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Dietary Flavonoids and Respiratory Outcomes: Evidence from the BOLD Study

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Coordinator: Professor Simone Accordini

Signature _____

Tutor: Professor Maria Elisabetta Zanolin

Signature _____

Supervisor: Professor Vanessa Garcia Larsen

Signature _____

PhD candidate: Mulubirhan Assefa Alemayohu

Signature _____

* For the list of Disciplinary Sectors (SSD), see Ministerial Decree 04/10/2000 Appendix A "*List of Disciplinary Sectors*" available on the Ministry of Education, University and Research website at: http://www.miur.it/atti/2000/alladm001004_01.htm

Dietary Flavonoids and Respiratory Outcomes: Evidence from the BOLD Study

Alemayohu Mulubirhan Assefa

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SUMMARY (in Italian)

Il peso della broncopneumopatia cronica ostruttiva (BPCO) è cresciuto drammaticamente ed è ora la terza causa di morte, con quasi dieci anni di anticipo

rispetto all'anno previsto dall'Organizzazione Mondiale della Sanità (OMS). La BPCO è stata riconosciuta essere un killer silenzioso nei Paesi a basso e medio reddito, dove si verificano 9 decessi su 10 per BPCO. I progressi in campo medico compiuti negli ultimi decenni non sono stati sufficienti e, per ottenere una riduzione significativa dei tassi di incidenza, è necessario un nuovo paradigma incentrato sulla salute pubblica e sugli stili di vita. In linea con questo cambiamento di paradigma, le ultime evidenze indicano che i fattori dietetici, identificati come fattori modificabili, possono influenzare lo sviluppo e la progressione della malattia ostruttiva polmonare. In questa tesi si vuole indagare l'associazione tra l'assunzione di flavonoidi nella dieta e gli esiti respiratori nell'indagine multinazionale Burden of Obstructive Lung Disease (BOLD I).

In primo luogo, è stata effettuata un'analisi dei dati per valutare il peso della BPCO nei Paesi a basso e medio reddito nell'Africa Subsahariana (SSA) utilizzando i dati dello studio Global Burden of Diseases, Injuries, and Risk Factors Study (GBD). La prevalenza della BPCO nei Paesi dell'Africa subsahariana è aumentata costantemente negli ultimi trent'anni e rimane un importante carico per la salute pubblica, con un contributo significativo alla morbosità e alla mortalità prematura in tutta la regione.

È stato dimostrato che i flavonoidi hanno molteplici effetti benefici, tra cui un'azione antinfiammatoria, antiossidante, antimicrobica e antinvecchiamento, che svolgono un ruolo importante nei cambiamenti patologici che portano a limitazioni progressive e persistenti del flusso aereo. Stime dell'assunzione di flavonoidi basate sulla popolazione sono presenti solo nei Paesi ad alto reddito, come gli Stati Uniti e alcuni paesi europei. Le stime dell'apporto dietetico basate sulla popolazione dipendono da quali tabelle di composizione degli alimenti (FCT) vengono impiegate e il contenuto di flavonoidi può variare a seconda della FCT utilizzata. Migliorare la nostra comprensione delle variazioni tra le FCT di riferimento utilizzate per stimare l'assunzione di flavonoidi può contribuire a ridurre le incongruenze nelle associazioni tra flavonoidi ed esiti di salute che si possono trovare nella letteratura scientifica.

Abbiamo perciò condotto uno studio di confronto per analizzare in che misura il contenuto di flavonoidi degli alimenti inclusi nel Food Frequency Questionnaire

(FFQ) di BOLD varia in base alle diverse FCT internazionali. Abbiamo eseguito una ricerca completa delle FCT con dati sui flavonoidi utilizzando motori di ricerca riconosciuti a livello internazionale come risorsa per trovare dati sulla composizione degli alimenti: PubMed Central, i database elettronici Scopus e il motore di ricerca Google. Sono state selezionate quattro FCT con dati comparabili sui flavonoidi e si sono ricavate le stime sui flavonoidi per gli alimenti inclusi nel BOLD FFQ e disponibili in ciascuna tabella; sono stati inoltre effettuati confronti per gli alimenti comuni tra le tabelle. Il contenuto di flavonoidi negli alimenti variava notevolmente tra le tabelle internazionali. E' stata riscontrata un'elevata eterogeneità nei livelli di stima dei flavonoidi tra le diverse FCT e queste differenze devono essere tenute in considerazione quando si ricavano le stime dell'assunzione di flavonoidi nelle indagini sulla popolazione.

Per ottenere l'assunzione giornaliera di flavonoidi totali e delle loro sottoclassi, la tabella di composizione alimentare dei flavonoidi è stata ricavata principalmente dai database dei flavonoidi del Dipartimento dell'Agricoltura degli Stati Uniti (USDA) e ampliata per includere ulteriori sottoclassi di flavonoidi e alimenti da Phenol-Explorer, The Bioactive Substances in Food Information Systems (eBASIS) e The Indian Food Composition Table (IFCT). È stata stimata l'assunzione giornaliera di flavonoidi nella dieta degli adulti partecipanti all'indagine dietetica BOLD I e sono state esaminate le principali fonti alimentari e la loro distribuzione tra i siti BOLD. L'assunzione giornaliera di flavonoidi totali più alta e più bassa è stata riscontrata rispettivamente in Kirghizistan (Chui e Naryn) e a Tirana in Albania.

Per analizzare l'associazione tra l'assunzione giornaliera di flavonoidi con la dieta e gli esiti respiratori è stata eseguita una metanalisi in due fasi sui dati individuali dei partecipanti. Il metodo di metanalisi a varianza inversa a effetti casuali stima i dati aggregati specifici del sito nella prima fase e poi, nella seconda fase, produce una stima totale ponderata. La metanalisi ha mostrato che un aumento di 10 mg nell'assunzione giornaliera di flavoni era inversamente associato all'ostruzione cronica delle vie aeree (FEV1 / FVC <LLN), mentre non è stata riscontrata alcuna altra associazione tra i flavonoidi (flavonoidi totali e altre sottoclassi) e gli esiti respiratori negli adulti che hanno partecipato all'indagine BOLD I. L'analisi non ha

mostrato alcuna evidenza di eterogeneità tra i singoli siti nelle associazioni tra l'assunzione di flavonoidi con la dieta (totali e sottoclassi) e gli esiti respiratori.
I risultati di questa tesi ampliano le nostre conoscenze su (i) il modello e la distribuzione geografica della BPCO nei Paesi a basso e medio reddito, (ii) l'entità della variazione del contenuto di flavonoidi negli alimenti in base all'uso della FCT, (iii) l'assunzione di flavonoidi nella dieta e la sua distribuzione e (iv) l'associazione tra flavonoidi nella dieta ed esiti respiratori. Questi risultati indicano che il carico della BPCO, l'assunzione di flavonoidi nella dieta e il loro ruolo nella riduzione dell'ostruzione cronica delle vie aeree potrebbero essere presi in considerazione per una riduzione della BPCO. In conclusione, questi risultati indicano che l'aumento dell'assunzione giornaliera di una particolare categoria di flavonoidi, i flavoni, può svolgere un ruolo significativo nella riduzione della BPCO e forniscono indicazioni per ulteriori studi sulla popolazione.

ABSTRACT (in English)

The burden of chronic obstructive pulmonary disease (COPD) has grown dramatically and is now the third leading cause of death, nearly ten years ahead of the year predicted by the World Health Organization (WHO). COPD has been

recognized as a silent killer in low- and middle-income countries where 9 out of 10 COPD deaths occur. Despite the burden, the progress made in recent decades is not enough and a new paradigm focused on public health and lifestyle approaches is needed to achieve significant reductions in incidence rates. In line with these paradigm shifts, emerging evidence indicates that the identification of dietary factors as modifiable factors may influence the development and progression of obstructive pulmonary disease. This thesis was designed to investigate the association of dietary flavonoid intake with respiratory outcomes in adults participating in multinational Burden of Obstructive Lung Disease (BOLD I) survey.

First of all, an analysis of data to assess the burden of COPD in low-middle income countries was done for Sub-Saharan Africa (SSA) countries using the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) data estimates. The results shown that the prevalence of COPD in SSA has had a steady increase in number of cases over the past three decades, and it remains a major public health burden with a significant contribution to premature morbidity and mortality across the region.

Flavonoids have been demonstrated to have multiple beneficial effects including anti-inflammatory, antioxidant, antimicrobial, and anti-aging actions, which play an important role in pathological changes resulting in progressive and persistent airflow limitations. Population-based estimate of flavonoid intake are lacking or are found only in high income countries, particularly in United States and some European countries. Population-based estimates of dietary intake depend on which food composition tables (FCTs) are considered and the flavonoid content can vary depending on which FCT is being used. Improving our understanding on the variations between reference FCTs used to estimate flavonoid intake can contribute to reduce inconsistencies in the associations of flavonoids and health outcomes that can be found in the scientific literature.

A comparison study was conducted to examine to what extent the flavonoid content of foods included in BOLD's Food Frequency Questionnaire (FFQ) varies according to the different international FCTs. A comprehensive FCT search with flavonoid data was performed using internationally recognized website engines as

a resource for food composition data and complemented using PubMed Central, Scopus electronic databases and the Google search engine. Four FCTs were selected for their comparable flavonoid data and the flavonoid estimates were derived for the foods included in the BOLD FFQ and available in each table, and comparisons were made for common foods among the tables. Food content of flavonoids varied considerably across international tables. There was a high heterogeneity in the levels of flavonoid contents of food items between FCTs and these differences should be taken into account when deriving the estimates of flavonoid intake in population surveys.

To obtain daily intake of total flavonoids and subclasses, the food composition table on flavonoid was derived primarily from the United States Department of Agriculture (USDA) flavonoid databases and expanded to include further subclasses of flavonoids and food items from Phenol-Explorer, The Bioactive Substances in Food Information Systems (eBASIS) and The Indian Food Composition Table (IFCT). The daily dietary flavonoid intake of adults participating in BOLD I dietary survey was estimated, and the main food sources and their distribution across BOLD sites were examined. The highest and lowest daily total flavonoids intake was found in Kyrgyzstan (Chui and Naryn) and Tirana in Albania, respectively. Most of the overall variability in the distribution of total flavonoid and other subclasses intake was observed within the BOLD sites.

A two-stage individual participant data meta-analysis was performed to analyze the association of daily dietary flavonoid intake and respiratory outcomes. This random effect inverse variance approach estimates site-specific aggregated data in the first step and then, in the second step, pooled overall summary estimates are produced. The meta-analysis indicated that a 10 mg increase in daily flavone intake was inversely associated with chronic airflow obstruction (FEV1 / FVC <LLN), while no association was found between other dietary flavonoids (total flavonoids and other subclasses) intake and respiratory outcomes in adults participating in the BOLD I survey. The I^2 statistics showed no evidence of heterogeneity between individual sites in the associations of dietary flavonoid intake (total and subclasses) and respiratory outcomes.

The findings of this thesis expand our knowledge on (i) the pattern and geographic

distribution of COPD in low- and middle-income countries, (ii) the extent of variation in flavonoid content of foods according on which FCT is used, (iii) dietary flavonoid intake and its distribution, and (iv) the association between dietary flavonoids and respiratory outcomes. These findings inform that the COPD burden, improvement of flavonoid content, and intake estimation and role in lowering the proportion of chronic airflow obstruction should be taken into account in paradigm shifts for a significant reduction of COPD. Moreover, these results indicate that increasing daily flavone intake may play a significant role in COPD reduction and provide indication for further population-based studies.

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Introduction

Noncommunicable Diseases (NCDs) currently pose the biggest threats to health and development globally and, in the developing world (1), they account for more than 73% of the total deaths in 2017 (1, 2). Chronic respiratory diseases are the third major contributor to total cause deaths following cardiovascular diseases and neoplasms (2). The prevalence of chronic respiratory disease, globally, in 2017 increased by 39·8% compared to 1990, Chronic Obstructive Pulmonary Disease

(COPD) being responsible for about 55% of them (3). In 2019, COPD is the third leading cause of death worldwide, responsible for approximately 6% of total deaths and causing 3.23 million deaths (4). Low and middle-income countries (LMICs) bear a disproportionately high burden of global morbidity and mortality (5), and over 80% of COPD deaths occurred in low- and middle-income countries (LMIC)(4, 6).

The greater share of COPD-attributable burden is explained by cigarette smoking and other environmental factors such as household air pollution, ambient air pollution, occupational particulates, and second-hand smoke. Except for sub-Saharan Africa, smoking accounted for the largest fraction of COPD- attributable morbidity in all super-regions(3). Despite the increased rate in smoking cessation observed throughout Europe (7), the majority of European countries have not seen reductions in COPD between 2001 and 2017 (8) and the projected incidence estimates are foreseen to worsen over time with a 39.6% increase in prevalence in 2050 (9). Smoking cessation was not associated with a lower incidence of COPD in a prospective population-based study (10). Besides, smoking cessation was significantly associated with weight and BMI gains (11) which may in turn increase the risk of COPD and/or attenuate the mortality benefit of the cessation (12). Being obese was positively associated with COPD and other chronic respiratory diseases (13, 14). Such results would seem to indicate that nutritional interventions aimed at increasing the intake of certain nutrients and controlling obesity might have beneficial outcomes in primary prevention and management of lung impairment(15).

There is evidence documenting a relationship between a healthy dietary intake and the maintenance of lung function and the prevention of COPD(15). Findings suggest that a healthy diet(16), dietary shift to higher-antioxidant food intake (17), nutritional interventions encouraging taking fruits, and probably fish, and dietary fiber (18) might be considered useful intervention strategies in COPD management. A population-based cohort study found that a 100 g increase in fruit intake was associated with a 24% lower COPD mortality risk (19). A dietary inflammatory index might be clinically used as a predictor for the risk of COPD(20). Targeting the inflammation associated with COPD with nutrients that have powerful anti-

inflammatory effects might be a novel approach to the treatment (15). Oxidant/antioxidant imbalance along with malnutrition and underweight in COPD are signals for considering antioxidant therapy along with nutritional management (21). Reactive oxygen and nitrogen species (RONS) promote corticosteroid insensitivity by disrupting glucocorticoid receptor (GR) signaling and augmenting proinflammatory responses. Antioxidant-based therapies may complement corticosteroids to reduce their need in prolonged high dose regimens in patients with severe asthma and COPD(22).

Although ample epidemiological evidence supports the knowledge that diet might affect COPD outcomes through modulating the impact of oxidative stress and other adverse environmental factors on the lung, the majority of studies come from developed countries. Moreover, dietary flavonoids are a new promising area of diet-COPD association studies because of their anti-allergic, anti-inflammatory, anti-platelet aggregation, anti-tumor, and antioxidant behavior. This thesis, therefore, was designed to estimate intake of dietary flavonoid and investigate its association with pulmonary function and COPD in adults participating in the Burden of Obstructive Lung Disease (BOLD-I) survey.

Thesis structure

The thesis structure is organized in introduction, internal chapters, and conclusions based on the University of Verona's PhD Thesis layout guideline.

Introduction – this section introduces the research topic addressed within this thesis and provides an outline of each chapter throughout the thesis.

Internal chapters – these chapters are organized in four chapters and the last three chapters present three distinct research papers. ***Chapter 1*** presents the background of the thesis that includes a review of the existing literature on the research area, research problem (gap identified), and the research aim to address research questions and the contribution foreseen from this thesis. It also provides a summary of similar studies in relation to their study designs and setting, study populations, dietary intake assessments, intake comparisons, respiratory outcomes, and main findings. ***Chapter 2*** provides result on the burden of COPD and its risk factors based on modelled-approach data sources from Global Burden of Diseases (GBD) to give an overview of the burden trend and established risk factors of COPD in low-middle

income countries. ***Chapter 3*** is a methodological paper on the comparison of international flavonoid food composition tables to inform the construction of expanded flavonoid food composition tables that are employed for dietary flavonoid intake estimation in chapter 4. ***Chapter 4*** presents the daily flavonoid intake and its association with respiratory outcomes. The last three chapters, encompassed as internal chapters in this thesis, have been submitted for publication or prepared for submission.

Conclusions – Conclusions provide a summary of the main findings in relation to the research questions and present the recommendations for future work on the research area.

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Chapter 1 Background

1.1. Definition and diagnostic criteria of COPD

The definition of chronic obstructive pulmonary disease (COPD) and diagnostic criteria to establish the definition itself are important to understand the disease states to set prevention measures. The definition of COPD is pragmatic (1), and several definitions (2, 3) have been adopted and modified (1, 4) in time. Airflow obstruction, irreversible airflow obstruction, obstructive lung disease, and airflow limitation have been used as common terms for spirometrically established COPD in various published studies. Chronicity and progressive trend have been emphasized as common definition terms. To date, there is no gold standard definition /diagnostic criterion/reference equation. There are the three most used guidelines, namely those of American Thoracic Society/European Respiratory Society (ATS/ERS), those of the British Thoracic Society/National Institute for Health and Care Excellence (BTS/NICE), and those of The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. These three guidelines share in common (5) the following: (i) airflow obstruction as the primary physiologic characteristic of COPD, (ii) the progressive nature and irreversibility of the obstruction over time, (iii) importance of symptoms and exposure history in making diagnosis, and (iv) requirement of spirometry to confirm airflow obstruction. Despite of those similarities, these guidelines have key differences in establishing spirometry-based diagnostic criteria for COPD definition. The ATS/ERS guidelines are most suitable in an epidemiological setting with due consideration on reference value selection(6) and could reduce the risk of over-diagnosis of COPD in elderly people(7), while BTS/NICE and GOLD are suggested as practical threshold for identifying clinically relevant COPD (8). On the another hand, identifying more false-negative (9) particularly in elderly is the major limitation of ATS/ERS, whereas the major limitation of GOLD is to find more false-positive (9) mainly in general populations.

1.2. Literature review

1.2.1 Prevalence of COPD and impaired lung function

Epidemiological studies estimate that 65 million people have moderate to severe COPD each year(10, 11) with a heterogeneous distribution worldwide (12). Recent

findings from a multinational study corroborates the heterogeneousness of the prevalence of COPD ranging in men from 3.5% in Saudi Arabia to 23.2% South Africa, while in women, from 2% in Tunisia to 19.4% in Austria(13). In other Burden of Obstructive Lung Disease (BOLD) participating countries, the reported prevalence of COPD was 6.5% in Malaysia(14), 7.7% in Nigeria (15), 12.6% in Morocco(16) and 17.3% in North India(17). Such heterogeneity is also evident among countries in the Eastern Mediterranean Region where the reported prevalence of COPD was 5.4% and the highest was reported in Pakistan, 13.8% (18). Not only at regional or at country level, the variation on the prevalence of COPD was also displayed at subnational level from Jiangsu (11.8%)(19) to Shenzhen (5.9%)(20) in China. In India, the overall prevalence of COPD was reported to be 7%(21), while in Odisha India(22) it was reported to be 22.4%.

1.2.2 Risk factors for impaired lung function and COPD

Several epidemiological studies demonstrated that demographic and socio-economic factors such as age(23-30), being a male (19, 25-27, 30-32), low educational level (15, 27, 29, 31, 33, 34), rural residence (35, 36), occupation (25, 26, 31, 37-42), household income or poverty (24, 33-35, 43), and being underweight (24, 25, 29, 31) or obese (34, 44) were important predictors of impaired lung function and COPD. History of tuberculosis (15, 23, 24, 26, 30, 45), asthma (15, 24, 25), allergy (31), childhood respiratory (27, 31), recurrent infection (31) and family history of respiratory disease (27, 31) were also independently associated with impaired lung function and COPD. Most epidemiological studies had consistently reported increased risk of COPD with age increase, low educational level, occupational exposure, low socioeconomic level, low BMI, and previous history of tuberculosis whereas they were inconsistent on association of sex and residence to COPD.

The structural and physiological lung changes with increasing age result in gradual declines of lung function (46). A multicounty study by Buist et al. estimated a 94% increase in the prevalence of COPD per 10-year increase in age (30). Another study by Danielsson et al. also estimated a similar increase (100%) of COPD per 10-year increase in age (23). The prevalence of COPD was significantly higher among males (19, 25, 30, 32) with percentage differences ranging from 42% to 53%

compared to females (26, 27, 31) while other studies conducted by Woldeamanuel et al.(28) and Karki et.al (29) found no significant difference between sexes. The likelihood of having COPD is 23% and 15.8% higher among rural residents in United States (35) and Nepal(36), respectively, compared to urban residents. Inconsistently, another study conducted in Nepal (29) and China (19) reported almost identical or no significant difference in COPD prevalence between rural and urban residents.

Pathogenesis of COPD could also be linked to an imbalance between oxidants and antioxidants (47) where cigarette smoking interplays a crucial mechanism to increase oxidants in the respiratory tract (48). Cigarette smoke induces pulmonary inflammation by reactive oxygen species ROS released from activated inflammatory cells such as neutrophils, macrophages, and resident cells (47) and by damaging the respiratory epithelial barrier (49). Cigarette smoking was the leading risk factor for COPD (24, 31, 50), and the risk increased with the numbers of cigarette packs per year of smoking (14, 16, 23, 26, 27, 29, 30, 51). The prevalence of COPD varies significantly by dose-response relationship observed between smoking years and number of cigarette packs (27, 29). For instance in Fez, Morocco, the population-estimated prevalence of COPD increased by 17.8% and 3.8% for smoking history of 20 pack-years and 10 pack-years, respectively(16). Current and/or former smokers showed a higher risk of COPD(19, 27-29, 32, 34) though epidemiological evidences were inconsistent on former smokers(52). Several studies reported that the prevalence of COPD among non-smokers was significantly lower compared to those who were former/current smokers, with a difference ranging from 4.2% - 10.5% (16, 19, 27, 32). Recently, Syamlal et al reported an estimate of 2.3 million of workers with COPD where 40% of them were never smokers(41). Globally, the increased COPD prevalence amongst non-smokers is a worrying concern(53).

Exposure to biomass heating and cooking also contributes to the prevalence of COPD and explain the location-specific variations(30). Being exposed to biomass smoke activates Toll-like receptor 2 (TLR2) on lung dendritic cells by increasing the response of T helper (Th)17 in the lungs of the COPD-modelled rats and this suggests the pathway for biomass smoke induced-COPD (54). J Pu and colleagues

showed that the risk of small airway dysfunction increased by chronic exposure to high-level black carbon aerosol with an estimate of 32.9% small airway dysfunction prevalence among the exposed compared to 19.6% of among the non-exposed (55). Exposure to biomass burning was associated with an increase in IL-6 (56), lower FEV1 /FVC ratio (56, 57), and FEF25–75 (57). Biomass fuel use (14, 21, 22, 28, 31, 36, 52, 58-61), years of exposure to biomass smoke(26, 28), and poor ventilated housing (31) and kitchen (28) were significantly associated with COPD as reported in several epidemiological studies. Besides that, individuals who have higher cooking ages and cooked for four and half hours or more in a day showed a 6.9% greater decline in FEV1/FVC ratio compared to those who engaged in cooking for a smaller number of years (22). The risk of COPD due to solid fuel exposure was higher in African and South Asian countries (59, 60), women who had been cooking for years (50, 58, 62, 63), men (unmarried) as using more biomass fuel for heating(27, 52), and for people living around polluted area (31). Furthermore, residents living in areas with PM2.5 concentration >75 mg/m^3 were at high risk of COPD (31). For instance, the FEV1/FVC has declined by 4.4 and 7% for an interquartile increase in PM2.5 and PM2.5 concentrations above 196.8 μg/m^3 (> 75th percentile), respectively(22). On the contrary, some population-based study had reported no association between domestic use of solid fuel and higher prevalence of COPD (15, 64, 65).

1.2.3 Diet and Impaired Lung Function, and COPD

Several scientific shreds of evidence have reported specific dietary factors as potential factors contributing to or protecting individuals against lung function decline and COPD due to their anti-inflammatory (66-68) and antioxidant effect(67, 68). An increased intake of fruits (69-78), vegetable (69, 72, 73, 75), tea (79-81), coffee (82), and fish intake (76, 83) has been reported as beneficial to reduce the risk of COPD and/or to improve lung function. On the other hand, the risk of COPD increases as the intake of soda (79, 84), coffee (79), and processed meat increased (69, 85-88). Individuals' eating behavior was associated with a higher risk of COPD (68, 69, 72, 73, 89-92) and lung function decline (68, 69) among those who consume unhealthy/western diet compared with those who consume healthy/prudent diet. Additionally, lower FVC and higher odds of spirometric

restriction were related to individuals with high household food insecurity (93).

A pooled analysis of studies conducted by Zhai and colleagues reported that individuals with the highest fruit intake had a 28% lower risk of COPD compared to those with the lowest intake (75). Another meta-analysis by Seyedrezazadeh et al. also reported a 26% lower risk of COPD for the highest intake group compared with the lowest intake group (76). In a prospective cohort study carried out in Sweden by Kaluza et al., women in the highest quintile of fruit consumption ($\geq$ 2.5 servings/day) would be 37% less likely than women in the lowest quintile of fruit consumption (<0.8 servings/day) to develop COPD(77). There is no consistency among these epidemiological studies on the relationship between vegetable intake and COPD: the meta-analysis by Seyedrezazadeh et al. and the prospective study by Kaluza et al. reported no association as opposed to the study by Zhai et al. that reported a 24% lower risk of COPD for the highest versus the lowest level of vegetables intake (75).

After adjusting for covariates, the prevalence of COPD decreased with increasing the consumption of tea (79-81), and a dose-response relationship was observed (80, 81). A 65% decrease in the odds of COPD was observed with consuming ≥3 cups of tea per day and a 38% lower likelihood of having COPD among people who consumed green tea ≥2 times per day in a study conducted by Ng et al. (80) and Oh CM et al. (81), respectively. The study conducted by Oh CM et al. also reported that the increase of green tea consumption frequencies from never to ≥2 times per day diminished the incidence of COPD from 14.1% to 5.9% (81). Besides, an increase of FEV_1/FVC ratio was observed as the intake of green tea increased (79, 81). There are controversial findings on the relationship between coffee intake and pulmonary function; the mean ratio of FEV_1/FVC decreased (79) and pulmonary function values increased (82) with increased coffee intake. Furthermore, a positive association was observed between COPD prevalence and coffee intake (79).

Studies demonstrated that the intake of soda (79, 84) and processed meat (69, 85-88) were positively associated with COPD and also reported a joint effect with smoking (79, 85, 87). The odd of having COPD among those who consumed more than half a liter of soft drinks per day was 79% more likely than those who did not consume soft drinks (84) with a reduced mean ratio of FEV_1/FVC (79). A 29%

increased risk of COPD was reported among those who served processed meat at least once per week compared with those who never served it (85). An 8% higher risk of COPD for each 50 gram per week increase in processed red meat intake was reported in a dose-response meta-analysis conducted by Salari-Moghaddam et al (86). Another study conducted by Jiang et al showed a positive dose-response relationship between cured meat consumption and COPD; 14%, 15%, 40%, and 51% higher risk of COPD among 1–3 servings per month, 1 serving per week, 2–3 servings per week, and $\geq$ 4 servings per week, respectively compared with never or almost never (88). A hazard ratio of 6.32 for COPD was reported in individuals who smoke and consumed unhealthy diet and processed meat compared to individuals with none of those three lifestyle factors (85) with a significant interaction effect of smoking and processed meat intake (87).

Several epidemiological studies showed positive effects of healthy/prudent dietary patterns in preserving lung function and preventing COPD compared with unhealthy/western diets (68, 69, 72, 73, 89-92). The likelihood of having COPD was reduced by 22% (89), 25% (73), 33% (92), 45% (91), and 50% (72) in participants who ate the healthiest/prudent diet compared with those who ate either unhealthy/western or those who ate the less healthy diet. Moreover, the risk of COPD was positively increased by 31% (73) and 112% (91) for the highest quintile of Western pattern compared with the lowest quintile.

An experimental study by Jang et al revealed a beneficial role of high-fiber diets in the gut microbiota-metabolite modulation and subsequently, in attenuating emphysema progression and inflammatory response (94). A higher intake of dietary fibers is associated with decreased risk of COPD (69, 76, 90, 95-100) and beneficial to lung function (96, 99, 100) which varied by fiber sources (98, 100). A 35% lower risk of COPD among those who consume the highest dietary fiber was observed in a study conducted by Seyedrezazadeh et al (76). Another study conducted by Varraso et al also reported that there was a 33% reduction in the risk of COPD in the highest total dietary fiber consuming group compared to the lowest intake group (98). Besides, 60.2 ml and 55.2 ml higher FEV1 and FVC, respectively, were observed among individuals in the highest quintile of total fiber intake compared with those in the lowest quintile (100). Compared to the lowest quintile group, those

in the highest quintile had reported a 0.4% higher FEV_1/FVC ratio with 1.4% and 1.8% higher FVC% predicted and FEV1% predicted, respectively (100).

Vitamin C and other nutrients play an essential role in the pathogenesis of COPD by improving average lung function (69, 101) or preventing airway dysfunction (55). In epidemiological studies, a higher intake of vitamin C shows protective effects against decreased pulmonary function (55, 69, 99, 101) and/or risk of COPD (74, 76, 90, 97). A 6% lower risk of airway dysfunction was observed for every 10 mg per day increase in vitamin C intake (55) while an 8.3% increased risk of COPD for a 10% decrease in the daily recommended intake of vitamin C (97). In a paradox, a study conducted by Walda et al reported no effect for the intake of vitamin C against COPD (71). Studies reported inconsistent findings on the effect of vitamin E (69, 71, 74, 76, 90, 99, 102), and β-carotene(69, 71, 76, 99, 103) against COPD and/or impaired lung functions. In a randomized trial, a 10% reduction of chronic lung diseases for women who received 600 IU of vitamin E was observed (102). Vitamin D intake also revealed a beneficial effect on improving pulmonary function (69) and lowering the risk of COPD (104).

1.2.4 Flavonoid and their benefits on Lung Health

1.2.4.1. Role of flavonoids in COPD

A progressive persistent airflow limitation is the key feature of chronic obstructive pulmonary disease (COPD) and resulting from varying degrees of pathological changes associated with the imbalance between oxidants and antioxidants (105-108) mucus hypersecretion (109), excessive elastase release (110), increased lipid peroxidation (105). Flavonoids have been demonstrated to have multiple potentially beneficial effects against several chronic diseases due to their well-described antioxidant (111-113), anti-inflammatory (114, 115) anti-mutagenic properties, as well as their role in modulating metabolic pathways (114, 116).

Several experimental studies including rat and cell models evaluate the beneficial effects of dietary intake flavonoids or their dietary sources with several important health outcomes including better quality of sleep (117), reduced inflammation in obese individuals (118), better lung function (70, 119), and lower risk of several non-communicable diseases such as autoimmune diseases (120), and chronic obstructive pulmonary disease (COPD) (78, 121-124).

Oxidative stress resulted from the imbalance between oxidants and antioxidants (108, 125) implicated in the pathobiology of COPD (126-128). Reactive oxygen species (ROS) (129), reactive nitrogen species (130), and other free radicals are the main agents responsible for oxidative stress (131). Heme oxygenase 1, glutathione S transferase, and lipid peroxidation products were reported among the oxidative stress biomarkers involved in lung function decline(108).

Flavonoids have been beneficial to neutralize the negative effects of free radicals and maintain the oxidant/antioxidant balance, through their antioxidant properties (132). Experimental evidence demonstrates that flavonoid compounds such as quercetin(133), baicalin (134), oroxylin A (135), hesperidin (136), can reduce the effect of oxidative damage induced by ROS (131) and reactive nitrogen species (134) through induction of heme oxygenase (HO)-1 (133), reducing oxidant malondialdehyde (MDA) production (134), and inhibiting augmenting glutathione (GSH) level (135).

The innate immune response of alveoli and airways is likely to be formed from inflammation-associated cells such as macrophages, neutrophils, and eosinophil cells (128). A review conducted by Wang et al. found a beneficial effect of 31 bioactive compounds including epigallocatechin-3-gallate (EGCG), kaempferol, isorhamnetin, and quercetin, mainly through regulating various signaling pathways to inhibit infection, inflammation in a series of lung-related diseases (137).

Quercetin has been proven to be an excellent anti-inflammatory by inhibiting lipopolysaccharide (LPS) induced cytokine production in macrophages and lung cells (A549) (138), human neutrophil elastase (HNE)-induced MUC5AC gene expression in human airway epithelial cells (109), human neutrophil degranulation (110). Myricetin also induces an anti-inflammatory effect by inhibiting dose-dependent elastase release through neutrophil degranulation (110).

Other flavonoid compounds such as oroxylin A (135), baicalin (139), phloretin (140), hesperidin (136), and genistein (141) could inhibit inflammation by reducing Cigarette smoke (CS) -induced inflammatory cytokine production (135), suppressing the nuclear factor-kappa B (NF-κB) pathway (139, 141), suppressing the mucus hypersecretion (140), and regulating cytokines in bronchoalveolar lavage fluid (BALF) (136).

