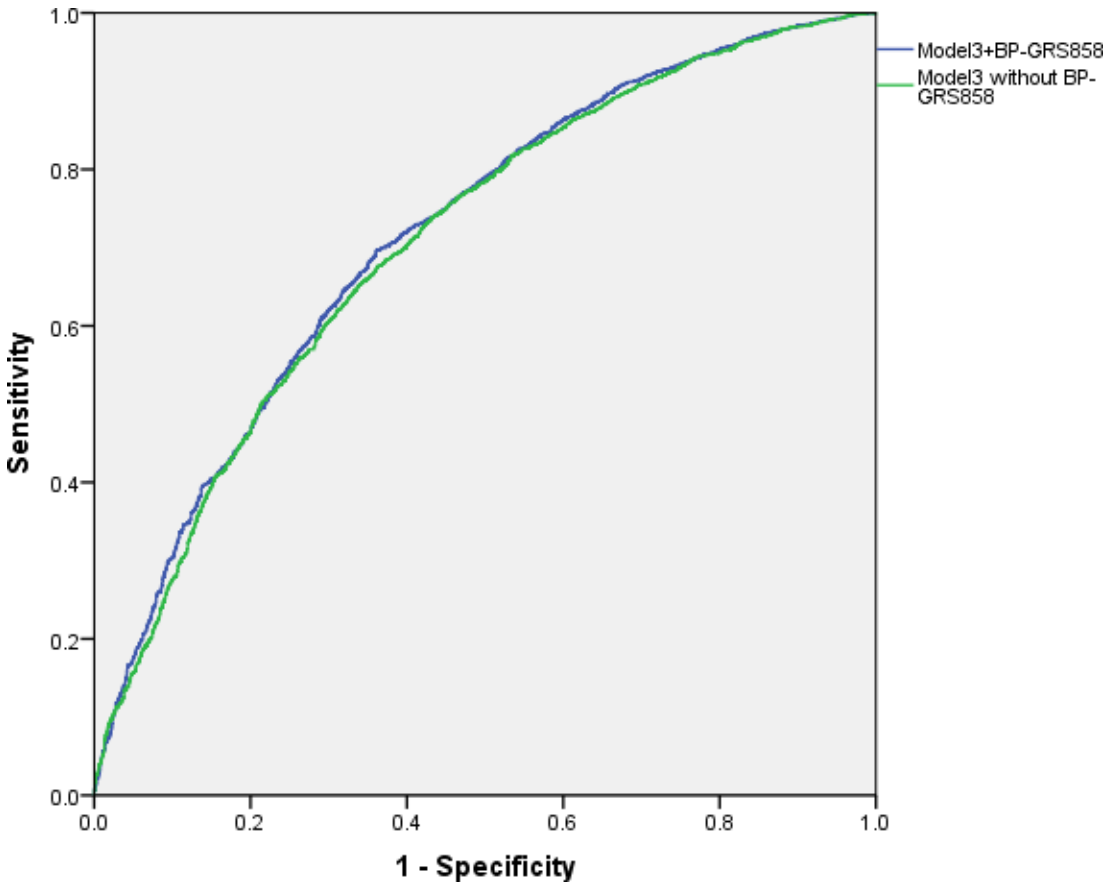
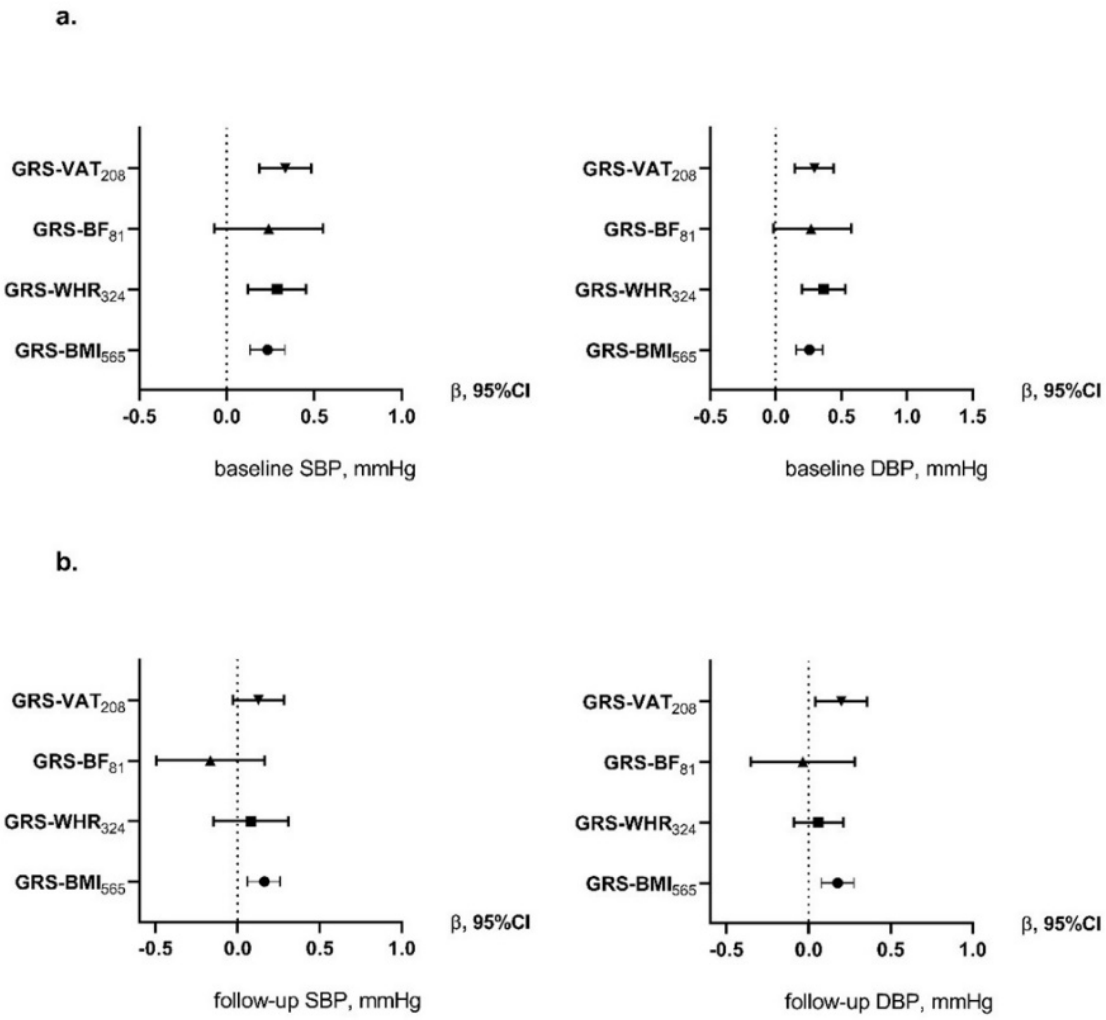


Figure 10. ROC curve of model 3 with (green line) and without (blue line) adding BP-GRS858 [93]



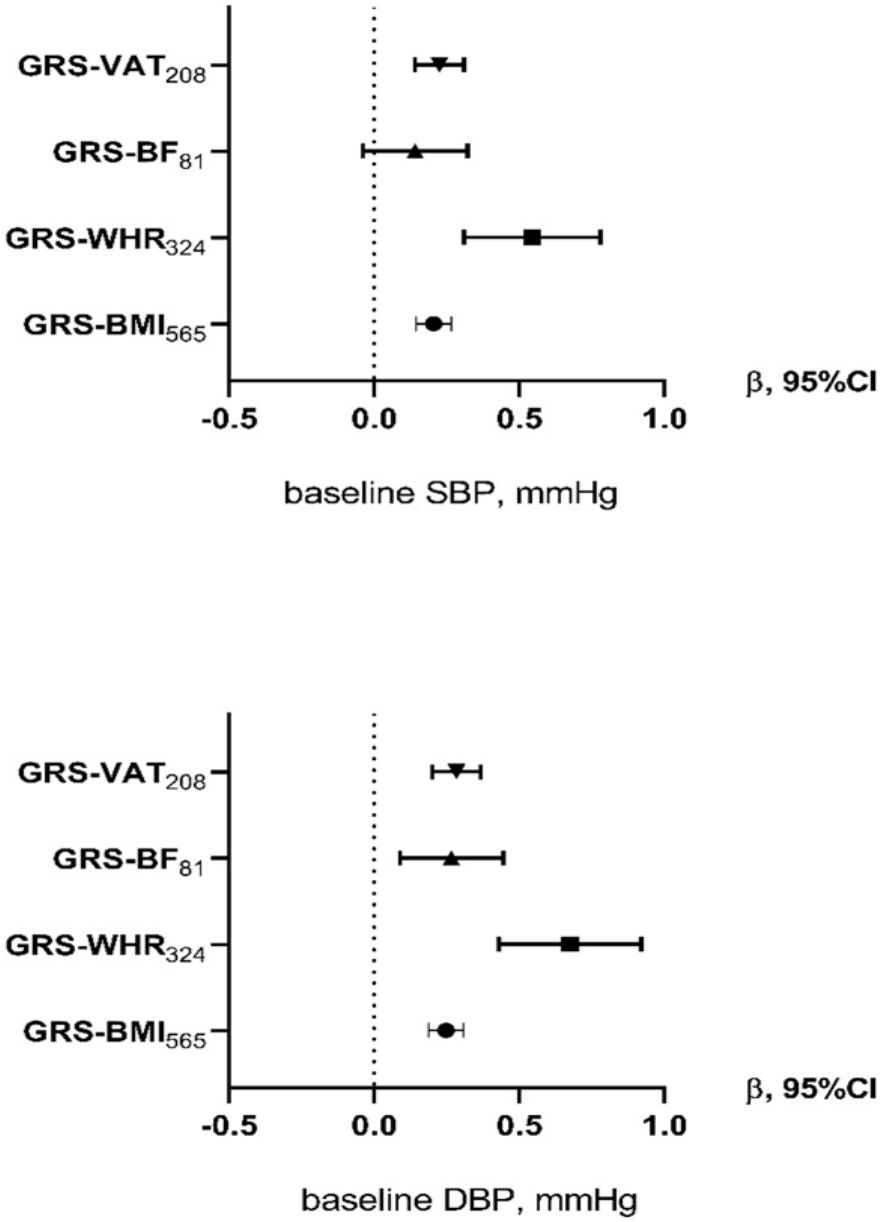
## Study II

Figure 11 . Causal association from 2SLS MR between the GRSs and BP traits, in the MPP cohort [94]



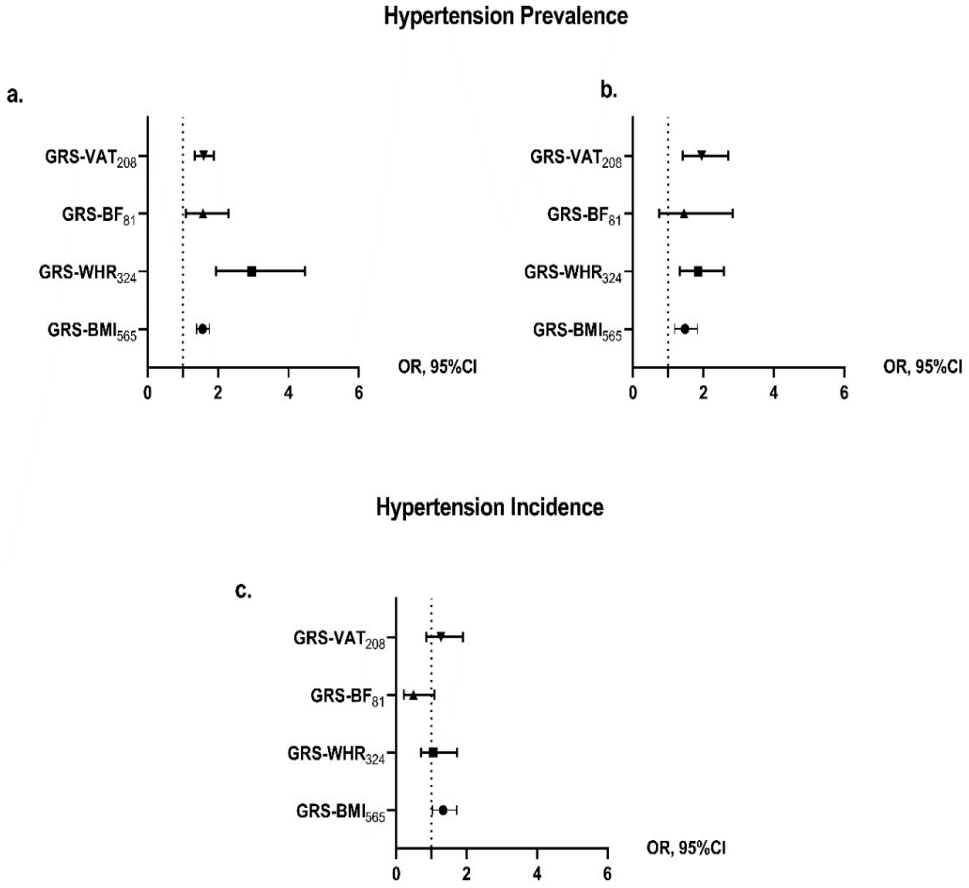

Legend: DBP, diastolic blood pressure; GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; SBP, systolic blood pressure. Each Forest plot shows the causal estimates (β) from the 2SLS regression of the four GRSs with baseline (a.) and follow-up (b.) blood pressure outcomes (SBP or DBP) in the MPP cohort for the model 2 (adjustment for age, sex, age2, age*sex). I.e. an increase of 1 SD in GRS-VAT208 is associated with an SD increase of 0.326 of SBP.

Figure 12 Causal association from 2SLS MR between the GRSs and BP traits, in the MDC cohort [94]




Legend: DBP, diastolic blood pressure; GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; SBP, systolic blood pressure. Each Forest plot shows the causal estimates (β) from the 2SLS regression of the four GRSs with blood pressure outcomes (SBP or DBP) in the MDC cohort for model 2 (adjustment for age, sex, age2, age*sex). I.e. an increase of 1 SD in GRS-VAT208 is associated with an SD increase of 0.236 of SBP.

Figure 13. Forest plot of the association of the four GRSs with the prevalence of hypertension at baseline in the two cohorts and with the incidence of hypertension at follow-up in the MPP cohort [94]




Legend: GRS-VAT208, Genetic risk score for Visceral Adipose Tissue based on 208 SNPs; GRS-BF81, Genetic risk score for Body Fat based on 81 SNPs; GRS-WHR324 Genetic Risk Score for Waist Hip Ratio based on 324 SNPs; GRS-BMI565, Genetic Risk Score for Body Mass Index based on 565 SNPs; OR, Odds ratio.