1.2.4.2. Dietary Flavonoid Intake and impaired lung function, COPD

Flavonoids are a large class of bioactive compounds, polyphenolic, non-nutrients, and ubiquitously distributed plant secondary metabolites, with fruits and vegetables being their richest sources (142-144). Fruit consumption accounts for around 54% of dietary flavonoid intake (145) and of which, pome fruits (78, 145-147) and citrus fruits (145, 146, 148) had been reported as the major contributing food items. Vegetables followed by legumes and beverages (including alcohols) are major sources of flavonoids and account for 40% of the flavonoid intake (145). Tea was also reported as the major dietary flavonoid source in several dietary intake studies (78, 147-149) with a percentage contribution of 75% to monomer intake (147). Dietary flavonoid intakes varied by age (149, 150), sex (148), level of education (148, 150), socioeconomic status (150), and other sociodemographic factors (148, 150). Dietary flavonoid intake also varied across regions and/or countries (147-152).

Population-level estimates of flavonoid intake mostly rely on the use of food composition tables (FCTs) to derive their content. These tools allow quantifying the intake of a wide variety of nutrients and non-nutrient bio-compounds, providing reference values that are often calculated within the research facilities linked to the specific FCT or compiled through scientific literature searches (153). As such, the content of flavonoids reported in FCTs is likely to show variations, which might be influenced by the differences in the analytical methods used to estimate their content in food, by the chemical form (e.g. aglycones or glycosides), the completeness of flavonoid FCTs, and by other factors related to seasonality and harvest (154). In addition to the specific methodological variations in the quantification of flavonoids, the epidemiological tools used to ascertain dietary intake (e.g., food frequency questionnaires (FFQ), 24-hour recall questionnaires) can also affect estimates (145).

Findings from epidemiological studies suggest that increased dietary flavonoid intake was associated with a lower risk of COPD(78, 155, 156), airway restriction (119), and a slower rate of lung function decline (70, 78, 119, 155-158). Compared to the lowest intake, FEV1(78, 155, 157), FVC(70, 157), FEV_1/FVC(119) were positively associated with a higher intake of total flavonoid (119, 155), total

catechins (70, 78), anthocyanin (157), flavonols(78), flavone(78) and pro-anthocyanidins(119).

In a study conducted by Mehta et al (157), participants in the fourth quartile of anthocyanin intake reported having a 23 mL/y and 37 mL/y slower decline rate of FEV1 and FVC, respectively compared with participants in the first quartile. Moreover, the decline rate in FEV1 and FVC was attenuated by 22.5 mL/y and 37.9 mL/y, respectively, in participants who consumed >2 servings of anthocyanin-rich blueberries per week compared with no or very low consumption (157).

A population-based study by Garcia-Larsen et al reported that 42% and 53% lower odds of having airway restriction (FVC < LLN) for those with higher intakes of total flavonoid and pro-anthocyanidin, respectively(119). Another study conducted by Sanderson et al demonstrated that the odds of having COPD decreased by 5.9% for every 1% increase in the daily total flavonoid intake (155). A habitual intake of isoflavones had reduced the prevalence of COPD by 64% as reported in a study conducted by Hirayama et al (156).

Table 1.1 summarize the characteristics of epidemiological evidence on the association between fruits, vegetables and dietary flavonoids intake with lung function and COPD. In this review, five important gaps have been identified; (i) almost all studies have been concentrated in European countries and United States and no study reported from low middle income countries, (ii) the variation on flavonoid contents of foods by food composition table was not considered, (iii) except very few studies, the majority didn't addressed all subclass of flavonoid, (iv) in majority studies, the impact of potential covariate have not addressed, and (v) the data used in the majority studies was not up to date.

1.3. Research Problem

Although numerous laboratory and experimental studies have demonstrated the beneficial effect of flavonoids on COPD and other lung health outcomes, still there is a paucity of population-based epidemiological evidence. Literature regarding the comparability of FCTs that are currently available to derive estimates of flavonoids is lacking and varied by inconsistent in terms of nutrient/compound identification, comparability of existing food composition datasets, dietary intake estimation method, and controlling for potential confounders. These are additional gaps to

which we have been identified in our literature review described in previous sections.

1.4. Research Aim, research questions and hypotheses

The primary aim of this PhD thesis was to investigate the association of dietary flavonoid intake with respiratory outcomes in adults participating in the Burden of Obstructive Lung Disease (BOLD-I) survey. In support of this aim, (i) a comparison study was designed to examine the extent of variations among international food composition tables; (ii) a modelled-approach data was analyzed to estimate the prevalence, mortality, disability, and risk factors associated with COPD in sub-Saharan African countries.

1.4.1 Objectives

1. To compare the extent of variation between international flavonoid food composition tables on the flavonoid content of selected foods
2. To estimate dietary flavonoid intake and explore the variation across participating sites
3. To investigate the association of dietary flavonoid intake and respiratory outcomes among adults participating in BOLD I survey
4. To analyze the burden and risk factors of COPD in sub-Saharan African countries

1.4.2 Research questions and hypotheses

RQ-I: To what extent the flavonoid contents of selected food item vary across the food composition tables.

- *H0-I*: There is no variation in the flavonoid contents of selected foods across the international flavonoid food composition tables
- *H1-I: There is a variation on the* flavonoid contents of selected foods across the international flavonoid food composition tables

RQ-II: What is the daily flavonoid intake among adults participating in BOLD I survey and how this vary between sites?

- *H0-II*: There is no between-sites and within-sites variation in daily total and subclasses flavonoid intake in adults participating in BOLD I survey
- *H1-II:* There is between-sites and within-sites variation in *the* daily total and subclasses flavonoid intake in adults participating in BOLD I survey

RQ-*III*: what is the relationship between dietary flavonoids intake and pulmonary function and COPD?

- *H0-IIIa*: There is no statistical evidence that support the association of dietary flavonoid intake and spirometry-defined airflow obstruction among adults participating in BOLD-I survey after adjusting for potential confounders
- *H1-IIIa:* There is statistical evidence that support the association of dietary flavonoid intake and spirometry-defined airflow obstruction among adults participating in BOLD-I survey after adjusting for potential confounders
- *H0-IIIb*: There is no statistical evidence that support the association of dietary flavonoid intake and FVC (ml) among adults participating in BOLD-I survey after adjusting for potential confounders
- *H1-IIIb:* There is statistical evidence that support the association of dietary flavonoid intake and mean of FVC (ml) among adults participating in BOLD-I survey after adjusting for potential confounders
- *H0-IIIc*: There is no statistical evidence that support the association of dietary flavonoid intake and FEV_1/FVC (%) among adults participating in BOLD-I survey after adjusting for potential confounders
- *H1-IIIc:* There is statistical evidence that support the association of dietary flavonoid intake and mean of FEV_1/FVC (%) among adults participating in BOLD-I survey after adjusting for potential confounders

RQ-*IV*: What is the burden of COPD across sub-Saharan African countries from 1990 to 2019? What is the percentage contribution of risk factors towards COPD burden across sub-Saharan African countries from 1990 to 2019?

- *H0-IV*: There is no variation on the burden of COPD by risk factors across sub-Saharan African countries
- *H1-IV:* There is variation on the burden of COPD by risk factors across sub-Saharan African countries

1.5. Significance

This study will contribute to the understand the role of dietary flavonoid intake on pulmonary function and COPD. This will help address the knowledge gap on the risk factors of COPD that provide clues to understand the determinants for the prevention of the disease; and insight into the effective management of health-care resources. Subsequently, this will contribute to the sustainable development goal of reducing the mortality from NCDs by 30% by the year 2030. Moreover, this study will shed light the research gaps which needs further investigation.

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Table 1.1 Characteristics of epidemiological studies investigating fruits, vegetables and dietary flavonoids intakes and outcomes of lung function, and COPD.

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
Bondonno NP, et al (2022) (1)	Prospective cohort using Danish nationwide registers	Denmark	• 57,053 participants • 50–65 years • Male and female	• FFQ • 174 food items	• Phenol-Explorer • Total flavonoid (219 flavonoid compounds), all flavonoid subclasses	Median flavonoid intake in quintile	Physician-diagnosed COPD	Age, sex, BMI, smoking status, smoking pack-years, physical activity, pure alcohol intake (g/d), education, income, and dietary factors such as energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids, and saturated fatty acids	• Daily median [IQR] habitual flavonoid intake was 496 mg (287 – 805) • Lower risk of COPD for both current and former smokers with the highest intake of flavonoids

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
Garcia-Larsen V, et al (2018) (2)	Multi-centric population-based study (GA^{2}LEN screening survey)	European Countries (Denmark, Finland, Sweden, UK, Portugal, Belgium, Germany, The Netherlands, Poland)	• 2599 adults • Age: 15–74 years • Male and female	• FFQ • 250 foods	• USDA • Total flavonoids, flavanones, anthocyanins, flavan-3-ols, flavonols, flavones and polymers	Higher vs. lowest quintile intake	FVC, FEV_1/FVC, FVC < LLN), and Spirometrically-defined COPD (FEV_1/FVC < LLN) NHANES III norms for Caucasians used as reference equations	Height, age, sex, BMI, smoking status, occupation, age at completion of full-time education, use of nutritional supplements, total fruit and vegetable intake, and total energy intake	• Median intake of total flavonoids was 291 mg/person/day • Total flavonoid and pro-anthocyanidins intake associated with a higher FEV1/FVC and a lower risk of spirometric restriction (FVC < LLN). • A lower risk of airway obstruction (FEV1/FVC < LLN) was

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
									observed among those with A higher intake of pro-anthocyanidins.
Sanderson TA, et al (2017)(3)	Cross-sectional study using 2007–2010 NHANES	US	• 5,172 participants • Age: 30 years and above • Male and female	24-hour dietary recalls	• USDA • Total flavonoid	Mean daily flavonoid intake	Spirometry defined COPD using GOLD (2015) guidelines (FEV1/FVC < 70%), and COPD Severity (FEV1% predicted)	Age, BMI, dietary fiber intake, education level, gender, race/ethnicity, and smoking status	• Mean daily flavonoid intake was 249.3 mg/day • Total daily flavonoid intake was inversely associated with COPD, OR declined from 7.1% to 5.9%
Mehta et al. (2016) (4)	Longitudinal analysis using data from the VA (Veterans	US	• 839 participants • Age: 49–92 • Male only	• Semi-quantitative FFQ	• USDA • Anthocyanins, flavanones, flavan-3-ols,	Quartiles (lowest quartile as reference)	FEV1 (mL) and FVC (mL) based on ATS	Race, smoking status, pack-years smoked, physician	• The median intake of Anthocyanins was 1.3, 4.4,

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
	Affairs) Normative Aging Cohort Study			• 126 food items	flavonols, flavones, and polymers		Guidelines	diagnosis of chronic bronchitis or asthma or emphysema, age at first visit, height (cm), total energy intake, and time since first visit, use of medication for asthma, use of statins, years of education, percentage of census tract below poverty level, total fruit intake, total vegetable intake, and physical activity	13.6 and 25.3 mg/day for 1st, 2nd, 3rd and 4th quartile, respectively. • Higher intake of dietary anthocyanin reduces age-related lung function decline

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
Garcia-Larsen V, et al (2015) (5)	Cross-sectional study as part of non-concurrent longitudinal study	Chile	• 1232 adults • Age: 22–28 years • Male and female	• Semi-quantitative FFQ • 65 food items	• Dutch food composition data for flavonoid content of foods • Flavonols, flavones and catechins	Highest vs. lowest quintile of intake	FEV1, FVC, and FEV1/FVC based on American Thoracic Society guideline	Height, sex, age, current smoking, overcrowding, years of fulltime education, socio-economic status, birth weight, body mass index (BMI), and total energy intake	• Daily average dietary intake of total catechins and Flavonols was 17.1 and 26.2 mg7day for males, and 21.2 and 24.7 mg/day for females, respectively. • Total fruits and catechins intake positively associated with lung function
F. Hirayama et al (2010) (6)	A case–control study	Japan	• 278 patients with COPD diagnosed and 340 community-	• FFQ • 138 food items	• Japanese food composition tables • Isoflavones (Genistein,	Highest (≥ 55.41) versus lowest (≤ 7.68) levels	Spirometry defined COPD based on GOLD	Age, gender, BMI of 5 years ago, education level, cigarette smoking,	• The mean habitual dietary isoflavone intake was

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
			based controls • Age: aged 50–75 years • Male and female		Daidzein)	of total isoflavone intake	guidelines, lung function measures (FEV1 and FVC)	smoking pack-years, alcohol drinking status and total energy intake	27.82 ± 20.66, and 39.57± 39.21 for cases and controls, respectively • Lower habitual intakes of isoflavones (genistein and daidzein) were observed among COPD patients compared to control subjects. Positive association between lung function and dietary intakes of

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
									total isoflavone, genistein, daidzein
Tabak, Arts, Smit, et al (2001) (7)	Cross-sectional analysis from MORGEN-EPIC	The Netherlands	• 13,651 adults • Age: 20 – 59 years • Male and female	• Semi-quantitative FFQ • 178 food items	• Specific food composition tables • Total catechin, Flavonols, Flavone	Fifth versus the first quintile of intake	Spirometry based Pulmonary function (FEV1) based on ERS guidelines, COPD symptoms	Age, sex, height, BMI, energy intake, smoking, pack-years of smoking	• 58 mg/d (SD=46) was the average intake of catechin, flavonols, and flavone • Positive association of total catechin, flavonols, flavone with FEV1 whereas inversely associated with chronic cough and breathlessness

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
Fruits and Vegetables Intake									
Kaluza J, et al (2018) (8)	Cross-sectional analysis using data population-based prospective Swedish Mammography Cohort and Swedish health register	Sweden	• 34,739 participants • Age: 48–83 years • Female only	• FFQ • 67 and 96 food items in 1987 and 1997, respectively	na	Highest vs lowest quintile of consumption (≥ 2.5 vs <0.8 servings/day)	Diagnosed COPD based on ICD codes	Age, education, BMI, total physical activity, smoking status and pack-years of smoking, energy intake, dietary supplement use, alcohol intake, and modified Recommended Food Score (RFS) and Non-Recommended Food Score (Non-RFS)	• Women in the highest quintile of long-term fruit and vegetables consumptions had median of 2.9 and 3.7 servings/day, respectively compare to a median consumption of 0.6 and 0.9 servings/day for women in the lowest quintile respectively • Long-term consumption

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
									of fruits inversely associated with COPD incidence but not vegetables
H. Meteran et al (2018) (9)	Cross-sectional analysis using data from two Danish cohorts namely The Middle Age Danish Twin (MADT) and The Middle Age Danish Twin (MIDT)	Denmark	• 12,449 twins • Age: 40–80 years • Male and female	Self-reported weekly intake	na	Low (weekly consumption or less) versus high intake (daily)	FEV1, FVC, FEV1/FVC-ratio, Spirometry defined COPD (FEV1/FVC < LLN) based on ATS/ERS guidelines	Sex, age, BMI, smoking, alcohol consumption, physical activity	Low intake of fruit and vegetables associated with an increased risk of COPD
Kaluza J, et al (2017)(10)	population-based prospective Cohort of Swedish, Swedish	Sweden	• 4,335 men • Age: 45–79 years • Male only	• FFQ • 96 food items in 1997	na	Highest vs lowest (≥5.3 servings/day versus <2 servings/	Diagnosed COPD based on ICD codes	Age, smoking, education, BMI, total physical activity, energy intake, alcohol intake, modified	Lower risk of COPD was observed among current and ex-smokers with those high

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
	Patient Register, and the Swedish Cause of Death Register					day), median values of each quintile of consumption		RFS and non-RFS	consumption of fruits and vegetables compare to low intake.
E. Keranis et al. (2010) (11)	Prospective study, randomized trial of increased consumption of fresh fruit and vegetables as intervention group (IG)) or a free diet as control group (CG))	Greece	120 COPD patients	• FFQ • 38 food items	na	Mean consumption of foods	FEV1% GOLD criteria	Sex, age, smoking status, morbid conditions, and exacerbations	Lung function has improved with dietary shift to higher-antioxidant food intake
F. Hirayama et al (2009)(12)	Case–control study	Japan	• 278 COPD patients as cases and 400	• FFQ • 138 food items	na	Highest versus lowest quartile of	Spirometric defined COPD vs non-COPD	Age, gender, BMI of five years ago, education level,	Inverse association between vegetable consumption and

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
			community-dwelling adults as controls • Age 50–75 years • Males and females			intake	based on GOLD (FEV1 / FVC < 0.7)	life-long physical activity involvement, smoking status, smoking pack-years, alcohol drinking status and, daily dietary intake of fish, red meat, and chicken	the risk of COPD
L. Watson et al. (2002) (13)	Case-control study	UK	• 150 cases and 116 controls • Age: above 45 years • Male and female	• FFQ • 77 food items	na	Tertile (the lowest third of intake as reference)	Spirometry based COPD vs non-COPD using the BTS Guidelines	Sex, age, social class and BMI	Fruit and vegetable consumption is inversely associated with COPD
C. Tabak et al (2001) (14)	Cross-sectional study using data from MORGEN	The Netherlands	• 13 651 men and women • Age: 20 -59 years • Male and female	• FFQ • 178 food items	na	Food intake dichotomized favorable vs.	FEV_1 using ERS guidelines and prevalence of COPD	Age, gender, height, smoking, BMI, and energy intake	Fruit intake showed independent beneficial effects with COPD (*P*-trend < 0.001)

Table 1.1 …(Continued)

Author(s)	Study design and characteristics	Country	Study population	Dietary intake assessment	Food composition table(s) and flavonoid studied	Intake comparison	Respiratory outcome	Confounders included	Result(s)
						unfavorable	symptoms		
Tabak, Smit, Räsänen, et al (1999) (15)	Cross sectional study using data from two Finnish cohorts, Italian and Dutch cohort	Three European countries (Finland, Italy, and The Netherlands)	• 1248, 1386, and 691 men in Finland, Italy, and the Netherlands, respectively • Age: 40–59 years • Men	Cross-check dietary history method	na	high versus low intakes of fruit and vegetables using above or below the median	FEV (In Finland and Italy $FEV_{0.75}$ was measured whereas In the Netherlands FEV_1 was measured. The term FEV was used assuming that the relation with diet is the same for $FEV_{0.75}$ and FEV_1)	Smoking, BMI, alcohol consumption, and energy intake	A higher FEV was observed among men with intakes of fruit and vegetables above the median than those with a low intake

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Chapter 2 Burden and risk factors of chronic obstructive pulmonary disease in Sub-Saharan countries, 1990-2019

2.1. Introduction

Noncommunicable Diseases (NCDs) represent the biggest threats to health and development globally, particularly in developing countries(1) accounting for more than 73% of the total deaths in 2017(1, 2). Chronic respiratory diseases are the third major contributor of deaths(2). Globally, an estimated 454 million people had chronic respiratory diseases in 2019, of which 46·7%, 212 million(3), were COPD cases. Regions with a low socio-demographic index were reported to have the greatest burden of chronic respiratory diseases (4, 5). Current evidence suggests that Sub-Saharan countries are at the dawn of the epidemiological transition(6) and an increase of 31·5% of chronic obstructive pulmonary disease (COPD) cases over a decade that is attributable to ageing alone(7). Despite the steady increase in the number of COPD cases, there are few studies collecting population-based data on COPD in Sub-Saharan African Countries (SSA)(8-10). Available evidence shows that COPD is associated with a high mortality, accounting for 95·90 deaths/1000 person-years in Uganda(11) and stage 4 disease at baseline was the strongest risk factor associated with death(11, 12).

Epidemiological studies reported(7, 10, 13-20) that the prevalence of COPD in Sub-Saharan African countries (SSA) shows large variations, ranging from 1·1% to 23·8% (21). Some of this variation is due to differences in the definitions and criteria used to ascertain the prevalence of spirometry-defined COPD(18). In a prospective cross-sectional study conducted by van Gemert *et al.* in Uganda(17), COPD prevalence was 16·2% and 12·4%, depending on whether it was defined by the American Thoracic Society/European Respiratory Society (ATS/ERS), or Global initiative for chronic obstructive lung disease (GOLD) guideline, respectively. Similarly, the mean age of COPD patients was estimated about 55·5 and 46·7 years, when using the ATS/ERS and GOLD guideline, respectively(17). Another study conducted by North *et al.* in Uganda(15), however, found that prevalence of COPD was 2%, which was unchanged when defining COPD as $FEV_1/FVC<0.7$.

The variation of COPD prevalence by age was observed on these epidemiological

surveys using the GOLD(14, 16) and showed a six-fold higher prevalence in old compare to youngest age group(16), except in study conducted by Magitta et.al(19). A history of prior active TB(16, 19), smoking(14, 17, 19), biomass exposure(13, 14, 16), poor ventilated kitchen(14) were associated factors with COPD. The correlation between age and years of exposure to biomass smoke, and hours per day exposure to biomass smoke had reported more participants with COPD than without COPD(14).

Lack of generalizability(11, 14, 16, 20), limited sample size(11, 12, 19, 20), high non-participation rate(12, 13, 19, 20), challenges to identify causal risk factors risk factors(11, 13, 15), over- and under-diagnosis(14-17, 19, 21, 22) and self-reported age(14, 17) have been described as some of the major limitations to understand the distribution and risk factors for COPD in Africa. An estimated 98·3% and 81·4% of spirometrically defined COPD cases were undiagnosed in Ife, Nigeria and Cape Town, South Africa, respectively(22). Moreover, inconsistent diagnostic criteria and variable methods and methodological quality(18) and the heterogeneity in spirometrically defined COPD within and/or between studies(13-17, 20). Those poses additional challenge not only to the paucity of nationally representative population based studies(7, 18, 22) but to the understanding of the current status and progress being made at the country level (23).

The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) provides a systematic scientific assessment of published, publicly available, and contributed data(3). In SSA however, analyses on the burden and attributable risk factors of COPD are limited. The primary objective of this GBD paper is to address this evidence gap, by estimating the mortality, prevalence, risk factors, and disability associated with COPD in SSA, examining the variations observed in the period between 1990 and 2019.

2.2. Methods

2.2.1 Overview

SSA is amongst the seven super-regions where the Global Burden of Disease (GBD) estimate was produced. In this paper, as part of the GBD 2019 round, we have studied the GBD estimate of COPD in SSA, as classified by the World Bank. The methods applied in this paper are the same as those described for the GBD 2019, mentioned elsewhere (3, 24, 25). Additional methodological details are available as a supplementary appendix on the GBD 2019 Capstones: Diseases and Injuries(3), and Risk Factors(24).

2.2.2 Non-fatal Estimation for COPD: Prevalence and YLDs

The GOLD spirometry-based post-bronchodilation measurement (<0.7 FEV_1/FVC) was used as case definition and severity grading for COPD (26). An alternative case definition was also used from GOLD Pre-bronchodilation, Lower Limit of Normal (LLN) Pre and Post bronchodilation, and European Respiratory Society (ERS) guidelines(27). Furthermore, the International Classification of diseases (ICD) versions 9 and 10 codes associated with COPD were enrolled as methods of evaluating whether individual has COPD. The codes 491-492, & 496 from ICD-9, and J41, J42, J43, J44, & J47 from ICD-10. Codes J40 & 490 (Bronchitis, not specified as acute or chronic) and J47 & 494 (Bronchiectasis) were excluded.

Prevalence, incidence, remission, and hospital claims data were the main data sources obtained either from systematic reviews or from data contributed by GBD collaborators. A spirometry-based measure was used as inclusion criteria for all data. For Sub-Saharan Africa, five distinct datapoints were listed as input source for COPD prevalence estimation in GBD's Global Health Data Exchange repository. Of those input source, the data from the Burden of Obstructive Lung Disease (BOLD)(28) was the only population-based survey data source.

DisMod-MR version 2.1, an updated Bayesian meta-regression analytical tool, was used to estimate COPD prevalence by location, age, sex, and year. Prior to actual modelling, datapoint and bias adjustment was performed using; (1) age-sex and sex split to disaggregate data reported not disaggregated into age and sex (2) a Meta-Regression—Bayesian, Regularised, Trimmed (MR-BRT) model for direct comparison of study design and case definitions. The detailed procedure for both

data and bias adjustment was well documented in previous GBD paper (3).

The prevalence of COPD was estimated in two steps. In the first step, the prevalence was calculated using the DisMod-MR 2.1 model. The model has set with 0 for remission noting that individuals do not recover from COPD. Furthermore, the model setting also includes a series of country-level covariates with an assumption to apply Spatiotemporal Gaussian process regression (ST-GPR) for countries that were missing complete datasets. Healthcare Access and Quality (HAQi) index, standardised exposure variables (SEV) for COPD, and the proportion of elevation over 1500m were included as country-level covariates. In the second step, the GOLD class groupings in DisMod-MR 2.1 were used to estimate proportions of severities for COPD.

Following these two distinct steps, the Years Lived with Disability (YLDs) due to COPD was estimated as a product of the prevalence of each sequela and the disability weight (DW) of the relative severity of the sequela on a scale between 0 and 1; i.e., 0 implies a state equivalent to full health, and 1, a state equivalent to death. An uncertainty was computed for YLDs considering uncertainty in prevalence and uncertainty in the DW. 1000 samples of the YLD distribution were generated using 1000 samples of comorbidity corrected YLDs and 1000 samples of the DW assuming no correlation in the uncertainty in prevalence and DW. The supplementary appendix for 2019 GBD Capstone provides further methodological details on Nonfatal health outcome estimation(3).

2.2.3 COPD mortality estimation: Death and years of life lost (YLLs)

Vital registration was the main data input source to derive the Causes of Death due to COPD using the standard CODEm modelling approach. Datapoints with high or low implausible, or with substantial conflict from established age or temporal patterns, or with substantial conflicted with other data sources but from the same locations or locations with similar Socio-demographic Index were excluded as outliers.

Potential covariates were included in the model by their influence either as a positive standardized beta (increased death) or a negative (decreased death) standardized beta. A scalar of summary exposure to risk for COPD, smoking prevalence, total number of cigarettes smoked (5, 10, & 20 years), indoor air

pollution, and the proportion of elevation over 1,500m were covariates with a positive standardized beta whereas healthcare access and quality index, socio-demographic index, 10-year income per capita, and education were covariates with a negative standardized beta.

The death estimation adjustment was performed by CoDCorrect using unadjusted death estimate from COPD, the overall sum of death estimate from chronic respiratory diseases, and all-cause death derived from demographic estimation. YLLs due to COPD was calculated by multiplying the death due to COPD by the remaining life expectancy in GBD's standard life table based on lowest observed mortality rate at each stage in any population over five million people. Further methodological details on the cause of death estimation was explained in the methods appendix for GBD 2019 capstone(3).

2.2.4 DALYs Estimation

DALYs was obtained by adding YLLs and YLDs for each age-sex-location. Uncertainty was estimated by assuming the uncertainty in YLLs to be independent of uncertainty in YLDs. 1000 samples of DALYs were generated using the sum of 1000 samples for YLLs and YLD. The estimation was computed by recalculating every outcome of interest 1000 times, drawing from distribution of the sampling error around input data, correction for measurement error, and estimates of residual non-sampling error and, model selection in case of cause of death estimate. 95% UIs were computed by using the 25th and 975th ordered draw of the DALY uncertainty distribution(3).

2.2.5 Risk factor attributable burden estimation

Seven risk factors namely smoking, second-hand smoking, household air pollution from solid fuels, occupational particulate matter, ambient particulate matter, ozone, and low temperature were included in risk estimation for COPD. Those risk factors were included based on the World Cancer Research Fund criteria for convincing or probable evidence of risk–outcome pairs(29) and the comparative risk assessment framework(25). Distinct datapoints for household air pollution from solid fuels (388), smoking (280), second-hand smoke (191), Occupational particulate matter, gases, and fumes (81), Ambient particulate matter pollution (24), and one datapoint for Low temperature were available as exposure data input sources. There is no

datapoint available for Ambient ozone pollution exposure. It, however, obtained through simulation modelling of ozone ground measurement data from the Tropospheric Ozone Assessment Report (TOAR). Population survey was used as the main exposure data source for smoking, second-hand smoke, and household air pollution whereas the exposure to ambient PM2.5 was measured from satellite. Exposure data, relative risk of outcome, and a theoretical minimum level of exposure were enrolled to estimate the population attributable fraction of COPD (**Figure 2.1**). Further risk specific methodological details described in 2019 GBD risk factors capstone(24).

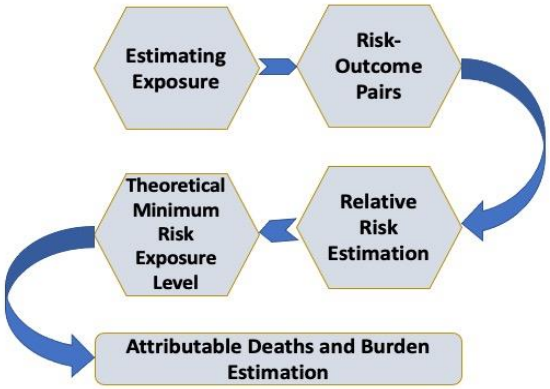

Figure 2.1 Flowchart shows risk factor attributable estimation using GBD comparative risk assessment framework

2.2.6 Data Presentations

Findings were reported based on data obtained from GBD result tool(30). The reporting complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) statement(31). GBD compare was used to explore the level and trend of estimates. In this study, COPD estimates such as prevalence, YLDs, Deaths, YLLs, and DALYs) were reported for Sub-Saharan African countries, and four regions. Those measures presented at country-level, group level (age or sex), change over time, and at-risk specific using metrics: number, rate, and percentage. Estimates had reported with 95% uncertainty intervals when needed which computed by ordering 1000 draws of a given estimate. Percentage change was estimated to show the trend of COPD estimates from 1990 to 2019. Furthermore, the percentage of COPD estimates attributable by risk factors was reported to ascertain the risk factor that bring the greatest burden by sex and locations (at country and regions level).

2.3. Results

2.3.1 Nonfatal health loss attributable to COPD in Sub-Saharan Africa

In 2019, all-age prevalent cases of COPD in SSA were estimated at 10·3 million people (95% UI 9·7 million to 10·9 million), which increased by 117% compared with the number of all-age COPD cases in 1990 (**Table 2.1**). COPD prevalence rate was estimated to be 1,705 (95% UI 1,820 – 1,598) per 100,000 which differed by country and sex. Sao Tome and Principe, and Ethiopia had the highest and lowest age-standardized COPD prevalence rate for both sexes, respectively [**Figure 2.2**].

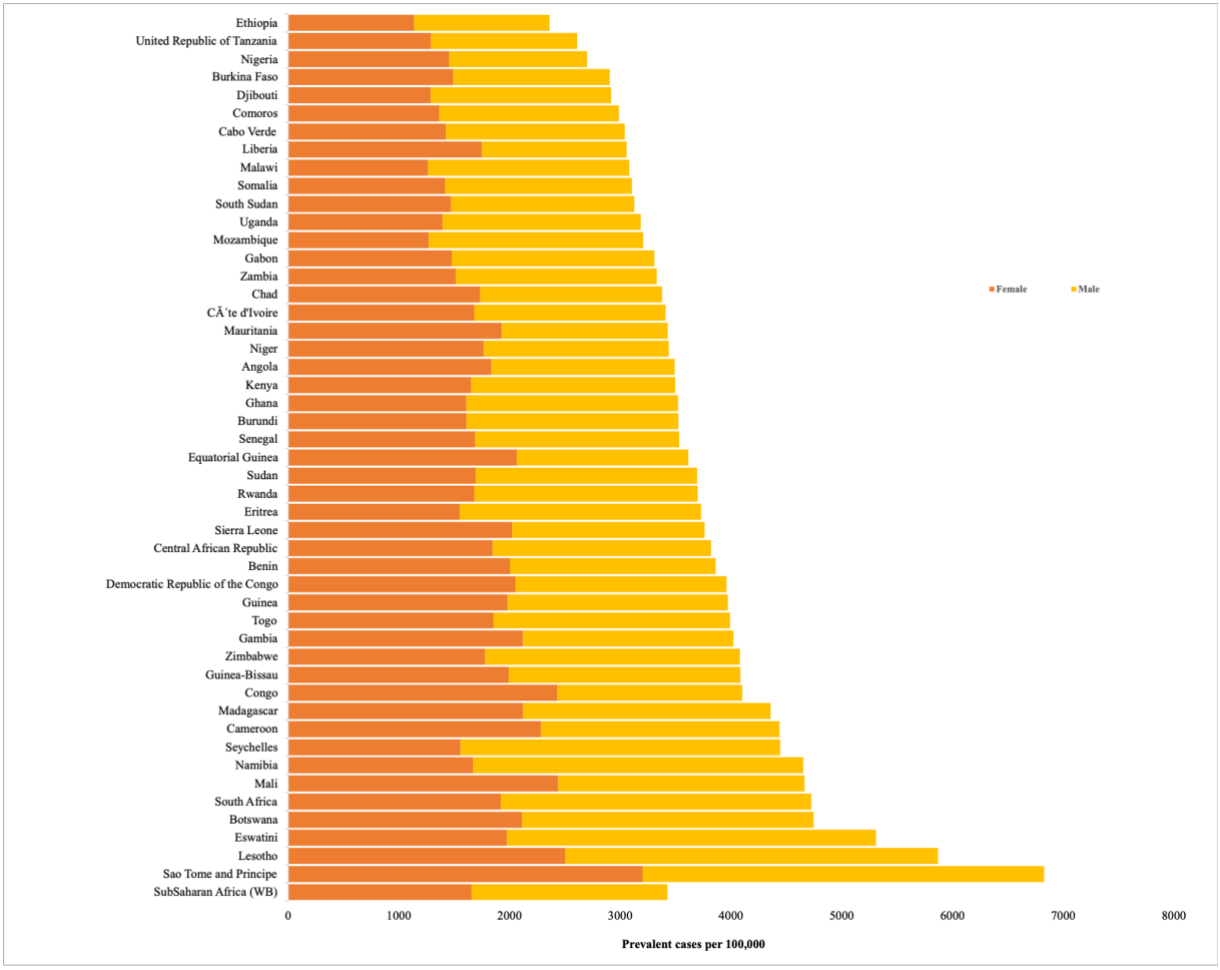

Figure 2.2 Age-standardized prevalence of COPD across sub-Saharan African countries (World Bank Classification) in 2019

The age-specific prevalence of COPD starts to increase at age 45 years for both sexes. Important percentage differences in COPD prevalence were observed between males and females from age 75 years ranging from 13% to 31% and reaching the peak at age 90—94 years [**Figure 2.3**]. From 1990 to 2019 the prevalence rate of COPD was stable in Eastern and Western Sub-Saharan Africa,

whereas there was a decreasing trend in Southern Sub-Saharan African countries [**Figure 2.4**]. Central sub-Saharan Africa countries showed an increase in age-standardized COPD prevalence since 2000 which reached a peak in 2019[**Figure 2.4**].

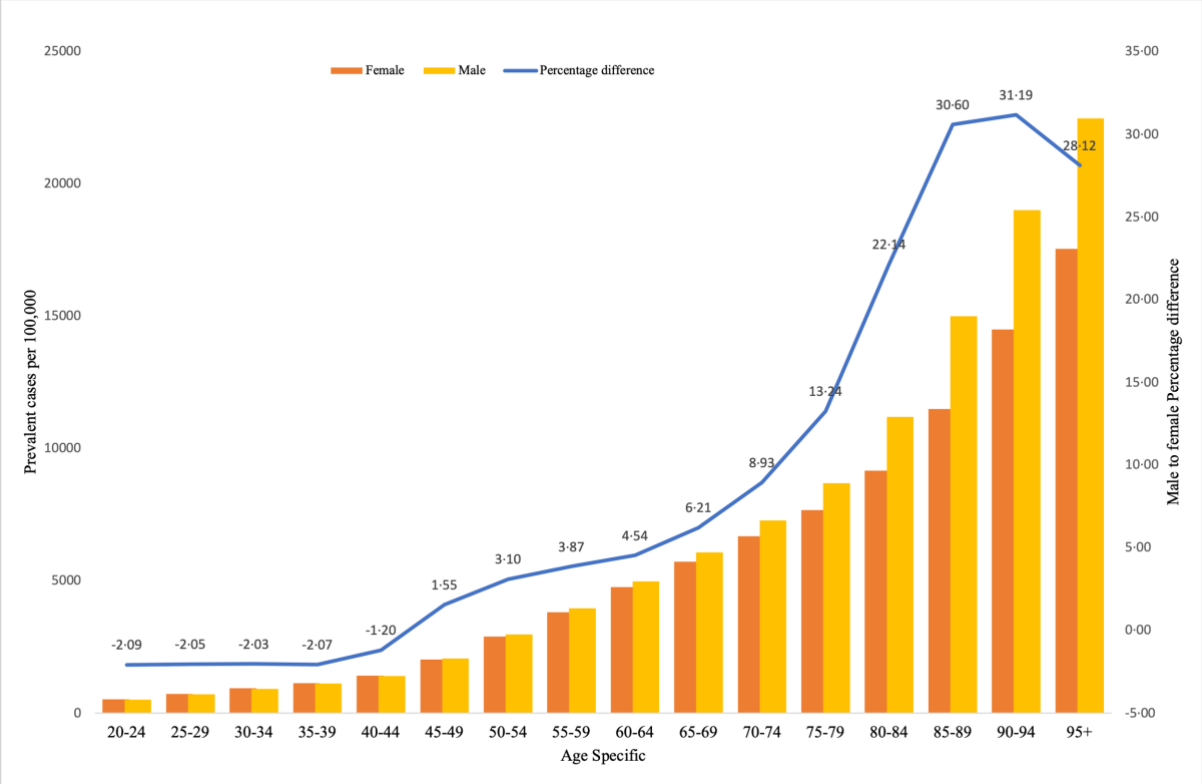

Figure 2.3 Age-specific prevalence of COPD by sex in Sub-Saharan Africa, 2019 (percentage difference was estimated to show percentage increase or decrease in male compared to female by age-specific)

In 2019, sub-Saharan Africa counted 1·2 millions (95% UI 1·1 millions to 1·4 millions) years lived with disabilities (YLDs) dues to COPD. Nigeria followed by South Africa and Democratic Republic Congo had the highest YLDs due to COPD in 2019. From 1990 to 2019, Sub-Saharan African countries presented an increased percentage change in all-age YLDs due to COPD ranging from 41% in Lesotho to 203% in Equatorial Guinea (**Table 2.1**). In Sub-Saharan Africa, Ethiopia exhibited the highest reduction in percentage change of age standardized YLDs due to COPD among males from 1990–2019 accounts for 28·7%. Whereas in Ghana, the percentage change of age standardized YLDs due to COPD among males increased by 46·8% (**Appendix Table A.1**).

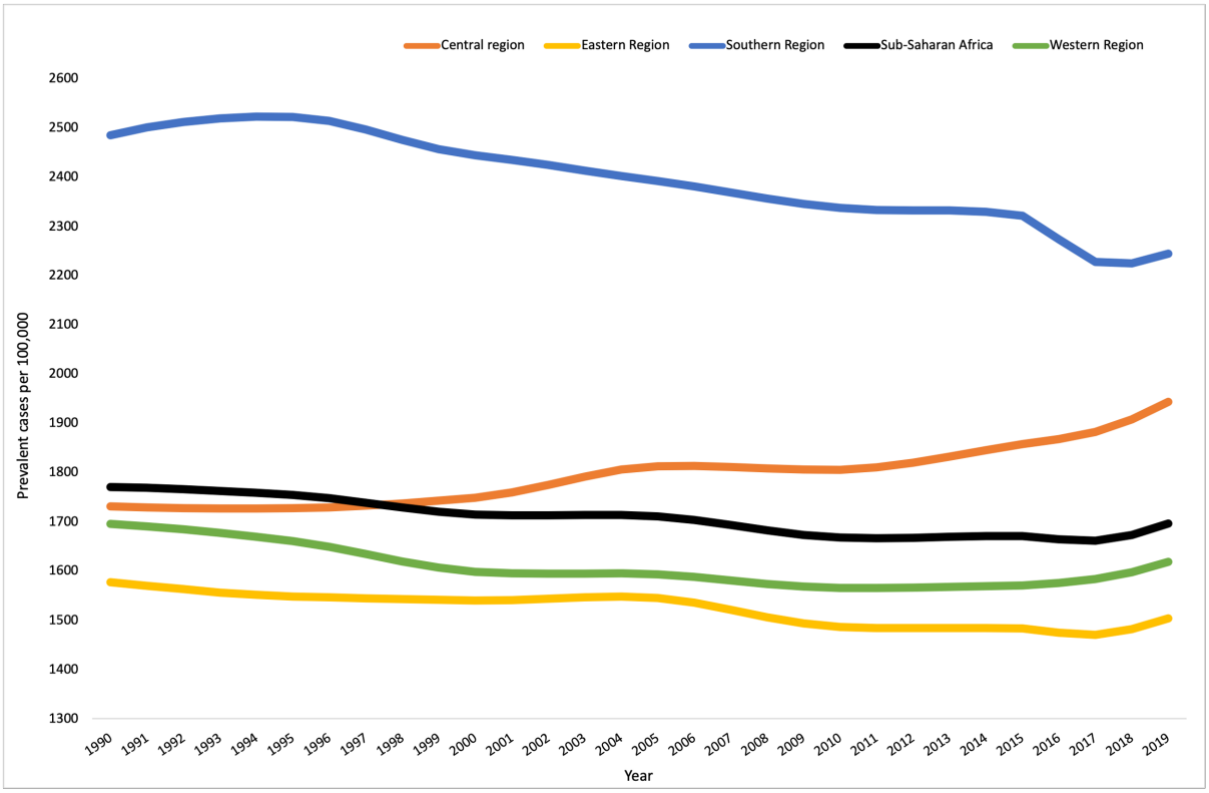

Figure 2.4 Trend in age-standardized prevalence rate of COPD by region in sub-Saharan Africa, 1990-2019

Seven risk factors had established based on the GBD comparative risk assessment framework. In 2019, household air pollution from solid fuel followed by smoking was the major contributor of the age standardized YLDs rate per 100,000 in sub-Saharan Africa (**Figure 2.5**). Smoking followed by ambient particulate matter pollution accounts for the major fraction of COPD attributable YLDs in southern sub-Saharan Africa (**Appendix Table A.4**). In Eastern Sub-Saharan Africa household air pollution from solid fuel was major contributor to the percentage of COPD related YLDs among Females responsible for 51% whereas smoking responsible for 4·4% (**Appendix Table A.4**).

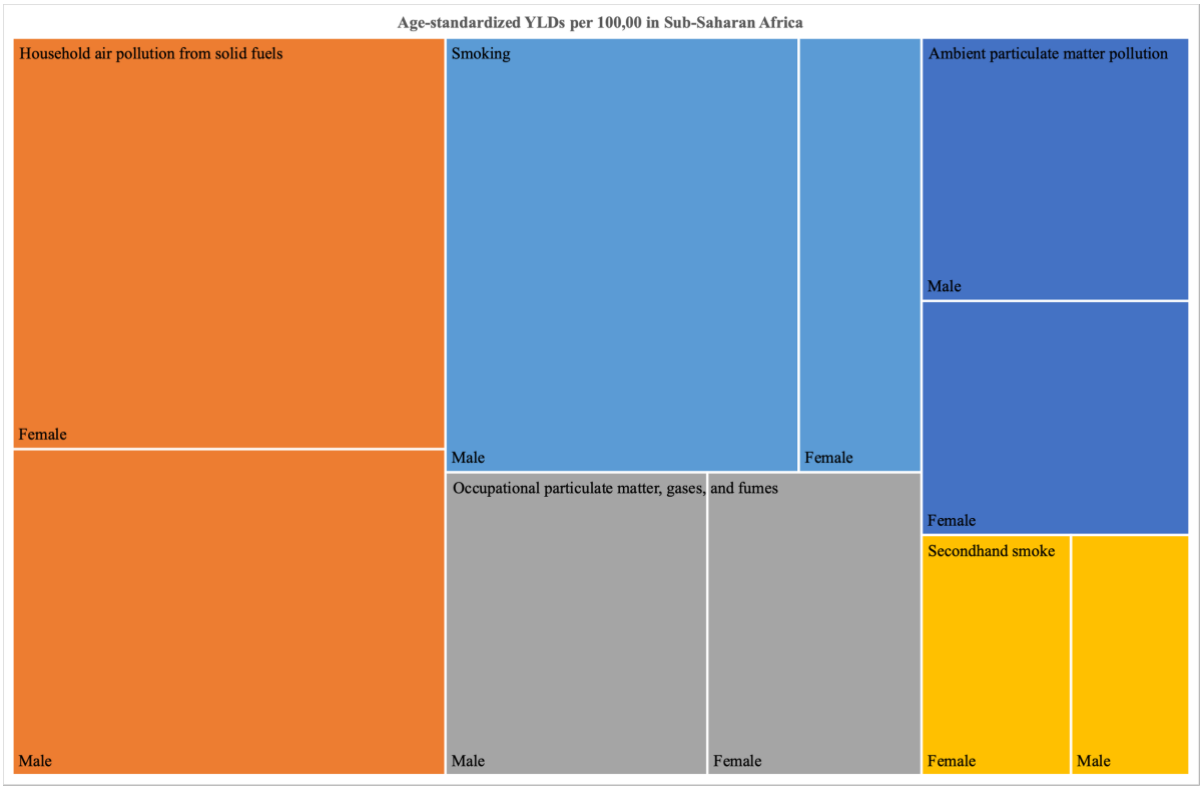

Figure 2.5 Age-standardized YLDs due to COPD attributable to risk factors by sex in sub–Saharan Africa in 2019 (the shaded area indicates the age-standardized years lived with disability rate attributable to the specific risk factor by sex)

2.3.2 Deaths and Years Life lost (YLLs) due to Chronic obstructive pulmonary disease

In 2019, about 107 thousand people (95% UI 92 thousand to 123 thousand) died due to COPD in Sub-Saharan Africa, with a 21% decrease in age-standardized death rate compared to 1990 (**Table 2.2**). The highest reduction of COPD age-standardized death rate was reported in Cabo Verde (48.5%) followed by Rwanda (42.6%) and Equatorial Guinea (42.5%) in 2019 compared to the age standardized death rate in 1990. While only in Sao Tome and Principe COPD age standardized death rate increased by 1.5% (**Table 2.2**). Cabo Verde had the highest reduction in age-standardized deaths rate for both sexes (**Appendix Table A.2**). Sub-Saharan African countries presented a reduction in COPD caused YLLs, age-standardized, in females ranging from 0·8% in Lesotho to 55·0% in Cabo Verde, 1990 to 2019 (**Appendix Table A.2**). From 1990 to 1998, Southern Sub-Saharan African exhibited a rapid increase in rate of deaths due to COPD and then a decrease since 1999 [**Figure 2.6**]. In 2019, household air pollution followed by smoking and occupational particulate matters was responsible for the largest fraction of the age-

standardized death and YLLs rate due to COPD in sub–Saharan Africa (**Figure 2.7**, **Appendix Table A.5**, **Appendix Table A.6**).

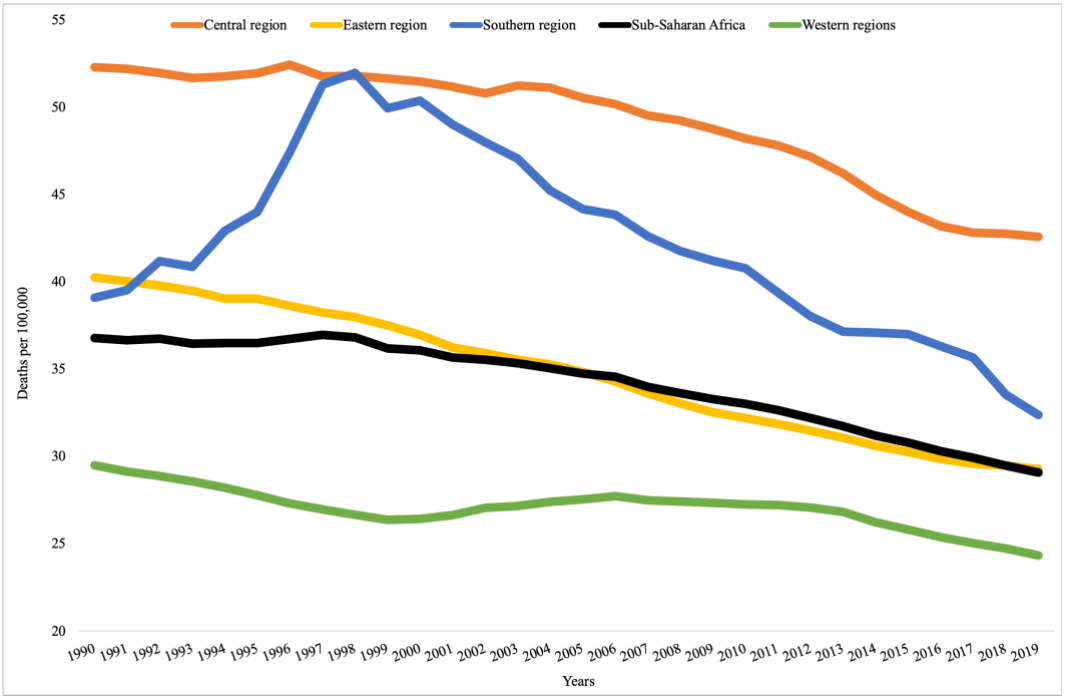

Figure 2.6 Trends in age standardized death due to COPD across Sub Saharan African regions, 1990-2019

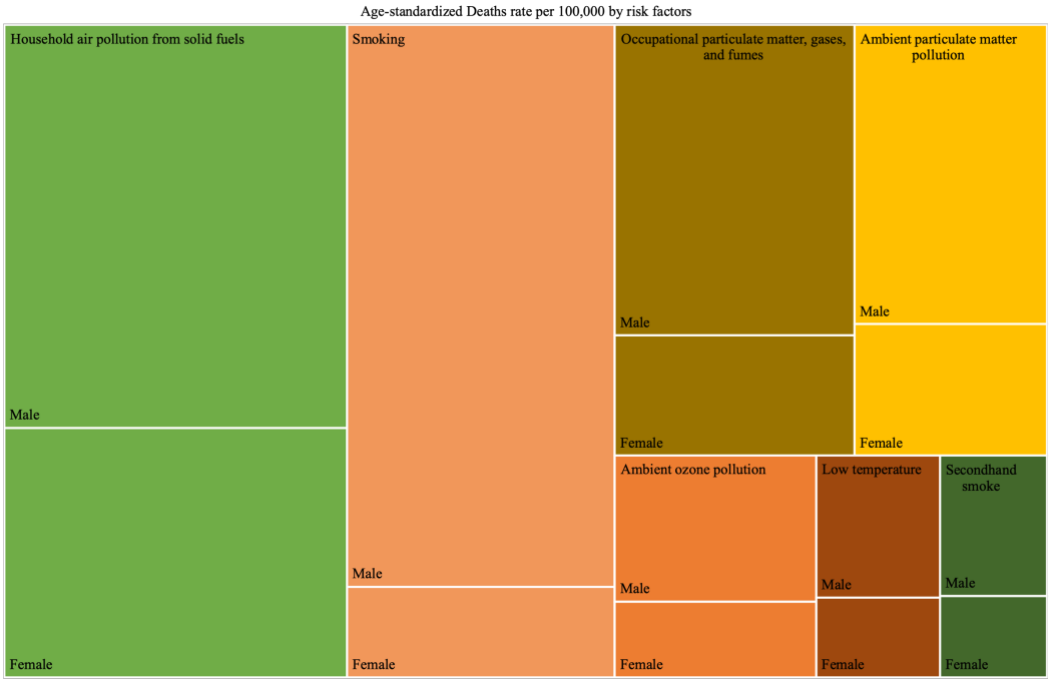

Figure 2.7 Contribution risk factors age-standardized Death rate due to COPD (the shaded area indicates the age-standardized deaths rate attributable to the specific risk factor by sex)

2.3.3 DALYs due to Chronic Obstructive pulmonary disease

In 2019, COPD was responsible for 715 [880 in males, 577 in females] DALYs rate

per 100,000 in Sub-Saharan Africa. Lesotho had the highest rate of DALYs attributable to COPD for males [2329 per 100,000] and females [1279 per 100,000] whereas Liberia [495 per 100,000] and Mauritius [304 per 100,000] had the lowest rate of DALYs for males and females, respectively [**Figure 2.8**]. All Sub-Saharan countries except Mozambique, and Sao Tome and Principe showed a reduction in COPD related DALYs rate where Ethiopia and Ghana showed the highest and lowest percentage reduction, respectively (**Appendix Table A.3**). The percentage reduction in age standardized DALYs rate showed a variation by sex (**Appendix Table A.3**).

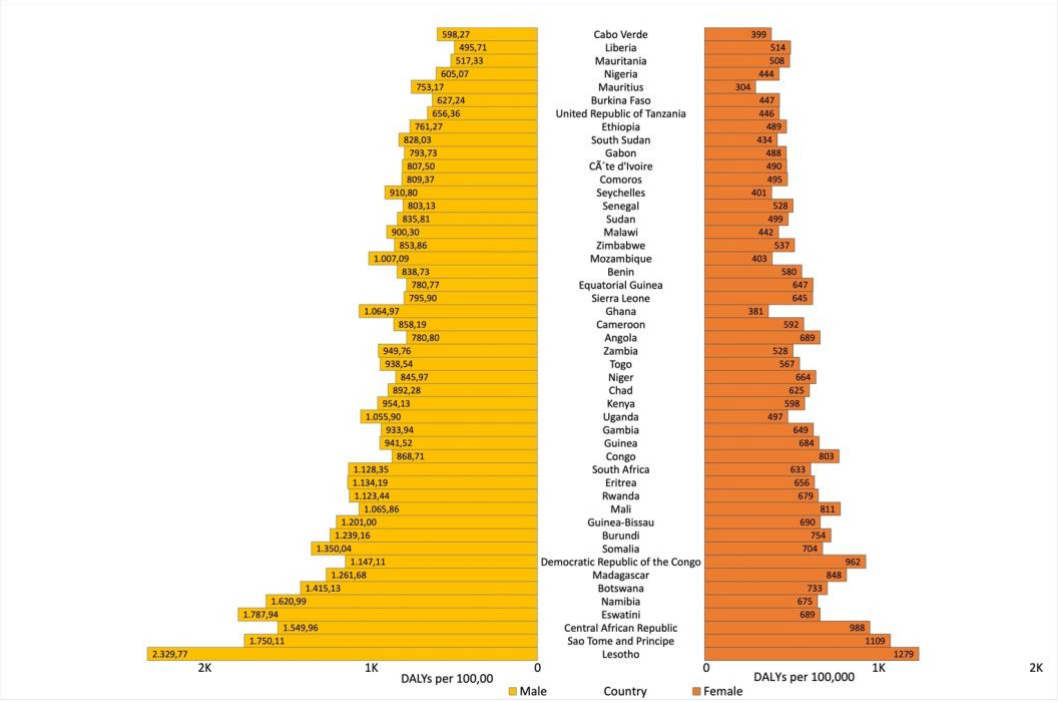

Figure 2.8 Age standardized DALYs due to COPD by sex across sub–Saharan Africa, 2019

COPD related to household air pollution risk contributed to a higher rate of DALYs per 100,000 in Sub-Saharan Africa followed by smoking, occupational and ambient particulate matter pollution [**Figure 2.9**]. Smoking and Ambient particulate matter were ranked 1st and 2nd for rate of DALYs attributable to COPD across Southern sub-Saharan Africa in 2019 [**Figure 2.9**]. The reduction of percentage contribution of household air pollution exhibited similar trend to the reduction of age-standardized DALY rate due to COPD in SubSaharan africa(**Figure 2.10**). In Somalia, household air pollution from solid fuel responsible for 80-85% of age-standardized DALYs rate due to COPD (**Appendix Table A.7**).

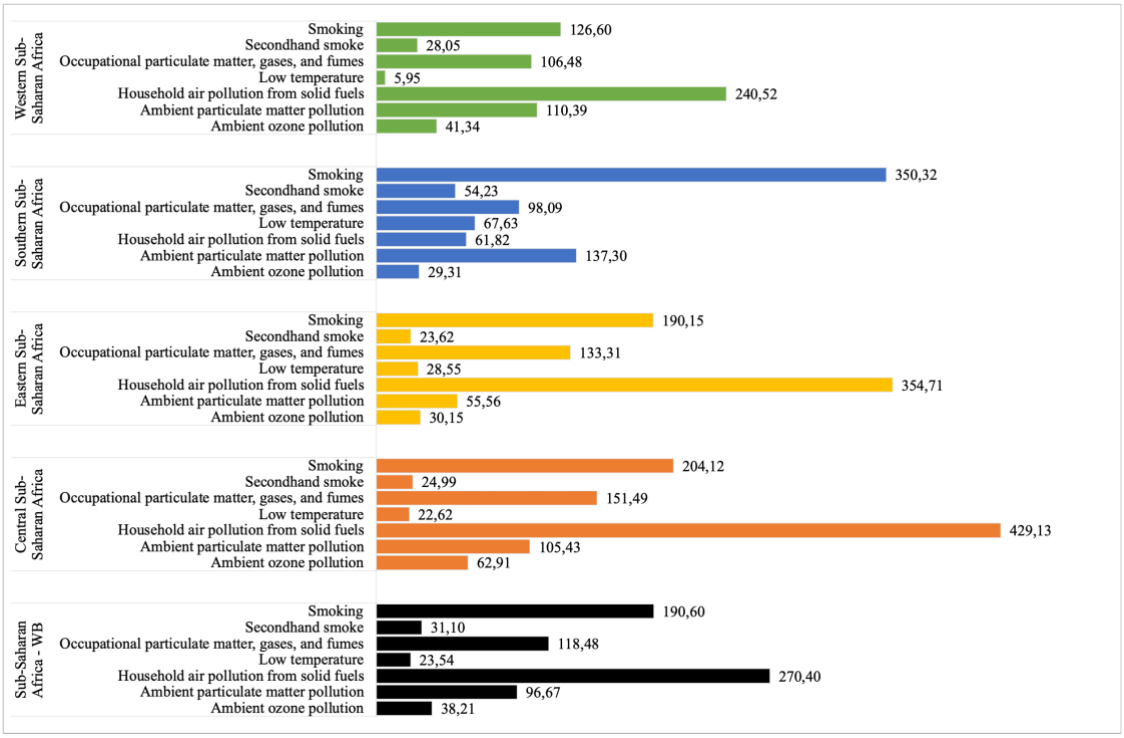

Figure 2.9 Age standardized DALYs rate (per 100,000) due to COPD attributable by risk factors among Sub-Saharan Africa regions in 2019

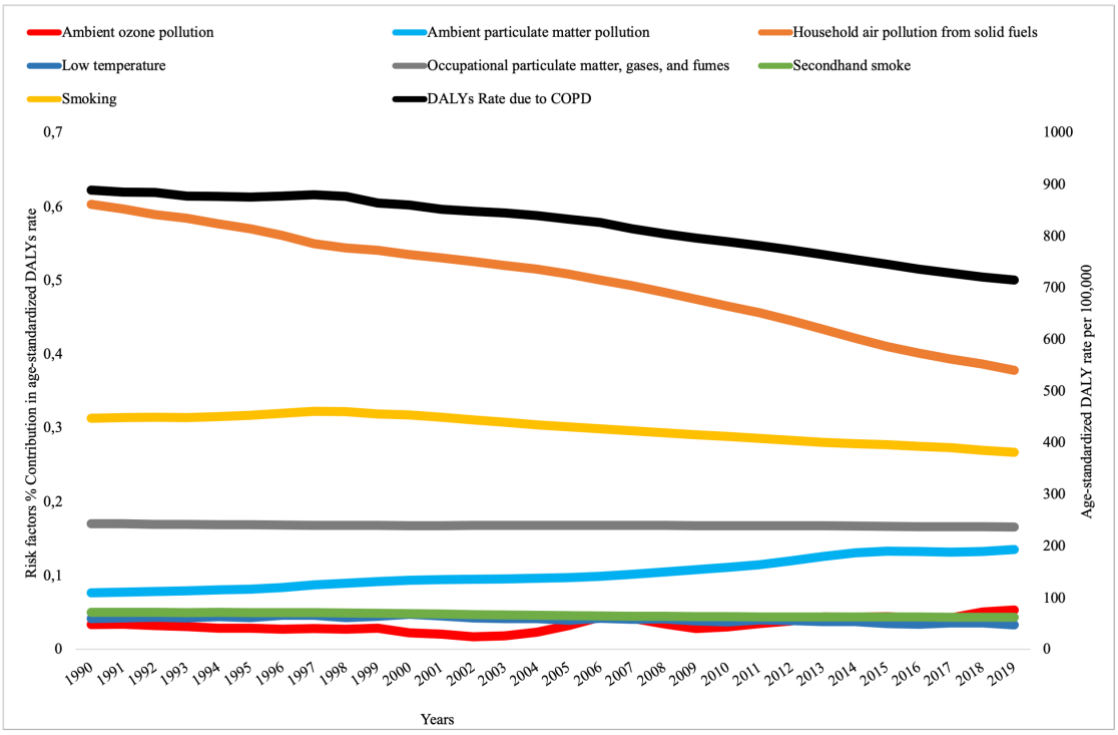

Figure 2.10 Trend in age-standardized DALYs rate due to COPD and risk factors percentage contribution in age-standardized DALYs rate in sub-Saharan Africa, 1990 to 2019

2.4. Discussion

This GBD analysis shows that the burden of COPD in SSA is substantial, with an estimated 10·3 million people having COPD (1·74% prevalence). The number of all-age prevalence cases of COPD in SSA was increased by 117% in 2019 compared to COPD cases in 1990 whereas the age-standardized COPD prevalence rate shown a decline by 3·3%. There was a significant variation in COPD prevalence between regions and countries, with the highest age-standardized COPD prevalence rate was observed in Southern SSA, and in Sao Tome and Principe. COPD had a significant contribution to disease burden and about two-thirds were due to premature mortality from COPD. In 2019, COPD was responsible for 715 DALY rate per 100,000 people across SSA, with the highest DALY observed in Central SSA.

Over the past 30 years, the age-standardized DALY rate due to COPD declined by 19·6% in SSA with the largest reduction observed in the Eastern, and in Ethiopia. Household air pollution from solid fuel was the primary risk factors that responsible for 270·4 DALY rate per 100,000 people due to COPD. There were large variations on risk factor contribution to the burden attributed to COPD by sex, region, and country. Amongst women, over half of deaths due to COPD in Eastern and Central SSA were attributed to household air pollution from solid fuel, whilst smoking contributed to 12·8% and 6% in each of these two areas. In Southern SSA, 28·2% of deaths due to COPD in women were explained by smoking, whilst in men, smoking was responsible for more than half of premature mortality and DALYs due to COPD.

As discussed by Adeloye D *et al*, aging alone can attribute as much as 31% to the increase on the prevalence of COPD in Africa(7). This could be one potential reason for the prevalence rate difference among all-age and age-standardized in which the later adjust age structure difference. Similar prevalence rate difference due to the difference in age structure and/or population growth had also reported in other study(32). The prevalence of COPD reported in this GBD paper differs from the results from several population-based studies conducted in other countries from SSA(7, 10, 14-17, 19, 20). Population-based estimates collected by the BOLD study using standardized protocols, reported a prevalence of COPD of 3·6% in Malawi(33) and 7·7% in Nigeria(34). The estimates from this GBD report showed

a slower prevalence of 1·54% and 1·38% in Malawi and Nigeria, respectively. The systematic analysis for GBD 2019 round was based on GBD 2016 iterations(3) and in this study, COPD prevalence was estimated based on five distinct datapoints. The estimate in this GBD study is also based on country-level covariates such as HAQi and SEV for COPD which could contribute to the differences observed with the results from the BOLD study. These differences highlight the need to harmonise the methodologies used in the GBD framework to improve their representativeness in the general population.

Our study found that there was a significant variation in COPD prevalence between regions, and countries. Aaron *et al* showed that known risk factors such as sex, age, and smoking explained 64% of variability in COPD prevalence(35). In our study, the highest age-standardized COPD prevalence rate was observed in Southern SSA. This might be partly driven by the 4-10 percentage change observed in tobacco use in several countries in the region, including Botswana, Lesotho and Zimbabwe(24). Our results also show an increasing COPD prevalence in those countries since 2017. Similarly, there was an increasing trend in COPD attributable to smoking in Sao Tome and Principe where the highest age-standardized COPD prevalence rate was observed compared to other sub-Saharan countries. Tobacco was being listed among the top 10 risks factors contributing to total number of disease burden in Sao Tome and Principe with an increase of 30% in percentage change in 2019 from 2009(24). From 2009 to 2019, there was an increasing trend in tobacco attributable burden among countries in Central SSA with a percentage change increase from 6.4 to 36.6%(24). This increase in smoking might have contributed to the 12% increase in age-standardized prevalence rate of COPD observed in Central SSA between 1990 to 2019.

A recent study estimated that in low and middle income countries, as much as 8·6 million deaths from 61 conditions could be averted by a Universal Health Coverage (UHC) system(36). In SSA, countries differ in their coverage and effectiveness of UHC. Cabo Verde for example, delivers effective, essential health services with 62·2% performance on UHC effective coverage index(37), whilst Lesotho has a much lower performance of 38·7%. The difference in the performance of delivering essential health care services could also contribute to those countries having the

lowest (Cabo Verde) and highest (Lesotho) death rate due to COPD.