Each Forest plot shows the causal estimates in odds ratio, from the 2-stage logistic regression of the four GRSs with the prevalence of hypertension at baseline in the MDC (a.) and the MPP (b.) and with the incidence of hypertension at follow-up in the MPP cohort (c.) for the model 2 (adjusted for age, sex, age2, age*sex). I.e. the increase of 1 SD in GRS-VAT208 is associated with an OR of 2.01 for hypertension prevalence

Figure 14. Forest plot of the association of the four GRSs with the prevalence of hypertension at baseline in the MDC, stratified by tertiles of age [94]

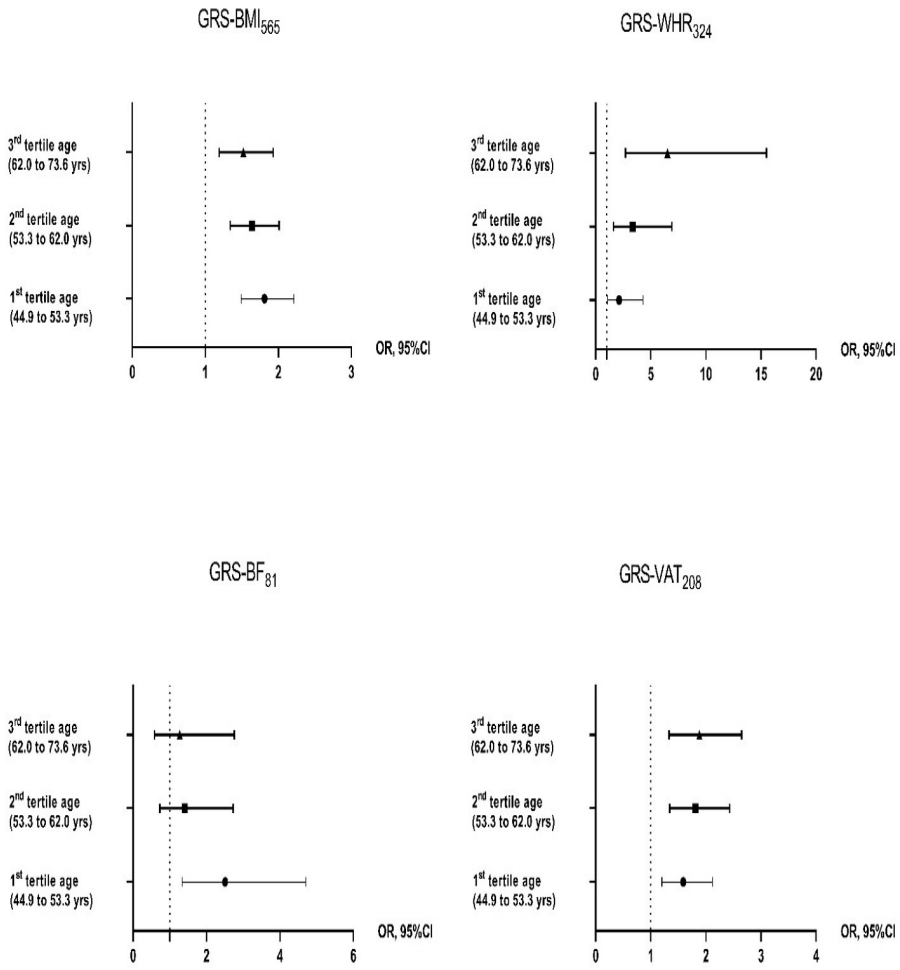
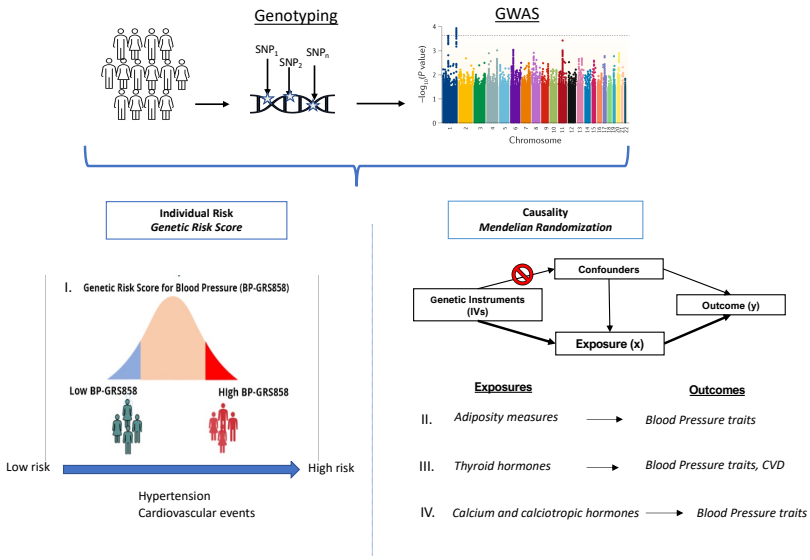


Figure 15 Graphical summary



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# APPENDIX

## Study I.

A1 List of SNPs with weights and effect allele used to compute the SBP-GRS474 [93]

| rsID | Chr | BP | Effect allele | Beta | proxy | lead snps |
|---|---|---|---|---|---|---|
| rs1014988 | 1 | 1680219 | G | 0.204 | | |
| rs260508 | 1 | 2187085 | T | 0.149 | | |
| rs2252865 | 1 | 8422676 | T | 0.187 | | |
| rs1815614 | 1 | 9441838 | A | 0.241 | | |
| rs880315 | 1 | 10796866 | C | 0.508 | | |
| rs17367504 | 1 | 11862778 | A | 0.897 | | |
| rs3820068 | 1 | 15798197 | A | 0.294 | | |
| rs2807337 | 1 | 22577371 | T | 0.175 | | |
| rs79598313 | 1 | 27284913 | T | 0.593 | | |
| rs3737801 | 1 | 27960832 | C | 0.298 | | |
| rs6689862 | 1 | 28837443 | C | 0.327 | | |
| rs12569027 | 1 | 38449163 | T | 0.196 | | |
| rs11210029 | 1 | 41865293 | G | 0.148 | | |
| rs7515635 | 1 | 42408070 | T | 0.251 | | |
| rs839755 | 1 | 43856410 | C | 0.227 | | |
| rs11579440 | 1 | 49052423 | T | 0.212 | | |
| rs12125786 | 1 | 56616712 | C | 0.229 | | |
| rs7547570 | 1 | 67008495 | A | 0.168 | | |
| rs10923038 | 1 | 88651771 | A | 0.162 | | |
| rs10922502 | 1 | 89360158 | G | 0.286 | | |
| rs7514579 | 1 | 94051350 | A | 0.197 | | |
| rs17396055 | 1 | 94730954 | G | 0.173 | | |
| rs3790604 | 1 | 113046879 | A | 0.635 | | |
| rs76719272 | 1 | 156129796 | C | 0.239 | | |
| rs2179490 | 1 | 169109393 | G | 0.231 | | |
| rs1043069 | 1 | 180859368 | T | 0.200 | | |
| rs4651224 | 1 | 184585182 | T | 0.194 | | |
| rs12042924 | 1 | 197297417 | C | 0.162 | | |
| rs33996239 | 1 | 203109801 | C | 0.354 | | |
| rs7550273 | 1 | 207912179 | G | 0.194 | | |
| rs7555285 | 1 | 209970355 | C | 0.196 | | |
| rs2494184 | 1 | 210386892 | C | 0.169 | | |
| rs12088448 | 1 | 218546170 | C | 0.163 | | |
| rs1415293 | 1 | 219730006 | A | 0.175 | | |
| rs4926499 | 1 | 249155909 | C | 0.295 | | |
| rs67720684 | 2 | 18975439 | A | 0.204 | | |

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|---|---|---|---|---|---|---|
| rs1344653 | 2 | 19730845 | G | 0.253 | | |
| rs7255 | 2 | 20878820 | T | 0.192 | | |
| rs55701159 | 2 | 25139596 | T | 0.396 | | |
| rs1275988 | 2 | 26914364 | C | 0.541 | | |
| rs9678851 | 2 | 27887034 | C | 0.172 | | |
| rs7562 | 2 | 28635740 | T | 0.231 | | |
| rs13408514 | 2 | 37203006 | C | 0.206 | | |
| rs13420463 | 2 | 37517566 | A | 0.314 | | |
| rs7601637 | 2 | 37993304 | G | 0.218 | | |
| rs2192768 | 2 | 40525932 | T | 0.231 | | |
| rs76326501 | 2 | 43167878 | A | 0.527 | | |
| rs35590893 | 2 | 43716933 | G | 0.215 | | |
| rs687914 | 2 | 45878760 | T | 0.277 | | |
| rs6545155 | 2 | 50429861 | T | 0.169 | | |
| rs10189186 | 2 | 53025757 | A | 0.143 | | |
| rs2920899 | 2 | 55279681 | T | 0.185 | | |
| rs13431149 | 2 | 56193665 | A | 0.206 | | |
| rs6730325 | 2 | 59315828 | G | 0.110 | | |
| rs66723505 | 2 | 60063763 | A | 0.213 | | |
| rs2540949 | 2 | 65284231 | A | 0.233 | yes | rs111524356 |
| rs2300481 | 2 | 66782467 | T | 0.195 | | |
| rs6731373 | 2 | 68503044 | A | 0.182 | | |
| rs72847885 | 2 | 86326717 | A | 0.218 | | |
| rs57874285 | 2 | 112012672 | A | 0.156 | | |
| rs28377357 | 2 | 112769721 | G | 0.186 | | |
| rs11688682 | 2 | 121347612 | G | 0.222 | | |
| rs750416 | 2 | 121997698 | C | 0.150 | | |
| rs72844590 | 2 | 138421227 | T | 0.208 | | |
| rs10928240 | 2 | 145820470 | G | 0.216 | | |
| rs2848657 | 2 | 158495349 | T | 0.242 | | |
| rs79523138 | 2 | 161368213 | G | 0.263 | | |
| rs55732192 | 2 | 162278233 | G | 0.240 | | |
| rs73029563 | 2 | 165008166 | C | 0.358 | | |
| rs10184004 | 2 | 165508389 | C | 0.205 | | |
| rs11694601 | 2 | 174949358 | G | 0.191 | | |
| rs55799551 | 2 | 177010551 | G | 0.203 | | |
| rs1837164 | 2 | 178716601 | A | 0.150 | | |
| rs12474446 | 2 | 182994685 | T | 0.276 | | |
| rs6739913 | 2 | 185033065 | A | 0.168 | | |
| rs28558491 | 2 | 187816321 | C | 0.187 | | |
| rs6434404 | 2 | 191494411 | A | 0.311 | | |
| rs61345672 | 2 | 191507014 | A | 0.228 | yes | rs142457531 |
| rs296797 | 2 | 201102905 | T | 0.165 | | |
| rs55780018 | 2 | 208526140 | C | 0.278 | | |

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|---|---|---|---|---|---|---|
| rs1047891 | 2 | 211540507 | C | 0.196 | | |
| rs12694277 | 2 | 213188795 | C | 0.177 | | |
| rs1250259 | 2 | 216300482 | T | 0.452 | | |
| rs2571445 | 2 | 218683154 | A | 0.205 | | |
| rs1870123 | 2 | 219187698 | G | 0.153 | | |
| rs2943646 | 2 | 227099534 | G | 0.283 | | |
| rs10182307 | 2 | 227875360 | G | 0.164 | | |
| rs1044822 | 2 | 230629138 | C | 0.228 | | |
| rs139354822 | 2 | 242344695 | T | 0.547 | | |
| rs347591 | 3 | 11290122 | T | 0.318 | | |
| rs6793656 | 3 | 13823342 | G | 0.266 | | |
| rs729639 | 3 | 13826854 | C | 0.121 | | |
| rs11128722 | 3 | 14958126 | G | 0.287 | | |
| rs189267552 | 3 | 20073193 | T | 0.783 | | |
| rs4858758 | 3 | 20117233 | C | 0.232 | | |
| rs2643826 | 3 | 27562988 | C | 0.411 | | |
| rs12638085 | 3 | 30405936 | A | 0.213 | | |
| rs267539 | 3 | 37582252 | G | 0.178 | | |
| rs6788984 | 3 | 41107173 | A | 0.256 | | |
| rs112912733 | 3 | 42054910 | C | 0.421 | | |
| rs34877991 | 3 | 45643648 | G | 0.173 | | |
| rs11716779 | 3 | 47606215 | A | 0.271 | yes | rs111499603 |
| rs6774721 | 3 | 49381898 | G | 0.252 | | |
| rs3821843 | 3 | 53558012 | G | 0.334 | | |
| rs4681794 | 3 | 56776908 | C | 0.211 | | |
| rs4499560 | 3 | 70920485 | T | 0.201 | | |
| rs9857362 | 3 | 74710462 | A | 0.151 | | |
| rs1375564 | 3 | 85656311 | T | 0.234 | | |
| rs1882289 | 3 | 114461208 | G | 0.216 | | |
| rs6438253 | 3 | 115115932 | A | 0.174 | | |
| rs3772840 | 3 | 124550364 | C | 0.185 | | |
| rs4854572 | 3 | 132801239 | G | 0.182 | | |
| rs863930 | 3 | 135949737 | G | 0.189 | | |
| rs357489 | 3 | 153884517 | T | 0.210 | | |
| rs78151625 | 3 | 158316726 | C | 0.211 | | |
| rs56394279 | 3 | 160171092 | C | 0.236 | | |
| rs12638862 | 3 | 169477506 | A | 0.258 | | |
| rs262986 | 3 | 183435713 | G | 0.186 | | |
| rs231708 | 4 | 2694773 | G | 0.228 | | |
| rs2610990 | 4 | 18008232 | G | 0.257 | | |
| rs4572866 | 4 | 26795603 | T | 0.202 | | |
| rs2291435 | 4 | 38387395 | C | 0.262 | | |
| rs12511987 | 4 | 46595623 | G | 0.215 | | |
| rs13141523 | 4 | 48789269 | G | 0.195 | | |

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|---|---|---|---|---|---|---|
| rs60991988 | 4 | 54801228 | T | 0.318 | yes | rs7671947 |
| rs693367 | 4 | 56260662 | G | 0.178 | | |
| rs55940751 | 4 | 77365891 | C | 0.212 | yes | rs568240689 |
| rs10857147 | 4 | 81181072 | A | 0.630 | | |
| rs12649662 | 4 | 83896818 | T | 0.219 | | |
| rs2014912 | 4 | 86715670 | T | 0.477 | | |
| rs13149209 | 4 | 89750668 | T | 0.251 | | |
| rs1347345 | 4 | 95938386 | G | 0.179 | | |
| rs17248480 | 4 | 102435265 | G | 0.733 | | |
| rs13107325 | 4 | 103188709 | C | 0.553 | | |
| rs144317085 | 4 | 105806108 | T | 0.451 | | |
| rs13112725 | 4 | 106911742 | C | 0.414 | | |
| rs78866112 | 4 | 109021269 | A | 0.188 | yes | rs67372037 |
| rs6815273 | 4 | 111337478 | G | 0.328 | | |
| rs3097937 | 4 | 124794644 | A | 0.159 | | |
| rs7439567 | 4 | 138464842 | T | 0.236 | | |
| rs72719160 | 4 | 144051276 | T | 0.234 | | |
| rs6823767 | 4 | 151295085 | C | 0.173 | | |
| rs3796592 | 4 | 156631345 | T | 0.295 | | |
| rs17035181 | 4 | 157678511 | T | 0.295 | | |
| rs869398 | 4 | 169688069 | A | 0.208 | | |
| rs4957026 | 5 | 361148 | A | 0.198 | | |
| rs10069690 | 5 | 1279790 | T | 0.274 | | |
| rs1173771 | 5 | 32815028 | G | 0.632 | | |
| rs74774746 | 5 | 33411769 | G | 0.171 | | |
| rs1694068 | 5 | 53283630 | A | 0.234 | | |
| rs256904 | 5 | 55810305 | T | 0.206 | | |
| rs13179413 | 5 | 55868097 | T | 0.205 | | |
| rs10062049 | 5 | 61553881 | T | 0.235 | | |
| rs6875372 | 5 | 64079015 | A | 0.134 | | |
| rs3121685 | 5 | 65662133 | C | 0.148 | | |
| rs1159201 | 5 | 66311339 | A | 0.209 | | |
| rs246973 | 5 | 68007803 | T | 0.224 | | |
| rs34797797 | 5 | 77853085 | G | 0.247 | | |
| rs10059921 | 5 | 87514515 | G | 0.425 | | |
| rs709668 | 5 | 96174186 | G | 0.253 | | |
| rs1871190 | 5 | 97953719 | T | 0.140 | | |
| rs10477931 | 5 | 108093529 | A | 0.212 | | |
| rs10077885 | 5 | 114390121 | C | 0.259 | | |
| rs4235771 | 5 | 114393594 | G | 0.241 | yes | rs147202915 |
| rs13359291 | 5 | 122476457 | A | 0.433 | | |
| rs62373688 | 5 | 127352807 | A | 0.261 | | |
| rs6595838 | 5 | 127868199 | A | 0.323 | | |
| rs702395 | 5 | 140086677 | T | 0.191 | | |

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|---|---|---|---|---|---|---|
| rs10477176 | 5 | 141790325 | A | 0.185 | | |
| rs34070447 | 5 | 147871508 | G | 0.197 | | |
| rs1036190 | 5 | 148387612 | G | 0.217 | | |
| rs11953630 | 5 | 157845402 | C | 0.453 | | |
| rs1422799 | 5 | 158321121 | G | 0.263 | yes | rs368910700 |
| rs12153395 | 5 | 179411477 | G | 0.111 | | |
| rs2745599 | 6 | 1613686 | A | 0.191 | | |
| rs9349379 | 6 | 12903957 | A | 0.225 | | |
| rs9368222 | 6 | 20686996 | A | 0.230 | | |
| rs6911827 | 6 | 22130601 | T | 0.238 | | |
| rs198851 | 6 | 26104632 | T | 0.351 | | |
| rs6914824 | 6 | 27139048 | T | 0.209 | | |
| rs76106973 | 6 | 27904345 | A | 0.775 | | |
| rs7889 | 6 | 31605448 | G | 0.250 | | |
| rs73744859 | 6 | 34208190 | C | 0.375 | | |
| rs7763558 | 6 | 43349215 | A | 0.353 | | |
| rs78648104 | 6 | 50683009 | C | 0.429 | | |
| rs4712120 | 6 | 56092916 | T | 0.197 | | |
| rs6454092 | 6 | 79701972 | G | 0.228 | | |
| rs9449350 | 6 | 82281417 | C | 0.219 | | |
| rs35410524 | 6 | 96885405 | T | 0.337 | | |
| rs2012071 | 6 | 112087768 | G | 0.158 | | |
| rs9401025 | 6 | 117989145 | C | 0.203 | | |
| rs1626650 | 6 | 118654588 | C | 0.307 | yes | rs149379258 |
| rs9401090 | 6 | 119113317 | T | 0.164 | | |
| rs10782230 | 6 | 126228512 | A | 0.200 | | |
| rs9398815 | 6 | 127097775 | T | 0.361 | | |
| rs9885632 | 6 | 131311909 | T | 0.210 | | |
| rs12194247 | 6 | 133996536 | C | 0.378 | | |
| rs7763294 | 6 | 140383733 | G | 0.180 | | |
| rs7765526 | 6 | 147713764 | A | 0.201 | | |
| rs113397083 | 6 | 150984741 | G | 0.518 | | |
| rs2207232 | 6 | 152340288 | C | 0.375 | yes | rs34862067 |
| rs9356632 | 6 | 170589803 | G | 0.274 | | |
| rs6963853 | 7 | 1858725 | A | 0.197 | | |
| rs2107595 | 7 | 19049388 | A | 0.417 | | |
| rs12979 | 7 | 24738164 | C | 0.274 | | |
| rs6969780 | 7 | 27159136 | C | 0.296 | | |
| rs3735533 | 7 | 27245893 | C | 0.652 | yes | rs60772526 |
| rs10274928 | 7 | 28142088 | A | 0.159 | | |
| rs10233127 | 7 | 30933453 | A | 0.303 | | |
| rs76206723 | 7 | 40447971 | G | 0.412 | | |
| rs2075066 | 7 | 44265179 | A | 0.251 | | |
| rs10260816 | 7 | 46010100 | G | 0.351 | | |