In a study conducted by Hystad *et al* use of solid fuel use was associated with fully adjusted hazard ratios of 1·14 for fatal or nonfatal respiratory disease compared with electricity or gas(38). Another study also showed that COPD prevalence was higher among women using biomass, women aged >40 years, and was determined by year of exposure(13). In our study, COPD attributable DALYs rate in most countries in Eastern SSA was due to household air pollution from solid fuel. A significant reduction of COPD was observed on women using improved cookstoves which accounts for 36% of risk reduction(39). The highest reduction in DALY rate due to COPD attributed to household air pollution from solid fuel could be potential reason to compare the reduction between Ethiopia and Ghana where the later had stable trend over the past 30 years with a lowest DALY rate reduction. These findings differ from the recent BOLD results showing that there was no association between airflow obstruction and use of solid fuels for cooking or heating(40). The definition used for indoor biomass use in the GBD was drawn from a systematic review that reported publication bias in their studies, and from pooled data that showed 85% heterogeneity, therefore the findings on this risk factor need to be interpreted with caution.

Our study provides up-to-date evidence on the burden of COPD across sub-Saharan countries and regions, and the contribution of the major risk factors to the premature morbidity and mortality. Observing the increasing trends in COPD change over the past thirty years is important to improve the understanding of the status and progress being made in Africa, a region facing some of the greatest public health and climate change challenges. The subsequent implication is to identify and prioritize policy options using the evidence we have on the contribution of risk factors towards the achievements of sustainable development goals (SDG), particularly SDG 3.4(1). Our study has also show that the heterogeneous distribution of COPD and its inconsistencies highlighted the importance for further studies with standard definitions of airflow obstruction and of risk factors representative of the general population in SSA.

This analysis has some limitations, including the paucity of population-based studies where the prevalence estimate was derived using five datapoints and

country-level covariates, which have been observed in other regional analyses.(32) Albeit the GBD methodology has greatly contributed to improve our understanding of the distribution of disease and their impact on mortality, there are some methodological limitations that need to be considered. The GBD rely heavily on the WHO mortality data, but it is unlikely that these represent mortality associated with chronic airflow obstruction. Data from systematic reviews need to consider the limitations of the original studies e.g., publication bias, and suitability of meta-analysis when the heterogeneity is too great. We were unable to examine the role of other important environmental risk factors such as diet, poverty, education, and history of tuberculosis, which have been shown to be important attributable factors for COPD in studies of the general population (41).

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Table 2.1 Number and percentage change of all age COPD prevalence and COPD attributable YLDs in 2019 by Sub-Saharan Africa country

	Number of prevalent cases in all-age, 2019 (95%UI)	Percentage change in all-age prevalent cases, 1990-2019	YLDs in all-age, 2019 (95%UI)	Percentage change in all-age YLDs, 1990-2019
Sub-Saharan Africa	1034097 (9741174 to 10947696)	117·0	1264690 (1054269 to 1435013)	117·1
Angola	254081 (236617 to 271195)	189·2	31766 (26304 to 36398)	191·1
Benin	122253 (116116 to 128660)	162·8	14729 (12258 to 16806)	165·0
Botswana	33850 (31750 to 36001)	127·7	4463 (3711 to 5087)	129·5
Burkina Faso	180238 (170496 to 189858)	148·8	21904 (18287 to 25112)	150·7
Burundi	106070 (99945 to 112433)	92·7	13097 (10804 to 15002)	92·7
CÃ´te d'Ivoire	248534 (236502 to 261568)	141·1	29846 (24830 to 34166)	143·6
Cabo Verde	7318 (6951 to 7690)	78·0	901 (746 to 1015)	77·0
Cameroon	333003 (315180 to 351183)	175·2	39824 (33428 to 45642)	176·6
Central African Republic	52811 (49579 to 56338)	92·6	6484 (5389 to 7440)	93·8
Chad	128055 (121772 to 134579)	133·2	15366 (12941 to 17510)	133·4
Comoros	8091 (7559 to 8638)	98·3	1003 (833 to 1152)	97·8
Congo	63447 (59272 to 67413)	146·6	7891 (6520 to 9043)	147·3
Democratic Republic of the Congo	868445 (808523 to 929199)	165·3	106944 (89130 to 122971)	166·3
Equatorial Guinea	11740 (10799 to 12645)	197·8	1462 (1207 to 1685)	203·0
Eritrea	67089 (63358 to 71102)	161·3	8268 (6756 to 9485)	162·0
Eswatini	16362 (15605 to 17119)	78·9	2111 (1770 to 2395)	74·2
Ethiopia	683970 (612886 to 751405)	62·8	86388 (70077 to 101068)	65·9
Gabon	19732 (18295 to 21159)	93·9	2406 (1999 to 2768)	93·3
Gambia	24182 (22965 to 25460)	170·4	2901 (2405 to 3312)	170·0
Ghana	353063 (335031 to 371410)	193·9	40968 (33983 to 46466)	193·8
Guinea	134216 (126884 to 141604)	105·2	16198 (13509 to 18503)	105·2
Guinea-Bissau	19764 (18753 to 20857)	91·3	2378 (1972 to 2725)	92·8
Kenya	488588 (452563 to 528500)	165·7	61034 (50552 to 70346)	164·1
Lesotho	38827 (37057 to 40680)	42·2	5043 (4196 to 5717)	41·5
Liberia	42788 (40388 to 45276)	160·9	5110 (4267 to 5829)	162·2
Madagascar	304017 (286418 to 321707)	147·7	37925 (31200 to 43165)	149·3
Malawi	147080 (137355 to 156496)	105·9	18258 (15192 to 20946)	105·3
Mali	247544 (232568 to 261553)	139·5	29672 (24863 to 33898)	140·9
Mauritania	42163 (39788 to 44643)	95·3	5101 (4293 to 5789)	95·9
Mauritius	32393 (30706 to 34221)	83·0	3294 (2653 to 3799)	79·3
Mozambique	234441 (220557 to 247596)	144·9	28838 (23886 to 32900)	143·7
Namibia	33664 (31536 to 35779)	78·8	4337 (3591 to 4966)	77·0
Niger	179661 (169575 to 189387)	185·9	21792 (18106 to 24915)	187·1
Nigeria	1587744 (1449908 to 1718545)	85·6	192661 (158614 to 222305)	89·0
Rwanda	134377 (126021 to 143261)	93·9	16705 (13834 to 19161)	94·9
Sao Tome and Principe	3934 (3787 to 4087)	124·8	466 (389 to 523)	123·1
Senegal	159836 (151194 to 168298)	130·2	19073 (15936 to 21762)	130·5

	Number of prevalent cases in all-age, 2019 (95%UI)	Percentage change in all-age prevalent cases, 1990-2019	YLDs in all-age, 2019 (95%UI)	Percentage change in all-age YLDs, 1990-2019
Seychelles	2377 (2249 to 2512)	115·0	245 (199 to 282)	112·6
Sierra Leone	86262 (81988 to 90499)	129·7	10367 (8708 to 11739)	130·8
Somalia	147261 (136640 to 157532)	161·9	18403 (15194 to 21312)	163·4
South Africa	1046594 (970945 to 1127782)	76·9	135801 (112436 to 155679)	73·8
South Sudan	79130 (73518 to 84549)	58·1	9709 (8066 to 11166)	59·9
Sudan	428128 (401529 to 455381)	141·5	40242 (32532 to 46905)	139·4
Togo	91070 (86074 to 96044)	177·6	10964 (9134 to 12440)	177·5
Uganda	303362 (278483 to 326245)	130·5	37877 (30979 to 43760)	132·8
United Republic of Tanzania	423197 (389806 to 453143)	141·4	53252 (43694 to 61474)	142·9
Zambia	152038 (141443 to 161813)	157·1	18848 (15572 to 21698)	155·4
Zimbabwe	168183 (157789 to 179080)	73·4	22375 (18389 to 25608)	73·8

Notes: YLDs-years lived with disabilities. 95% UI-95% uncertainty intervals. COPD-chronic obstructive pulmonary disease

Table 2.2 COPD attributable Deaths and YLLs in 2019 and percentage change from 1990 to 2019 across Sub-Saharan Africa country

	Number, all-age, 2019 (95%UI)		Age-standardized rate per 100,000 in 2019 (95%UI)		% Change in Age-standardized, 1990 - 2019	
	Deaths	**YLLs**	**Deaths**	**YLLs**	**Deaths**	**YLLs**
Sub-Saharan Africa	107899 (92406 to 123565)	2337318 (1967700 to 2722757)	29 (25 to 33)	510 (436 to 587)	-21·0	-24·7
Angola	2245 (1673 to 2864)	50767 (37555 to 64790)	31 (23 to 39)	515 (384 to 654)	-36·1	-41·8
Benin	1016 (779 to 1321)	22788 (16740 to 30713)	26 (20 to 33)	464 (352 to 612)	-31·3	-32·3
Botswana	405 (276 to 540)	8893 (5780 to 12182)	39 (27 to 52)	706 (477 to 947)	-30·4	-30·5
Burkina Faso	1391 (1122 to 1724)	33244 (25736 to 43299)	19 (16 to 23)	350 (282 to 434)	-16·3	-14·9
Burundi	1464 (1100 to 1924)	34901 (25324 to 48141)	43 (32 to 55)	784 (588 to 1033)	-29·6	-33·9
CÃ´te d'Ivoire	1950 (1472 to 2498)	45903 (33350 to 60748)	25 (20 to 31)	447 (335 to 574)	-33·3	-34·8
Cabo Verde	73 (58 to 100)	1227 (1005 to 1681)	18 (14 to 25)	296 (243 to 403)	-48·5	-53·6
Cameroon	2311 (1583 to 3034)	53612 (34746 to 72911)	25 (18 to 32)	453 (307 to 599)	-33·3	-32·8
Central African Republic	802 (535 to 1137)	20399 (13494 to 29091)	53 (35 to 79)	1003 (669 to 1424)	-13·9	-15·7
Chad	1405 (1045 to 1831)	32536 (24055 to 43439)	31 (23 to 40)	568 (417 to 741)	-14·2	-15·4
Comoros	109 (84 to 141)	2095 (1584 to 2750)	26 (20 to 33)	451 (347 to 588)	-33·5	-35·2
Congo	619 (449 to 800)	13239 (9162 to 17632)	35 (26 to 44)	579 (420 to 748)	-36·2	-41·6
Democratic Republic of the Congo	11865 (7720 to 18665)	257781 (167118 to 383962)	47 (30 to 77)	801 (520 to 1251)	-12·7	-14·3
Equatorial Guinea	101 (65 to 164)	1995 (1247 to 3140)	30 (20 to 51)	474 (303 to 771)	-42·5	-52·1
Eritrea	637 (447 to 820)	15980 (11273 to 20931)	33 (23 to 42)	621 (435 to 799)	-19·6	-26·4
Eswatini	192 (143 to 253)	4300 (3102 to 5765)	42 (31 to 55)	779 (572 to 1026)	-27·5	-27·1
Ethiopia	9309 (7480 to 10922)	189662 (150989 to 229253)	28 (23 to 33)	484 (386 to 573)	-38·9	-48·7
Gabon	204 (141 to 263)	4019 (2696 to 5350)	26 (18 to 33)	427 (295 to 560)	-35·5	-39·6
Gambia	244 (185 to 311)	5138 (3777 to 6655)	30 (23 to 38)	542 (405 to 697)	-11·4	-12·5

Table 2.2 …Continued

	Number, all-age, 2019 (95%UI)		Age-standardized rate per 100,000 in 2019 (95%UI)		% Change in Age-standardized, 1990 - 2019	
	Deaths	**YLLs**	**Deaths**	**YLLs**	**Deaths**	**YLLs**
Ghana	3286 (1973 to 4138)	74523 (44339 to 94611)	26 (16 to 32)	471 (281 to 592)	-11·3	-10·4
Guinea	1478 (1123 to 1863)	32228 (24009 to 41774)	31 (24 to 39)	574 (432 to 733)	-15·1	-14·6
Guinea-Bissau	197 (144 to 256)	4991 (3537 to 6617)	34 (26 to 44)	671 (491 to 872)	-30·8	-33·1
Kenya	5081 (3957 to 6680)	111390 (86236 to 147048)	31 (24 to 41)	542 (422 to 713)	-6·0	-4·3
Lesotho	712 (504 to 972)	15846 (10939 to 22023)	71 (50 to 95)	1315 (921 to 1803)	-4·6	-2·6
Liberia	292 (213 to 405)	6481 (4562 to 9216)	18 (14 to 25)	325 (236 to 453)	-14·3	-19·3
Madagascar	3317 (2390 to 4440)	81550 (58547 to 109571)	43 (31 to 56)	775 (557 to 1037)	-9·2	-12·2
Malawi	1450 (1148 to 1769)	31668 (24456 to 39694)	25 (20 to 30)	449 (352 to 550)	-20·1	-21·4
Mali	2476 (1849 to 3175)	59059 (41107 to 79482)	34 (26 to 42)	667 (482 to 866)	-11·1	-14·6
Mauritania	320 (246 to 405)	6098 (4478 to 8097)	19 (15 to 23)	308 (231 to 401)	-38·8	-45·6
Mauritius	293 (230 to 377)	4833 (3783 to 6263)	19 (15 to 25)	298 (234 to 385)	-38·4	-41·3
Mozambique	2182 (1662 to 2900)	50412 (37358 to 68322)	25 (20 to 33)	471 (355 to 632)	-4·3	-2·8
Namibia	534 (403 to 686)	10259 (7637 to 13323)	45 (34 to 58)	777 (585 to 1008)	-28·4	-30·3
Niger	1790 (1281 to 2557)	43149 (29852 to 62560)	31 (22 to 43)	547 (389 to 790)	-18·4	-23·7
Nigeria	14120 (10738 to 17549)	286800 (216038 to 367679)	22 (17 to 27)	362 (274 to 456)	-13·1	-19·0
Rwanda	1620 (1265 to 2093)	35938 (27489 to 46777)	36 (28 to 46)	629 (490 to 816)	-42·6	-48·5
Sao Tome and Principe	48 (37 to 60)	996 (738 to 1244)	58 (44 to 72)	1014 (761 to 1261)	1·5	0·1
Senegal	1579 (1240 to 1948)	32742 (24919 to 42053)	26 (20 to 31)	451 (350 to 567)	-27·9	-29·9
Seychelles	23 (19 to 27)	420 (338 to 491)	25 (21 to 29)	411 (335 to 479)	-23·6	-28·3
Sierra Leone	802 (591 to 1054)	17996 (12734 to 24335)	27 (20 to 35)	494 (359 to 658)	-23·3	-23·2
Somalia	1991 (1263 to 3200)	51568 (31587 to 86630)	40 (26 to 63)	771 (491 to 1219)	-23·4	-24·4

Table 2.2 …Continued

	Number, all-age, 2019 (95%UI)		Age-standardized rate per 100,000 in 2019 (95%UI)		% Change in Age-standardized, 1990 - 2019	
	Deaths	**YLLs**	**Deaths**	**YLLs**	**Deaths**	**YLLs**
South Africa	11843 (10780 to 13332)	225719 (206694 to 253944)	32 (29 to 36)	536 (490 to 605)	-16·2	-19·3
South Sudan	757 (511 to 1048)	16093 (10751 to 23267)	27 (18 to 36)	456 (305 to 638)	-26·5	-31·3
Sudan	4390 (2883 to 6190)	97251 (62467 to 139562)	29 (19 to 40)	510 (332 to 725)	-21·5	-27·3
Togo	717 (527 to 942)	17134 (12156 to 23224)	26 (20 to 34)	479 (350 to 633)	-25·9	-25·0
Uganda	3322 (2431 to 4316)	73369 (51430 to 98685)	30 (22 to 39)	537 (390 to 704)	-31·6	-32·4
United Republic of Tanzania	4259 (3417 to 5100)	91879 (72713 to 113177)	21 (17 to 25)	381 (300 to 458)	-19·3	-21·2
Zambia	1462 (1150 to 1793)	33147 (25578 to 41889)	29 (23 to 35)	520 (407 to 638)	-19·5	-21·1
Zimbabwe	1217 (842 to 1582)	25305 (16898 to 33012)	24 (17 to 31)	404 (279 to 525)	-9·5	-7·6

Notes: YLLs-years life lost; 95% UI-95% uncertainty intervals; COPD-chronic obstructive pulmonary disease; WB- World Bank.

Chapter 3 Comparison of flavonoid contents of selected foods across International Food Composition Tables

3.1. Introduction

Flavonoids are a large class of bioactive compounds, polyphenolic, non-nutrients, and ubiquitously distributed plant secondary metabolites, with fruits and vegetables being their richest sources (1-3). Extensive scientific evidence shows that flavonoids have been demonstrated to have multiple potentially beneficial effects against several chronic diseases due to their well described antioxidant (4-6), anti-inflammatory (7, 8) anti-mutagenic properties, as well as their role in modulating metabolic pathways (7, 9). Findings from epidemiological studies suggest that dietary intake of flavonoids or of their dietary sources, is associated with several important health outcomes including better quality of sleep (10), reduced inflammation in obese individuals (11), better lung function (12, 13), and lower risk of several non-communicable diseases such as autoimmune diseases (14), and chronic obstructive pulmonary disease (COPD) (15, 16).

Population-level estimates of flavonoid intake mostly rely on the use of food composition tables (FCTs) to derive their content. These tools allow quantifying the intake of a wide variety of nutrients and non-nutrient bio-compounds, providing reference values that are often calculated within the research facilities linked to the specific FCT or compiled through scientific literature searches (17). As such, the content of flavonoid reported in FCTs is likely to show variations, which might be influenced by the differences in the analytical methods used to estimate their content in food, by the chemical form (e.g. aglycones or glycosides), the completeness of flavonoid FCTs, and by other factors related to seasonality and harvest (18). In addition to the specific methodological variations in the quantification of flavonoids, the epidemiological tools used to ascertain dietary intake (e.g., food frequency questionnaires (FFQ), 24-hour recall questionnaires) can also affect estimates (19).

These challenges highlight the need to improve our understanding of the comparability of FCTs that are currently available to derive estimates of flavonoids. We therefore investigated the variations in the content of flavonoids reported by four international FCTs commonly used in epidemiological studies. As part of the multinational Burden of Lung Disease (BOLD) survey (20), a standardized, and

validated FFQ (21) was adapted to be used in six countries in Europe, Africa and Asia participating in BOLD I. The FFQ contains a wide range of plant-based foods commonly consumed across participant countries, as well as specific foods representative of each country's dietary habits. Their content of flavonoids was examined using different food composition tables.

3.2. Methods

3.2.1 Selection of foods included for the determination of flavonoid content

The foods that were used as a basis for the flavonoid content comparison were selected from the FFQ used in the BOLD Survey. Detailed was described in Chapter 4 Section 4.2.1.

3.2.2 Search strategy and identification of eligible FCTs with flavonoid content

An exhaustive search of FCTs with flavonoid data was carried out using website engines internationally recognized as a resource for food composition data, namely INFOODs/FAO (22-24) , EuroFIR (25) and LANGUAL™ (26). Country specific food composition tables were examined to identify if they included flavonoid data. Additional searches were carried out in PubMed Central, Scopus electronic databases and Google search engine to identify relevant literature on FCT with flavonoid content. FCTs were considered eligible if they included original flavonoid composition data. FCTs that compiled flavonoid data from pre-existing tables/databases were excluded.

We identified six potentially eligible FCTs with original estimates of flavonoid content: (1) The US Department of Agriculture (USDA) database describes flavonoid content in three separate datasets, (i) flavonoids(27) (which contains five sub-classes: Flavan-3-Ols, Flavanones, Flavones, Flavonols, and Anthocyanidins), (ii) isoflavones(28), and (iii) proanthocyanidins(29). It contains worldwide food composition data on the seven main flavonoid classes (27-29). (2) Phenol-Explorer is the second most commonly used database, which contains data on three additional flavonoid classes (chalcones, dihydrochalcones, and dihydroflavonols) with respect to USDA (30, 31). (3) The Bioactive Substances in Food Information Systems (eBASIS) (32, 33), an internet-deployed database with both compositional and biological activity data for bioactive substances. It contains flavonoid compositional data on seven subclasses. (4) The Indian Food Composition Table (IFCT) was built on the principle of 'key foods approach' to include those foods

contribute up to 75% of the population's intake in India (34). These compositional databases comprise flavonoid data on five subclasses. These four FCTs were included in the comparison of flavonoid content. Another two identified databases, namely the EPIC FCT (35) and FLAVIOLA (36) were excluded because their flavonoid data were obtained from Phenol Explorer and from the USDA flavonoid databases.

3.2.3 Matching of foods, data extraction and aggregation of flavonoid data

The main version of the FFQ used in the BOLD survey contained 250 food items classified into 32 groups, which included separate sections to enquire consumption of fruits, vegetables, legumes, cereals, and other food groups, as per the EFCOSUM guidelines. Due to local adaptations to reflect consumption of traditional foods relevant to each country, the final list of foods was comprised of 396 items. Of these, 138 foods were recognized to have some content of flavonoids and were therefore selected for this methodological study. Fitness of matching of each of these foods was investigated across all FCTs. A flavonoid-containing food included in the BOLD survey was matched to a food in a FCT if the name provided in the FCT clearly represented the food under consideration. This approach was used for the matching of all eligible foods, across all FCTs. Each FCT contained flavonoid estimates (per 100g food) for each of the foods available in that table. To standardize the flavonoid content in each FCT, the raw (uncooked) form or the most generic form ('average') option was chosen for all foods. For example, for all fruits and vegetables, the reference food item used in each FCT was that reported for fresh (uncooked) fruit. The matching process review was routinely discussed within the research team to address queries and disagreements in the matching. For some traditional foods that did not have an obvious English translation, the Latin name was used to match it to its closest corresponding food in the FCTs. Subclasses of flavonoids were derived and aggregated to estimate the total flavonoid content of each food.

Data on flavonoid content in each of the four FCTs under comparison was harmonized to ensure that the content expressed in mg/100g foods. In eBASIS, content of flavonoid was expressed in mg/kg or µg/kg, therefore the content of flavonoids was converted into the standard mg/100g foods, using the conversion formula from FAO/INFOODS Guideline (37). Similarly, as the flavonoid content

of some foods in Phenol Explorer was available as mg/100ml, FAO/INFOODS Guideline (37) and a density factor from FAO/INFOODS density database version 2 (38) were used to standardize the content into mg/100 g of food. Foods that only reported flavonoid content as dry weight were excluded from comparisons.

The Flavonoid content was reported as aglycones and/or glycosides in three of the four studied FCTs, namely Phenol Explorer(30, 31), eBASIS(32, 33), and IFCT(34), whereas the USDA(27-29) reported flavonoid content as aglycones only. In all FCTs, the content of catechins and epicatechins was expressed as gallic acid esters i.e., as epicatechin gallate and epigallocatechin gallate, respectively (27-34).

3.2.4 Statistical Analyses

Levels of agreement in the content of total and subclass flavonoid content of each table were used to examine variations in flavonoid content (per 100g of food) between FCTs. Comparisons were carried out across foods that were common (present) in all four tables, and between specific tables. For the latter, the USDA and the Phenol Explorer were used as reference tables for the US and Europe, respectively, and their flavonoid content was compared to that of each of the other three FCTs. Variations of flavonoid content were also investigated between the IFCT and eBASIS.

Bias percentage and a two-way mixed-effect model of intra-class correlation coefficients (ICCs; 95% confidence intervals [95%CI]) were calculated to quantify limit of agreement (LoA) in the content of flavonoids in each pair of FCTs under comparison. Bland-Altman plots were used to illustrate the magnitude of the mean differences between the FCTs. (39) ICC was categorized as indicating low (<0.5), moderate (0.50-0.75), good (0.76-0.90), or excellent (>0.90) reliability (40). The lower bound for 95%CI of ICCs was truncated at zero value when the computed value was negative. The analyses were performed using Stata/IC 16.0.

3.3. Results

3.3.1 General characteristics of the FCTs studied

The general characteristics of the four FCTs included in this study namely USDA, Phenol-Explorer, eBASIS, and Indian Food Composition Table (IFCT), are described in **Table 3.1**. These databases have been set up with similar goals. USDA and IFCT present their polyphenol composition data as a single figure for each food item with a matched food description, allowing comparison with standard nutrient databases. However, Phenol Explorer and eBASIS provide the user with more detailed information on ranges, allowing a greater use for a variety of users. Phenol-Explorer includes useful summary statistics, whereas eBASIS covers raw data, enabling the user to choose their preferred methods of aggregation and statistical analysis of bioactive composition and bio-effects. Except for the IFCT, all tables used multinational data from peer-reviewed articles and from lab-confirmed estimates of flavonoid content to compile the datasets. The IFCT used national data from original lab-confirmed estimates (**Table 3.1)**. The USDA table had flavonoid data available for most foods (n=133), whilst the IFCT had data available for the fewest (n=70) (**Figure 3.1**).

Across tables, there were variations in the number of bio-compounds included in each subclass of flavonoids (**Appendix Table B.1**). The eBASIS and Phenol-Explorer tables included an extensive number of bio-compounds within the anthocyanin and flavonols subclasses compared to the USDA table. The IFCT did not include anthocyanins.

There were 42 foods common to all four FCTs (**Appendix Table B.2**), with the number of foods available for comparison between FCTs varying (**Table 3.2**). The comparison of the flavonoid content of these 42 foods showed that the highest estimates of total flavonoid content was reported by eBASIS (934.33 mg/100g) followed by Phenol Explorer (596.06 mg/100g), IFCT (486.18 mg/100g) and USDA (426.67 mg/100g) (**Table 3.2**).

Table 3.1 Summary characteristics of included food composition tables

	Food composition table included in the study comparison			
	eBASIS	**IFCT**	**Phenol Explorer**	**USDA**
Tables and/or databases version	EuroFIR BASIS	2017 Updated version	version 3.6	Flav_R03-3; Isoflav_R2-1; PA02-1
Coverage	Multi-country	India	Multi-country	Multi-country
Data Source	Extracted from peer-reviewed publications	Survey and laboratory-based	Collected from scientific publications	Obtained from published and unpublished data
No of food items reported with measurable data	215	247	326	506; 560; 285
Unit of expression used to report values	mg/kg; µg/kg; mg/l; µg/l; µmole/kg[Π]; µmole/l;	mg/100g	mg/100g; mg/100ml	mg/100g
Value reported	Individual	Aggregated*	Aggregated*	Aggregated*
Quality evaluation#	A, B, C, U	na	Acceptable	A, B, C, D
Flavonoid reporting form				
Aglycon	✓	✓	✓	✓
Glycosylation	✓	✓	✓	✕
Fresh weight	✓	✓	✓	✓
Dry weight	✓	✕	✕	✕
Flavonoid subclasses (mg/100g)				
Anthocyanins	✓	✕	✓	✓
Flavanols	✓	✓	✓	✓
Flavonols	✓	✓	✓	✓
Flavanones	✓	✓	✓	✓
Flavones	✓	✓	✓	✓

	Food composition table included in the study comparison			
	eBASIS	**IFCT**	**Phenol Explorer**	**USDA**
Chalcones	✕	✕	✓	✕
Dihydrochalcones	✕	✕	✓	✕
Isoflavones	✓	✓	✓	✓
Dihydroflavonols	✕	✕	✓	✕
Proanthocyanidins	✓	✕	✓	✓

[*] *Mean content values were reported by aggregating reported data for various foods with matched food descriptions. This reports a single value estimate for specific flavonoid compound of a given food.*

[#] *Flavonoid compositional data were evaluated for quality and were categorized based on the information retrieved from the primary data source. (1)* ***eBASIS****: 'A'-reliable and meet all five criteria being rated as acceptable, 'B'- study with some limitations, 'C' study with serious limitations, and 'U'-insufficient information; (2)* ***USDA****: the quality was rated and categorized based on quality index as 'A'- 75-100, 'B' 74-50, 'C' 49-25, and 'D'<25. (3)* ***Phenol Explorer****: The data filling specified minimal requirements set were considered as acceptable and selected for aggregation. In the case of* ***IFCT****, it is not applicable.*

II - In eBASIS for individual compounds a conversion is made from mole to mg to help the user

Table 3.2: Flavonoid content of common foods by food composition tables under study

	Total flavonoid content estimate of foods (mg)			
	eBASIS	**IFCT**	**Phenol Explorer**	**USDA**
Total Flavonoids (n=42)	934.33	486.18	596.06	426.67
Flavanols (n=17)	121.24	92.71	67.49	106.00
Flavanones (n=2)	173.35	94.53	75.95	50.08
Flavones (n=12)	223.53	33.03	56.65	39.80
Flavonols (n=28)	310.32	141.92	325.37	178.95
Isoflavones (n=6)	4.13	0.96	*	10.05

n -number of food items common for tables under comparison

[*]*No isoflavones estimates available in Phenol-Explorer for the foods common to the other three tables*

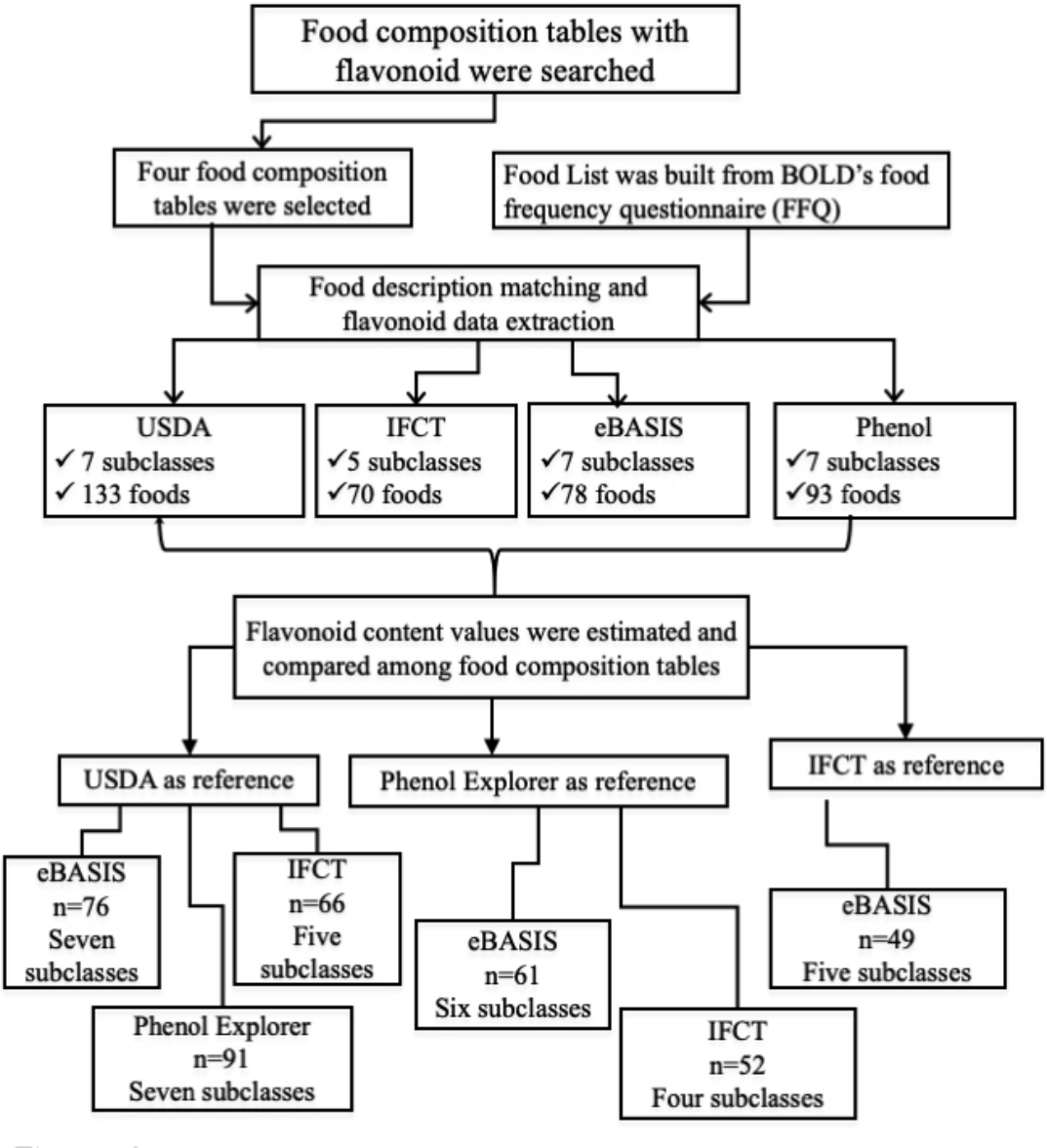

Figure 3.1: Flowchart illustrating the comparison of flavonoid content for selected foods across the FCTs under study

3.3.2 Comparison of Food Composition Tables for their flavonoid contents for selected foods

3.3.2.1. USDA as reference

The number of foods for total flavonoid content available for comparison with the USDA Table varied between 66 (IFCT) and 91 (Phenol-Explorer). All three tables showed low-to-moderate reliability for total flavonoid estimates when compared to the USDA tables (**Table 3.3**). Compared to USDA, Phenol-Explorer and IFCT table showed moderate-to-good reliability for flavanones and low reliability for the flavonols (**Table 3.3**). eBASIS and IFCT tables showed moderate reliability for

isoflavones and low reliability for the flavones (**Table 3.3**).