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|---|---|---|---|---|---|---|
| rs6593297 | 7 | 56122058 | A | 0.158 | | |
| rs6963105 | 7 | 75097488 | G | 0.178 | | |
| rs7796089 | 7 | 77512098 | G | 0.221 | | |
| rs42377 | 7 | 92243672 | G | 0.258 | | |
| rs17477177 | 7 | 106411858 | C | 0.735 | | |
| rs4728142 | 7 | 128573967 | G | 0.181 | | |
| rs34072724 | 7 | 130432469 | G | 0.218 | | |
| rs13238550 | 7 | 131059056 | A | 0.257 | | |
| rs1860509 | 7 | 139478175 | T | 0.268 | | |
| rs12703989 | 7 | 140238048 | A | 0.152 | | |
| rs11771693 | 7 | 150050111 | A | 0.167 | | |
| rs3918226 | 7 | 150690176 | T | 0.509 | | |
| rs10224002 | 7 | 151415041 | G | 0.367 | | |
| rs1870735 | 7 | 155744303 | C | 0.170 | | |
| rs4875958 | 8 | 1721090 | A | 0.226 | | |
| rs62491354 | 8 | 9730663 | A | 0.257 | | |
| rs2898290 | 8 | 11433909 | T | 0.312 | | |
| rs6557876 | 8 | 25900675 | C | 0.416 | | |
| rs2979470 | 8 | 30288272 | T | 0.162 | | |
| rs66963240 | 8 | 32392283 | T | 0.190 | yes | rs527953512 |
| rs1906672 | 8 | 38130025 | A | 0.272 | | |
| rs34473019 | 8 | 51704077 | T | 0.252 | yes | rs12547335 |
| rs6996733 | 8 | 60535824 | T | 0.188 | | |
| rs2354862 | 8 | 64501744 | A | 0.192 | | |
| rs13253358 | 8 | 68920135 | T | 0.173 | | |
| rs7837090 | 8 | 74221406 | C | 0.220 | | |
| rs1449544 | 8 | 76591880 | A | 0.219 | | |
| rs72688070 | 8 | 81393697 | C | 0.241 | | |
| rs62526122 | 8 | 92769569 | A | 0.211 | | |
| rs142449193 | 8 | 102750597 | C | 0.388 | | |
| rs35783704 | 8 | 105966258 | G | 0.462 | | |
| rs11775209 | 8 | 120453012 | A | 0.262 | yes | rs566791419 |
| rs56123029 | 8 | 124673630 | C | 0.192 | | |
| rs62523863 | 8 | 126520544 | A | 0.232 | | |
| rs4598218 | 8 | 129483956 | T | 0.180 | | |
| rs1036821 | 8 | 135650483 | A | 0.214 | | |
| rs4129585 | 8 | 143312933 | A | 0.175 | | |
| rs3802228 | 8 | 143992218 | A | 0.214 | | |
| rs520015 | 9 | 211762 | C | 0.120 | | |
| rs60191654 | 9 | 753648 | G | 0.173 | | |
| rs28558845 | 9 | 4334791 | G | 0.218 | | |
| rs1332813 | 9 | 9350706 | T | 0.197 | | |
| rs111791351 | 9 | 19111187 | T | 0.205 | | |
| rs2780841 | 9 | 20612516 | C | 0.184 | | |

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|---|---|---|---|---|---|---|
| rs9886665 | 9 | 22942770 | T | 0.151 | | |
| rs7042283 | 9 | 71518027 | G | 0.220 | | |
| rs7045409 | 9 | 95201540 | T | 0.182 | | |
| rs111245230 | 9 | 113169775 | C | 0.749 | | |
| rs10448275 | 9 | 116702866 | T | 0.171 | | |
| rs16927927 | 9 | 127943338 | C | 0.282 | | |
| rs7023828 | 9 | 128498594 | C | 0.244 | | |
| rs1891730 | 9 | 130309028 | C | 0.179 | | |
| rs184457 | 9 | 131940019 | G | 0.166 | | |
| rs6271 | 9 | 136522274 | C | 0.411 | | |
| rs821317 | 9 | 140488634 | A | 0.200 | | |
| rs56352451 | 10 | 5804865 | T | 0.199 | | |
| rs11256837 | 10 | 10840535 | A | 0.211 | | |
| rs12258967 | 10 | 18727959 | G | 0.453 | | |
| rs3802517 | 10 | 28233469 | A | 0.190 | | |
| rs34130368 | 10 | 48411796 | G | 0.272 | | |
| rs72831344 | 10 | 63518378 | C | 0.337 | | |
| rs7090758 | 10 | 65335315 | C | 0.149 | | |
| rs11000752 | 10 | 75470355 | G | 0.358 | | |
| rs4746172 | 10 | 75855842 | C | 0.171 | | |
| rs7096715 | 10 | 82195949 | T | 0.172 | | |
| rs10788569 | 10 | 89604732 | T | 0.228 | | |
| rs11187142 | 10 | 94468685 | T | 0.331 | | |
| rs932764 | 10 | 95895940 | G | 0.430 | | |
| rs57866767 | 10 | 96023077 | C | 0.306 | | |
| rs4917612 | 10 | 96591284 | C | 0.341 | yes | rs199562446 |
| rs112184198 | 10 | 102604514 | G | 0.663 | | |
| rs3218248 | 10 | 103528244 | A | 0.575 | | |
| rs11191548 | 10 | 104846178 | T | 1.098 | | |
| rs111790405 | 10 | 106445445 | T | 0.870 | | |
| rs7903146 | 10 | 114758349 | T | 0.221 | | |
| rs1801253 | 10 | 115805056 | G | 0.272 | | |
| rs11197813 | 10 | 118523933 | G | 0.180 | | |
| rs11592107 | 10 | 122968964 | A | 0.302 | | |
| rs72834453 | 10 | 124235226 | G | 0.276 | | |
| rs7912283 | 10 | 133773019 | A | 0.194 | | |
| rs1133400 | 10 | 134459388 | G | 0.261 | | |
| rs12770172 | 10 | 134499718 | A | 0.252 | | |
| rs661348 | 11 | 1905292 | C | 0.445 | | |
| rs10743086 | 11 | 8774923 | G | 0.183 | | |
| rs173396 | 11 | 9759918 | A | 0.264 | yes | rs58068637 |
| rs7129220 | 11 | 10350538 | A | 0.500 | | |
| rs1401454 | 11 | 16250183 | T | 0.550 | | |
| rs414992 | 11 | 16894090 | T | 0.313 | | |

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|---|---|---|---|---|---|---|
| rs757081 | 11 | 17351683 | G | 0.343 | | |
| rs10766533 | 11 | 19224677 | A | 0.167 | | |
| rs871004 | 11 | 28512458 | A | 0.200 | | |
| rs11031051 | 11 | 30355707 | C | 0.190 | | |
| rs190194639 | 11 | 34068037 | T | 0.275 | | |
| rs3740781 | 11 | 45255926 | T | 0.226 | | |
| rs1585453 | 11 | 46884713 | T | 0.389 | | |
| rs11039216 | 11 | 47406592 | T | 0.313 | | |
| rs59652089 | 11 | 47907350 | C | 0.404 | | |
| rs11040595 | 11 | 49878757 | G | 0.278 | | |
| rs4385883 | 11 | 51539339 | A | 0.233 | | |
| rs75905900 | 11 | 55113534 | A | 0.388 | | |
| rs11229457 | 11 | 58207203 | C | 0.317 | | |
| rs7125196 | 11 | 61272565 | C | 0.264 | | |
| rs4980515 | 11 | 63744609 | T | 0.209 | | |
| rs3741378 | 11 | 65408937 | C | 0.409 | | |
| rs67976715 | 11 | 68023742 | C | 0.197 | | |
| rs11263441 | 11 | 69252000 | G | 0.402 | | |
| rs72931748 | 11 | 69825414 | A | 0.300 | | |
| rs7927515 | 11 | 76125330 | A | 0.227 | | |
| rs10830278 | 11 | 89216425 | A | 0.259 | | |
| rs10895001 | 11 | 100533021 | G | 0.374 | yes | rs35571646 |
| rs4754196 | 11 | 107096777 | G | 0.288 | | |
| rs7128382 | 11 | 117023487 | A | 0.269 | | |
| rs896693 | 11 | 120067082 | G | 0.166 | | |
| rs1106243 | 11 | 122611430 | G | 0.181 | | |
| rs11222084 | 11 | 130273230 | T | 0.299 | | |
| rs11571376 | 12 | 1059556 | G | 0.188 | | |
| rs736107 | 12 | 12627410 | G | 0.173 | | |
| rs2024385 | 12 | 12888438 | T | 0.233 | | |
| rs28621435 | 12 | 13860990 | G | 0.193 | | |
| rs60691990 | 12 | 20368269 | T | 0.353 | | |
| rs7976167 | 12 | 24210599 | T | 0.164 | | |
| rs11168516 | 12 | 48702065 | T | 0.247 | | |
| rs1126930 | 12 | 49399132 | C | 0.638 | | |
| rs10747570 | 12 | 50509937 | A | 0.293 | | |
| rs61926181 | 12 | 50767037 | G | 0.547 | | |
| rs73099903 | 12 | 53440779 | T | 0.469 | | |
| rs7297416 | 12 | 54443090 | A | 0.376 | | |
| rs10437954 | 12 | 58003922 | G | 0.347 | | |
| rs9669278 | 12 | 66374587 | T | 0.217 | yes | rs113744258 |
| rs4143175 | 12 | 67782397 | T | 0.180 | | |
| rs7963801 | 12 | 79685226 | C | 0.203 | | |
| rs7964067 | 12 | 79904658 | A | 0.250 | | |

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|---|---|---|---|---|
| rs17249754 | 12 | 90060586 | G | 0.845 |
| rs10858966 | 12 | 90567026 | C | 0.254 |
| rs5742643 | 12 | 102837863 | C | 0.224 |
| rs11064687 | 12 | 110441730 | G | 0.378 |
| rs11066320 | 12 | 112906415 | A | 0.246 |
| rs2384550 | 12 | 115352731 | G | 0.168 |
| rs35444 | 12 | 115552437 | G | 0.367 |
| rs117206641 | 12 | 133086888 | T | 0.216 |
| rs2480171 | 13 | 21559858 | T | 0.205 |
| rs606950 | 13 | 22298923 | A | 0.232 |
| rs1331012 | 13 | 27115424 | T | 0.204 |
| rs9508495 | 13 | 30146201 | C | 0.224 |
| rs9603376 | 13 | 32181957 | A | 0.326 |
| rs4274337 | 13 | 41967193 | G | 0.220 |
| rs9532959 | 13 | 42543516 | A | 0.314 |
| rs73187288 | 13 | 42738672 | C | 0.256 |
| rs912434 | 13 | 47189928 | T | 0.215 |
| rs9526707 | 13 | 51489186 | G | 0.194 |
| rs75961402 | 13 | 56398286 | A | 0.182 |
| rs78474310 | 13 | 73826901 | G | 0.483 |
| rs7988232 | 13 | 79808655 | A | 0.148 |
| rs9549328 | 13 | 113636156 | T | 0.267 |
| rs7331680 | 13 | 115000650 | T | 0.386 |
| rs17115145 | 14 | 30122409 | T | 0.157 |
| rs8904 | 14 | 35871217 | A | 0.212 |
| rs34983854 | 14 | 39858442 | G | 0.162 |
| rs72683923 | 14 | 50735947 | T | 0.977 |
| rs9888615 | 14 | 53377540 | C | 0.274 |
| rs8016306 | 14 | 63928546 | A | 0.189 |
| rs11623535 | 14 | 72462381 | A | 0.202 |
| rs11622562 | 14 | 77517148 | C | 0.176 |
| rs8009025 | 14 | 98631171 | T | 0.283 |
| rs10149871 | 14 | 100111955 | T | 0.213 |
| rs8014182 | 14 | 103859962 | C | 0.340 |
| rs11629850 | 15 | 40317075 | A | 0.200 |
| rs2925345 | 15 | 41311799 | T | 0.234 |
| rs1018148 | 15 | 48903126 | G | 0.431 |
| rs1440371 | 15 | 66941084 | A | 0.217 |
| rs72756346 | 15 | 69597932 | G | 0.205 |
| rs1378942 | 15 | 75077367 | C | 0.324 |
| rs11634028 | 15 | 76276150 | A | 0.226 |
| rs2759308 | 15 | 81016227 | A | 0.316 |
| rs3743157 | 15 | 85680532 | A | 0.260 |
| rs11632436 | 15 | 86295286 | C | 0.206 |

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|---|---|---|---|---|---|---|
| rs2071382 | 15 | 91428197 | T | 0.409 | | |
| rs62020769 | 15 | 93280491 | C | 0.174 | | |
| rs12906962 | 15 | 95312071 | T | 0.232 | | |
| rs4965529 | 15 | 100145224 | C | 0.250 | | |
| rs11248866 | 16 | 1365341 | G | 0.173 | | |
| rs140869992 | 16 | 2158570 | G | 1.472 | | |
| rs2379829 | 16 | 3538873 | G | 0.202 | | |
| rs1034906 | 16 | 4128853 | G | 0.207 | | |
| rs77997837 | 16 | 4944256 | T | 0.267 | yes | rs558074929 |
| rs35450617 | 16 | 6889675 | G | 0.161 | | |
| rs2188717 | 16 | 24730230 | C | 0.332 | | |
| rs34294937 | 16 | 49883927 | A | 0.208 | | |
| rs34941092 | 16 | 50550137 | G | 0.230 | | |
| rs62049427 | 16 | 70334172 | A | 0.559 | | |
| rs1012089 | 16 | 74171973 | G | 0.131 | | |
| rs12449170 | 16 | 75463012 | T | 0.302 | | |
| rs7187540 | 16 | 85318302 | C | 0.177 | | |
| rs731749 | 16 | 86356582 | A | 0.320 | | |
| rs3851018 | 16 | 86437811 | G | 0.118 | | |
| rs6540125 | 16 | 87993889 | T | 0.164 | | |
| rs10852858 | 17 | 1357751 | T | 0.229 | | |
| rs4790309 | 17 | 1966889 | C | 0.244 | yes | rs12952051 |
| rs12937989 | 17 | 6479453 | G | 0.231 | | |
| rs2428362 | 17 | 7180274 | T | 0.241 | | |
| rs62059712 | 17 | 7740170 | T | 0.394 | | |
| rs4925159 | 17 | 18185510 | A | 0.228 | | |
| rs1551355 | 17 | 30032420 | T | 0.193 | | |
| rs9899540 | 17 | 30777924 | A | 0.201 | | |
| rs12946454 | 17 | 43208121 | T | 0.413 | | |
| rs17608766 | 17 | 45013271 | C | 0.497 | | |
| rs7406910 | 17 | 46688256 | C | 0.435 | | |
| rs9912738 | 17 | 47510584 | T | 0.204 | | |
| rs34430710 | 17 | 56876627 | T | 0.207 | | |
| rs1292058 | 17 | 57957982 | T | 0.277 | | |
| rs1036902 | 17 | 58950791 | C | 0.227 | | |
| rs8068318 | 17 | 59483766 | T | 0.420 | | |
| rs8078112 | 17 | 60720362 | T | 0.191 | | |
| rs4291 | 17 | 61554194 | T | 0.206 | | |
| rs112260610 | 17 | 64252393 | T | 0.222 | | |
| rs3744010 | 17 | 73840243 | G | 0.276 | | |
| rs9302885 | 17 | 76799898 | A | 0.195 | | |
| rs112280096 | 17 | 79367409 | C | 0.171 | | |
| rs34413141 | 18 | 777282 | T | 0.308 | | |
| rs1154214 | 18 | 24546824 | G | 0.203 | | |