Amongst flavonoid subclasses, the best reliability was observed with flavanones (Phenol-Explorer and IFCT), and with proanthocyanidins (Phenol-Explorer). Narrow confidence intervals for 95% limit of the agreement were reported in eBASIS, Phenol Explorer, and Indian FCT for isoflavones, flavones, and flavonols, respectively, when compared to the USDA table (**Table 3.3**, **Figure 3.2**, **Figure 3.3**, **Figure 3.4**).

Table 3.3 Bias, ICCs and LoA of flavonoid FCTs using USDA as reference.

Flavonoids	n	%bias$^{\phi}$	ICCs (95%CI)	95% LoA
USDA and eBASIS				
Total Flavonoids*	76	-5.24	0.46 (0.32, 0.61)	-172.62 to 185.65
Anthocyanidins	22	56.59	0.33 (0.12, 0.55)	-202.13 to 262.57
Flavanols	27	24.68	0.02 (0.00^{T}, 0.20)	-35.49 to 45.42
Flavanones	7	32.22	0.27 (0.00^{T}, 0.59)	-78.60 to 115.78
Flavones	34	44.68	0.31(0.27, 0.35)	-51.56 to 63.00
Flavonols	50	47.03	0.004 (0.00^{T}, 0.08)	-116.02 to 142.50
Isoflavones	66	73.71	**0.72 (0.66, 0.77)**	-1.19 to 0.99
Proanthocyanidins	11	-133.34	0.02 (0.00^{T}, 0.010)	-193.57 to 70.17
USDA and Phenol Explorer				
Total Flavonoids*	91	-18.75	**0.50 (0.35, 0.63)**	-366.81 to 404.56
Anthocyanidins	18	27.39	0.14 (0.00^{T}, 0.61)	-233.77 to 259.22
Flavanols	57	-14.54	0.03 (0.00^{T}, 0.01)	-371.48 to 426.87
Flavanones	19	-23.55	**0.87 (0.77, 0.95)**	-14.15 to 19.21
Flavones	59	15.95	**0.57 (0.47, 0.67)**	-12.46 to 16.16
Flavonols	68	-12.64	0.21 (0.01, .40)	-41.43 to 49.85
Isoflavones	9	6.82	0.32 (0.00^{T}, 0.76)	-147.39 to 111.70
Proanthocyanidins	45	4.43	**0.89 (0.83, 0.95)**	-171.37 to 161.83
USDA and IFCT				
Total Flavonoids*	66	46.15	**0.57 (0.44, 0.70)**	-44.25 to 45.89
Flavanols	22	7.38	**0.55 (0.26, 0.85)**	-9.73 to 8.85
Flavanones	5	68.51	**0.73 (0.26, 0.98)**	-23.25 to 41.48

Flavonoids	n	%bias$^{\phi}$	ICCs (95%CI)	95% LoA
Flavones	31	106.73	0.38 (0.21, 0.54)	-9.32 to 10.42
Flavonols	50	38.77	0.47 (0.28, 0.66)	-16.5 to 15.28
Isoflavones	9	-47.11	**0.61 (0.48, 0.73)**	**-111.02 to 77.09**

$^{\phi}$% bias- Flavonoid estimate absolute difference divided by the mean of estimate
n -number of food items common for tables under study and the Target in intraclass correlation coefficients estimation
** Total Flavonoids – Flavonoid estimated from 7 subclasses except for IFCT from 5 subclasses*
In bold- moderate to excellent reliability
^{T} A common ad-hoc method of truncating at zero value was applied when the lower bound for 95%CI of ICCs was computed as negative

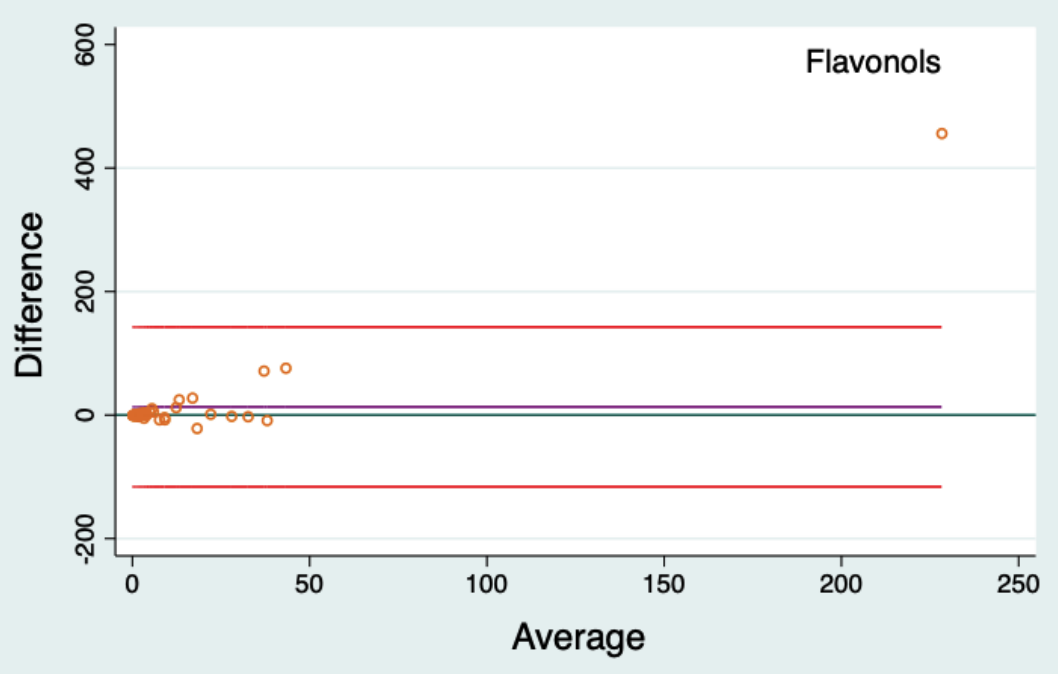

Figure 3.2 Bland-Altman agreement between eBASIS and USDA for flavonol content (mg) for 50 food items common

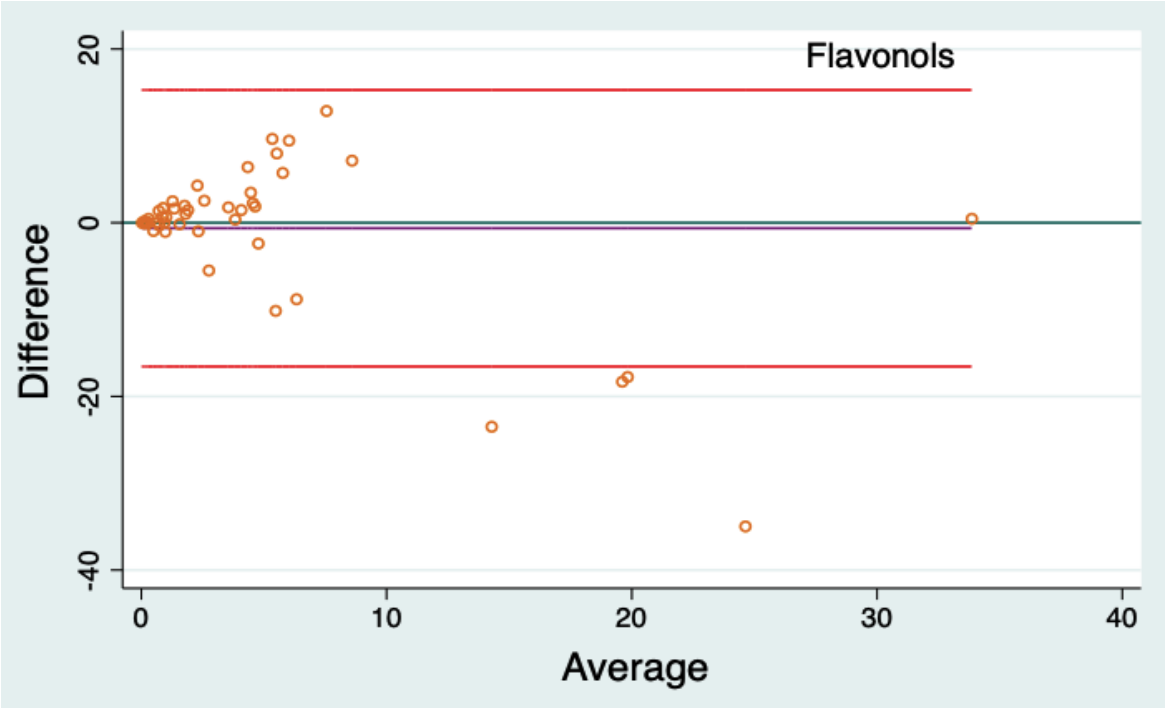

Figure 3.3 Bland-Altman agreement between IFCT and USDA for flavonol content (mg) for 50 food items common

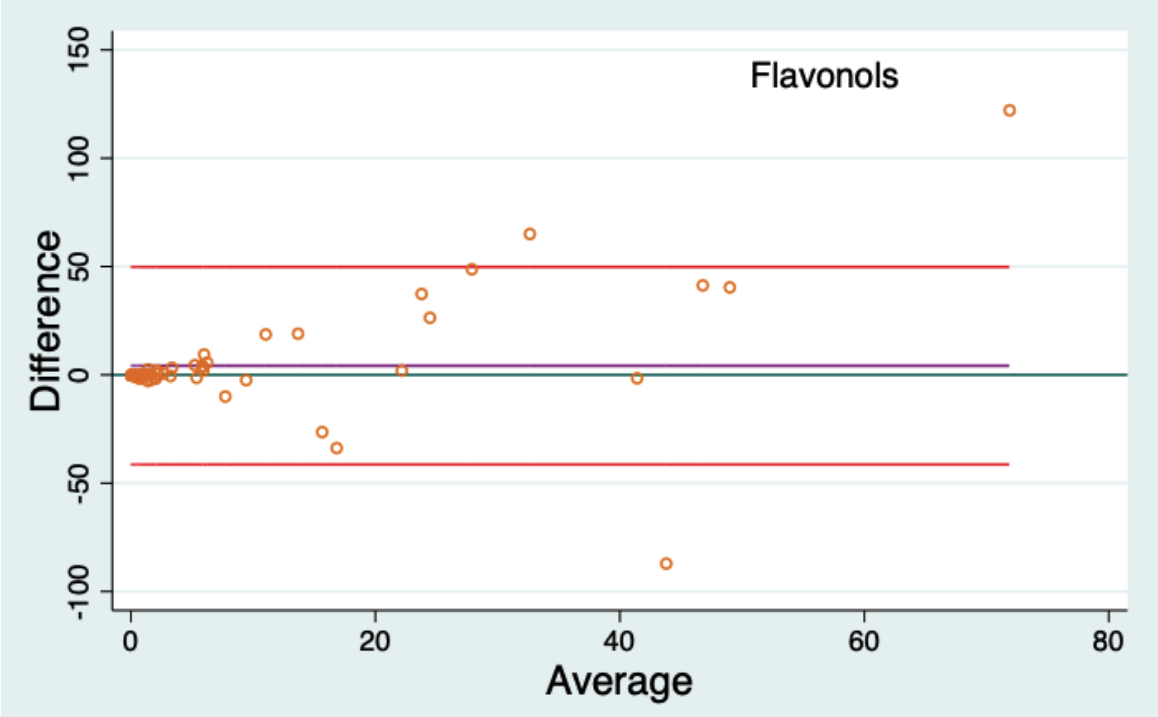

Figure 3.4 Bland-Altman agreement between Phenol Explorer and USDA for flavonols content (mg) for 68 food items common

3.3.2.2. Phenol-Explorer table as a reference

Compared to Phenol-Explorer, eBASIS and IFCT overestimated the content of most flavonoid subclasses (**Table 3.4**). The percentage bias for total flavonoids and for flavonoid subclasses of eBASIS and IFCT respect to Phenol Explorer varied from 10% to 117%. There was moderate-to-excellent reliability in the content of total flavonoids and anthocyanidins between Phenol-Explorer and eBASIS. IFCT showed moderate-to-good reliability for flavanols and flavanones, and low reliability for the other subclasses when compared to Phenol Explorer (**Table 3.4**). Flavanols in eBASIS and IFCT showed a narrow confidence interval for 95% limit of agreement when compared to Phenol Explorer (**Table 3.4**, **Figure 3.5**, **Figure 3.6**).

Table 3.4 Bias, ICCs and LoA of flavonoid FCTs using Phenol Explorer as reference

Flavonoids	n	%bias$^{\phi}$	ICCs (95%CI)	95% LoA
Phenol Explorer and eBASIS				
Total Flavonoids*	61	10.16	**0.67 (0.51, 0.79)**	-172.66 to 177.98
Anthocyanidins	10	55.29	**0 .85 (0.51, 0.96)**	-164.78 to 204.61
Flavanols	26	31.66	0.30 (0.00^{T}, 0.60)	-33.16 to 48.41
Flavanones	6	11.11	0.35 (0.00^{T}, 0.88)	-98.33 to 118.18
Flavones	28	89.78	0.42 (0.06, 0.68)	-57.25 to 65.50
Flavonols	40	77.91	0.24 (0.00^{T}, 0.51)	-121.16 to 142.71
Isoflavones$^{\theta}$	1	-		-
Proanthocyanidins	9	-117.10	0.04 (0.00^{T}, 0.56)	-247.11 to 102
Phenol Explorer and IFCT				
Total Flavonoids*	52	50.15	0.38 (0.12, 0.59)	-55.92 to 51.52
Flavanols	23	17.39	**0.71 (0.42, 0.86)**	-19.70 to 20.01
Flavanones	4	14.18	**0.85 (0.00^{T}, 0.99)**	-29.12 to 38.20
Flavones	25	91.83	0.16 (0.00^{T}, 0.52)	-21.32 to 22.31
Flavonols	43	60.21	0.03 (0.00^{T}, 0.32)	-55.35 to 44.85
Isoflavones$^{\theta}$	1	-		-

$^{\phi}$% bias- Flavonoid estimate absolute difference divided by the mean of estimate; n -number of food items common for tables under study and the Target in intra-class correlation coefficients estimation
** Total Flavonoids – Flavonoid estimated from 7 subclasses except for IFCT from 5 subclasses*
$^{\theta}$ Isoflavones have not been estimated for insufficient data (food in common) for this comparison
In bold- moderate to excellent reliability
^{T} A common ad-hoc method of truncating at zero value was applied when the lower bound for 95%CI of ICCs was computed as negative.

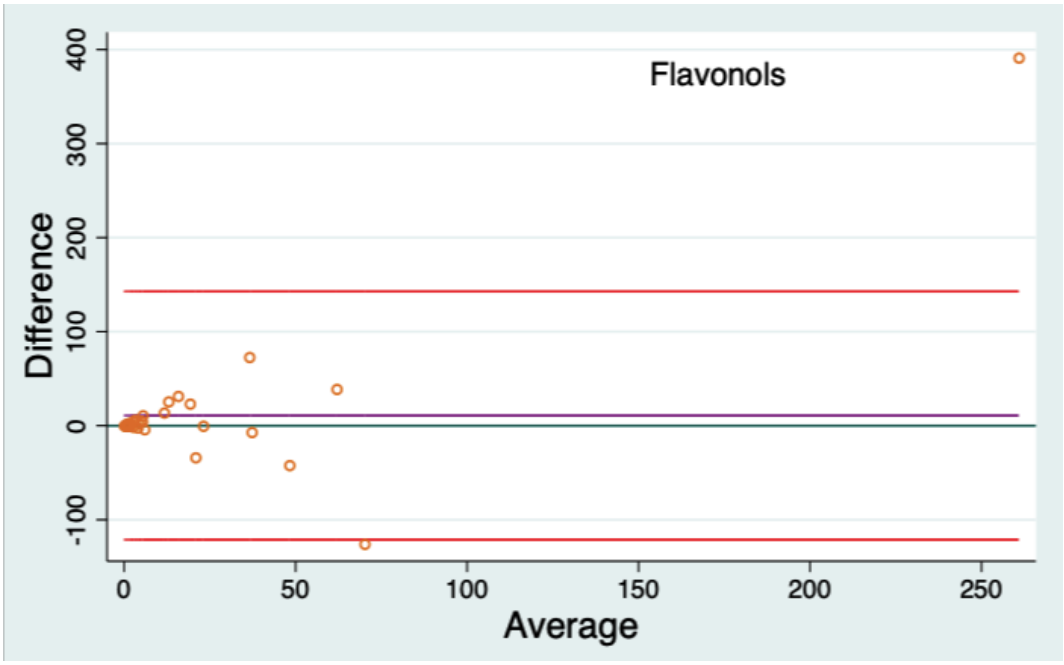

Figure 3.5 Bland-Altman agreement between eBASIS and Phenol Explorer for flavonols content (mg) for 40 food items common

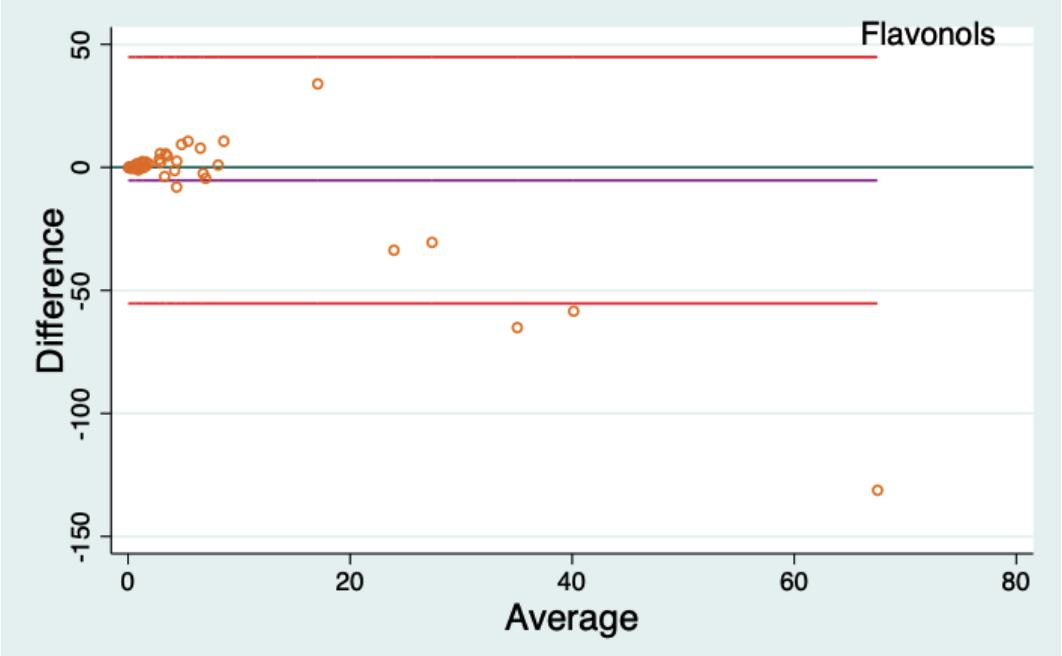

Figure 3.6 Bland-Altman agreement between IFCT and Phenol Explorer for flavonols content (mg) for 43 food items common

3.3.2.3. IFCT as reference, compared to eBASIS

Table 3.5 shows the comparison between IFCT and eBASIS. The reliability for total flavonoid estimates between these two tables was poor, but eBASIS showed moderate-to-good reliability for flavanone and flavanol estimates. There was low reliability for other flavonoid subclasses. Compared to IFCT, flavonols and isoflavones were overestimated by nearly 28% and 19%, respectively in eBASIS, whilst the content of flavones was underestimated by around 42% (**Table 3.5**). For isoflavones, the Bland-Altman plots showed narrow confidence intervals for a 95% limit of agreement in eBASIS (**Figure 3.7**).

Table 3.5 Bias, ICCs and LoA of flavonoid FCTs comparing IFCT and eBASIS

Flavonoids	**n**	**%Bias$^{\phi}$**	**ICCs (95%CI)**	**95% LoA**
Total Flavonoids*	49	-18.01	0.37 (0.11, 0.58)	-65.65 to 83.38
Flavanols	19	-6.38	**0.89 (0.73, 0.95)**	-12.8 to 16.01
Flavanones	2	-1.06	**0 .67 (0.00^{T}, 0.99)**	-101.65 to 180.47
Flavones	17	-41.70	0 .07 (0.00^{T}, 0.52)	-82.18 to 103.78
Flavonols	37	28.19	0 .33 (0.03, 0.58)	-22.53 to 31.27
Isoflavones	6	18.66	0 .34 (0.00^{T}, 0.86)	-1.80 to 2.86

$^{\phi}$% Bias- Flavonoid estimate absolute difference divided by the mean of estimate; n -number of food items common for tables under study and the Target in intra-class correlation coefficients estimation
** Total Flavonoids – Flavonoid estimated from 7 subclasses except for IFCT from 5 subclasses*
In bold- moderate to excellent reliability, ^{T} A common ad-hoc method of truncating at zero value was applied when the lower bound for 95%CI of ICCs was computed as negative

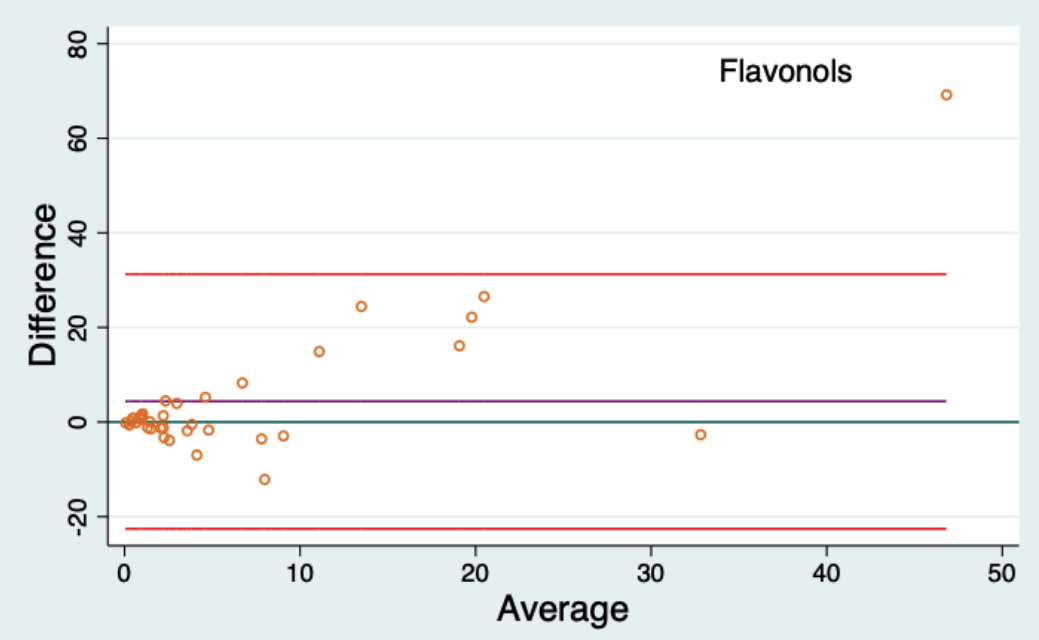

Figure 3.7 Bland-Altman agreement between eBASIS and IFCT for flavonols content (mg) for 37 food items common

3.4. Discussions

In our first paper, we investigated variations in the content of flavonoid estimates (mg/100g edible food) in four international FCTs commonly used to derive intake of these bio-compounds in population-based surveys. We examined levels of agreement and variations in net content of total and subclasses of flavonoids from an extensive list of foods with known flavonoid content included in the BOLD FFQ. Our findings showed that there were variations in the content of flavonoids between tables. Compared to the USDA Table for example, the total flavonoid content (mg/100g edible food), varied between 4.43% and 133.34% in eBASIS, IFCT, and Phenol Explorer. Despite the net differences in flavonoid content estimates, there was a strong level of agreement between FCTs, with moderate-to-excellent reliability between the USDA and the other three tables (eBASIS, IFCT, and Phenol-Explorer), and moderate-to-good reliability being observed between Phenol Explorer, eBASIS, and IFCT.

There are several similarities in our findings and those from other studies. Ivey *et al.* (41) reported a strong level of agreement between the USDA and Phenol Explorer for total flavonoid, flavanol, flavanone and anthocyanidin estimates in a study of elderly women. Another survey using dietary data estimated from adults (42) showed that total flavonoid intake estimated by the USDA and Phenol-Explorer were similar (56.32 mg/day and 64.22 mg/day, respectively), whilst a study by Witkowska *et al.* (43) reported that the flavonoid intake estimated using the USDA table was 30% higher than the estimates generated with Phenol-Explorer. When comparing these two FCTs, we confirmed good reliability for flavanone estimates, and found lower reliability for total flavonoids, flavanols and anthocyanidins.

Differences in the estimated flavonoid content of foods among surveys are likely to be influenced by several factors. These include the number and type of foods with flavonoid content included, the dietary instruments used to ascertain dietary intake (19), differences in the versions used for the comparisons between FCT (e.g. older versions might have fewer estimates, and newer versions might include updated or more accurate estimates), analytical methods used to quantify content of flavonoids). Our study included an extensive list of food items from an FFQ specifically designed to capture dietary intake of flavonoids. The larger number of

foods we studied might have contributed to the greater differences observed in total flavonoid content.

Because of the wide range of potential benefits of some subclasses of flavonoids, researchers might be interested in specific flavonoid content of foods. Our study showed that FCTs had variations in the number of foods with flavonoid content, which is a relevant point to consider when deriving intake estimates in population-based surveys. There were only 42 food items with total flavonoid intake estimates common to all FCTs, and there were at least 66 foods available for comparison between FCTs. Except for the IFCT, all tables had data on anthocyanidins and proanthocyanidins. Regional representativeness of flavonoid data might be important to consider when deriving flavonoid intake estimates in low-middle income countries. The IFCT is one of the few sources of flavonoid data outside high-income countries. The table showed relatively low levels of agreement in the estimates of total flavonoid and of flavone content compared to the other three tables. These differences should be taken into consideration in studies ascertaining flavonoid intake in India, as the use of other tables might overestimate the consumption of flavonoids in nutritional surveys in this country. The IFCT includes flavonoid content of foods representative of the country's usual diet.

Another methodological aspect that influences variations in the content of flavonoids in FCTs refers to the chemical form (aglycones or glycosides) included for flavonoids. Aglycone describes the core flavonoid, phenolic acid, lignan or stilbene, without the linked sugars or polyols. Although all four FCTs included flavonoid data in aglycone form, there were variations in the extent to which this information was available for all flavonoid subclasses across tables. In addition, some of the sources of flavonoid content were similar between tables, but they also used original or unpublished data. These factors might explain some of the biases we found in the reporting of anthocyanidin content.

FCTs of flavonoid content remain the main, and possibly one of the most helpful sources of information to estimate intake in population-based surveys. However, the limitations inherent to the variations in the methods and reporting of flavonoid data across FCTs, and those related to dietary instruments might reduce their reliability. To this end, new potential markers of flavonoid intake identified in urine and blood could contribute to improving the accuracy in the measurement of intake

(44, 45). Using the FFQ that is being administered in the BOLD study, we have identified several candidate markers of flavonoid and polyphenolic compounds in sera, which can be used to calibrate the information provided in FCTs (46).

Flavonoid intakes vary greatly within and between populations (18, 47), and improving our understanding on the variations between reference FCTs used to estimate flavonoid intake can contribute to reduce inconsistencies in the associations of flavonoids and health outcomes. Our study shows that there was a relatively good levels of agreement across FCTs, but it also highlights the complexities associated with harmonizing data, and that content of flavonoid might differ across databases and specific foods (48). It is, therefore, important to understand the particularities, advantages, and disadvantages of each database regarding the measurement of flavonoid (42).

To our knowledge, this is the first study to compare the levels of agreement and variations in net estimates of flavonoids using four international FCTs. The findings from this study suggest that the choice of FCTs can influence the differences observed in the estimates of flavonoid content of foods. Our study has some limitations. Although we tried to harmonize the foods and flavonoids classes under comparison, unaccounted differences in data aggregation and comparability criteria within each table might have influenced some of the differences observed. Some of the aggregation of composition data, might have resulted in over- or under-estimation. For example, the food item “apple” may have several composition variations due to its variety in pigments and species. In our study, the flavonoid estimate in different varieties of apples was aggregated into a single value, to give a generic estimate of this food item.

Due to the differences in reporting of flavonoid content (aglycones or glycosides), we were unable to consistently estimate content in one or the form for all foods across all FCTs. International harmonization of chemical forms of flavonoids would facilitate comparisons that account for a specific composition (49).

In conclusion, our study found that several flavonoid subclasses showed moderate to excellent levels of agreement between FCTs, whilst others (including total flavonoid intake) had lower levels of agreement.

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Chapter 4 Dietary Flavonoids intake and Respiratory Outcome

Dietary flavonoid intake estimation and its association with respiratory outcomes in adults participating in Burden of Obstructive Lung Disease (BOLD-I) survey

4.1. Introduction

Globally, chronic obstructive pulmonary disease (COPD) is causing 3.23 million deaths in 2019 which placed COPD the third leading cause of death (1) that had not predicted by World Health Organizations (WHO) to occur until 2030 (2). COPD has been recognized as a silent killer in low-middle income countries(2, 3) where 90% of COPD deaths in those under 70 years of age occur (1). The progress made to reduce the burden of lung diseases for the past decades is not enough (4) and to achieve significant reductions, a new paradigm focused on public health(4) and lifestyle approach is needed (3, 5). The identification of modifiable risk factors is important and urgent for the prevention and treatment of COPD (6). Emerging evidence indicates dietary factors as a modifiable factor that can affect the development and progression of obstructive lung diseases (6-9).

Flavonoids are dietary factors belong to the polyphenols with variety of beneficial properties (10-12) including anti-inflammatory(13, 14), anti-oxidants (15), antimicrobial (16), and anti-ageing(17, 18) which plays important role on the pathogenic processes of chronic obstructive pulmonary disease(19-21). There are promising findings reported from observational studies where total flavonoids(22, 23), anthocyanins, flavonols, flavanones, flavones(22), isoflavones (24), and proanthocyanidins(25) intake exposures were inversely associated with COPD. Lung function measures (such as FEV_1, FVC and FEV_1/FVC) were positively associated with increased intake of antioxidants-rich food (26), Total flavonoid (25), flavanols (27), total catechins (28, 29), flavonols (28), isoflavones (24), and proanthocyanidins(25).

Those scientific sources published to date are promising with notable discrepancies in design setting and approach, results obtained, and geographic coverage where almost all are from high-income countries. There is/are no studies, to the best of our knowledge, on dietary flavonoid intake and respiratory outcomes conducted in those countries that participated in the Burden of Obstructive Lung Disease (BOLD I) dietary survey. This study, therefore, was designed to estimate dietary flavonoid intake and investigate its associations with respiratory outcome in adults

participating in BOLD I dietary survey.

4.2. Methods

4.2.1 The Burden of Obstructive Lung Disease (BOLD) Survey

4.2.1.1. Study design and population

A multinational population-based survey, Burden of Obstructive Lung Disease (BOLD), was designed to describe the variations in the prevalence of COPD across the world, and to identify its risk factors across several regions , mostly in low- and middle-income countries(30). BOLD was conducted among non-institutional adults aged 40 years and above using standardized and validated methods and tools. As per BOLD protocol, the minimum sample size was 600 persons randomly selected from a meaningful defined administrative boundary with at least 150,000 subjects. The BOLD Operations Centre (OC) reviewed and approved the sampling methodology of each participating site.

In this paper, we have used BOLD I survey data from six countries namely Albania, India, Kirgizstan, Morocco, Pakistan, and the United Kingdom (UK) (**Figure 4.1**).