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|---|---|---|---|---|---|---|
| rs356833 | 18 | 26323525 | A | 0.172 | | |
| rs7226575 | 18 | 31168982 | C | 0.300 | | |
| rs7245273 | 18 | 42074522 | G | 0.235 | | |
| rs12958173 | 18 | 42141977 | A | 0.295 | | |
| rs1025686 | 18 | 48147127 | A | 0.214 | | |
| rs11876341 | 18 | 48799991 | G | 0.223 | | |
| rs599550 | 18 | 53252388 | G | 0.283 | | |
| rs10048404 | 18 | 54578482 | C | 0.228 | | |
| rs6567160 | 18 | 57829135 | T | 0.154 | | |
| rs12454712 | 18 | 60845884 | T | 0.204 | | |
| rs10460108 | 18 | 73034151 | A | 0.212 | | |
| rs3810409 | 19 | 2180515 | A | 0.645 | yes | rs576345045 |
| rs2613765 | 19 | 5066330 | G | 0.234 | | |
| rs4247374 | 19 | 7252756 | C | 0.635 | | |
| rs10409243 | 19 | 10332988 | C | 0.113 | | |
| rs167479 | 19 | 11526765 | G | 0.412 | | |
| rs17638167 | 19 | 11584818 | C | 0.478 | | |
| rs8104223 | 19 | 15363477 | A | 0.214 | | |
| rs3745348 | 19 | 17212410 | T | 0.260 | | |
| rs8104559 | 19 | 22205167 | C | 0.228 | | |
| rs8105753 | 19 | 31927547 | A | 0.218 | | |
| rs7256564 | 19 | 33889593 | A | 0.153 | | |
| rs7412 | 19 | 45412079 | C | 0.326 | | |
| rs10423928 | 19 | 46182304 | A | 0.198 | | |
| rs73046792 | 19 | 49605705 | G | 0.282 | | |
| rs138877676 | 19 | 50935809 | G | 0.656 | | |
| rs1764975 | 20 | 4101290 | A | 0.216 | | |
| rs6054200 | 20 | 6365645 | A | 0.164 | | |
| rs1887320 | 20 | 10965998 | A | 0.311 | | |
| rs6141767 | 20 | 31225069 | C | 0.286 | | |
| rs6031435 | 20 | 42797358 | G | 0.259 | | |
| rs6021247 | 20 | 50108980 | A | 0.204 | | |
| rs6026739 | 20 | 57739469 | T | 0.390 | | |
| rs13039439 | 20 | 62703490 | C | 0.326 | yes | rs146216988 |
| rs1882961 | 21 | 16556367 | T | 0.235 | | |
| rs11701033 | 21 | 33788341 | G | 0.219 | | |
| rs220249 | 21 | 43472148 | A | 0.159 | | |
| rs162366 | 21 | 44935383 | G | 0.242 | | |
| rs758374 | 22 | 19971552 | C | 0.210 | | |
| rs9608690 | 22 | 28921347 | G | 0.371 | | |
| rs12321 | 22 | 29453193 | G | 0.195 | | |
| rs28578714 | 22 | 50727921 | T | 0.195 | | |

Table A2 List of SNPs with weights and effect allele used to compute the DBP-GRS474
[93]

| rsID | Chr | BP | EA | Beta | proxy | lead snps |
|---|---|---|---|---|---|---|
| rs4970449 | 1 | 1353632 | A | 0.4383 | | |
| **rs2493292** | 1 | 3328659 | T | 0.2481 | | |
| rs4908678 | 1 | 7739250 | C | 0.1124 | | |
| rs191602286 | 1 | 11843008 | C | 0.3061 | | |
| **rs6686889** | 1 | 25030470 | T | 0.1918 | | |
| rs1565716 | 1 | 29549216 | A | 0.2012 | | |
| **rs4660293** | 1 | 40028180 | G | 0.0998 | | |
| rs12142296 | 1 | 46541679 | G | 0.1716 | | |
| rs4926923 | 1 | 48109225 | T | 0.1918 | | |
| rs6681713 | 1 | 51527684 | T | 0.4074 | | |
| rs34370185 | 1 | 59656909 | T | 0.2019 | | |
| rs34517439 | 1 | 78450517 | C | 0.233 | | |
| rs2065152 | 1 | 90228519 | T | 0.1103 | | |
| rs2932538 | 1 | 113216543 | G | 0.237 | | |
| rs12078697 | 1 | 117015118 | G | 0.1083 | | |
| rs1886914 | 1 | 119541452 | G | 0.1106 | | |
| rs72704264 | 1 | 145713305 | C | 0.1173 | | |
| rs13796 | 1 | 154245917 | C | 0.1626 | | |
| rs2171690 | 1 | 164740099 | T | 0.1181 | | |
| rs7524019 | 1 | 167367193 | T | 0.1036 | | |
| rs12405515 | 1 | 172357441 | G | 0.1698 | | |
| rs150816167 | 1 | 179571862 | C | 0.2873 | | |
| rs41475048 | 1 | 183058452 | G | 0.1233 | | |
| rs882624 | 1 | 201735913 | C | 0.1536 | | |
| rs2169137 | 1 | 204497913 | C | 0.1588 | | |
| rs2629665 | 1 | 207220800 | C | 0.1193 | | |
| **rs12408022** | 1 | 217718789 | T | 0.1483 | | |
| rs35981664 | 1 | 218549354 | T | 0.1542 | | |
| rs9431431 | 1 | 221358796 | G | 0.134 | | |
| **rs2760061** | 1 | 228191075 | A | 0.1771 | | |
| **rs2004776** | 1 | 230848702 | T | 0.2513 | | |
| **rs6429422** | 1 | 243472801 | G | 0.246 | | |
| rs56236159 | 2 | 3636478 | T | 0.1265 | | |
| rs10176996 | 2 | 19708692 | C | 0.2275 | | |
| rs13035244 | 2 | 25134009 | T | 0.1606 | | |
| rs1607644 | 2 | 34679626 | G | 0.1035 | | |
| rs2707238 | 2 | 38094149 | C | 0.1019 | | |
| **rs4952611** | 2 | 40567743 | C | 0.1401 | | |
| rs11681462 | 2 | 42352567 | C | 0.1325 | | |
| **rs76326501** | 2 | 43167878 | A | 0.3618 | | |

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|---|---|---|---|---|
| **rs17737768** | **2** | **46357133** | C | 0.2621 |
| **rs1975487** | 2 | 55809054 | G | 0.141 |
| **rs11899888** | **2** | **56102744** | G | 0.2549 |
| rs7608483 | 2 | 61836235 | A | 0.1171 |
| rs13014371 | 2 | 64217786 | C | 0.1176 |
| rs12052761 | 2 | 69065841 | G | 0.1229 |
| rs10193543 | 2 | 72483329 | T | 0.1391 |
| **rs1876487** | 2 | 73114352 | C | 0.1099 |
| **rs2579519** | 2 | 96675166 | C | 0.1818 |
| rs4851462 | 2 | 98357163 | C | 0.1138 |
| **rs6722745** | 2 | 108875244 | C | 0.0926 |
| rs62158170 | 2 | 114082175 | A | 0.1645 |
| rs10864859 | 2 | 121440218 | T | 0.1962 |
| rs13001283 | 2 | 127183454 | A | 0.1513 |
| rs4954192 | 2 | 135632981 | C | 0.1225 |
| rs7606205 | 2 | 144146311 | C | 0.1207 |
| **rs1438896** | 2 | 145646072 | T | 0.195 |
| rs34570306 | 2 | 146272860 | C | 0.1115 |
| rs62169544 | 2 | 146950908 | G | 0.1207 |
| rs12990959 | 2 | 148572160 | C | 0.1271 |
| rs1220128 | 2 | 158499902 | C | 0.1733 |
| rs2390258 | 2 | 166250129 | G | 0.1031 |
| rs6758859 | 2 | 173965056 | T | 0.1211 |
| **rs79146658** | 2 | 179786068 | C | 0.3344 |
| rs10184839 | 2 | 181946115 | T | 0.1398 |
| **rs16823124** | 2 | 183224127 | A | 0.2276 |
| **rs7592578** | 2 | 191439591 | G | 0.1998 |
| rs2162003 | 2 | 205077128 | T | 0.1279 |
| rs1263671 | 2 | 207996447 | C | 0.1394 |
| rs1250259 | 2 | 216300482 | T | 0.4275 |
| rs4674114 | 2 | 217659266 | G | 0.1808 |
| **rs1063281** | 2 | 218668732 | C | 0.1623 |
| rs1996992 | 2 | 219651349 | G | 0.2964 |
| rs12474050 | 2 | 220362557 | T | 0.1142 |
| rs4507125 | 2 | 239864732 | C | 0.1244 |
| rs9865843 | 3 | 7489993 | G | 0.0906 |
| rs4634143 | 3 | 23163749 | T | 0.1129 |
| **rs13082711** | 3 | 27537909 | C | 0.1778 |
| rs72851229 | 3 | 29374219 | G | 0.1364 |
| rs3774372 | 3 | 41877414 | C | 0.0254 |
| **rs2683696** | **3** | **41914898** | C | 0.3962 |
| rs113134141 | 3 | 46861939 | G | 0.1569 |
| rs13094615 | 3 | 47534921 | T | 0.4073 |
| **rs6797587** | 3 | 48197614 | G | 0.2378 |

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|---|---|---|---|---|
| **rs36022378** | 3 | 49913705 | C | 0.1765 |
| rs9821489 | 3 | 53575728 | A | 0.4962 |
| **rs9810888** | 3 | 53635595 | G | 0.1151 |
| **rs9827472** | 3 | 56726646 | C | 0.133 |
| rs12486605 | 3 | 57706503 | C | 0.1437 |
| rs3774702 | 3 | 63856870 | A | 0.147 |
| **rs918466** | 3 | 64710253 | G | 0.1402 |
| rs11923667 | 3 | 101268080 | A | 0.1222 |
| rs28675079 | 3 | 111500002 | G | 0.1444 |
| rs55914222 | 3 | 128202943 | G | 0.5104 |
| **rs55688777** | 3 | 133886705 | T | 0.18 |
| **rs2306374** | 3 | 138119952 | C | 0.1774 |
| **rs16851397** | 3 | 141134818 | G | 0.3942 |
| rs73158427 | 3 | 153721493 | A | 0.1801 |
| **rs419076** | 3 | 169100886 | T | 0.2755 |
| rs7611674 | 3 | 179169230 | T | 0.1576 |
| **rs12374077** | 3 | 185317674 | C | 0.1748 |
| rs1706003 | 3 | 194299967 | T | 0.1326 |
| rs6777317 | 3 | 197070959 | A | 0.1147 |
| rs55829085 | 4 | 2165493 | C | 0.2672 |
| rs28667801 | 4 | 26785356 | T | 0.1449 |
| rs1878825 | 4 | 36091370 | G | 0.1072 |
| rs1718845 | 4 | 57943153 | G | 0.0963 |
| rs6551716 | 4 | 63575696 | A | 0.1478 |
| rs10008637 | 4 | 77414144 | T | 0.1879 |
| **rs16998073** | 4 | 81184341 | T | 0.494 |
| rs7694000 | 4 | 95324968 | T | 0.0954 |
| rs17248480 | 4 | 102435265 | G | 0.5064 |
| rs13107325 | 4 | 103188709 | C | 0.6747 |
| rs223361 | 4 | 103769304 | T | 0.1522 |
| rs7694643 | 4 | 109017528 | G | 0.1209 |
| **rs6825911** | 4 | 111381638 | C | 0.202 |
| rs4834735 | 4 | 119958809 | T | 0.1511 |
| **rs66887589** | 4 | 120509279 | C | 0.161 |
| **rs4292285** | 4 | 145271954 | T | 0.1073 |
| **rs13139571** | 4 | 156645513 | C | 0.2408 |
| rs954767 | 5 | 3706050 | C | 0.1389 |
| rs12515541 | 5 | 57095011 | T | 0.1104 |
| rs1848510 | 5 | 57754005 | A | 0.1256 |
| rs10062049 | 5 | 61553881 | T | 0.2113 |
| rs4286632 | 5 | 66291370 | A | 0.127 |
| **rs10078021** | 5 | 75038431 | G | 0.1534 |
| rs62380354 | 5 | 89484911 | A | 0.1825 |
| rs1579036 | 5 | 122921103 | A | 0.1714 |

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|---|---|---|---|---|---|---|
| **rs6891344** | 5 | 123136656 | A | 0.2182 | | |
| **rs12521868** | 5 | 131784393 | G | 0.1403 | | |
| rs55747751 | 5 | 132397351 | G | 0.2159 | | |
| rs34070447 | 5 | 147871508 | G | 0.1126 | | |
| **rs9687065** | 5 | 148391140 | A | 0.2199 | | |
| rs114503346 | 5 | 172192350 | C | 0.2678 | | |
| **rs72812846** | 5 | 173377636 | T | 0.2053 | | |
| rs28362590 | 5 | 176731452 | T | 0.1242 | | |
| **rs1799945** | 6 | 26091179 | G | 0.3888 | | |
| rs13191474 | 6 | 27413345 | C | 0.326 | yes | rs547190239 |
| **rs926552** | 6 | 29548089 | G | 0.2501 | | |
| **rs805303** | 6 | 31616366 | G | 0.228 | | |
| rs115245297 | 6 | 34244132 | C | 0.3148 | | |
| rs4714224 | 6 | 39186743 | G | 0.139 | | |
| rs9472135 | 6 | 43809802 | T | 0.1444 | | |
| **rs13205180** | 6 | 51832494 | T | 0.1721 | | |
| **rs12203179** | **6** | **55994237** | C | 0.219 | | |
| rs504691 | 6 | 72206620 | C | 0.1177 | | |
| **rs10943605** | 6 | 79655477 | A | 0.1723 | | |
| rs7753695 | 6 | 80818531 | T | 0.1031 | | |
| rs72613227 | 6 | 106320771 | T | 0.1884 | | |
| rs3822857 | 6 | 116313931 | G | 0.1194 | | |
| rs2693560 | 6 | 117523671 | G | 0.1475 | | |
| **rs9372498** | 6 | 118572486 | A | 0.2731 | | |
| **rs12208772** | **6** | **122125427** | C | 0.2679 | | |
| **rs13209747** | 6 | 127115454 | T | 0.3017 | | |
| rs668459 | 6 | 139835689 | C | 0.1219 | | |
| **rs17080102** | 6 | 151004770 | G | 0.4853 | | |
| rs7766549 | 6 | 152395963 | T | 0.2259 | | |
| rs9479509 | 6 | 153427265 | G | 0.1152 | | |
| rs598682 | 6 | 154418759 | G | 0.1153 | | |
| rs9456648 | 6 | 161712235 | C | 0.1166 | | |
| rs1322639 | 6 | 169587103 | A | 0.2352 | | |
| rs73033340 | 7 | 1195692 | A | 0.4615 | | |
| rs6959688 | 7 | 1966831 | G | 0.2002 | | |
| **rs2969070** | 7 | 2512545 | G | 0.1791 | | |
| rs73049928 | 7 | 4669949 | G | 0.1167 | | |
| rs1468520 | 7 | 7290732 | G | 0.1638 | | |
| rs13240040 | 7 | 14375977 | A | 0.1186 | | |
| rs12705091 | 7 | 19045397 | G | 0.2078 | | |
| rs4507656 | 7 | 22156538 | G | 0.1487 | | |
| rs342989 | 7 | 35467896 | A | 0.1631 | | |
| rs73105827 | 7 | 45036785 | G | 0.1878 | | |
| rs2854746 | 7 | 45960645 | C | 0.228 | | |