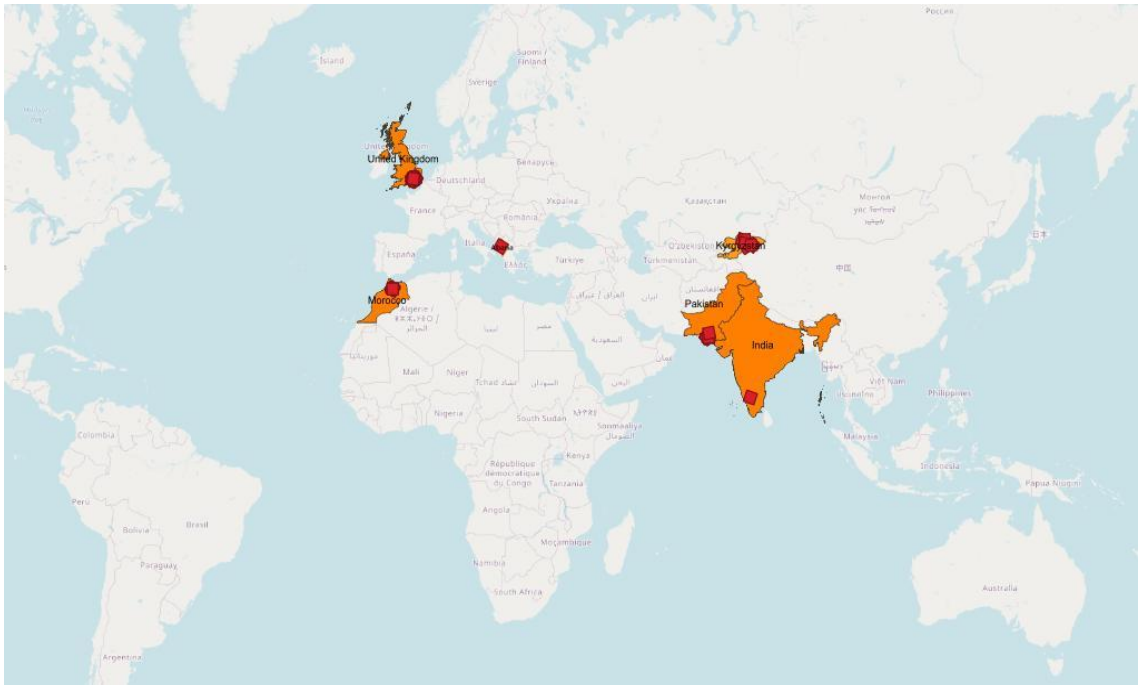

Figure 4.1 BOLD I survey Participating countries selected in our study

In all BOLD I dietary survey participating sites selected for this analysis, except UK(London), a cluster sampling strategy has been applied to select study participants from non-institutionalized individuals living within their target population. A stratified random sampling method was used in UK(London). **Figure**

4.2 show the procedure followed to extract eligible study participants for this specific analysis.

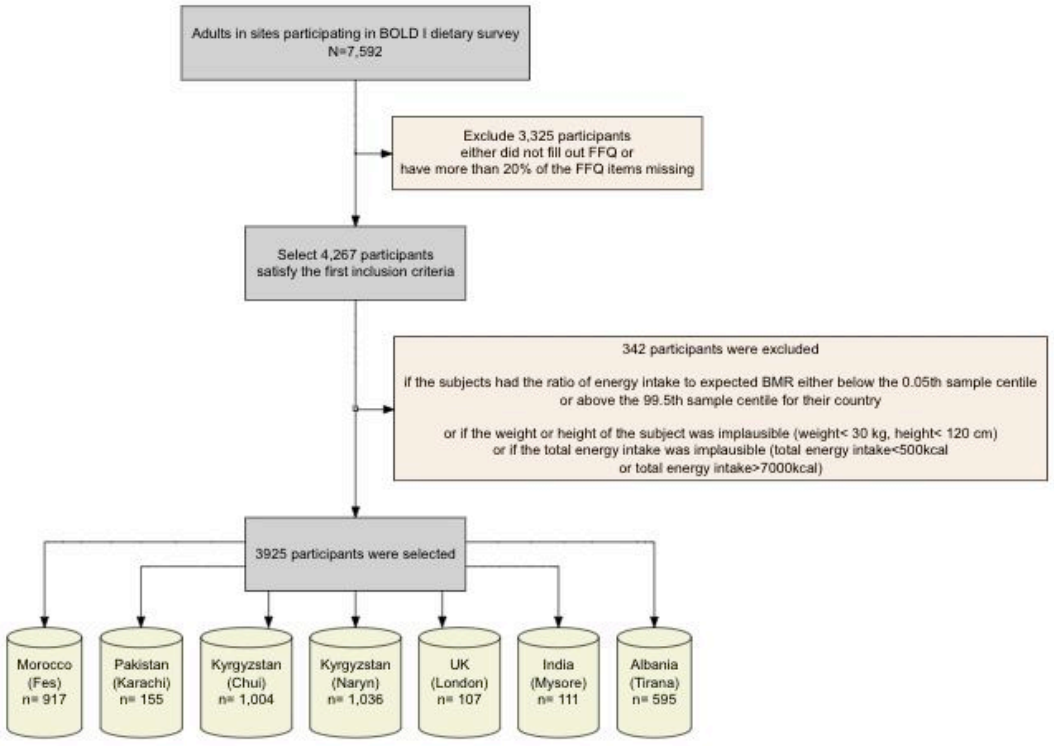

Figure 4.2 Flowchart showing study participants selection procedure from BOLD I dietary survey participating sites.

4.2.1.2. Data collection tools and procedures

Data was collected using a validated questionnaire and spirometry tests (pre-and post-bronchodilator). Detailed data collection and management procedures were described in further detail elsewhere(30). Participants were expected to respond to trained staff administering BOLD Spirometry, Core, Cigarette Smokers', Biomass and fuel, and occupational questionnaires. A locally modified dietary survey was also designed as part of the multinational population-based BOLD I survey.

4.2.1.3. Food Frequency Questionnaire (FFQ)

As part of BOLD survey(30), a standardized, and validated FFQ (31) was adapted to be used across all participant countries in Europe, Africa, and Asia participating in BOLD I. The GA^{2}LEN food frequency questionnaire (FFQ) (31) is an internationally validated, semi-quantitative questionnaire that was used as a common, standardized tool to ascertain dietary intake across all research sites participating in the BOLD study. The FFQ has been further validated to show that dietary intake of flavonoids was highly correlated with several novel potential

markers of flavonoid intake in serum (32). The food group classification (n=32) was based on the European Food Consumption Survey Method (EFCOSUM) recommendations, facilitating international comparisons of dietary intake (33). Six countries, namely Pakistan, Morocco, Albania, India, Kyrgyzstan, and UK implemented the FFQ, and translated it to the local language. The FFQ contains a wide range of plant-based foods commonly consumed across participant countries, as well as specific foods representative of each country's dietary habits. The frequency of food consumption was categorized as +4 per day, 2-3 per day, once per day, 5-6 per week, 2-4 per week, once per week, 1-3 times a month, and rarely or never.

4.2.2 Dietary Flavonoid Intake Exposure

Dietary flavonoid intake exposure were estimated using a flavonoid food composition table derived from The US Department of Agriculture (USDA) database describing flavonoids content in three separate datasets: (i) flavonoids(34) (containing five sub-classes: Flavanols, Flavanones, Flavones, Flavonols, and Anthocyanidins), (ii) isoflavones(35), and (iii) proanthocyanidins(36). The USDA flavonoid database was expanded using the finding from comparison study to include additional flavonoid subclasses (Chalcones, Dihydrochalcones, Dihydroflavonols), gallic acid and food items using Phenol-Explorer (37, 38), The Bioactive Substances in Food Information Systems (eBASIS) (39, 40), and The Indian Food Composition Table (IFCT) (41).

The participant's actual food intake was estimated using the mean serving per day obtained from the FFQs multiplied by grams per portion for each food item. The estimated participant's food intake was then multiplied by flavonoid content of each food item to obtain daily flavonoid intake.

4.2.3 Covariates

Potential covariates such age, sex, educational level, smoking status, BMI, wealth index, total energy intake, β-Carotene, vitamin C, vegetable and fruit diversity scores were included for adjustment in the final analysis model. Wealth index was measured from 15-items BOLD questionnaire on household assets (42): out of the 15 items of asset ownership that satisfy Mokken scale requirements(43) were chosen using an automated item selection procedure(44). Further details were

described elsewhere(42, 45).

Total energy intake, β-Carotene, and vitamin C were estimated by multiplying the nutrient contents obtained from McCance and Widdowson's food composition tables(46, 47) complemented by USDA National Nutrient Database for Standard Reference(48), Moroccan food composition tables(49), and IFCT (41) by food consumption amount from BOLD FFQs and gram per portion of food items. Vegetable and fruit diversity scores were defined by one point score attributed to individual vegetables and fruits consumed at least once per day and summed separately for vegetables and fruits to obtain diversity scores.

4.2.4 Outcome Measurement

Given that BOLD[1] is a population-based study using standardized methods and tools(30), we used ATS/ERS-LLN guidelines to define COPD. The detailed quality check and measurement procedure have been mentioned elsewhere (30, 50-52). FVC, FEV_1/FVC%, and Chronic airflow obstruction (FEV_1/FVC < LLN) were the primary outcomes we studied. Chronic airflow obstruction (CAO) was defined using Post-BD FEV1/FVC <LLN (53) based on the reference equation from the Third National Health and Nutrition Examination Survey (NHANES III) for age and sex(54).

4.2.5 *Statistical Analyses*

Descriptive analyses for continuous variables were calculated as mean and standard deviation or median and inter-quartile range, according to the distribution of data (presence or absence of normality). Frequencies and percentages were used for the description of categorical variables.

Our analyses focused on three respiratory outcomes: FVC, FEV_1/FVC% and CAO. All the three analytical analyses were adjusted for 14 potential covariates selected based on prior information from literature review and p-value (<0.2) from univariate analysis. The selected covariates were sex, age, educational level, smoking, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity

[1] https://www.boldstudy.org/

score. Direct Acyclic Graphs (DAGs) were also used to identify a minimal sufficient adjustment for estimating the total effect of dietary flavonoid intake on CAO (FEV1/FVC < LLN).

The association of dietary flavonoid intake (total flavonoids and seven main subclasses) with FVC, FEV_1/FVC was studied by multiple linear regression analysis, while the relationship with the presence of CAO by multiple logistic regression. A meta-analysis across BOLD I dietary survey participating sites was used with the random-effects inverse-variance model. The inverse-variance approach was performed by a two-stage individual participant data meta-analysis which allows to examine participant-level covariates (55). In first stage, it calculates the site-specific aggregate data, and then produces pooled summary estimates and a forest plot (56, 57). The total variation in effect estimate (odds ratio or coefficient) due to between-sites heterogeneity was displayed using I^2 statistic based on Q-test (58).

All analysis were performed using Stata/BE 17.0 (StataCorp, College Station, Texas USA) and R 4.1.1 (RStudio, PBC, Boston, MA USA).

4.3. Results

A total of 3,925 adults, of which 59% was female, from six countries has enrolled for this study. The general characteristics on sociodemographic, comorbidities and respiratory outcomes of adults participating in BOLD I dietary survey are presented in **Table 4.1**. The overall reported mean (±SD) age was 54.3(±10.7) years with the highest and lowest mean age reported in London in UK (63.6±9.3) and Mysore in India (45.8±4.7), respectively. The majority (71%) of adults participating in BOLD I dietary survey had never smoked. A total of 669 (17%) of adults had never attended a school.

4.3.1 Dietary flavonoids intake estimation and their major food sources

In Table 4.2, the median dietary intake of adults participating in BOLD I is described for each site. Both BOLD Sites in Kyrgyzstan (Chui and Naryn) had the highest median daily intake of total flavonoids, 1579 mg, and 1328 mg, respectively, whereas the lowest was reported in Tirana in Albania (273 mg), among the BOLD sites participating in BOLD I Dietary survey. The highest daily median intake of anthocyanidin (61.4 mg) was observed in Fes (Morocco) followed by Chui in Kyrgyzstan (55.5 mg) and London in UK (32 mg). **Appendix Table C.1** presents the mean daily total flavonoids and subclasses intake with an overall mean daily total flavonoids was reported to be 989.1(±599.4).

From **Figure 4.3** to **Figure 4.10** show the distribution of dietary flavonoid intake in each site participating in BOLD I dietary survey. Most of the total variation in the distribution of total flavonoid intake was observed within BOLD sites and only 34% of the total variability was due to variation between BOLD sites [**Figure 4.3**]. Subclasses variation due to between BOLD sites ranges from 14% for intake of anthocyanidins [**Figure 4.5**] to 51% for the intake of isoflavones [**Figure 4.9**].

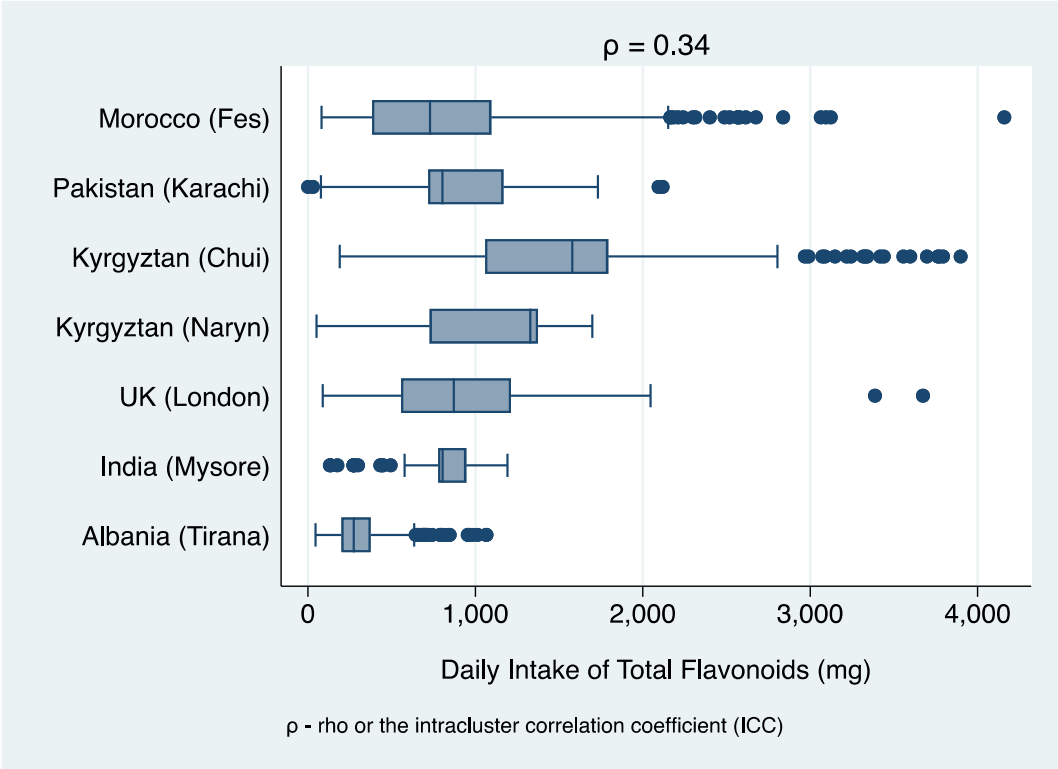

Figure 4.3: Distribution of daily intake of total flavonoids in each site participating in BOLD I dietary survey

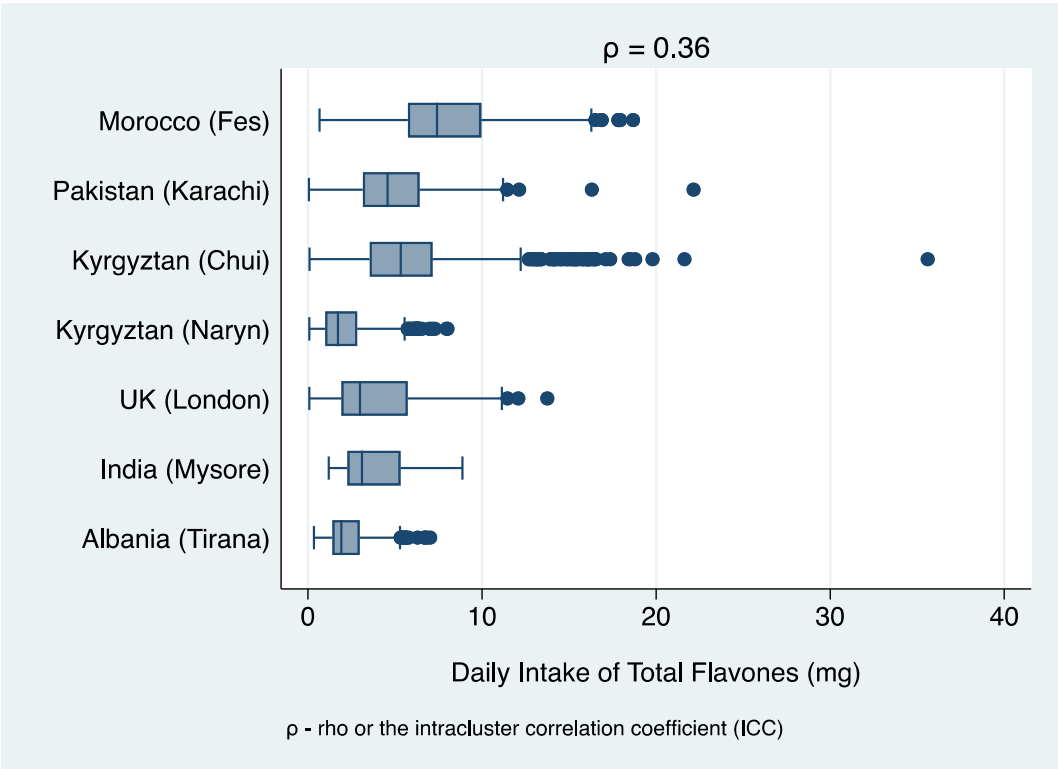

Figure 4.4*:* distribution of daily intake of flavones in each site participating in BOLD I dietary survey

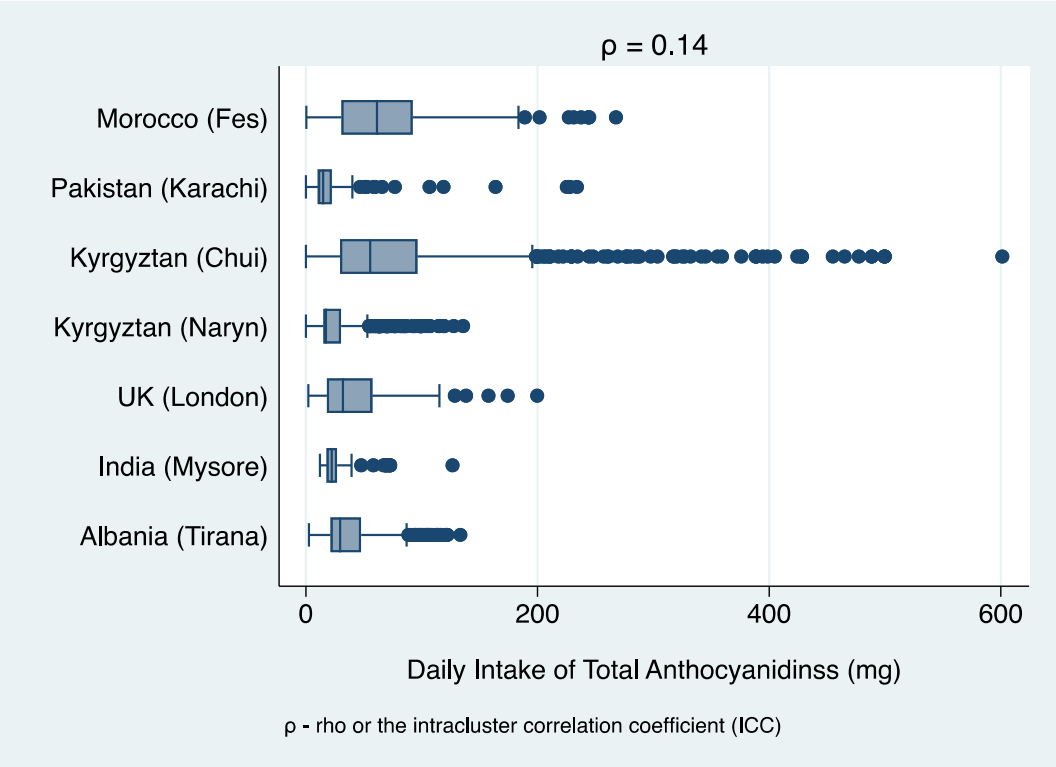

Figure 4.5*:* distribution of daily anthocyanidins intake in each site participating in BOLD I dietary survey

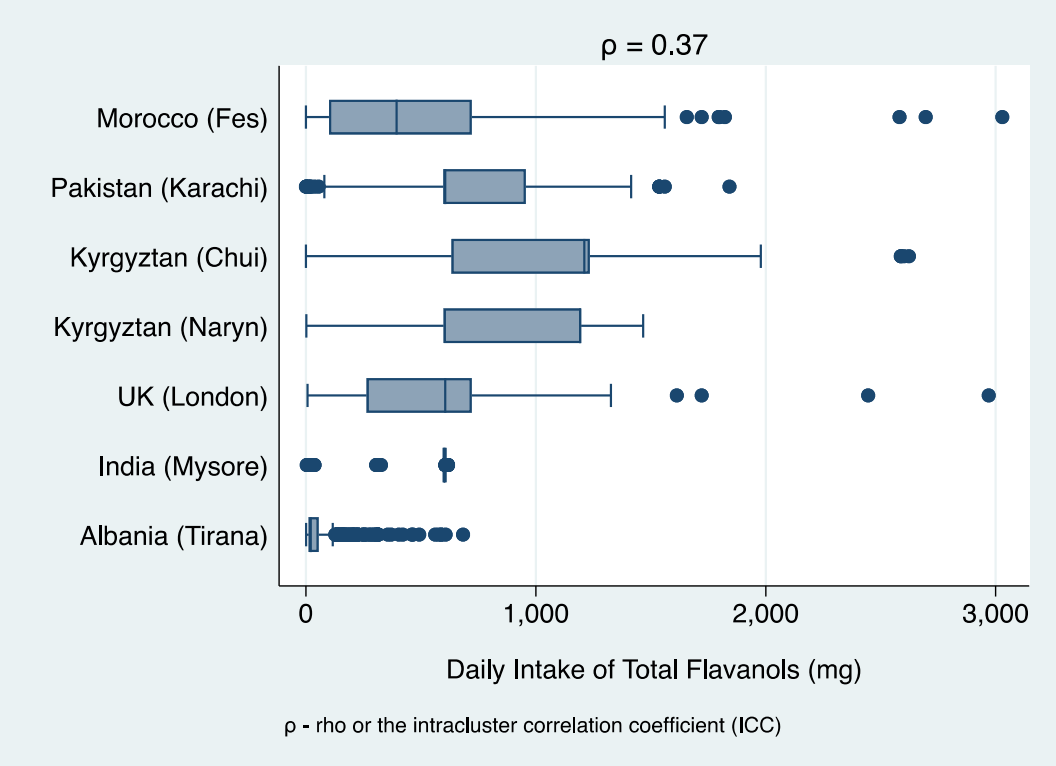

Figure 4.6*:* distribution of daily Flavanols intake in each site participating in BOLD I dietary survey

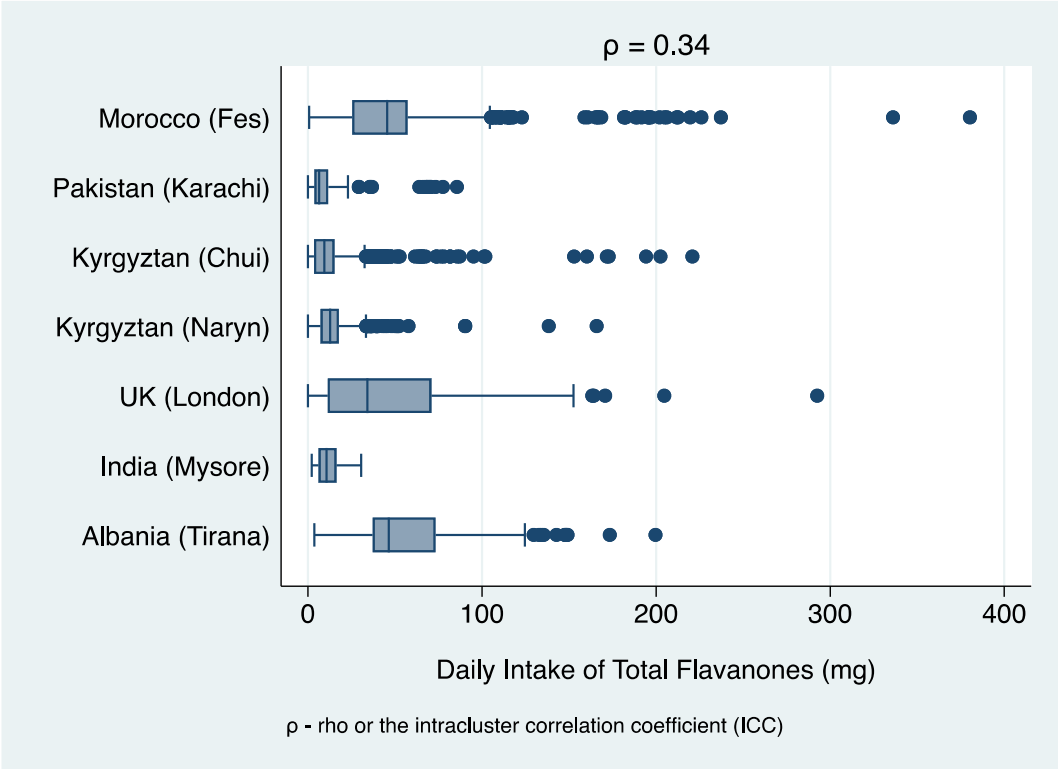

Figure 4.7*:* distribution of daily intake of flavanones in each site participating in BOLD I dietary survey

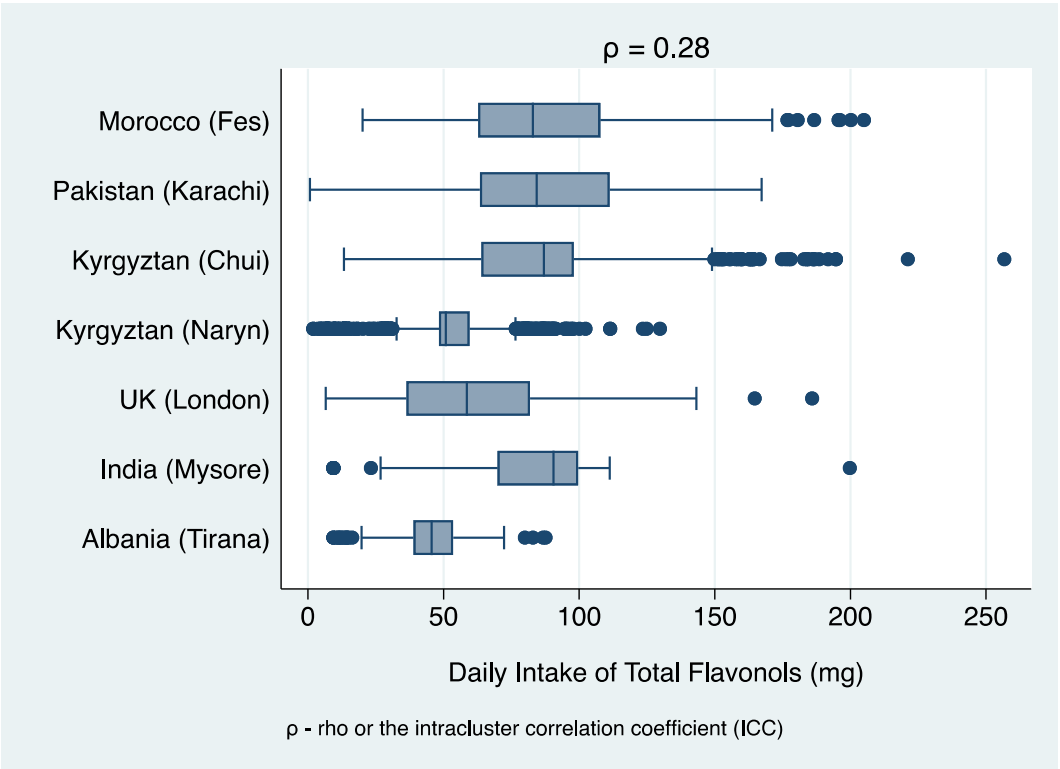

Figure 4.8*:* distribution of daily intake of flavonols in each site participating in BOLD I dietary survey

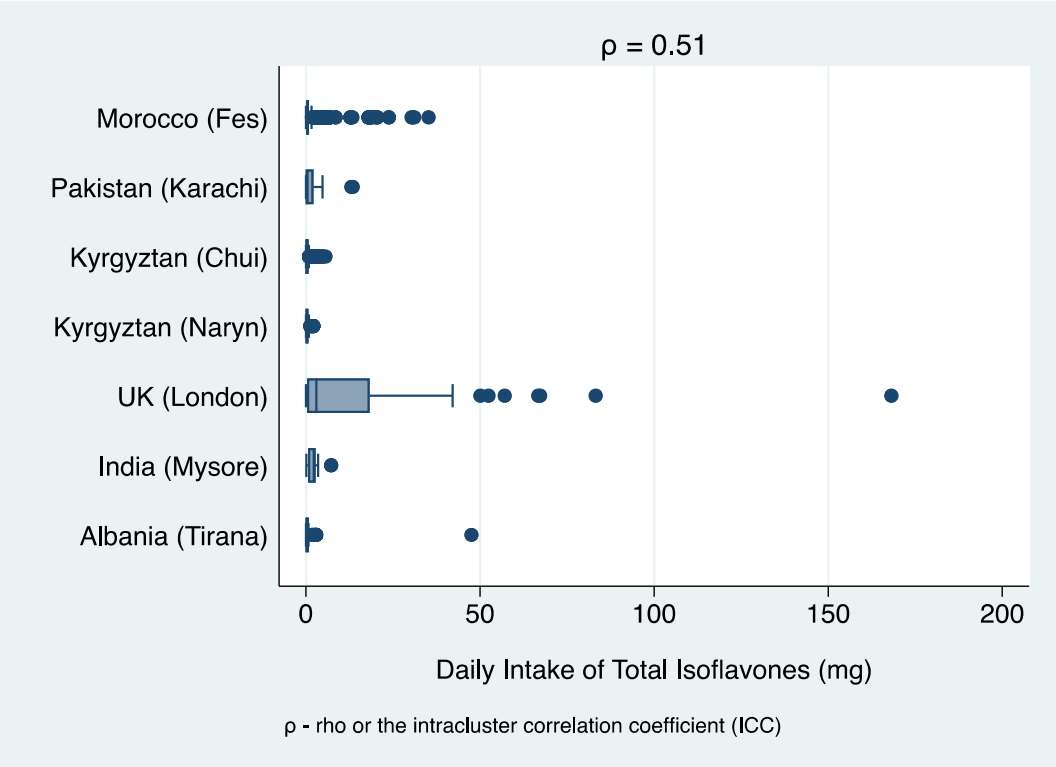

Figure 4.9*:* distribution of daily intake of isoflavones in each site participating in BOLD I dietary survey

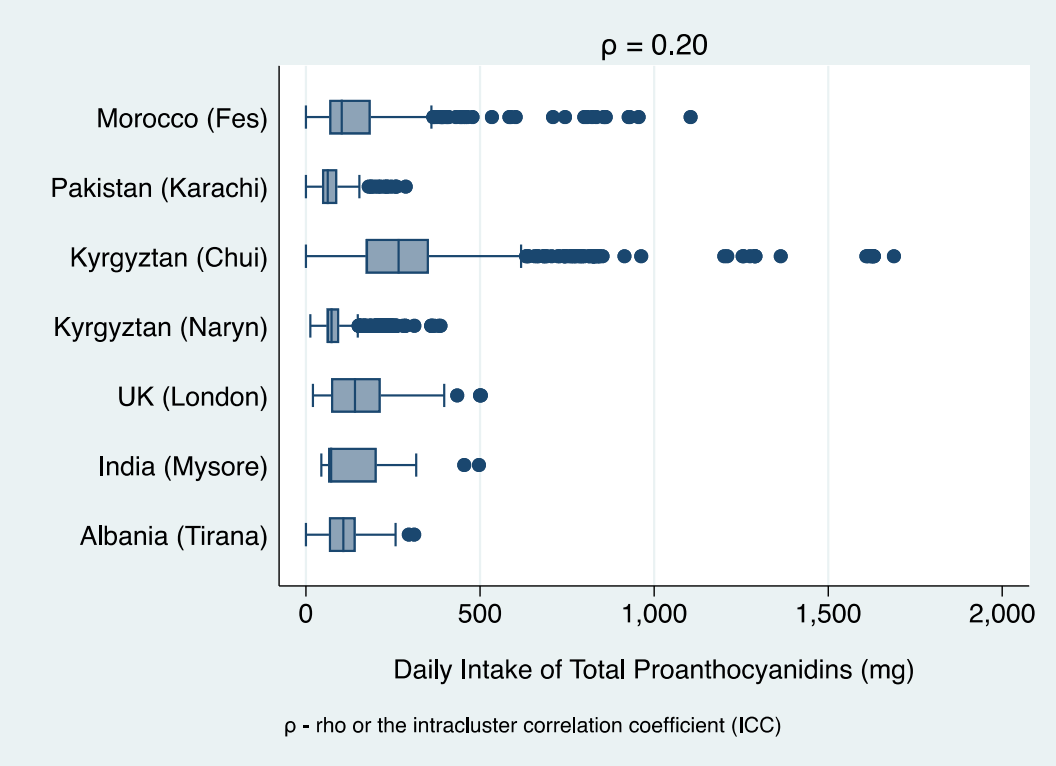

Figure 4.10: distribution of daily intake of proanthocyanidins in each site participating in BOLD I dietary survey

Table 4.3 presents the main food sources and their contribution to daily intake of total flavonoids and main subclasses. Tea was the main food source of total flavonoids in almost all sites, except in Albania (Tirana) and contributed to the total flavonoid intake from 57% in Morocco (Fes) to 86% in Kyrgyzstan (Naryn). In Albania (Tirana) fruits were the main food sources of total flavonoids accounting for 60%. **Figure 4.11** also provides the percentage contribution of specific food items to the daily intake of total flavonoids.