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|---|---|---|---|---|---|---|
| rs17454517 | 7 | 50915776 | A | 0.1216 | | |
| rs2222544 | 7 | 69769369 | C | 0.0987 | | |
| rs34324971 | 7 | 74107374 | A | 0.1199 | | |
| rs2282978 | 7 | 92264410 | C | 0.1578 | | |
| rs1947228 | 7 | 96461649 | C | 0.1451 | | |
| rs2526620 | 7 | 100472380 | C | 0.2072 | yes | rs6963129 |
| rs2392929 | 7 | 106414069 | G | 0.2573 | | |
| **rs11556924** | 7 | 129663496 | C | 0.181 | | |
| rs1722886 | 7 | 134215259 | A | 0.1166 | | |
| **rs3918226** | 7 | 150690176 | T | 0.6117 | | |
| **rs891511** | 7 | 150704843 | G | 0.2109 | | |
| rs9638084 | 7 | 156311745 | A | 0.1107 | | |
| rs2922895 | 8 | 6379932 | C | 0.1317 | | |
| rs75902664 | 8 | 17427186 | G | 0.3546 | | |
| rs1047030 | 8 | 22428708 | A | 0.1291 | | |
| rs62503324 | 8 | 23400615 | T | 0.1931 | | |
| rs17321041 | 8 | 26445194 | T | 0.2313 | | |
| rs56345595 | 8 | 82814156 | A | 0.1887 | | |
| rs2142141 | 8 | 90940205 | G | 0.1054 | | |
| **rs2978098** | 8 | 101676675 | A | 0.1548 | | |
| rs2513877 | 8 | 103883630 | G | 0.1294 | | |
| rs11780200 | 8 | 120458521 | G | 0.3319 | | |
| **rs894344** | 8 | 135612745 | G | 0.1267 | | |
| rs6578061 | 8 | 141045732 | A | 0.1465 | | |
| rs10087782 | 8 | 141858620 | T | 0.1211 | | |
| **rs34591516** | 8 | 142367087 | T | 0.3121 | | |
| **rs62524579** | 8 | 144060955 | G | 0.1656 | | |
| rs56233017 | 8 | 144981488 | G | 0.2669 | | |
| rs12216886 | 9 | 2493751 | T | 0.1292 | | |
| rs35287509 | 9 | 10594635 | C | 0.1082 | | |
| **rs4364717** | 9 | 21801530 | G | 0.1006 | | |
| rs1537373 | 9 | 22103341 | G | 0.1397 | yes | rs9644861 |
| **rs76452347** | 9 | 35906471 | C | 0.2246 | | |
| rs11141731 | 9 | 89888472 | C | 0.1258 | | |
| rs7020564 | 9 | 109670016 | T | 0.1105 | | |
| rs7043304 | 9 | 112358150 | T | 0.176 | | |
| rs1861881 | 9 | 119312256 | T | 0.115 | | |
| **rs687621** | 9 | 136137065 | A | 0.1327 | | |
| **rs6271** | 9 | 136522274 | C | 0.4313 | | |
| rs11145807 | 9 | 139520789 | A | 0.155 | | |
| rs10906391 | 10 | 13523937 | T | 0.121 | | |
| **rs4373814** | 10 | 18419972 | C | 0.1595 | | |
| **rs1813353** | 10 | 18707448 | T | 0.2772 | | |
| rs1265842 | 10 | 28924901 | T | 0.1113 | | |

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|---|---|---|---|---|
| rs2505084 | 10 | 30335520 | G | 0.1735 |
| rs76164690 | 10 | 32590362 | G | 0.154 |
| **rs2246438** | 10 | 45273079 | G | 0.1119 |
| **rs10761530** | **10** | **62390726** | T | 0.0955 |
| **rs1530440** | 10 | 63524591 | C | 0.4983 |
| **rs10995311** | 10 | 64564934 | C | 0.2017 |
| rs77413490 | 10 | 89681688 | T | 0.473 |
| **rs4494250** | 10 | 96563757 | A | 0.1917 |
| rs603424 | 10 | 102075479 | A | 0.1717 |
| rs72847884 | 10 | 103115345 | A | 0.2664 |
| **rs4387287** | 10 | 105677897 | A | 0.1575 |
| rs191784289 | 10 | 106894942 | T | 0.7062 |
| rs111777102 | 10 | 111965826 | T | 0.214 |
| **rs1801253** | 10 | 115805056 | C | 0.3183 |
| rs72842207 | 10 | 121433675 | C | 0.2112 |
| rs4411245 | 10 | 126712781 | A | 0.1023 |
| rs17224476 | 11 | 4673788 | A | 0.1547 |
| rs2929184 | 11 | 6289118 | A | 0.1164 |
| **rs110419** | 11 | 8252853 | A | 0.112 |
| rs360153 | 11 | 9762274 | C | 0.1917 |
| **rs900145** | 11 | 13293905 | T | 0.1493 |
| **rs4757391** | 11 | 16302939 | C | 0.3041 |
| **rs381815** | 11 | 16902268 | T | 0.2043 |
| rs11026586 | 11 | 22515533 | A | 0.2606 |
| **rs11030119** | 11 | 27728102 | G | 0.1679 |
| rs919045 | 11 | 31111810 | T | 0.1193 |
| **rs7103648** | 11 | 47461783 | G | 0.235 |
| **rs751984** | 11 | 61278246 | T | 0.3937 |
| **rs4601790** | 11 | 65353906 | A | 0.0197 |
| **rs67330701** | 11 | 69079707 | C | 0.2798 |
| rs875106 | 11 | 70005641 | G | 0.1217 |
| rs504217 | 11 | 72006086 | T | 0.2745 |
| rs2298807 | 11 | 73068571 | T | 0.1233 |
| rs4420291 | 11 | 74374950 | A | 0.0937 |
| rs59986178 | 11 | 77359909 | A | 0.176 |
| rs2450128 | 11 | 77940075 | G | 0.1505 |
| rs2289124 | 11 | 89224477 | A | 0.2199 |
| rs11021221 | 11 | 95308854 | T | 0.1772 |
| **rs633185** | 11 | 100593538 | C | 0.376 |
| rs61892344 | 11 | 101100768 | C | 0.1162 |
| rs12362593 | 11 | 111586091 | G | 0.1275 |
| rs12797557 | 11 | 117254122 | A | 0.177 |
| rs12574332 | 11 | 122521123 | T | 0.1747 |
| **rs11222084** | **11** | **130273230** | A | 0.2736 |

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|---|---|---|---|---|---|---|
| rs78998485 | 12 | 434755 | G | 0.2036 | | |
| rs55935819 | 12 | 2521579 | A | 0.1088 | | |
| rs75507123 | 12 | 5417856 | G | 0.1396 | | |
| rs7132012 | 12 | 8832203 | A | 0.148 | | |
| rs7313556 | 12 | 15297359 | A | 0.090 | | |
| rs61912333 | 12 | 19554817 | C | 0.1191 | | |
| **rs12579720** | 12 | 20173764 | G | 0.2865 | | |
| **rs6487543** | 12 | 26438189 | A | 0.1325 | | |
| rs1098708 | 12 | 27321112 | G | 0.0931 | | |
| rs7965392 | 12 | 42540280 | A | 0.0972 | | |
| rs11168245 | 12 | 48204499 | C | 0.1822 | | |
| **rs7302981** | 12 | 50537815 | A | 0.2652 | | |
| rs7137749 | 12 | 57098040 | T | 0.132 | | |
| rs149723171 | 12 | 94830475 | T | 0.2933 | yes | rs144449115 |
| rs11108209 | 12 | 96109855 | C | 0.1901 | | |
| rs7134060 | 12 | 96717095 | G | 0.0999 | | |
| rs12184466 | 12 | 111281636 | T | 0.2533 | | |
| rs3184504 | 12 | 111884608 | T | 0.4999 | | |
| **rs10850411** | 12 | 115387796 | T | 0.1856 | | |
| **rs35444** | 12 | 115552437 | A | 0.2671 | | |
| **rs11067763** | 12 | 116198341 | A | 0.2177 | | |
| rs3898618 | 12 | 120813921 | C | 0.2532 | | |
| rs28498002 | 12 | 122599796 | C | 0.1566 | | |
| **rs1060105** | 12 | 123806219 | C | 0.1894 | | |
| rs1271309 | 12 | 124820705 | G | 0.1786 | | |
| rs55641580 | 13 | 25257917 | T | 0.1745 | | |
| rs9549297 | 13 | 41397482 | G | 0.14720 | | |
| rs12583637 | 13 | 50564490 | G | 0.1671 | | |
| rs9563529 | 13 | 58316637 | T | 0.1173 | | |
| rs3861113 | 13 | 72364382 | A | 0.2126 | | |
| rs1215469 | 13 | 80707408 | C | 0.1219 | | |
| rs55684003 | 13 | 97988689 | A | 0.1193 | | |
| rs7987651 | 13 | 110448501 | C | 0.1329 | | |
| rs17880989 | 14 | 23313633 | A | 0.3648 | | |
| rs365990 | 14 | 23861811 | A | 0.1937 | | |
| rs4424827 | 14 | 35110857 | C | 0.0948 | | |
| rs11628933 | 14 | 60700903 | G | 0.1338 | | |
| rs731681 | 14 | 68010224 | G | 0.1071 | | |
| rs57786342 | 14 | 69260028 | A | 0.1423 | | |
| rs8014161 | 14 | 92393198 | A | 0.2163 | | |
| rs34161718 | 14 | 104620193 | C | 0.1319 | | |
| rs10873612 | 15 | 26105602 | C | 0.1096 | | |
| rs4924570 | 15 | 41974660 | C | 0.1548 | | |
| rs9806323 | 15 | 48766015 | A | 0.2172 | yes | rs60317590 |

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|---|---|---|---|---|---|---|
| rs956006 | 15 | 62808539 | T | 0.1595 | | |
| **rs7178615** | 15 | 66869072 | G | 0.1371 | | |
| rs62004794 | 15 | 68454523 | G | 0.0948 | | |
| rs11853359 | 15 | 71621524 | G | 0.1608 | | |
| rs61653296 | 15 | 74557817 | G | 0.1405 | | |
| **rs1378942** | 15 | 75077367 | C | 0.388 | | |
| **rs62012628** | 15 | 79070000 | C | 0.238 | | |
| **rs2034618** | 15 | 83799632 | C | 0.1157 | | |
| rs7180952 | 15 | 85162551 | C | 0.0984 | | |
| **rs2521501** | 15 | 91437388 | T | 0.3693 | | |
| rs873122 | 15 | 92702020 | C | 0.1147 | | |
| **rs12906962** | 15 | 95312071 | C | 0.2378 | | |
| rs4984496 | 15 | 96635898 | T | 0.1584 | | |
| rs9932866 | 16 | 706067 | A | 0.1098 | | |
| rs28590346 | 16 | 2080653 | T | 0.1786 | | |
| **rs12921187** | 16 | 4943019 | G | 0.175 | | |
| rs57327054 | 16 | 14487036 | C | 0.1173 | | |
| rs59333122 | 16 | 19149996 | A | 0.1087 | | |
| **rs13333226** | 16 | 20365654 | A | 0.2965 | | |
| rs6565174 | 16 | 30111904 | C | 0.1821 | | |
| **rs72799341** | 16 | 30936743 | A | 0.1599 | | |
| rs10468291 | 16 | 49768046 | C | 0.1166 | | |
| rs9932220 | 16 | 51758116 | G | 0.1591 | | |
| rs12598649 | 16 | 56320824 | G | 0.1519 | yes | rs62039274 |
| rs45474499 | 16 | 66914492 | T | 0.3433 | | |
| rs7185555 | 16 | 69131281 | G | 0.1537 | | |
| rs77870048 | 16 | 69965021 | C | 0.4982 | | |
| **rs8059962** | 16 | 81574197 | C | 0.1397 | | |
| rs7500448 | 16 | 83045790 | A | 0.2134 | | |
| **rs1126464** | 16 | 89704365 | C | 0.2071 | | |
| rs7215084 | 17 | 3880148 | T | 0.1196 | | |
| rs2009598 | 17 | 6470598 | G | 0.1674 | | |
| **rs78378222** | **17** | **7571752** | G | 1.0386 | | |
| rs8069739 | 17 | 8078765 | C | 0.1082 | | |
| rs941454 | 17 | 18230380 | C | 0.1569 | | |
| rs12938803 | 17 | 19204432 | C | 0.1598 | | |
| rs11080134 | 17 | 29161503 | G | 0.0974 | | |
| rs11874 | 17 | 45017193 | G | 0.2327 | yes | rs533030436 |
| rs16948048 | 17 | 47440466 | A | 0.260 | | |
| rs3786130 | 17 | 60765043 | T | 0.1571 | | |
| **rs4308** | 17 | 61559625 | A | 0.1753 | | |
| rs6504213 | 17 | 62381714 | C | 0.2441 | | |
| **rs2467099** | 17 | 73949045 | C | 0.1428 | | |
| **rs57927100** | 17 | 75317300 | C | 0.206 | | |

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|---|---|---|---|---|
| rs11665020 | 18 | 10879503 | G | 0.1371 |
| rs4800420 | 18 | 20158965 | A | 0.1114 |
| rs10164193 | 18 | 31161426 | G | 0.2196 |
| **rs2543029** | **18** | **43098275** | A | 0.2381 |
| **rs745821** | 18 | 48142854 | T | 0.189 |
| rs34163044 | 18 | 51851616 | A | 0.1488 |
| rs72930904 | 18 | 52607301 | C | 0.140 |
| rs12605156 | 18 | 53498114 | A | 0.1418 |
| rs7235890 | 18 | 55732115 | G | 0.1692 |
| rs2009733 | 19 | 8398714 | A | 0.1054 |
| **rs167479** | 19 | 11526765 | G | 0.362 |
| rs3745318 | 19 | 16436262 | T | 0.1396 |
| **rs2304130** | 19 | 19789528 | G | 0.2396 |
| rs6511291 | 19 | 21950402 | C | 0.1158 |
| **rs62104477** | 19 | 30294991 | T | 0.1703 |
| rs1821295 | 19 | 32590773 | C | 0.1347 |
| rs12983238 | 19 | 39438532 | G | 0.1266 |
| **rs6108168** | 20 | 8626271 | C | 0.1901 |
| **rs1327235** | 20 | 10969030 | G | 0.3018 |
| rs1232482 | 20 | 11886643 | C | 0.1155 |
| rs2618647 | 20 | 17882452 | G | 0.0983 |
| rs3790228 | 20 | 19469150 | G | 0.1759 |
| **rs6060114** | 20 | 30169673 | T | 0.1689 |
| rs13042148 | 20 | 32298286 | C | 0.1543 |
| rs4810332 | 20 | 40268334 | T | 0.1562 |

## Study III

Table A3 List of genetic instruments associated to TSH, FT4, Hyperthyroidism, Hypothyroidism and TPOAb [95]

| SNP | POS | EA | OA | EAF | BETA | SE | P | exposure |
|---|---|---|---|---|---|---|---|---|
| rs17020122 | 1:108357391 | T | C | 0,09 | 0,1 | 0,01 | 5,32E-20 | TSH |
| rs12089835 | 1:19771438 | T | C | 0,35 | 0,07 | 0,01 | 1,27E-28 | TSH |
| rs10917469 | 1:19843576 | A | G | 0,84 | 0,11 | 0,01 | 3,95E-39 | TSH |
| rs334725 | 1:61610049 | A | G | 0,95 | 0,17 | 0,01 | 2,45E-32 | TSH |
| rs11255790 | 10:8682180 | T | C | 0,3 | -0,04 | 0,01 | 6,83E-10 | TSH |
| rs4933466 | 10:89849519 | A | G | 0,6 | 0,04 | 0,01 | 5,13E-10 | TSH |
| rs4445669 | 11:115045237 | T | C | 0,46 | -0,04 | 0,01 | 5,76E-11 | TSH |
| rs12284404 | 11:45228686 | A | G | 0,27 | -0,07 | 0,01 | 2,48E-22 | TSH |
| rs7329958 | 13:24782080 | T | C | 0,35 | -0,04 | 0,01 | 1,13E-11 | TSH |
| rs398745 | 14:36536181 | A | C | 0,59 | -0,05 | 0,01 | 3,97E-17 | TSH |
| rs2254613 | 14:36713154 | T | G | 0,55 | -0,03 | 0,01 | 3,44E-08 | TSH |
| rs11159482 | 14:81490842 | T | C | 0,09 | 0,08 | 0,01 | 6,30E-11 | TSH |
| rs59334515 | 14:81594143 | T | C | 0,22 | -0,05 | 0,01 | 1,10E-13 | TSH |
| rs12893151 | 14:81619945 | A | C | 0,22 | -0,06 | 0,01 | 1,02E-15 | TSH |
| rs8015085 | 14:93585331 | A | G | 0,21 | 0,07 | 0,01 | 2,45E-18 | TSH |
| rs11639111 | 15:49749735 | T | C | 0,41 | 0,05 | 0,01 | 3,60E-13 | TSH |
| rs13329353 | 15:89113877 | T | C | 0,68 | 0,06 | 0,01 | 5,17E-21 | TSH |
| rs30227 | 16:14405428 | T | C | 0,61 | -0,05 | 0,01 | 7,59E-14 | TSH |
| rs1045476 | 16:4015313 | A | G | 0,18 | 0,05 | 0,01 | 2,36E-09 | TSH |
| rs17767491 | 16:79745487 | A | G | 0,68 | 0,09 | 0,01 | 3,35E-42 | TSH |
| rs1157994 | 17:59338574 | A | G | 0,05 | -0,09 | 0,02 | 5,28E-09 | TSH |
| rs1042673 | 17:70121339 | A | G | 0,52 | -0,05 | 0,01 | 3,57E-19 | TSH |
| rs4804413 | 19:7222655 | T | C | 0,44 | 0,05 | 0,01 | 8,64E-18 | TSH |