Fruits were the major sources for flavanones and proanthocyanidin, contributing almost 70% and 80% of the total daily intake, respectively. Vegetables were reported as the major food sources providing 74%, 82% and 55% of the total daily intake of anthocyanidins, flavones, and flavonols, respectively [**Table 4.3**].

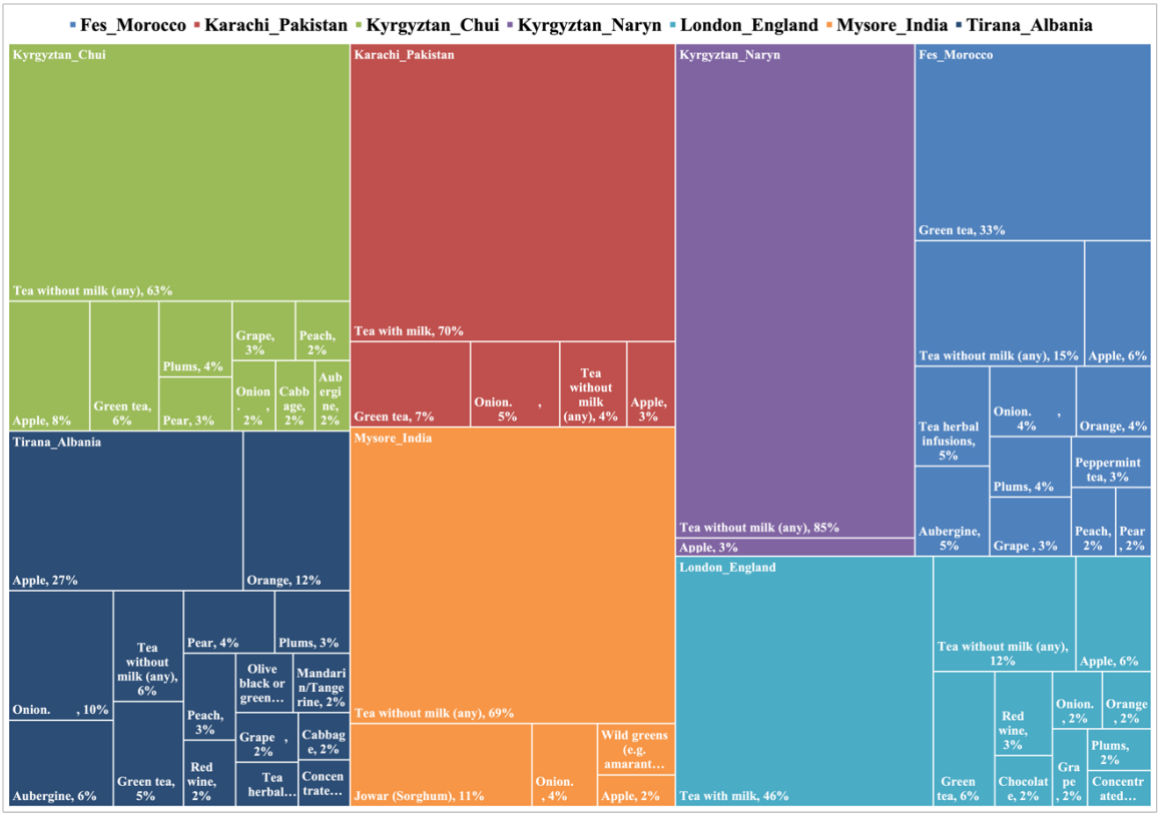

Figure 4.11 major food sources for daily intake total flavonoids in sites participating in BOLD I dietary survey [food items with 1% or less of contribution were excluded from this figure].

4.3.2 Association of dietary flavonoid intake and CAO

In all site samples participating in BOLD I dietary survey, except in Naryn from Kyrgyzstan, a higher median intake of total flavonoid was observed among adults without CAO compared to those with CAO [**Table 4.4**]. **Figure 4.12**, however,

show that there is no evidence to support the difference in the median intake of total flavonoid among those with and without CAO. There is also no evidence of heterogeneity between individual sites on the associations of daily total flavonoid intake with CAO (I^2=0%, p=0.94).

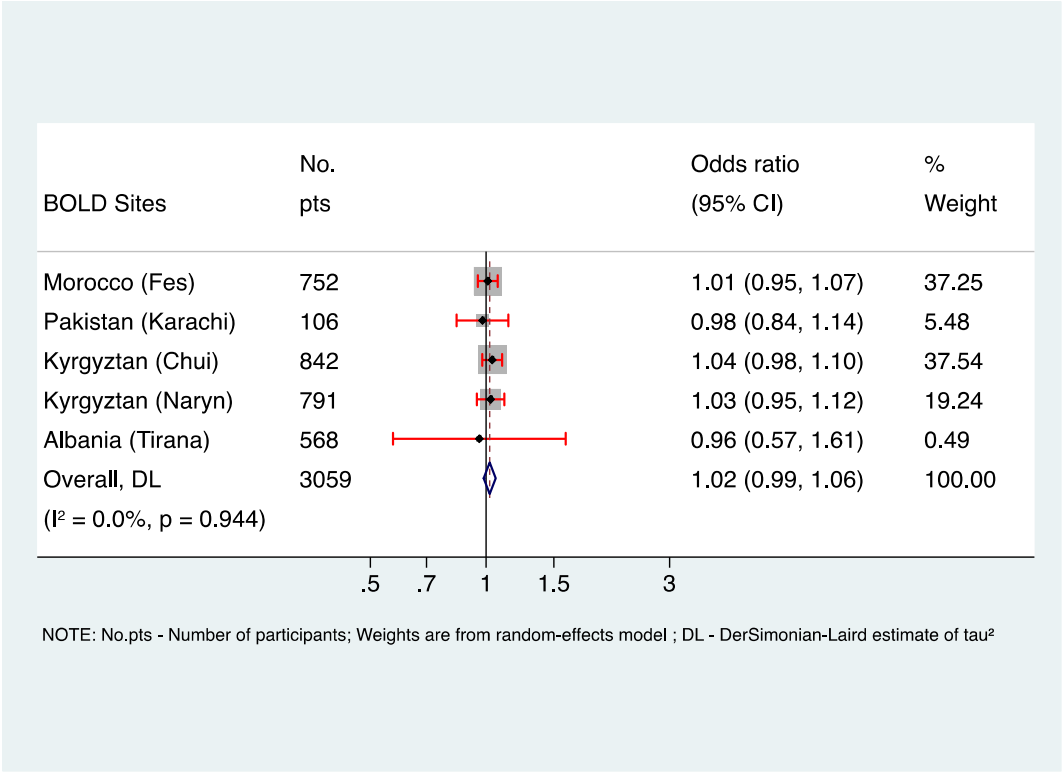

Figure 4.12 Association of daily total flavonoids intake (per 100 mg increase) and chronic airflow obstruction across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score]

There is a difference in the median intake of flavones among those with and without CAO [**Table 4.4**]. The random effect meta-analysis in **Figure 4.13** shows there is strong evidence on the adjusted association of a 10 mg increase in daily flavones intake a lower proportion of subjects having CAO with an adjusted OR 0.27(95%CI 0.09, 0.81) and no evidence of heterogeneity between sites (I^2=0%, p=0.47).

Table 4.5 gives the meta-analysis summary statistics on unadjusted and adjusted associations of daily intake of flavonoids (total and subclasses) with CAO. A 50 mg increase in daily intake of flavanones was associated with a lower proportion of subjects having CAO (unadjusted OR 0.74, 95%CI 0.58, 0.94; p<0.02), although, after adjustment, this association was no more significant.

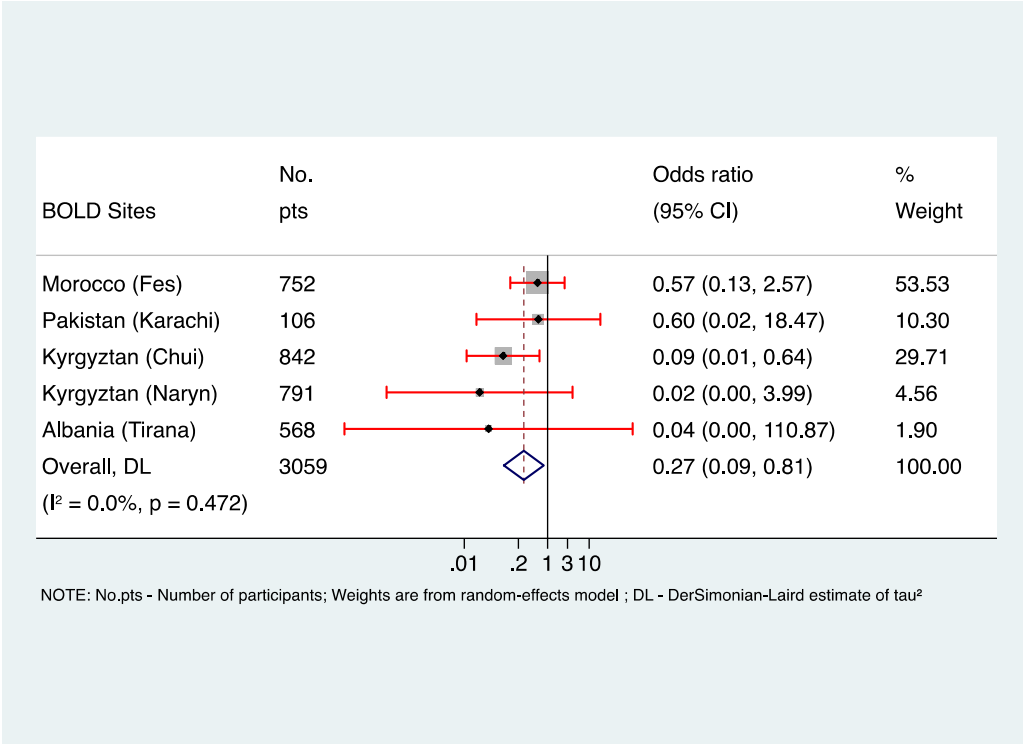

Figure 4.13 Association of daily flavones intake per (10 mg increase) and chronic airflow obstruction across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score.

4.3.3 Association of dietary flavonoid intake and FVC and FEV1/FVC

Figure 4.14 and **Figure 4.15** show the distribution of post-bronchodilator FVC and FEV_1/FVC ratio (expressed in percentage) by sites participating in BOLD I dietary survey. Only 20% and 12% of the total variation in FVC and FEV1/FVC (%) was due to between-site differences. The overall means of FVC and FEV1/FVC (%) were estimated as 3,380.9±902.1 ml and 77.8±8.4 %, respectively [**Figure 4.1**]. The highest and lowest means of FVC were observed in Tirana (Albania) and Mysore (India), respectively [**Figure 4.1**]. **Figure 4.16** and **Figure 4.17** present the meta-analysis on the adjusted associations of daily intake of total flavonoids with FVC and FEV_1/FVC%, respectively, per BOLD site and overall effect. There is no statistical evidence of an association between total flavonoid intake (per 100 mg increase) with FVC or FEV_1/FVC%. The data shows no heterogeneity between individual sites in the associations of total flavonoid intake with FVC and FEV_1/FVC%, with I^2 below 1% and $p>0.97$. A 50mg increase in daily intake of flavanone is positively associated with FEV_1/FVC% in unadjusted meta-analysis that yields a regression coefficient of 0.89 (95%CI 0.18, 1.60) [**Table 4.5**], while this association disappeared after the adjustment. There is no evidence of between-sites heterogeneity in the association of dietary flavonoids intake (total and all subclasses) with FVC (ml) and FEV1/FVC% [**Table 4.5**].

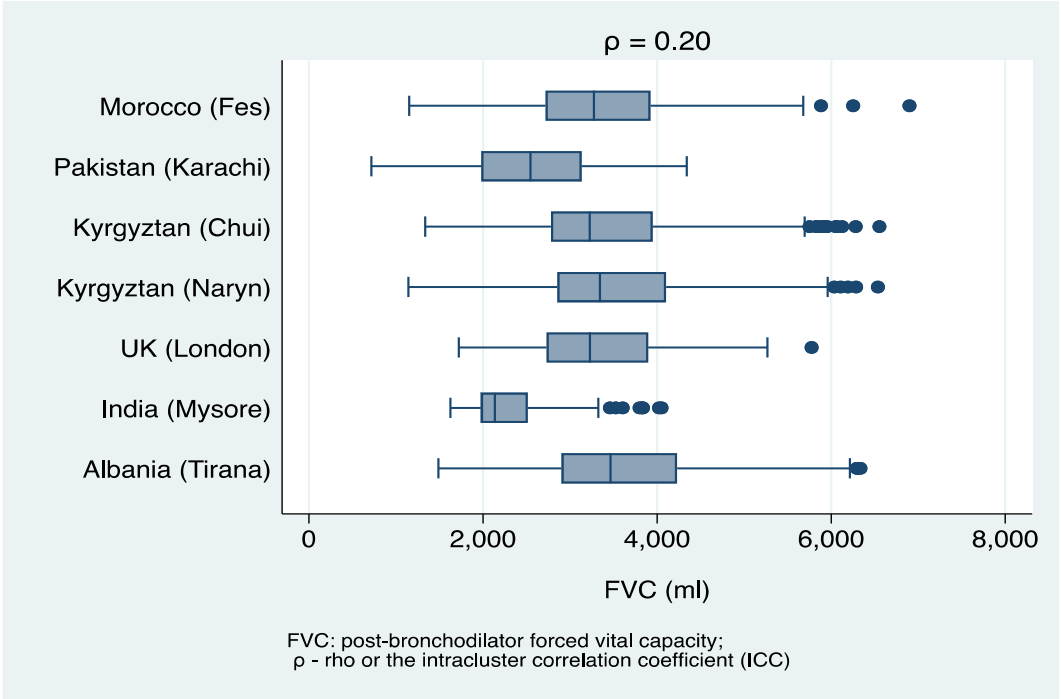

Figure 4.14 distribution of FVC (ml) in each site participating in BOLD I dietary survey

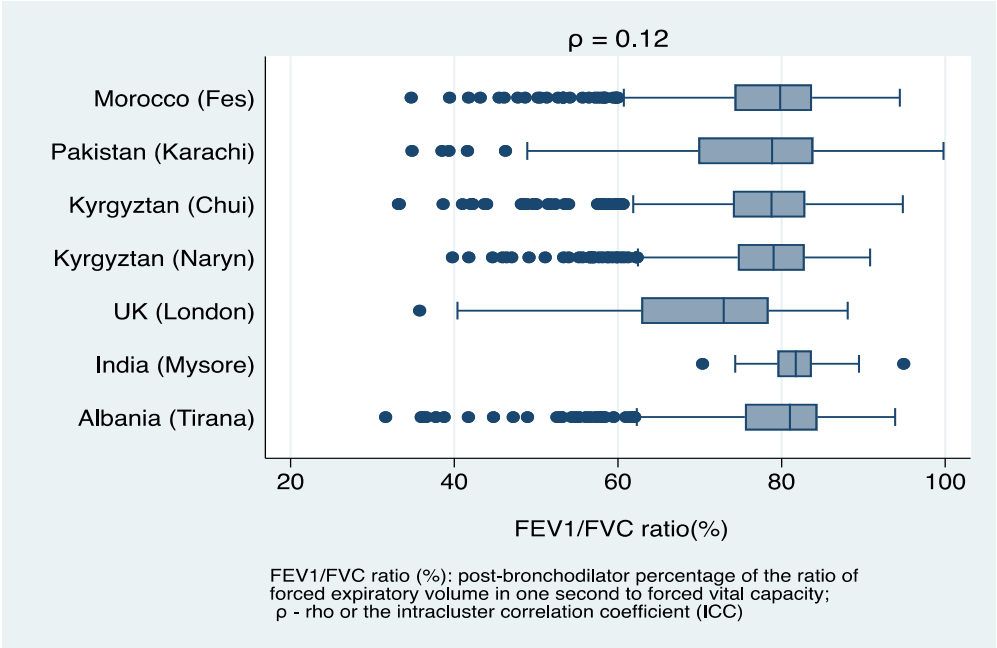

Figure 4.15 distribution of FEV1/FVC % in each site participating in BOLD I dietary survey

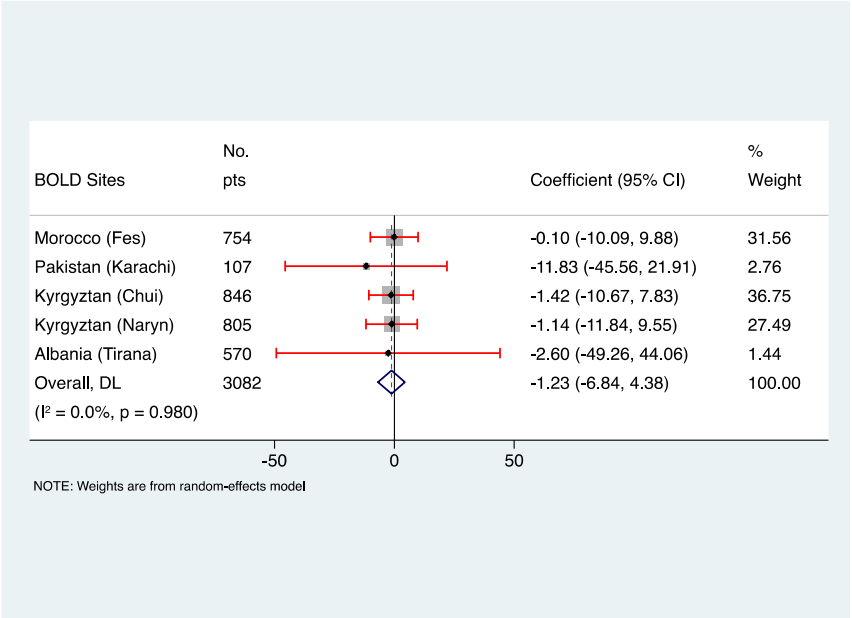

Figure 4.16 Association of daily total flavonoids intake (per 100 mg increase) and FVC (ml) across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in FVC (ml) per 100 mg increase in daily total flavonoid intake.]

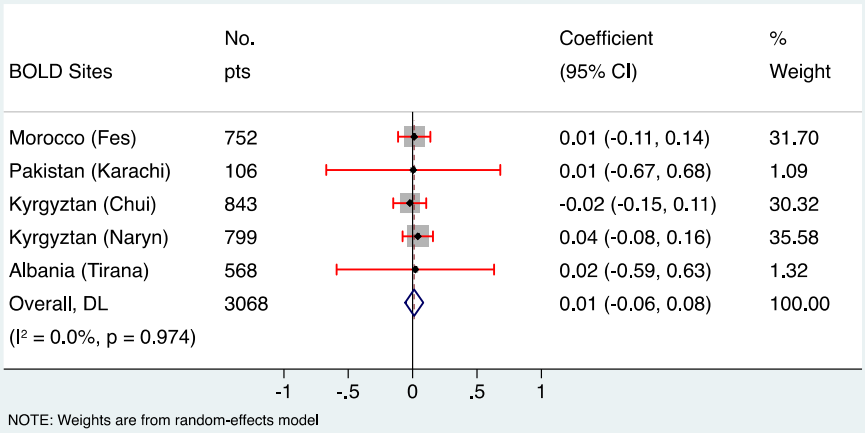

Figure 4.17 Association of daily total flavonoids intake (per 100 mg increase) and FEV1/FVC (%) across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in FEV1/FVC (%) per 100 mg increase in daily total flavonoids intake.]

4.4. Discussion

This multinational population-based study estimates daily dietary flavonoids intake and their associations with respiratory outcomes (FVC, FEV_1/FVC% and FEV_1/FVC<LLN). The overall mean daily total flavonoid intake was estimated to be 989.1±599.4 mg/d with the highest and lowest from Chui in Kyrgyzstan (1506.4±539.5) and Tirana in Albania (306.8±159.4), respectively. Flavanols (67.5%) followed by proanthocyanidins (16.4%) were the major contributor of daily total flavonoid intake. Tea was the major food group contributor to the daily total flavonoid intake representing 70% except for Tirana in Albania where fruits were the primary food group source (60%) of total flavonoid intake. Vegetables were the main contributor to the intake of daily anthocyanidins, flavones and flavonols in all sites participate in BOLD I dietary survey. The most important source of daily flavanone intake was fruits and fruit juices varying from 67% in Mysore, India to 96% in Naryn, Kyrgyzstan. An unadjusted meta-analysis across the BOLD sites with information on diet showed that the daily intake of flavanones and flavones was inversely associated with chronic airflow obstructions (FEV_1/FVC < LLN). After adjustment by potential covariates, the association of daily intake of flavones with CAO remained significant. No associations were found between daily total flavonoid and other subclasses intake with respiratory outcomes (FVC, FEV_1/FVC, and CAO).

There is lack of prior population-based study on daily flavonoid intake and their food sources across countries participating in BOLD I dietary survey. Dietary flavonoid intake studies are growing and several of those studies were from US (23, 59-63), and European countries (25, 29, 64-66). The estimated mean daily total flavonoid intake in previous studies ranged from 58 mg/d (29) to 897 mg/d(66). However, the majority of studies reported a mean daily total flavonoid intake between 180 and 350 mg (23, 25, 59-64, 67-69) with the highest estimate of these latter studies reported by Grosso G et.al(66) and Murphy KJ et.al (70) in Australia and Poland, respectively.

The mean daily total flavonoid intake in our study is at least threefold higher than the intake reported by majority of studies but moderately consistent with the estimate reported by Grosso G et.al (66). In our study, the total flavonoid intake was

derived from ten subclasses and around 150 food items: the higher number of flavonoid subclasses and food items considered in our study could be the potential reason to the observed discrepancy in the intake estimation. Peterson et.al (71) demonstrated that total flavonoid estimate can be lowered by at least a third when proanthocyanidins and Thearubigins (flavanols-polymers) remained unmeasured. In our study, flavanol-polymers and proanthocyanidins has contributed 402 mg/d and 162 mg/d to the total flavonoids, respectively. On top of that, in our study we have used the latest available flavonoid food composition tables according to our comparison study on international flavonoid food composition tables. Completeness of flavonoid food composition tables (in terms of food items and flavonoid compounds) were reported as contributor to the variation of flavonoid intake estimation in US and European cohorts(71).

This study found that flavanols were the main contributor to the daily intake of total flavonoids, providing 667.5mg/d of the total intake and of which, 60.3% was from flavanol-polymers (thearubigins and theaflavins). Our study is consistent with various studies (59, 61-63, 70, 72) that reported flavanols as major source of dietary flavonoids, accounting from 75% to 86.5% of total flavonoids. Large portion of the daily total flavonoid intake was obtained from tea, presenting 70% of total flavonoids followed by 19% from fruits. A study conducted by Zamora-Ros et.al(73) shows that total flavonoid intake estimation could be influenced by black tea consumptions, the main dietary source of Thearubigins. In our study, those sites with the higher daily consumption of tea had reported also higher total flavonoid intake whilst the lower daily consumption tea and total flavonoid was reported in Tirana in Albania. Similarly, tea was identified as major flavonoid source in several intake studies(59-63, 65, 66, 70, 72).

Previous studies have demonstrated that higher intake of dietary flavonoid could be beneficial in terms of a better lung function (24-29) and/or a lower risk of COPD (22-25, 29, 74) regardless of their consistency and geographic coverage. Our finding is consistent with Garcia-Larsen et.al (25) where chronic airflow obstruction ($FEV_1/FVC<LLN$) was not associated with total flavonoid intake exposure whilst inconsistent with the study by Bondonno et.al (22) that showed that the risk of COPD was lowered up to 20% in participants with higher total flavonoid

intake compared to participants with lower intake and by Sanderson et al(23) where a 7.1% decrease in the odds of having COPD was observed in every 1% increase in total daily flavonoid intake. The inconsistency could be explained by study setting and design applied, food composition table employed, exposure assessment (mainly tools and comparison methods used) and outcome measurement performed. For instance, Johns and his colleagues(75) reported that the evidence on the misclassification of COPD in general practice could be related to a diagnosis not being based on objective spirometry and in our study, an objective spirometric was used to define CAO. Exposure assessment assuming homogeneity of risks within categories, using quantile, leads to inaccurate estimation as reported in a study by Bennette and Vickers (76) and a homogeneity of risks within categories was not assumed in our study.

Apigenin, a common flavone, was reported to have a beneficial role to decline age-related lung diseases such as COPD through increasing the activation ratio of silent information regulator 1 (SIRT1) and reducing the impact of senescent cells (77). The study by Chen et.al (78) has found that the potent anti-inflammatory properties of flavone luteolin can be used to treat inflammatory disorders in lung. These results have been supported by our findings that showed strong evidence on the association of daily flavones intake and chronic airflow obstruction. Our findings are consistent with the study of Bondonno et.al (22) where a lower risk of COPD was associated with a higher intake of flavones, and Tabak et.al (29) where flavones intake was inversely associated with COPD symptoms. In a study conducted by Hirayama et.al(74) a substantial reduction in COPD risk was found by increasing daily total vegetable intake. In our study more than 70% of flavones was obtained from vegetables: this result is similar to other studies that reported vegetables as the main contributors to the intake of flavones(25, 68). Taking this into consideration, our findings are in line with other studies(74, 79-81) where vegetable consumption is inversely associated with COPD.

This study found that there is no association between daily intake of other flavonoid subclasses (such as anthocyanidins, flavanols, flavanones, flavonols, isoflavones and proanthocyanidins) with respiratory outcomes (FVC, FEV_1/FVC% and FEV_1/FVC<LLN). These findings are inconsistent with other studies where a

higher intake of anthocyanin reduces age-related lung function decline (27), higher intake of pro-anthocyanidins is associated with a lower risk of airway obstruction (FEV1/FVC < LLN) (25), catechins intake is positively associated with lung function (28), and a lower habitual intakes of isoflavones are observed among COPD patients (24). Inconsistency of findings across studies may be explained by the discrepancy of studies in terms of mainly; (i) study setting and design such as multicenter, cross-sectional, case-control, prospective/ longitudinal, high vs low middle income countries (ii) exposure ascertainment including number of food items, dietary assessment tool, choice of food composition tables, and categorization approaches, and (iii) outcome assessment (objective spirometric vs clinical diagnosis).

To our best knowledge this study is the first multinational population-based study that address low-middle income countries where there is a lack of similar studies. It uses a standardized and validated food frequency questionnaire across all sites. This study, however, has limitations such as nature of cross-sectional study and FFQs: In the former, it is impossible to make causal inference and it is also prone for bias due to non-responder and interviewer whereas recall bias and inability to reflect eating pattern of population are major drawbacks to the latter. Small sample size in some sites could decrease statistical power mainly when several covariates included in a model for adjustment.

In conclusion, this study presents a complete description of dietary flavonoid intake in adults participating in BOLD I dietary survey using the latest and expanded version of flavonoid food composition tables. This study has found that there is strong evidence on the association of flavones intake with chronic airflow obstruction, while no associations were found between other subclasses and respiratory outcomes. Further research is highly suggested to elucidate the inconsistency across similar studies.