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|---|---|---|---|---|---|---|---|---|
| rs16856540 | 2:217580413 | T | C | 0,84 | -0,05 | 0,01 | 7,81E-11 | TSH |
| rs13015993 | 2:217625523 | A | G | 0,73 | 0,08 | 0,01 | 4,52E-32 | TSH |
| rs6724073 | 2:218236786 | T | C | 0,74 | 0,05 | 0,01 | 1,35E-10 | TSH |
| rs1203944 | 20:22596879 | T | C | 0,23 | -0,05 | 0,01 | 2,42E-12 | TSH |
| rs1663070 | 3:12239852 | T | C | 0,74 | -0,05 | 0,01 | 3,49E-11 | TSH |
| rs28502438 | 3:149220109 | T | C | 0,57 | 0,03 | 0,01 | 3,70E-08 | TSH |
| rs59381142 | 3:193916181 | A | G | 0,24 | -0,06 | 0,01 | 1,70E-14 | TSH |
| rs6535624 | 4:149587905 | A | G | 0,44 | 0,04 | 0,01 | 1,60E-11 | TSH |
| rs11732089 | 4:149665602 | T | C | 0,8 | 0,12 | 0,01 | 1,73E-51 | TSH |
| rs62362610 | 5:76439961 | C | G | 0,08 | 0,07 | 0,01 | 7,73E-10 | TSH |
| rs1119208 | 5:76488613 | T | C | 0,37 | 0,05 | 0,01 | 6,65E-13 | TSH |
| rs139424329 | 5:76495539 | A | G | 0,01 | -0,2 | 0,03 | 5,14E-10 | TSH |
| rs2127387 | 5:76532571 | A | G | 0,41 | 0,14 | 0,01 | 1,10E-117 | TSH |
| rs7702192 | 5:76554807 | A | C | 0,47 | 0,07 | 0,01 | 2,61E-30 | TSH |
| rs113974964 | 5:76652403 | T | C | 0,05 | -0,12 | 0,01 | 2,06E-17 | TSH |
| rs139149784 | 5:76660193 | A | G | 0,03 | 0,16 | 0,03 | 4,97E-08 | TSH |
| rs9497965 | 6:148521292 | T | C | 0,4 | 0,04 | 0,01 | 9,81E-13 | TSH |
| rs73022105 | 6:165973757 | T | C | 0,95 | 0,1 | 0,02 | 1,20E-11 | TSH |
| rs1079418 | 6:166047034 | A | G | 0,69 | 0,1 | 0,01 | 8,23E-53 | TSH |
| rs1265091 | 6:31108129 | T | C | 0,2 | 0,06 | 0,01 | 3,20E-11 | TSH |
| rs744103 | 6:43805362 | A | T | 0,69 | 0,09 | 0,01 | 6,73E-41 | TSH |
| rs9381266 | 6:43905037 | T | C | 0,74 | 0,07 | 0,01 | 1,84E-25 | TSH |
| rs118039499 | 8:133771635 | A | C | 0,98 | 0,18 | 0,02 | 1,99E-14 | TSH |
| rs2739067 | 8:133951991 | A | G | 0,6 | -0,04 | 0,01 | 2,43E-11 | TSH |
| rs56009477 | 8:23356964 | A | G | 0,84 | 0,05 | 0,01 | 3,72E-10 | TSH |
| rs2439301 | 8:32433013 | A | G | 0,23 | -0,06 | 0,01 | 8,15E-15 | TSH |
| rs10957494 | 8:70365025 | A | G | 0,69 | -0,04 | 0,01 | 1,10E-09 | TSH |
| rs9298749 | 9:16214340 | A | C | 0,59 | -0,04 | 0,01 | 8,80E-10 | TSH |

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|---|---|---|---|---|---|---|---|---|
| rs10814915 | 9:4290544 | T | C | 0,44 | 0,04 | 0,01 | 5,06E-12 | TSH |
| rs145019385 | 1:54252139 | T | C | 0,98 | 0,181 | 0,032 | 1,10E-08 | FT4 |
| rs12033572 | 1:54369674 | C | G | 0,05 | 0,115 | 0,017 | 1,40E-11 | FT4 |
| rs2235544 | 1:54375570 | A | C | 0,52 | 0,139 | 0,007 | 4,20E-101 | FT4 |
| rs954878 | 1:54578401 | G | A | 0,55 | 0,058 | 0,007 | 4,80E-19 | FT4 |
| rs4149056 | 12:21331549 | C | T | 0,66 | 0,051 | 0,009 | 1,30E-08 | FT4 |
| rs12323871 | 14:101852075 | C | T | 0,16 | 0,047 | 0,008 | 1,40E-08 | FT4 |
| rs11626434 | 14:101998443 | C | G | 0,18 | 0,058 | 0,007 | 4,10E-17 | FT4 |
| rs150816132 | 14:80464293 | G | A | 0,64 | 0,22 | 0,04 | 3,50E-08 | FT4 |
| rs978055 | 14:80534869 | A | T | 0,01 | 0,038 | 0,007 | 1,10E-08 | FT4 |
| rs225014 | 14:80669580 | T | C | 0,62 | 0,054 | 0,007 | 1,80E-15 | FT4 |
| rs12907106 | 15:63873658 | G | C | 0,36 | 0,041 | 0,007 | 3,70E-08 | FT4 |
| rs8063103 | 16:12703395 | G | C | 0,73 | 0,052 | 0,009 | 1,60E-08 | FT4 |
| rs1080094 | 18:29173795 | G | A | 0,47 | 0,042 | 0,007 | 4,10E-10 | FT4 |
| rs113107469 | 18:29306737 | T | C | 0,4 | 0,2 | 0,022 | 1,00E-19 | FT4 |
| rs56069042 | 18:57914644 | A | G | 0,97 | 0,106 | 0,019 | 1,20E-08 | FT4 |
| rs4954192 | 2:135632981 | C | T | 0,04 | 0,041 | 0,007 | 8,40E-09 | FT4 |
| rs6785807 | 3:181718601 | G | A | 0,57 | 0,059 | 0,009 | 2,50E-10 | FT4 |
| rs6854291 | 4:170992760 | A | G | 0,15 | 0,117 | 0,011 | 1,30E-24 | FT4 |
| rs17185536 | 6:100620931 | T | C | 0,24 | 0,073 | 0,008 | 1,90E-19 | FT4 |
| rs10946313 | 6:19381386 | T | C | 0,63 | 0,046 | 0,007 | 2,30E-11 | FT4 |
| rs9356988 | 6:25777481 | G | A | 0,73 | 0,051 | 0,007 | 3,60E-12 | FT4 |
| rs137964359 | 6:26001742 | C | T | 0,01 | 0,2 | 0,032 | 2,10E-10 | FT4 |
| rs67583169 | 8:61212179 | C | G | 0,87 | 0,061 | 0,01 | 1,00E-10 | FT4 |
| rs10739496 | 9:100552559 | T | C | 0,66 | 0,078 | 0,007 | 4,20E-30 | FT4 |
| rs10984606 | 9:100739117 | G | T | 0,5 | 0,04 | 0,007 | 1,20E-09 | FT4 |
| rs10818937 | 9:127015440 | C | T | 0,69 | 0,048 | 0,007 | 1,30E-11 | FT4 |
| rs4842131 | 9:139092679 | C | T | 0,55 | 0,104 | 0,008 | 7,70E-44 | FT4 |

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|---|---|---|---|---|---|---|---|---|
| rs55679545 | 9:139122363 | A | G | 0,27 | 0,044 | 0,008 | 8,40E-09 | FT4 |
| rs10119187 | 9:4223660 | T | C | 0,81 | 0,05 | 0,009 | 4,10E-09 | FT4 |
| rs11675342 | 2:1407628 | T | C | 0,43 | 0,16 | 0,025 | 1,50E-10 | Hypothyroidism |
| rs12449792 | 17:43302259 | T | C | 0,45 | 0,157 | 0,028 | 2,40E-08 | Hypothyroidism |
| rs1382879 | 5:76521868 | C | T | 0,39 | 0,153 | 0,026 | 2,10E-09 | Hypothyroidism |
| rs2983514 | 6:166050119 | A | G | 0,68 | 0,154 | 0,027 | 1,60E-08 | Hypothyroidism |
| rs4273946 | 9:100547627 | C | G | 0,68 | 0,248 | 0,027 | 5,50E-20 | Hypothyroidism |
| rs597808 | 12:111973358 | A | G | 0,48 | 0,18 | 0,026 | 3,50E-12 | Hypothyroidism |
| rs75491569 | 1:19836221 | C | T | 0,85 | 0,238 | 0,037 | 8,70E-11 | Hypothyroidism |
| rs78495697 | 1:108355719 | T | C | 0,1 | 0,316 | 0,041 | 2,60E-14 | Hypothyroidism |
| rs12138950 | 1:19839115 | C | A | 0,15 | 0,258 | 0,042 | 5,50E-10 | Hyperthyroidism |
| rs11038357 | 11:45237858 | A | T | 0,29 | 0,235 | 0,035 | 3,10E-11 | Hyperthyroidism |
| rs17477923 | 15:49711185 | C | T | 0,26 | 0,245 | 0,034 | 6,10E-13 | Hyperthyroidism |
| rs8077245 | 17:70376177 | T | G | 0,53 | 0,205 | 0,033 | 5,00E-10 | Hyperthyroidism |
| rs2046045 | 5:76535811 | T | G | 0,61 | 0,329 | 0,034 | 4,40E-22 | Hyperthyroidism |
| rs2983514 | 6:166050119 | G | A | 0,32 | 0,199 | 0,032 | 5,20E-10 | Hyperthyroidism |
| rs66760320 | 6:43906255 | T | C | 0,25 | 0,192 | 0,035 | 4,40E-08 | Hyperthyroidism |
| rs925488 | 9:100546391 | A | G | 0,68 | 0,19 | 0,033 | 1,10E-08 | Hyperthyroidism |
| rs11675434 | 2:1407815 | T | C | 0,32 | 0,02 | 0,005 | 7,40E-13 | TPOAb |
| rs2010099 | 3:124300257 | C | T | 0,91 | 0,024 | 0,008 | 3,1E10-8 | TPOAb |
| rs653178 | 12:112007756 | C | T | 0,5 | 0,015 | 0,004 | 3,50E-10 | TPOAb |
| rs9277555 | 6:33055605 | G | A | 0,74 | 0,02 | 0,005 | 3,90E-12 | TPOAb |

*EA, Effect Allele; EAF, Effect allele frequency; FT4, free tetraiodothyronine; OA, Other allele; TPOAb, anti-thyroid peroxidase antibodies; TSH, thyroid-stimulating hormone*

## Study IV

Table A4 List of instrumental variables associated with calcium level, Vitamin D, FGF23 and PTH [96]

| SNP | POS | EA | OA | EAF | BETA | SE | P | exposure |
|---|---|---|---|---|---|---|---|---|
| rs61766352 | 1:1086179 | C | T | 0.2787 | -0.002376 | 0.0002565 | 2.80E-22 | calcium |
| rs629301 | 1:109818306 | T | G | 0.778 | 0.00158 | 0.000272 | 9.40E-10 | calcium |
| rs10737767 | 1:116830250 | C | T | 0.4161 | 0.001402 | 0.0002306 | 6.50E-10 | calcium |
| rs760077 | 1:155178782 | T | A | 0.6011 | -0.002513 | 0.0002307 | 1.50E-26 | calcium |
| rs36086195 | 1:16510894 | T | C | 0.5791 | 0.001839 | 0.0002291 | 1.10E-15 | calcium |
| rs1434282 | 1:199010721 | T | C | 0.725 | 0.002059 | 0.0002543 | 9.20E-17 | calcium |
| rs4506486 | 1:200453320 | T | C | 0.6019 | 0.001539 | 0.0002312 | 3.50E-11 | calcium |
| rs1497826 | 1:217471419 | G | C | 0.3736 | 0.001792 | 0.0002351 | 2.80E-15 | calcium |
| rs12132412 | 1:21820042 | G | A | 0.3906 | 0.002386 | 0.0002337 | 1.70E-20 | calcium |
| rs3011 | 1:220085453 | C | G | 0.3689 | -0.001904 | 0.0002353 | 2.70E-16 | calcium |
| rs6667260 | 1:226923938 | C | A | 0.4579 | -0.0016 | 0.0002269 | 1.00E-13 | calcium |
| rs841572 | 1:43436051 | A | G | 0.4069 | 0.002805 | 0.0002307 | 1.60E-35 | calcium |
| rs112174050 | 1:51581471 | T | C | 0.02497 | 0.009962 | 0.0007328 | 1.70E-43 | calcium |
| rs148756772 | 1:68270398 | C | G | 0.03229 | 0.006967 | 0.0006552 | 4.10E-27 | calcium |
| rs1848837 | 1:78578550 | G | A | 0.2881 | -0.001482 | 0.0002502 | 3.70E-10 | calcium |
| rs2296436 | 10:100179851 | C | T | 0.08461 | -0.002759 | 0.000407 | 8.70E-12 | calcium |
| rs2419886 | 10:115841641 | T | C | 0.2555 | -0.001604 | 0.000261 | 1.90E-10 | calcium |
| rs3011642 | 10:22394843 | T | C | 0.2422 | 0.001886 | 0.0002649 | 1.10E-12 | calcium |
| rs2377965 | 10:50510522 | G | T | 0.5284 | -0.001871 | 0.000227 | 1.20E-16 | calcium |
| rs1262217 | 10:65483262 | A | G | 0.8256 | 0.001964 | 0.0002984 | 8.50E-12 | calcium |
| rs498490 | 10:8118677 | T | C | 0.1661 | -0.002636 | 0.0003052 | 8.80E-19 | calcium |
| rs9420589 | 10:94450233 | T | G | 0.4345 | 0.001641 | 0.0002289 | 4.10E-13 | calcium |
| rs2274224 | 10:96039597 | C | G | 0.4346 | -0.001703 | 0.0002285 | 2.70E-13 | calcium |
| rs7947953 | 11:10684060 | G | A | 0.6123 | 0.001311 | 0.0002323 | 1.20E-08 | calcium |

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|---|---|---|---|---|---|---|---|---|
| rs561830 | 11:119043745 | T | C | 0.2518 | -0.00216 | 0.0002617 | 5.10E-16 | calcium |
| rs11218721 | 11:122504717 | A | C | 0.3894 | 0.001554 | 0.0002337 | 1.30E-12 | calcium |
| rs7928577 | 11:126227723 | T | G | 0.07379 | -0.005488 | 0.0004333 | 2.50E-37 | calcium |
| rs2855799 | 11:128737694 | A | G | 0.8116 | -0.001643 | 0.0002906 | 1.10E-08 | calcium |
| rs11511848 | 11:13505549 | T | C | 0.6261 | 0.002855 | 0.0002342 | 1.70E-33 | calcium |
| rs12363232 | 11:47623890 | T | C | 0.3491 | -0.001991 | 0.000238 | 3.50E-18 | calcium |
| rs2298615 | 11:65352062 | T | C | 0.2324 | -0.00178 | 0.0002685 | 4.90E-12 | calcium |
| rs7115200 | 11:71752160 | G | T | 0.4384 | -0.001457 | 0.0002285 | 6.50E-11 | calcium |
| rs302650 | 11:87901236 | A | G | 0.4329 | -0.001847 | 0.0002285 | 3.40E-16 | calcium |
| rs17884869 | 12:123519112 | A | G | 0.02463 | -0.009579 | 0.0007304 | 8.00E-39 | calcium |
| rs4763297 | 12:12889289 | C | A | 0.4323 | 0.001603 | 0.0002299 | 6.10E-12 | calcium |
| rs12369443 | 12:20582651 | G | A | 0.199 | -0.001637 | 0.0002857 | 3.00E-09 | calcium |
| rs12320328 | 12:25408464 | G | A | 0.08462 | -0.002646 | 0.0004081 | 3.40E-11 | calcium |
| rs117213754 | 12:4006794 | A | G | 0.01472 | 0.00825 | 0.0009405 | 3.80E-19 | calcium |
| rs79295634 | 12:47180008 | G | A | 0.06783 | 0.002446 | 0.0004511 | 2.70E-08 | calcium |
| rs6580981 | 12:54723028 | A | G | 0.4584 | -0.00176 | 0.0002287 | 4.50E-14 | calcium |
| rs11172256 | 12:57976118 | G | A | 0.2558 | -0.00192 | 0.0002603 | 1.90E-13 | calcium |
| rs12583851 | 13:110504964 | C | T | 0.7503 | -0.002021 | 0.000262 | 6.40E-15 | calcium |
| rs7319447 | 13:42551508 | G | A | 0.1513 | -0.003277 | 0.0003162 | 2.00E-25 | calcium |
| rs78844280 | 13:50349898 | A | G | 0.02206 | -0.004317 | 0.0007712 | 1.70E-08 | calcium |
| rs8011945 | 14:21871999 | G | T | 0.9093 | 0.002638 | 0.0003955 | 9.00E-11 | calcium |
| rs11625026 | 14:24869746 | T | C | 0.3309 | 0.001541 | 0.000244 | 1.10E-09 | calcium |
| rs17718872 | 14:51000770 | T | C | 0.1445 | 0.001733 | 0.0003234 | 1.10E-08 | calcium |
| rs35852840 | 14:64595763 | A | C | 0.05802 | 0.002627 | 0.0004882 | 6.90E-09 | calcium |
| rs7144433 | 14:90850229 | T | C | 0.8923 | -0.002755 | 0.0003665 | 1.20E-14 | calcium |
| rs17127600 | 14:92279983 | G | T | 0.171 | -0.00233 | 0.0003027 | 7.80E-14 | calcium |
| rs28929474 | 14:94844947 | T | C | 0.01967 | 0.01164 | 0.0008173 | 1.70E-46 | calcium |
| rs147233090 | 15:44028047 | T | C | 0.02481 | 0.008869 | 0.0007339 | 1.10E-33 | calcium |

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|---|---|---|---|---|---|---|---|---|
| rs11632520 | 15:49358308 | T | C | 0.1692 | -0.002245 | 0.0003033 | 1.00E-13 | calcium |
| rs12911748 | 15:51493568 | T | C | 0.5221 | -0.001535 | 0.0002291 | 1.30E-12 | calcium |
| rs55754498 | 15:60883394 | T | C | 0.05317 | -0.003008 | 0.000507 | 2.00E-08 | calcium |
| rs11071896 | 15:66821250 | G | A | 0.25 | 0.001657 | 0.0002618 | 1.00E-09 | calcium |
| rs34066945 | 15:69612053 | T | C | 0.358 | -0.002096 | 0.0002369 | 1.40E-19 | calcium |
| rs12148513 | 15:75222225 | T | C | 0.3792 | 0.001276 | 0.0002357 | 1.70E-08 | calcium |
| rs11629876 | 15:96666402 | T | C | 0.331 | -0.001408 | 0.000241 | 3.70E-09 | calcium |
| rs41278174 | 16:16259596 | A | G | 0.02739 | 0.004561 | 0.0006946 | 1.00E-10 | calcium |
| rs2745205 | 16:1844226 | G | C | 0.6981 | -0.001306 | 0.0002475 | 4.10E-08 | calcium |
| rs16945716 | 16:47980267 | C | T | 0.04904 | -0.00359 | 0.0005266 | 5.90E-12 | calcium |
| rs12922549 | 16:54451747 | T | C | 0.2378 | -0.00225 | 0.0002722 | 6.50E-17 | calcium |
| rs1858800 | 16:73024276 | T | C | 0.3453 | 0.002785 | 0.0002399 | 4.90E-33 | calcium |
| rs35610022 | 16:81586901 | T | C | 0.5206 | 0.001374 | 0.0002283 | 1.20E-09 | calcium |
| rs12918968 | 16:88520452 | C | A | 0.4384 | -0.002643 | 0.0002288 | 1.90E-32 | calcium |
| rs34422500 | 16:89703797 | T | C | 0.1304 | 0.002444 | 0.0003467 | 7.10E-14 | calcium |
| rs11078597 | 17:1618363 | C | T | 0.1864 | 0.004854 | 0.0002912 | 2.50E-64 | calcium |
| rs12600694 | 17:18091019 | A | G | 0.1998 | 0.001871 | 0.0002833 | 4.10E-11 | calcium |
| rs66634575 | 17:27499881 | T | C | 0.1831 | 0.001721 | 0.0002939 | 3.60E-09 | calcium |
| rs7221118 | 17:47907641 | C | T | 0.2142 | -0.001846 | 0.0002773 | 3.40E-11 | calcium |
| rs9910998 | 17:55292765 | A | C | 0.07198 | 0.003908 | 0.0004403 | 2.00E-18 | calcium |
| rs2270114 | 17:59478776 | C | G | 0.7336 | -0.002299 | 0.0002567 | 9.20E-20 | calcium |
| rs77542162 | 17:67081278 | G | A | 0.02267 | -0.008596 | 0.0007621 | 3.10E-31 | calcium |
| rs10852764 | 17:73503489 | C | G | 0.9034 | 0.002144 | 0.0003836 | 2.60E-08 | calcium |
| rs689049 | 18:57168498 | C | T | 0.5811 | 0.001359 | 0.0002315 | 6.80E-09 | calcium |
| rs55722786 | 18:60206800 | T | G | 0.2847 | 0.001411 | 0.0002526 | 7.70E-09 | calcium |
| rs7252372 | 19:14172896 | C | G | 0.4429 | 0.001276 | 0.0002318 | 9.10E-09 | calcium |
| rs143333049 | 19:19800289 | G | A | 0.04016 | 0.004958 | 0.0005947 | 5.30E-16 | calcium |
| rs1672991 | 19:35556659 | G | A | 0.9336 | 0.006755 | 0.0004552 | 9.20E-52 | calcium |

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|---|---|---|---|---|---|---|---|---|
| rs142888784 | 19:38810744 | G | C | 0.02256 | -0.008762 | 0.0008414 | 7.90E-27 | calcium |
| rs7248167 | 19:43960114 | C | A | 0.217 | -0.001568 | 0.0002765 | 8.30E-09 | calcium |
| rs73036517 | 19:45744842 | G | A | 0.2596 | -0.001455 | 0.0002598 | 1.90E-08 | calcium |
| rs1448208 | 2:112263474 | T | C | 0.3358 | -0.001389 | 0.0002415 | 5.10E-09 | calcium |
| rs895418 | 2:114018320 | T | C | 0.4693 | 0.002143 | 0.0002275 | 2.40E-21 | calcium |
| rs11673819 | 2:121070729 | T | C | 0.7035 | -0.002192 | 0.0002485 | 8.40E-19 | calcium |
| rs13389219 | 2:165528876 | T | C | 0.3928 | -0.00139 | 0.0002313 | 1.30E-10 | calcium |
| rs12613807 | 2:191343763 | C | T | 0.4449 | 0.001483 | 0.0002275 | 4.30E-11 | calcium |
| rs7559013 | 2:213735555 | C | A | 0.1295 | 0.002221 | 0.0003373 | 8.70E-11 | calcium |
| rs838717 | 2:234296444 | A | G | 0.5667 | -0.003746 | 0.0002285 | 1.00E-60 | calcium |
| rs10197122 | 2:240285317 | T | C | 0.0721 | 0.002422 | 0.0004388 | 1.40E-08 | calcium |
| rs60624480 | 2:242297118 | A | G | 0.3596 | -0.002183 | 0.0002355 | 1.90E-21 | calcium |
| rs1260326 | 2:27730940 | C | T | 0.6051 | -0.004453 | 0.0002309 | 4.30E-87 | calcium |
| rs12467820 | 2:37572806 | T | G | 0.4936 | 0.001244 | 0.0002266 | 2.70E-09 | calcium |
| rs10193807 | 2:39601264 | C | T | 0.8402 | 0.001816 | 0.0003098 | 5.80E-09 | calcium |
| rs6545412 | 2:54727795 | T | A | 0.1538 | 0.002016 | 0.0003164 | 1.50E-10 | calcium |
| rs12468920 | 2:66197123 | G | A | 0.307 | 0.001388 | 0.0002464 | 2.20E-08 | calcium |
| rs111712978 | 2:91928755 | A | G | 0.04736 | -0.004198 | 0.0006374 | 1.70E-11 | calcium |
| rs6576983 | 2:97454650 | G | T | 0.3919 | -0.003502 | 0.0002315 | 2.30E-53 | calcium |
| rs3091842 | 20:39344272 | A | G | 0.04416 | 0.008099 | 0.0005697 | 2.40E-47 | calcium |
| rs3787267 | 20:45626851 | T | C | 0.6532 | -0.001364 | 0.000241 | 1.20E-08 | calcium |
| rs73078112 | 20:5547384 | T | C | 0.02722 | 0.004687 | 0.0006998 | 1.30E-11 | calcium |
| rs185799410 | 20:57466093 | T | G | 0.02602 | -0.00399 | 0.0007238 | 2.40E-08 | calcium |
| rs928760 | 21:35890958 | T | C | 0.3027 | -0.001714 | 0.0002475 | 3.70E-12 | calcium |
| rs219781 | 21:37832621 | T | G | 0.2632 | 0.001459 | 0.0002576 | 1.40E-08 | calcium |
| rs16853573 | 3:107233412 | C | T | 0.07673 | 0.004122 | 0.0004299 | 7.40E-22 | calcium |
| rs2271494 | 3:113300183 | T | A | 0.4164 | 0.001836 | 0.0002293 | 8.70E-17 | calcium |
| rs73186030 | 3:122013465 | C | T | 0.869623 | -0.0176658 | 0.000335171 | 2.7E-100 | calcium |

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|---|---|---|---|---|---|---|---|---|
| rs1801282 | 3:12393125 | G | C | 0.1197 | -0.00332 | 0.0003469 | 2.20E-22 | calcium |
| rs28519617 | 3:135874930 | G | T | 0.2703 | 0.002542 | 0.0002555 | 9.60E-24 | calcium |
| rs3773912 | 3:152180137 | T | C | 0.463 | -0.001284 | 0.0002267 | 1.00E-08 | calcium |
| rs13322435 | 3:156795468 | G | A | 0.4039 | 0.001779 | 0.0002313 | 1.90E-15 | calcium |
| rs2593813 | 3:186332571 | A | G | 0.6342 | 0.003279 | 0.0002344 | 5.70E-47 | calcium |
| rs35154162 | 3:4629789 | T | C | 0.7695 | -0.00191 | 0.0002681 | 1.90E-14 | calcium |
| rs11709284 | 3:52559705 | A | G | 0.5551 | 0.001386 | 0.0002271 | 3.60E-10 | calcium |
| rs12485738 | 3:56865776 | G | A | 0.629 | -0.001704 | 0.0002335 | 3.00E-13 | calcium |
| rs13107325 | 4:103188709 | T | C | 0.0758 | -0.006227 | 0.0004283 | 2.50E-48 | calcium |
| rs2713844 | 4:106287354 | A | G | 0.7632 | -0.00165 | 0.0002668 | 3.20E-10 | calcium |
| rs2388993 | 4:115379445 | G | T | 0.5869 | -0.001311 | 0.0002303 | 3.70E-09 | calcium |
| rs4320103 | 4:170910322 | G | A | 0.03895 | 0.00452 | 0.0005913 | 2.80E-13 | calcium |
| rs13108218 | 4:3443931 | G | A | 0.6157 | -0.003487 | 0.0002348 | 3.10E-51 | calcium |
| rs7688574 | 4:38533499 | T | C | 0.3707 | 0.001386 | 0.0002348 | 3.10E-09 | calcium |
| rs6841258 | 4:40565426 | T | C | 0.1678 | -0.003692 | 0.0003026 | 9.00E-36 | calcium |
| rs4864709 | 4:53879085 | C | T | 0.3711 | 0.001293 | 0.0002347 | 2.50E-08 | calcium |
| rs251391 | 5:127538116 | T | C | 0.7453 | 0.001483 | 0.0002613 | 4.50E-09 | calcium |
| rs12519940 | 5:133904597 | T | C | 0.2785 | -0.002307 | 0.0002545 | 3.60E-20 | calcium |
| rs6556313 | 5:176792491 | G | A | 0.3318 | 0.001649 | 0.0002409 | 1.30E-12 | calcium |
| rs10942734 | 5:74595194 | C | A | 0.4284 | 0.001531 | 0.0002294 | 2.20E-11 | calcium |
| rs6897362 | 5:76110217 | A | G | 0.5261 | -0.001326 | 0.0002268 | 2.10E-08 | calcium |
| rs4946137 | 6:116418112 | A | G | 0.4015 | 0.001687 | 0.0002315 | 3.60E-14 | calcium |
| rs9388399 | 6:125333797 | C | T | 0.3113 | -0.002087 | 0.0002454 | 4.10E-18 | calcium |
| rs7756870 | 6:130373648 | G | C | 0.6886 | -0.002046 | 0.000245 | 3.30E-18 | calcium |
| rs1763519 | 6:134518919 | C | G | 0.6065 | -0.002531 | 0.0002322 | 3.10E-29 | calcium |
| rs2327774 | 6:137275839 | C | T | 0.3792 | -0.001815 | 0.0002381 | 2.00E-14 | calcium |
| rs7742369 | 6:34165721 | G | A | 0.1748 | 0.003858 | 0.0002981 | 2.00E-37 | calcium |
| rs1214761 | 6:43354431 | G | A | 0.6787 | -0.00133 | 0.0002427 | 1.60E-08 | calcium |

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|---|---|---|---|---|---|---|---|---|
| rs4263551 | 6:74486371 | C | T | 0.5165 | -0.003464 | 0.0002267 | 1.60E-53 | calcium |
| rs511220 | 7:105314015 | A | T | 0.4081 | 0.001341 | 0.0002424 | 9.70E-09 | calcium |
| rs2283038 | 7:106835410 | T | C | 0.2367 | -0.002077 | 0.0002678 | 7.70E-15 | calcium |
| rs34372369 | 7:143092269 | A | G | 0.05172 | 0.003306 | 0.0005119 | 4.10E-11 | calcium |
| rs3857708 | 7:16140077 | A | G | 0.2998 | 0.001881 | 0.000249 | 4.90E-14 | calcium |
| rs4718271 | 7:65212402 | C | A | 0.4502 | 0.002856 | 0.0002279 | 5.50E-38 | calcium |
| rs7786368 | 7:77500734 | C | T | 0.4169 | -0.0019 | 0.00023 | 1.90E-16 | calcium |
| rs5745687 | 7:81359051 | T | C | 0.06607 | 0.002584 | 0.0004565 | 1.00E-08 | calcium |
| rs6993770 | 8:106581528 | T | A | 0.2871 | -0.001879 | 0.0002503 | 4.00E-15 | calcium |
| rs28601761 | 8:126500031 | G | C | 0.419 | -0.001306 | 0.0002324 | 9.30E-10 | calcium |
| rs62522556 | 8:145005450 | C | T | 0.3987 | 0.001577 | 0.000232 | 1.90E-11 | calcium |
| rs62493995 | 8:21946301 | G | T | 0.2876 | -0.001932 | 0.0002593 | 1.00E-13 | calcium |
| rs36104352 | 8:23377604 | C | A | 0.1205 | 0.002472 | 0.000348 | 2.40E-12 | calcium |
| rs9657190 | 8:38295928 | G | A | 0.2464 | 0.001851 | 0.0002629 | 3.90E-12 | calcium |
| rs74677734 | 8:72528849 | A | G | 0.04885 | 0.003259 | 0.0005262 | 4.60E-10 | calcium |
| rs4240624 | 8:9184231 | A | G | 0.9094 | 0.005811 | 0.0003957 | 1.00E-49 | calcium |
| rs6983263 | 8:98835226 | C | T | 0.4744 | -0.001321 | 0.0002288 | 6.00E-09 | calcium |
| rs10819178 | 9:129294976 | G | T | 0.6378 | 0.003035 | 0.0002375 | 2.40E-39 | calcium |
| rs13283282 | 9:131465481 | G | C | 0.146 | -0.001994 | 0.0003211 | 2.00E-10 | calcium |
| rs9411378 | 9:136145425 | A | C | 0.222 | -0.001617 | 0.0002843 | 1.40E-08 | calcium |
| rs77798356 | 9:4762052 | G | C | 0.1217 | 0.00211 | 0.0003565 | 5.10E-10 | calcium |
| rs11144001 | 9:71467135 | T | C | 0.4715 | -0.00216 | 0.0002281 | 3.10E-22 | calcium |
| rs4740965 | 9:903461 | A | G | 0.7668 | -0.002325 | 0.0002727 | 5.30E-18 | calcium |
| rs12337706 | 9:97523154 | G | A | 0.06085 | -0.005103 | 0.0004742 | 8.20E-29 | calcium |
| rs7528419 | 1:109817192 | G | A | 0.775329 | -0.0197401 | 0.00238729 | 1.3E-10 | Vit-D |
| rs140371183 | 1:152098428 | G | A | 0.967821 | -0.0870147 | 0.00565335 | 1.86E-43 | Vit-D |
| rs12123821 | 1:152179152 | T | C | 0.952473 | -0.0785529 | 0.00467652 | 2.55E-53 | Vit-D |
| rs61816761 | 1:152285861 | A | G | 0.984074 | -0.12315 | 0.00804767 | 7.35E-43 | Vit-D |

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|---|---|---|---|---|---|---|---|---|
| rs1933064 | 1:152301576 | A | G | 0.53039 | -0.015731 | 0.00203195 | 9.8E-10 | Vit-D |
| rs76798800 | 1:154994978 | T | G | 0.733745 | 0.0121989 | 0.00225962 | 0.00671438 | Vit-D |
| rs10908465 | 1:155389688 | T | C | 0.732668 | -0.0168816 | 0.00224924 | 6.1E-8 | Vit-D |
| rs35408430 | 1:17560195 | T | C | 0.657806 | 0.0214952 | 0.00209979 | 1.36E-14 | Vit-D |
| rs867772 | 1:220972343 | G | A | 0.315487 | 0.0146031 | 0.00215141 | 0.00000113945 | Vit-D |
| rs6672758 | 1:230303512 | T | C | 0.199128 | -0.0175857 | 0.00250898 | 0.000000023985 | Vit-D |
| rs6671730 | 1:2339139 | A | G | 0.565714 | 0.0147881 | 0.00201077 | 0.0000000019172 | Vit-D |
| rs11591147 | 1:55505647 | T | G | 0.981959 | -0.0450903 | 0.00747745 | 0.000163787 | Vit-D |
| rs2131925 | 1:63025942 | T | G | 0.356375 | 0.0229402 | 0.0020845 | 3.61E-18 | Vit-D |
| rs10887718 | 10:82042624 | T | C | 0.471787 | 0.0111219 | 0.00199828 | 0.00261047 | Vit-D |
| rs77532868 | 10:88081438 | T | C | 0.945958 | -0.0265692 | 0.00440069 | 0.000156513 | Vit-D |
| rs4418728 | 10:94839724 | T | G | 0.548312 | -0.0109611 | 0.00200006 | 0.00004244 | Vit-D |
| rs964184 | 11:116648917 | C | G | 0.131624 | -0.0431755 | 0.00294423 | 1.09E-38 | Vit-D |
| rs613808 | 11:116710968 | G | A | 0.280007 | -0.0264476 | 0.00223913 | 3.40E-22 | Vit-D |
| rs2847500 | 11:120114421 | A | G | 0.876497 | 0.021925 | 0.00302751 | 0.0000000442361 | Vit-D |
| rs116970203 | 11:14876718 | A | G | 0.972844 | 0.376873 | 0.00612043 | 0 | Vit-D |
| rs117576073 | 11:14912573 | T | G | 0.987265 | 0.147177 | 0.00886081 | 5.91E-52 | Vit-D |
| rs12794714 | 11:14913575 | A | G | 0.578197 | 0.0878964 | 0.00201629 | 0 | Vit-D |
| rs61891388 | 11:66079818 | G | T | 0.544079 | -0.0125532 | 0.00200799 | 0.0000406204 | Vit-D |
| rs78168201 | 11:70971149 | T | C | 0.986234 | -0.0893469 | 0.00864963 | 5.18E-15 | Vit-D |
| rs1660839 | 11:71094232 | A | G | 0.751151 | -0.0292665 | 0.00230557 | 6.40E-27 | Vit-D |
| rs12803256 | 11:71132868 | G | A | 0.223268 | -0.104243 | 0.00239998 | 0 | Vit-D |
| rs72997623 | 11:75488054 | A | C | 0.915338 | -0.0276158 | 0.00358139 | 0.00000000124917 | Vit-D |
| rs1149605 | 11:76485216 | C | T | 0.829603 | -0.0220166 | 0.00266133 | 0.0000000000013087 | Vit-D |
| rs73413596 | 12:111582630 | C | T | 0.926146 | -0.0216996 | 0.00382584 | 0.00141262 | Vit-D |
| rs12317268 | 12:21352541 | G | A | 0.848996 | 0.0208967 | 0.00278474 | 0.00000000618974 | Vit-D |
| rs11182428 | 12:38526387 | C | T | 0.480005 | 0.0125352 | 0.00199379 | 0.0000323406 | Vit-D |
| rs1038165 | 12:68665940 | T | C | 0.416651 | -0.0120567 | 0.002018 | 0.000230685 | Vit-D |

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|---|---|---|---|---|---|---|---|---|
| rs10859995 | 12:96375682 | C | T | 0.417366 | 0.0403465 | 0.0020206 | 1.05E-58 | Vit-D |
| rs12372115 | 12:97982701 | T | G | 0.929281 | 0.0217954 | 0.00387948 | 0.00193042 | Vit-D |
| rs12881545 | 14:101176212 | C | G | 0.326561 | -0.011822 | 0.00213142 | 0.00291383 | Vit-D |
| rs8018720 | 14:39556185 | C | G | 0.176673 | 0.0378247 | 0.00260904 | 1.26E-37 | Vit-D |
| rs325384 | 15:100229761 | T | C | 0.715795 | 0.0141728 | 0.00221789 | 0.0000016565 | Vit-D |
| rs261291 | 15:58680178 | C | T | 0.644772 | 0.0273653 | 0.00208561 | 2.50E-29 | Vit-D |
| rs1800588 | 15:58723675 | T | C | 0.784797 | 0.0329215 | 0.00242187 | 4.38E-34 | Vit-D |
| rs55829990 | 15:63790642 | C | T | 0.655996 | 0.0186013 | 0.00210294 | 9.1E-14 | Vit-D |
| rs62007299 | 15:77711719 | A | G | 0.287463 | 0.0133407 | 0.00219977 | 0.000132292 | Vit-D |
| rs77924615 | 16:20392332 | A | G | 0.806515 | 0.0166321 | 0.00255158 | 0.00000710834 | Vit-D |
| rs17231506 | 16:56994528 | T | C | 0.676894 | 0.0184236 | 0.00213148 | 54E-12 | Vit-D |
| rs11076175 | 16:57006378 | G | A | 0.821642 | -0.0230493 | 0.00260705 | 9.4E-10 | Vit-D |
| rs4327060 | 16:72807438 | T | C | 0.945604 | 0.0243589 | 0.00439221 | 0.00292392 | Vit-D |
| rs4575545 | 16:79755446 | A | G | 0.695172 | 0.0155823 | 0.00217312 | 7.4E-8 | Vit-D |
| rs11542462 | 16:82033810 | A | G | 0.865656 | 0.023334 | 0.00291776 | 1.2E-9 | Vit-D |
| rs10454087 | 17:40735641 | T | C | 0.715178 | 0.0135306 | 0.00220667 | 0.0000869545 | Vit-D |
| rs2952289 | 17:66464414 | T | C | 0.201968 | -0.017715 | 0.00249217 | 0.000000117512 | Vit-D |
| rs8091117 | 18:28919794 | A | C | 0.934702 | 0.0263626 | 0.0040284 | 0.00000598202 | Vit-D |
| rs4121823 | 18:47144223 | A | T | 0.154667 | 0.0192879 | 0.00277797 | 0.000000383415 | Vit-D |
| rs590215 | 18:57904088 | T | C | 0.734073 | 0.0129217 | 0.00225753 | 0.00104154 | Vit-D |
| rs2037511 | 18:61366207 | A | G | 0.833993 | -0.0181228 | 0.00267963 | 0.00000135002 | Vit-D |
| rs142158911 | 19:11190534 | A | G | 0.885392 | -0.0255317 | 0.00314553 | 0.0000000000478559 | Vit-D |
| rs187429064 | 19:19380513 | G | A | 0.988734 | -0.0648324 | 0.00947915 | 0.000000794845 | Vit-D |
| rs3814995 | 19:36342212 | T | C | 0.688405 | 0.012558 | 0.00214992 | 0.000518425 | Vit-D |
| rs7412 | 19:45412079 | T | C | 0.917927 | -0.0300485 | 0.00363434 | 1.3E-11 | Vit-D |
| rs212100 | 19:48376995 | C | T | 0.164001 | 0.0661522 | 0.00269018 | 1.61E-125 | Vit-D |
| rs10426 | 19:51517798 | A | G | 0.786567 | -0.0256629 | 0.00243056 | 4.6E-12 | Vit-D |
| rs11606 | 19:54658102 | G | C | 0.574838 | -0.0120363 | 0.00205119 | 0.000441191 | Vit-D |

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|---|---|---|---|---|---|---|---|---|
| rs7569755 | 2:118648261 | A | G | 0.70942 | -0.01425 | 0.00221206 | 0.0000117941 | Vit-D |
| rs1047891 | 2:211540507 | A | C | 0.684179 | 0.0152142 | 0.00214041 | 0.000000117671 | Vit-D |
| rs7604788 | 2:21190024 | T | C | 0.966567 | -0.0336737 | 0.0055518 | 0.000131653 | Vit-D |
| rs541041 | 2:21294975 | A | G | 0.180761 | 0.0154585 | 0.00258635 | 0.000227346 | Vit-D |
| rs2012736 | 2:234622379 | A | C | 0.919186 | 0.0483073 | 0.00366555 | 1.16E-31 | Vit-D |
| rs1260326 | 2:27730940 | C | T | 0.393435 | -0.0206128 | 0.00203644 | 4.41E-14 | Vit-D |
| rs11127186 | 2:28881407 | C | T | 0.504205 | -0.0109023 | 0.00203379 | 0.00829538 | Vit-D |
| rs727857 | 2:58981967 | A | G | 0.388511 | 0.0140184 | 0.00206152 | 0.00000104597 | Vit-D |
| rs2710651 | 2:63166379 | A | G | 0.471877 | 0.0114568 | 0.00199623 | 0.000951145 | Vit-D |
| rs2207132 | 20:39142516 | A | G | 0.96711 | 0.0345955 | 0.00557773 | 0.0000555966 | Vit-D |
| rs6123359 | 20:52714706 | G | A | 0.897775 | -0.0341831 | 0.00331429 | 6.10E-15 | Vit-D |
| rs17216707 | 20:52732362 | C | T | 0.817316 | 0.0376264 | 0.00263713 | 3.47E-36 | Vit-D |
| rs2585442 | 20:52737123 | G | C | 0.759346 | -0.0356675 | 0.00237687 | 6.70E-41 | Vit-D |
| rs2762943 | 20:52790786 | G | T | 0.076929 | -0.0457231 | 0.00373798 | 2.10E-24 | Vit-D |
| rs2229742 | 21:16339172 | C | G | 0.896549 | 0.0251483 | 0.00327069 | 0.00000000148302 | Vit-D |
| rs6003456 | 22:23356100 | A | T | 0.765336 | 0.013277 | 0.00236378 | 0.00194469 | Vit-D |
| rs2074735 | 22:31535872 | C | G | 0.935904 | -0.0278196 | 0.00407045 | 0.000000822761 | Vit-D |
| rs9861009 | 3:141654685 | C | T | 0.272485 | -0.0140213 | 0.00225294 | 0.0000486009 | Vit-D |
| rs13060130 | 3:84440527 | T | C | 0.860311 | 0.0149893 | 0.00287224 | 0.0180203 | Vit-D |
| rs6782190 | 3:85639672 | A | G | 0.352488 | 0.0172156 | 0.00208415 | 0.0000000000145368 | Vit-D |
| rs28364331 | 4:100201295 | G | A | 0.981914 | -0.068614 | 0.00747169 | 4.18E-10 | Vit-D |
| rs1229984 | 4:100239319 | C | T | 0.0248886 | 0.0450574 | 0.00637113 | 0.000000152584 | Vit-D |
| rs4364259 | 4:15892159 | A | G | 0.797852 | -0.0159119 | 0.00250595 | 0.0000215808 | Vit-D |
| rs78649910 | 4:3482213 | A | T | 0.893821 | 0.0211949 | 0.00325203 | 0.00000715189 | Vit-D |
| rs4616820 | 4:57745481 | T | C | 0.535046 | 0.012286 | 0.00201755 | 0.000113219 | Vit-D |
| rs35057908 | 4:69372082 | T | A | 0.568691 | -0.0110085 | 0.00202343 | 0.00053127 | Vit-D |
| rs705117 | 4:72608115 | T | C | 0.1477 | 0.0334179 | 0.00280601 | 1.06E-22 | Vit-D |
| rs1352846 | 4:72617775 | G | A | 0.708567 | 0.193471 | 0.00219074 | 0 | Vit-D |

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|---|---|---|---|---|---|---|---|---|
| rs11732896 | 4:88287993 | A | G | 0.701209 | 0.0160047 | 0.00217341 | 1.8E-8 | Vit-D |
| rs31612 | 5:108996643 | C | T | 0.825562 | 0.014528 | 0.00264902 | 0.00415128 | Vit-D |
| rs10070734 | 5:87940026 | C | T | 0.290469 | -0.0132137 | 0.00219753 | 0.000182146 | Vit-D |
| rs9490317 | 6:121859499 | C | T | 0.554106 | -0.011051 | 0.00201182 | 0.00395082 | Vit-D |
| rs2248551 | 6:131924689 | A | G | 0.834778 | 0.0233623 | 0.0026823 | 3.0E-16 | Vit-D |
| rs72834856 | 6:22801858 | G | T | 0.927936 | 0.0249871 | 0.00385103 | 0.00000867412 | Vit-D |
| rs78151190 | 6:25619007 | C | A | 0.871284 | 0.0168754 | 0.00297406 | 0.00139341 | Vit-D |
| rs9476310 | 6:57767576 | T | C | 0.488637 | -0.0117571 | 0.00200093 | 0.000420761 | Vit-D |
| rs75741381 | 7:100809458 | G | C | 0.852362 | 0.0166065 | 0.00282521 | 0.000415328 | Vit-D |
| rs6966728 | 7:104618318 | T | C | 0.537368 | 0.0117532 | 0.00203758 | 0.000801154 | Vit-D |
| rs2346264 | 7:133536351 | C | A | 0.217315 | 0.0138826 | 0.00243596 | 0.00120494 | Vit-D |
| rs10085881 | 7:21577960 | C | T | 0.717815 | 0.0145575 | 0.00223829 | 0.00000782905 | Vit-D |
| rs7784802 | 7:64015379 | T | A | 0.639009 | -0.0138131 | 0.00207209 | 0.00000262396 | Vit-D |
| rs804281 | 8:11611865 | G | A | 0.416395 | -0.0132996 | 0.00202139 | 0.00000472246 | Vit-D |
| rs12056768 | 8:116988527 | G | T | 0.417091 | 0.0234029 | 0.00202418 | 6.44E-21 | Vit-D |
| rs28692966 | 8:25892919 | A | G | 0.747064 | -0.0148311 | 0.00230018 | 0.0000113486 | Vit-D |
| rs2725371 | 8:30854033 | G | A | 0.302309 | -0.0118392 | 0.00218287 | 0.00583826 | Vit-D |
| rs4738684 | 8:59393273 | G | A | 0.334478 | -0.0124102 | 0.00211491 | 0.000441199 | Vit-D |
| rs34290760 | 8:9185179 | G | C | 0.970888 | 0.0334615 | 0.00593241 | 0.00001696 | Vit-D |
| rs13284054 | 9:107669073 | C | T | 0.882273 | -0.0175688 | 0.00313411 | 0.00207446 | Vit-D |
| rs17216707 | 20:52732362 | T | C | 0.8 | 0.054 | 0.005 | 3.0E-24 | FGF23 |
| rs2769071 | 9:136145974 | G | A | 0.37 | 0.037 | 0.005 | 6.1E-17 | FGF23 |
| rs11741640 | 5:176792743 | G | A | 0.73 | 0.039 | 0.005 | 1.6E-16 | FGF23 |
| rs17479566 | 9:71198014 | T | C | 0.22 | 0.031 | 0.005 | 2.0E-09 | FGF23 |
| rs9925837 | 16:79927303 | G | A | 0.13 | 0.035 | 0.006 | 5.1E-09 | FGF23 |
| rs219779 | 21:37833751 | G | A | 0.75 | 0.04 | 0.003 | 8.9E-22 | PTH |
| rs4074995 | 5:176797343 | G | A | 0.71 | 0.03 | 0.003 | 3.3E-23 | PTH |
| rs4443100 | 22:23372864 | G | C | 0.32 | 0.02 | 0.003 | 4.1E-13 | PTH |

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|---|---|---|---|---|---|---|---|---|
| rs6127099 | 20:52731402 | T | A | 0.34 | 0.07 | 0.003 | 2.4E-72 | PTH |
| rs73186030 | 3:122013465 | T | C | 0.14 | 0.03 | 0.003 | 1.2E-10 | PTH |

## PDF

PDF of studies I, II and III are available:

https://github.com/alice-gio/Thesis.git