4.5. References

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Table 4.1 General characteristics on socio-demographics, comorbidities, and respiratory outcomes across BOLD I site participating in the dietary survey (N = 3925)

Characteristics	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Age, years	54.3 (10.7)	56.0 (10.7)	51.9 (10.1)	52.7 (9.1)	54.7 (11.6)	63.6 (9.3)	45.8 (4.7)	54.5 (10.6)
Sex								
Male	1,617 (41%)	399 (44%)	72 (46%)	338 (34%)	414 (40%)	46 (43%)	50 (45%)	298 (50%)
Female	2,308 (59%)	518 (56%)	83 (54%)	666 (66%)	622 (60%)	61 (57%)	61 (55%)	297 (50%)
Educational Level								
None	669 (17%)	541 (59%)	72 (46%)	2 (0.2%)	46 (4.4%)	0 (0%)	3 (2.7%)	5 (0.8%)
Primary or Middle School	1,061 (27%)	252 (27%)	39 (25%)	190 (19%)	329 (32%)	10 (9.3%)	16 (14%)	225 (38%)
High or Some College School	1,702 (43%)	71 (7.7%)	38 (25%)	714 (71%)	521 (50%)	63 (59%)	75 (68%)	220 (37%)
Four Year College	492 (13%)	53 (5.8%)	6 (3.9%)	98 (9.8%)	139 (13%)	34 (32%)	17 (15%)	145 (24%)
Missing	1	0	0	0	1	0	0	0
Years of fulltime education	8.4 (4.5)	3.7 (5.1)	4.7 (4.8)	9.6 (1.3)	9.6 (1.9)	13.8 (3.5)	11.2 (5.8)	11.1 (3.9)
Missing	1	1	0	0	0	0	0	0
Cigarette Smoking Status								
current smoker	634 (16%)	74 (8.1%)	24 (15%)	214 (21%)	152 (15%)	22 (21%)	8 (7.2%)	140 (24%)
Ex-Smoker	497 (13%)	157 (17%)	22 (14%)	95 (9.5%)	90 (8.7%)	49 (46%)	0 (0%)	84 (14%)
Never Smoker	2,794 (71%)	686 (75%)	109 (70%)	695 (69%)	794 (77%)	36 (34%)	103 (93%)	371 (62%)
pack years of smoking	7.1 (16.4)	5.9 (14.5)	7.2 (22.2)	7.2 (16.1)	4.3 (11.1)	17.9 (27.2)	1.0 (3.8)	13.0 (21.6)
Missing	1	1	0	0	0	0	0	0
Have you ever smoked cigarettes?								
Yes	1,131 (29%)	231 (25%)	46 (30%)	309 (31%)	242 (23%)	71 (66%)	8 (7.2%)	224 (38%)
No	2,794 (71%)	686 (75%)	109 (70%)	695 (69%)	794 (77%)	36 (34%)	103 (93%)	371 (62%)
Anyone living in home smoked cigarette/pipe/cigar past 2 weeks?								
Yes	445 (11%)	124 (14%)	12 (7.7%)	70 (7.0%)	38 (3.7%)	14 (13%)	0 (0%)	187 (31%)
No	3,480 (89%)	793 (86%)	143 (92%)	934 (93%)	998 (96%)	93 (87%)	111 (100%)	408 (69%)
Wealth Index in Adulthood	6.6 (2.0)	7.4 (1.7)	7.5 (1.2)	6.1 (1.6)	5.1 (1.2)	NA (NA)	NA (NA)	8.8 (1.5)
Missing	219	0	0	1	0	107	111	0
Wealth Score during Childhood	1.5 (1.7)	0.8 (1.5)	1.1 (1.1)	2.2 (1.9)	1.9 (1.7)	NA (NA)	NA (NA)	1.0 (1.2)
Missing	517	8	11	77	200	107	111	3

Table 4.1 … Continued

Characteristics	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
BMI	27.6 (5.3)	27.9 (5.3)	25.9 (5.5)	28.3 (5.7)	26.9 (5.0)	27.9 (5.1)	25.8 (4.5)	28.0 (4.9)
Heart disease								
Yes	386 (9.8%)	61 (6.7%)	7 (4.5%)	157 (16%)	123 (12%)	11 (10%)	0 (0%)	27 (4.5%)
No	3,539 (90%)	856 (93%)	148 (95%)	847 (84%)	913 (88%)	96 (90%)	111 (100%)	568 (95%)
Hypertension								
Yes	1,005 (26%)	320 (35%)	56 (36%)	289 (29%)	161 (16%)	37 (35%)	2 (1.8%)	140 (24%)
No	2,920 (74%)	597 (65%)	99 (64%)	715 (71%)	875 (84%)	70 (65%)	109 (98%)	455 (76%)
Diabetes								
Yes	256 (6.5%)	127 (14%)	18 (12%)	51 (5.1%)	9 (0.9%)	13 (12%)	0 (0%)	38 (6.4%)
No	3,669 (93%)	790 (86%)	137 (88%)	953 (95%)	1,027 (99%)	94 (88%)	111 (100%)	557 (94%)
Stroke								
Yes	35 (0.9%)	1 (0.1%)	0 (0%)	15 (1.5%)	13 (1.3%)	3 (2.8%)	0 (0%)	3 (0.5%)
No	3,890 (99%)	916 (100%)	155 (100%)	989 (99%)	1,023 (99%)	104 (97%)	111 (100%)	592 (99%)
Tuberculosis								
Yes	48 (1.2%)	14 (1.5%)	1 (0.6%)	13 (1.3%)	8 (0.8%)	8 (7.5%)	0 (0%)	4 (0.7%)
No	3,877 (99%)	903 (98%)	154 (99%)	991 (99%)	1,028 (99%)	99 (93%)	111 (100%)	591 (99%)
hospitalized breathing problems prior age 10?								
Yes	73 (1.9%)	7 (0.8%)	4 (2.6%)	41 (4.1%)	14 (1.4%)	5 (4.7%)	0 (0%)	2 (0.3%)
No	3,540 (90%)	904 (99%)	150 (97%)	913 (91%)	977 (94%)	101 (94%)	111 (100%)	384 (65%)
Don't Know	312 (7.9%)	6 (0.7%)	1 (0.6%)	50 (5.0%)	45 (4.3%)	1 (0.9%)	0 (0%)	209 (35%)
Family diagnostic history of emphysema, COPD								
Yes	244 (6.2%)	86 (9.4%)	17 (11%)	71 (7.1%)	20 (1.9%)	23 (21%)	0 (0%)	27 (4.5%)
No	3,681 (94%)	831 (91%)	138 (89%)	933 (93%)	1,016 (98%)	84 (79%)	111 (100%)	568 (95%)
post-BD FEV1 (ml)	2,629.9 (745.4)	2,604.2 (725.7)	1,930.8 (667.0)	2,630.4 (700.3)	2,712.0 (705.2)	2,336.2 (712.3)	1,927.7 (492.2)	2,825.4 (796.0)
Missing	562	156	45	119	177	13	28	24
post-BD FVC (ml)	3,380.9 (902.1)	3,327.2 (871.4)	2,564.3 (741.6)	3,404.5 (872.6)	3,480.5 (882.8)	3,336.5 (872.4)	2,339.1 (588.6)	3,578.8 (900.1)

Table 4.1 … Continued

Characteristics	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Missing	594	162	48	124	192	14	29	25
post-BD FEV1/FVC%	77.8 (8.4)	78.1 (8.3)	75.6 (12.9)	77.4 (8.2)	78.0 (7.2)	70.5 (11.0)	81.9 (3.9)	78.8 (8.8)
Missing	608	164	49	127	198	14	29	27
Chronic Airflow Obstruction								
NO	3,009 (90%)	681 (90%)	80 (75%)	790 (90%)	781 (93%)	70 (65%)	82 (100%)	525 (92%)
Yes	322 (9.7%)	72 (9.6%)	26 (25%)	87 (9.9%)	57 (6.8%)	37 (35%)	0 (0%)	43 (7.6%)
Missing	594	164	49	127	198	0	29	27
GOLD COPD staging								
No COPD	3,009 (90%)	681 (90%)	80 (75%)	790 (90%)	781 (93%)	70 (65%)	82 (100%)	525 (92%)
Mild COPD	101 (3.0%)	20 (2.7%)	0 (0%)	21 (2.4%)	31 (3.7%)	15 (14%)	0 (0%)	14 (2.5%)
Moderate, Sever and very sever COPD	221 (6.6%)	52 (6.9%)	26 (25%)	66 (7.5%)	26 (3.1%)	22 (21%)	0 (0%)	29 (5.1%)
Missing	594	164	49	127	198	0	29	27
Spirometric Restriction								
NO	2,743 (82%)	602 (80%)	23 (21%)	773 (88%)	767 (91%)	88 (82%)	11 (13%)	479 (84%)
Yes	602 (18%)	153 (20%)	84 (79%)	107 (12%)	77 (9.1%)	19 (18%)	71 (87%)	91 (16%)
Missing	580	162	48	124	192	0	29	25

[1]Mean (SD); n (%)

Table 4.2 Dietary Intake of participants in the BOLD I survey, by center (N = 3925)

Estimated daily food and nutrient intake	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Cereals (g)	28.0 (25.0, 33.0)	39.0 (36.0, 44.0)	32.0 (27.5, 36.5)	26.0 (26.0, 29.0)	28.0 (26.0, 29.0)	25.0 (21.0, 29.0)	24.0 (20.0, 28.0)	19.0 (18.0, 21.0)
Nuts (g)	7.0 (4.0, 8.0)	11.0 (8.0, 15.0)	10.0 (7.0, 14.0)	4.0 (4.0, 8.0)	8.0 (6.0, 8.0)	8.0 (5.0, 10.0)	7.0 (7.0, 7.5)	1.0 (1.0, 2.0)
Legumes (g)	10.0 (8.0, 17.0)	19.0 (15.0, 23.0)	30.0 (26.0, 36.0)	8.0 (8.0, 10.0)	10.0 (8.0, 12.0)	22.0 (18.0, 25.0)	32.0 (31.0, 32.0)	3.0 (3.0, 3.0)
Vegetables total (g)	73.0 (62.0, 86.0)	95.0 (85.0, 103.0)	71.0 (63.5, 82.0)	76.0 (67.0, 83.0)	60.0 (52.0, 69.0)	84.0 (69.5, 97.0)	84.0 (80.0, 90.5)	65.0 (58.0, 73.0)
Fruits total (g)	60.0 (49.0, 73.0)	74.0 (65.0, 87.0)	58.0 (52.0, 66.0)	63.0 (53.0, 75.0)	48.0 (44.0, 56.0)	58.0 (47.0, 73.5)	57.0 (54.0, 58.0)	59.0 (51.0, 70.0)
Tea (g)	11.0 (9.0, 12.0)	14.0 (10.0, 19.0)	9.0 (9.0, 10.0)	11.0 (10.0, 11.0)	11.0 (10.0, 11.0)	12.0 (10.0, 15.0)	10.0 (10.0, 10.0)	4.0 (4.0, 7.0)
Wine (g)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 4.0)	0.0 (0.0, 0.0)	8.0 (4.0, 13.0)	4.0 (4.0, 4.0)	0.0 (0.0, 8.0)
Alcohol Intake(g)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	6.7 (0.0, 18.3)	0.0 (0.0, 0.0)	0.0 (0.0, 17.7)
Total fats (g)	93.2 (70.8, 122.4)	117.4 (89.7, 153.0)	56.6 (38.6, 77.3)	101.4 (80.4, 125.3)	93.3 (78.3, 119.7)	78.4 (56.6, 98.8)	50.6 (45.7, 54.2)	71.0 (58.4, 86.6)

Table 4.2 … Continued

Estimated daily food and nutrient intake	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Saturated FA Intake(g)	31.1 (22.0, 44.3)	37.2 (27.4, 49.4)	14.4 (8.7, 21.6)	35.7 (26.6, 46.4)	32.2 (26.6, 47.0)	28.0 (21.1, 38.1)	13.4 (12.2, 15.2)	20.1 (15.4, 29.3)
n6 PUFA (mg))	9.3 (6.0, 12.5)	7.4 (5.2, 11.4)	2.2 (1.4, 8.0)	11.1 (9.3, 16.1)	9.1 (5.5, 11.0)	4.5 (3.0, 6.9)	6.2 (6.2, 7.6)	9.6 (8.2, 15.9)
n3 PUFA (mg)	1.0 (0.5, 1.6)	1.7 (1.2, 2.3)	0.5 (0.4, 0.8)	0.9 (0.6, 1.4)	1.3 (0.8, 1.6)	1.2 (0.8, 1.7)	0.1 (0.1, 0.2)	0.4 (0.3, 0.5)
MUFA (g)	31.2 (23.2, 40.6)	44.8 (34.4, 57.4)	15.8 (10.3, 22.5)	32.2 (24.5, 40.5)	31.1 (25.0, 37.2)	28.8 (21.0, 35.3)	13.3 (12.0, 14.4)	23.4 (19.3, 28.1)
PUFAs (g)	17.6 (13.1, 22.3)	19.3 (14.3, 26.0)	10.4 (5.5, 17.2)	20.3 (16.2, 25.3)	17.2 (13.1, 21.2)	10.9 (7.7, 14.7)	13.0 (11.8, 13.8)	14.5 (11.1, 20.0)
Trans-fatty acids	1.2 (0.7, 1.9)	1.1 (0.8, 1.5)	0.4 (0.2, 0.7)	1.8 (1.2, 2.3)	1.6 (1.1, 2.4)	1.0 (0.7, 1.4)	0.3 (0.3, 0.3)	0.4 (0.3, 0.6)
Cholesterol (mg)	302.0 (204.6, 422.6)	435.2 (296.1, 574.5)	152.9 (105.7, 217.2)	355.2 (260.1, 449.6)	308.0 (221.0, 362.8)	259.3 (200.5, 328.3)	174.5 (134.0, 181.8)	193.9 (146.7, 249.3)
Magnesium (mg)	360.8 (279.2, 449.8)	521.9 (405.1, 664.8)	282.5 (208.1, 362.9)	383.7 (318.0, 458.4)	336.3 (285.3, 384.6)	343.8 (251.8, 422.5)	387.3 (358.9, 450.4)	215.3 (174.4, 269.3)

Table 4.2 … Continued

Estimated daily food and nutrient intake	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Phosphorus (mg)	1,582.1 (1,138.5, 2,059.1)	2,018.1 (1,579.9, 2,522.3)	1,025.4 (801.3, 1,305.4)	1,690.8 (1,388.0, 2,094.4)	1,742.1 (1,356.2, 2,045.6)	1,524.4 (1,135.7, 1,840.5)	725.2 (647.3, 884.0)	912.9 (757.7, 1,071.5)
Copper (mg)	1.5 (1.2, 1.9)	2.1 (1.6, 2.7)	1.2 (0.9, 1.6)	1.7 (1.4, 2.1)	1.4 (1.2, 1.6)	1.2 (0.9, 1.6)	1.3 (1.2, 1.4)	0.8 (0.6, 1.0)
Zinc (mg)	247.7 (11.3, 480.1)	479.4 (473.3, 486.5)	7.1 (5.4, 9.2)	478.4 (261.9, 486.9)	15.9 (13.6, 250.9)	9.6 (7.1, 11.8)	5.0 (4.4, 6.1)	6.6 (5.4, 9.1)
Selenium (µg)	58.2 (39.7, 77.9)	84.0 (63.8, 105.9)	40.6 (30.6, 55.5)	68.8 (54.4, 84.4)	55.9 (44.3, 62.3)	59.3 (45.1, 77.8)	31.5 (29.0, 42.6)	28.7 (23.4, 34.2)
Retinol (µg)	358.0 (228.9, 547.1)	314.0 (210.0, 447.1)	246.5 (137.7, 378.1)	370.8 (253.3, 549.6)	546.0 (351.7, 793.9)	415.9 (286.8, 552.3)	175.9 (156.2, 201.0)	274.4 (167.4, 374.6)
β-Carotene (µg)	5,571.9 (2,860.9, 9,647.6)	6,839.7 (4,700.9, 9,650.3)	3,462.7 (2,375.9, 5,440.0)	9,778.1 (5,177.1, 13,104.6)	3,628.8 (2,372.0, 8,666.9)	5,452.2 (2,750.7, 7,808.5)	4,889.5 (3,826.2, 5,963.1)	2,572.1 (1,902.6, 3,928.8)
Vitamin D (µg)	2.8 (1.8, 4.3)	5.6 (3.7, 7.4)	1.6 (1.1, 2.2)	3.5 (2.5, 4.5)	2.4 (1.7, 3.0)	3.9 (2.6, 5.6)	1.4 (1.1, 1.6)	1.6 (1.1, 2.1)
Vitamin E (mg)	13.3 (10.1, 17.3)	13.9 (10.6, 18.9)	8.0 (4.2, 13.1)	16.8 (14.0, 20.4)	11.9 (9.0, 14.2)	9.8 (7.2, 12.3)	11.0 (10.1, 12.2)	12.8 (9.6, 16.5)

Table 4.2 … Continued

Estimated daily food and nutrient intake	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Vitamin C (mg)	193.3 (108.0, 317.6)	335.8 (230.3, 464.8)	128.4 (90.3, 195.7)	299.5 (203.6, 374.7)	98.4 (62.4, 159.4)	165.2 (113.4, 257.0)	164.8 (149.5, 187.7)	135.7 (101.6, 189.7)
Total Flavonoids (mg)	903.0 (485.3, 1,399.1)	728.7 (382.3, 1,095.1)	803.5 (717.4, 1,144.0)	1,579.1 (1,058.2, 1,793.0)	1,328.1 (726.7, 1,375.0)	871.4 (558.2, 1,202.9)	804.1 (778.6, 945.7)	273.3 (200.4, 374.8)
Anthocyanidins (mg)	32.1 (17.6, 67.6)	61.4 (30.6, 92.2)	14.9 (10.4, 22.0)	55.5 (29.4, 96.2)	17.3 (15.1, 30.4)	32.0 (19.2, 57.0)	22.3 (17.9, 26.9)	29.5 (21.3, 47.5)
Flavanol Monomers (mg)	199.7 (95.1, 327.8)	358.0 (92.3, 512.4)	157.7 (149.7, 296.2)	321.3 (187.3, 347.3)	296.6 (151.1, 301.8)	179.8 (86.7, 282.8)	154.8 (154.6, 155.7)	20.1 (11.9, 40.8)
Flavanol polymers (mg)	447.9 (3.0, 895.9)	3.0 (0.0, 97.3)	447.9 (447.9, 449.2)	895.9 (447.9, 895.9)	895.9 (447.9, 895.9)	447.9 (176.0, 452.4)	447.9 (447.9, 447.9)	0.0 (0.0, 0.2)
Total flavanols (mg)	608.1 (156.8, 1,197.0)	394.5 (100.4, 721.2)	606.1 (597.7, 952.1)	1,211.1 (633.4, 1,234.7)	1,192.4 (599.0, 1,197.2)	605.9 (281.4, 715.5)	602.8 (602.5, 603.6)	20.7 (12.0, 55.5)
Flavanones (mg)	16.9 (8.3, 42.8)	45.5 (25.4, 57.2)	6.5 (3.8, 11.6)	9.4 (3.4, 15.3)	12.8 (7.2, 17.7)	34.2 (11.9, 70.6)	10.7 (6.1, 16.4)	46.5 (37.2, 73.2)

Table 4.2 … Continued

Estimated daily food and nutrient intake	Overall N = 3,925[1]	Morocco (Fes) N = 917[1]	Pakistan (Karachi) N = 155[1]	Kyrgyzstan (Chui) N = 1,004[1]	Kyrgyzstan (Naryn) N = 1,036[1]	UK (London) N = 107[1]	India (Mysore) N = 111[1]	Albania (Tirana) N = 595[1]
Flavones (mg)	3.8 (1.9, 6.5)	7.4 (5.7, 10.0)	4.6 (3.2, 6.4)	5.3 (3.6, 7.2)	1.7 (1.0, 2.8)	3.0 (1.9, 5.6)	3.1 (2.3, 5.3)	1.9 (1.4, 3.0)
Flavonols (mg)	63.4 (49.0, 90.2)	82.9 (62.8, 107.8)	84.3 (63.9, 111.2)	87.0 (63.9, 98.0)	50.8 (48.3, 59.6)	58.6 (36.6, 80.5)	90.5 (69.9, 99.6)	45.6 (38.9, 53.5)
Isoflavones (mg)	0.4 (0.2, 0.5)	0.4 (0.2, 0.8)	0.2 (0.1, 1.4)	0.3 (0.2, 0.5)	0.4 (0.2, 0.4)	3.0 (0.3, 18.3)	2.5 (0.6, 2.6)	0.3 (0.3, 0.5)
Proanthocyanidins (mg)	109.0 (67.5, 211.3)	102.7 (67.1, 186.2)	62.8 (46.2, 89.1)	266.1 (172.0, 353.3)	73.4 (59.7, 95.6)	140.8 (77.1, 212.9)	72.4 (63.6, 203.2)	107.5 (65.9, 142.7)
Chalcones (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Dihydrochalcones (mg)	2.6 (0.9, 6.0)	2.6 (0.9, 6.0)	0.9 (0.4, 2.6)	6.0 (2.6, 6.0)	0.9 (0.4, 1.1)	2.6 (0.9, 4.7)	0.4 (0.4, 0.4)	4.7 (2.6, 6.0)
Dihydroflavonols (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.3 (0.0, 1.8)	0.0 (0.0, 0.0)	0.0 (0.0, 0.6)
Gallic Acid (mg)	0.5 (0.2, 17.3)	34.6 (17.7, 103.4)	0.1 (0.1, 0.2)	0.6 (0.2, 1.1)	0.1 (0.1, 0.4)	2.2 (0.8, 5.6)	17.6 (0.5, 17.6)	0.5 (0.2, 2.5)

[1]Median (IQR)

Table 4.3 major food sources of dietary flavonoids in adults participating in BOLD I dietary survey

	Total Flavonoids	Anthocyanidins	Flavanols	Flavanones	Flavones	Flavonols	Isoflavone	Proanthocyanidin
BOLD Sites								
Bread and rolls							8%	
Breakfast and other cereals								2%
Chocolate							9%	4%
Fruit juices				21%				
Fruits	19%	23%	3%	70%	11%	9%		80%
Legumes					2%		19%	
Soya							50%	
Other milk products							2%	
Tea/Coffee	70%		97%	4%	4%	33%	9%	12%
Vegetables excluding potatoes	8%	74%		3%	82%	55%		
Morocco (Fes)								
Fruit juices				15%				
Fruits	25%	23%		76%	10%	10%		85%
Legumes							27%	
Soya milk							54%	
Tea/Coffee	57%		94%	5%	7%	19%	11%	9%
Vegetables excluding potatoes	14%	74%			82%	67%		
Pakistan (Karachi)								
Fruits	9%	17%		89%	5%			64%
Legumes					18%		91%	
Nuts								5%

Table 4.3 … Continued

	Total Flavonoids	Anthocyanidins	Flavanols	Flavanones	Flavones	Flavonols	Isoflavone	Proanthocyanidin
Tea/Coffee	81%		98%			29%		29%
Vegetables excluding potatoes	9%	78%			74%	66%		
Kyrgyzstan (Chui)								
Bread and rolls							30%	
Chocolate							47%	
Fruit juices				44%			5%	
Fruits	22%	26%		45%	13%	10%		84%
Legumes							8%	
Tea/Coffee	70%		96%	5%		42%	7%	11%
Vegetables excluding potatoes	7%	74%		5%	83%	47%		
Kyrgyzstan (Naryn)								
Bread and rolls							48%	
Chocolate							35%	6%
Fruit juices				47%			6%	
Fruits	8%	16%		49%	10%	5%		63%
Soya							6%	
Tea/Coffee	86%		99%			58%		29%
Vegetables excluding potatoes		83%			88%	36%		
UK (London)								
Chocolate								10%
Fruit juices				33%				
Fruits	18%	25%		58%	11%	9%		67%
Legumes					7%			

Table 4.3 … Continued

	Total Flavonoids	Anthocyanidins	Flavanols	Flavanones	Flavones	Flavonols	Isoflavone	Proanthocyanidin
Soya							92%	
Tea/Coffee	66%		95%			34%		11%
Vegetables excluding potatoes	6%	52%			77%	52%		
Wine		22%						9%
India (Mysore)								
Breakfast and other cereals	11%				11%			60%
Fruits	7%	12%		67%				25%
Legumes					16%		82%	
Starchy roots or Potatoes		14%						
Tea/Coffee	70%		98%	24%		23%	15%	12%
Vegetables excluding potatoes	10%	73%		7%	70%	74%		
Albania (Tirana)								
Bread and rolls							13%	
Fruit juices				11%				
Fruits	60%	25%	26%	83%	24%	17%		95%
Soya							20%	
Other milk products							10%	
Tea/Coffee	14%		69%	5%			53%	
Vegetables excluding potatoes	21%	69%			73%	77%		
Wine		6%						

Table 4.4 Dietary intake by CAO status (below LLN) in the BOLD I survey (N = 3,249)

Estimated daily food and nutrient intake	Morocco (Fes)		Pakistan (Karachi)		Kyrgyzstan (Chui)		Kyrgyzstan (Naryn)		UK (London)		Albania (Tirana)	
	NO N = 681[1]	Yes N = 72[1]	NO N = 80[1]	Yes N = 26[1]	NO N = 790[1]	Yes N = 87[1]	NO N = 781[1]	Yes N = 57[1]	NO N = 70[1]	Yes N = 37[1]	NO N = 525[1]	Yes N = 43[1]
Cereals (g)	40.0 (36.0, 44.0)	38.0 (34.0, 42.2)	31.0 (27.0, 36.0)	35.0 (28.5, 37.0)	26.0 (26.0, 29.0)	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	28.0 (26.0, 29.0)	24.0 (20.2, 29.0)	26.0 (23.0, 28.0)	19.0 (18.0, 21.0)	19.0 (19.0, 21.0)
Nuts (g)	12.0 (8.0, 15.0)	10.0 (8.0, 13.0)	11.0 (7.0, 14.0)	8.0 (7.0, 11.8)	4.0 (4.0, 8.0)	4.0 (4.0, 7.5)	8.0 (6.0, 8.0)	6.0 (4.0, 8.0)	8.0 (6.0, 10.0)	6.0 (4.0, 8.0)	1.0 (1.0, 2.0)	1.0 (1.0, 2.0)
Legumes (g)	20.0 (15.0, 23.0)	19.0 (14.8, 23.0)	28.0 (25.0, 35.2)	31.0 (26.2, 36.5)	8.0 (8.0, 10.0)	8.0 (8.0, 10.0)	10.0 (8.0, 12.0)	9.0 (8.0, 12.0)	22.0 (19.2, 25.8)	21.0 (17.0, 23.0)	3.0 (3.0, 3.0)	3.0 (3.0, 3.0)
Vegetables total (g)	95.0 (86.0, 103.0)	87.5 (82.0, 98.5)	72.5 (64.0, 85.0)	70.5 (64.0, 74.5)	75.0 (67.0, 83.0)	75.0 (66.5, 83.5)	60.0 (52.0, 69.0)	64.0 (53.0, 69.0)	84.0 (73.0, 97.0)	83.0 (65.0, 92.0)	65.0 (58.0, 73.0)	64.0 (57.5, 75.0)
Fruits total (g)	75.0 (65.0, 89.0)	72.0 (65.0, 79.0)	60.0 (52.8, 69.2)	59.0 (52.2, 64.0)	63.0 (53.0, 75.0)	58.0 (50.5, 74.5)	48.0 (44.0, 56.0)	48.0 (44.0, 55.0)	64.5 (53.0, 77.8)	49.0 (40.0, 65.0)	59.0 (51.0, 71.0)	52.0 (46.5, 62.5)
Tea (g)	14.0 (10.0, 19.0)	14.0 (10.0, 19.0)	9.0 (9.0, 10.0)	9.0 (9.0, 10.0)	11.0 (10.0, 11.0)	11.0 (10.5, 11.0)	11.0 (10.0, 11.0)	11.0 (10.0, 11.0)	12.0 (11.0, 16.0)	11.0 (9.0, 13.0)	4.0 (4.0, 7.0)	4.0 (4.0, 5.5)
Wine (g)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 4.0)	0.0 (0.0, 4.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	8.0 (4.0, 13.8)	8.0 (4.0, 12.0)	0.0 (0.0, 8.0)	5.0 (0.0, 7.5)
Alcohol Intake(g)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 1.0)	0.0 (0.0, 1.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	5.6 (0.0, 20.0)	8.1 (0.0, 16.2)	0.0 (0.0, 16.7)	12.6 (0.0, 18.7)
Total fats (g)	120.1 (90.4, 155.6)	103.1 (86.1, 138.6)	54.4 (36.3, 76.1)	62.2 (40.5, 82.0)	101.0 (81.6, 125.1)	95.6 (72.0, 117.2)	94.0 (78.6, 120.9)	88.7 (76.1, 107.9)	81.1 (61.9, 100.2)	69.2 (51.9, 89.8)	71.6 (58.4, 89.1)	66.6 (60.8, 76.2)
Saturated FA Intake(g)	37.9 (27.9, 50.5)	32.8 (25.3, 43.3)	13.6 (8.1, 21.0)	18.7 (9.9, 22.9)	35.8 (27.1, 46.4)	32.4 (24.3, 42.3)	32.2 (26.6, 47.2)	30.6 (25.9, 37.4)	29.4 (21.5, 37.8)	26.6 (21.0, 38.2)	20.7 (15.5, 29.9)	17.1 (13.9, 22.2)

Table 4.4 … Continued

Estimated daily food and nutrient intake	Morocco (Fes) NO N = 681[1]	Morocco (Fes) Yes N = 72[1]	Pakistan (Karachi) NO N = 80[1]	Pakistan (Karachi) Yes N = 26[1]	Kyrgyzstan (Chui) NO N = 790[1]	Kyrgyzstan (Chui) Yes N = 87[1]	Kyrgyzstan (Naryn) NO N = 781[1]	Kyrgyzstan (Naryn) Yes N = 57[1]	UK (London) NO N = 70[1]	UK (London) Yes N = 37[1]	Albania (Tirana) NO N = 525[1]	Albania (Tirana) Yes N = 43[1]
n6 PUFA (mg))	7.5 (5.3, 11.7)	7.6 (5.2, 11.0)	2.0 (1.4, 6.3)	2.9 (1.3, 13.7)	11.1 (9.4, 16.1)	10.3 (8.6, 16.1)	9.2 (5.5, 11.1)	9.0 (5.5, 10.4)	4.5 (3.2, 7.2)	4.4 (2.8, 6.0)	9.6 (8.1, 15.9)	10.5 (8.7, 15.8)
n3 PUFA (mg)	1.7 (1.2, 2.3)	1.7 (1.2, 2.0)	0.5 (0.4, 0.8)	0.6 (0.4, 0.8)	0.9 (0.6, 1.4)	0.8 (0.5, 1.2)	1.3 (0.8, 1.6)	1.1 (0.8, 1.5)	1.3 (0.9, 1.8)	1.1 (0.7, 1.6)	0.4 (0.3, 0.6)	0.3 (0.2, 0.5)
MUFA (g)	45.1 (34.6, 59.1)	40.1 (33.8, 52.0)	15.5 (9.7, 21.6)	18.7 (9.8, 22.8)	32.1 (25.0, 40.5)	29.6 (22.0, 38.4)	31.2 (25.0, 37.5)	30.3 (24.9, 36.1)	30.8 (23.4, 37.5)	25.5 (17.9, 31.6)	23.8 (19.5, 28.4)	21.5 (18.1, 25.8)
PUFAs (g)	19.5 (14.7, 26.9)	17.5 (14.2, 23.3)	8.6 (5.3, 16.0)	10.6 (4.3, 18.6)	20.2 (16.3, 25.1)	19.7 (14.5, 25.3)	17.3 (13.0, 21.4)	17.2 (14.2, 20.9)	11.2 (8.8, 15.0)	9.9 (7.5, 11.9)	14.5 (11.0, 20.0)	16.7 (12.2, 19.5)
Trans-fatty acids	1.2 (0.8, 1.5)	1.1 (0.7, 1.4)	0.4 (0.2, 0.7)	0.6 (0.3, 0.8)	1.8 (1.3, 2.3)	1.9 (1.2, 2.1)	1.6 (1.1, 2.5)	1.3 (1.1, 2.2)	1.1 (0.7, 1.5)	1.0 (0.7, 1.3)	0.4 (0.3, 0.6)	0.4 (0.3, 0.5)
Cholesterol (mg)	434.8 (296.3, 577.2)	438.6 (277.8, 566.3)	160.6 (108.1, 239.3)	150.8 (89.5, 194.6)	358.8 (266.0, 448.4)	345.7 (249.3, 432.3)	310.5 (221.1, 369.2)	276.6 (209.7, 364.7)	276.9 (209.5, 339.5)	240.5 (191.4, 314.6)	195.9 (147.0, 251.9)	186.1 (149.2, 243.2)
Magnesium (mg)	531.5 (409.7, 676.8)	453.5 (363.4, 574.9)	271.5 (200.7, 391.7)	289.1 (215.2, 357.8)	384.1 (321.8, 457.8)	366.0 (305.3, 436.5)	335.0 (283.7, 384.7)	326.6 (288.4, 376.2)	354.3 (282.4, 438.1)	308.2 (236.4, 389.3)	218.9 (177.1, 274.5)	195.4 (161.4, 233.1)
Phosphorus (mg)	2,028.1 (1,594.1, 2,546.2)	1,794.6 (1,470.1, 2,254.2)	985.8 (826.3, 1,406.4)	1,083.9 (855.5, 1,289.1)	1,687.0 (1,398.4, 2,091.2)	1,608.4 (1,225.8, 2,059.6)	1,720.3 (1,347.3, 2,053.2)	1,665.1 (1,277.5, 2,048.6)	1,573.5 (1,193.8, 1,868.7)	1,365.6 (989.3, 1,724.4)	923.3 (759.2, 1,084.5)	817.8 (738.4, 973.5)
Copper (mg)	2.1 (1.6, 2.8)	1.9 (1.4, 2.3)	1.2 (0.9, 1.6)	1.3 (0.9, 1.6)	1.7 (1.4, 2.1)	1.7 (1.3, 2.1)	1.4 (1.2, 1.6)	1.4 (1.3, 1.6)	1.3 (1.0, 1.6)	1.1 (0.8, 1.3)	0.8 (0.6, 1.0)	0.7 (0.6, 0.9)
Zinc (mg)	479.5 (473.2, 486.9)	476.2 (471.2, 483.6)	6.9 (5.4, 9.1)	7.8 (5.5, 8.9)	478.5 (262.6, 486.6)	477.5 (470.4, 486.1)	15.9 (13.4, 249.8)	15.9 (13.1, 475.3)	9.8 (7.9, 12.1)	9.2 (6.6, 10.7)	6.7 (5.4, 9.1)	6.2 (4.8, 8.5)
Selenium (µg)	84.8 (64.3, 106.9)	77.6 (60.9, 94.6)	39.6 (29.9, 55.8)	35.4 (23.4, 48.1)	69.0 (54.8, 84.3)	68.6 (51.1, 83.7)	55.9 (44.3, 62.2)	52.6 (40.1, 61.0)	60.6 (48.2, 81.7)	56.3 (40.2, 68.5)	29.0 (23.4, 34.5)	25.9 (23.7, 30.1)

Table 4.4 … Continued

Estimated daily food and nutrient intake	Morocco (Fes)		Pakistan (Karachi)		Kyrgyzstan (Chui)		Kyrgyzstan (Naryn)		UK (London)		Albania (Tirana)	
	NO	Yes	NO	Yes	NO	Yes	NO	Yes	NO	Yes	NO	Yes
	N = 681[1]	N = 72[1]	N = 80[1]	N = 26[1]	N = 790[1]	N = 87[1]	N = 781[1]	N = 57[1]	N = 70[1]	N = 37[1]	N = 525[1]	N = 43[1]
Retinol (µg)	316.4 (213.1, 457.7)	283.2 (175.2, 390.2)	263.6 (131.2, 429.2)	267.6 (183.1, 410.6)	377.6 (264.3, 553.1)	329.3 (207.5, 504.9)	550.2 (361.2, 801.2)	442.2 (321.2, 621.0)	414.3 (252.5, 583.5)	415.9 (308.9, 537.1)	278.8 (173.7, 383.6)	204.1 (129.0, 320.0)
β-Carotene (µg)	6,861.0 (4,700.9, 9,560.2)	6,116.1 (4,200.8, 8,314.4)	3,878.0 (2,420.4, 6,214.4)	3,151.3 (2,219.2, 4,125.2)	9,610.7 (5,145.5, 13,041.1)	9,652.1 (5,055.8, 13,060.8)	3,589.4 (2,363.9, 8,403.2)	5,213.6 (2,327.2, 9,434.7)	5,695.9 (2,711.5, 8,240.3)	5,078.6 (2,795.0, 6,325.9)	2,606.8 (1,902.3, 4,086.0)	2,499.4 (1,919.2, 4,041.0)
Vitamin D (µg)	5.5 (3.6, 7.4)	5.5 (3.5, 7.3)	1.7 (1.2, 2.3)	1.5 (1.0, 1.9)	3.5 (2.5, 4.5)	3.4 (2.2, 4.5)	2.5 (1.7, 3.0)	2.2 (1.7, 3.1)	3.9 (2.8, 6.2)	3.2 (2.2, 4.8)	1.7 (1.1, 2.1)	1.6 (1.0, 1.8)
Vitamin E (mg)	14.3 (10.6, 19.1)	12.7 (10.6, 15.8)	6.9 (4.3, 11.5)	8.7 (4.4, 14.8)	16.9 (14.1, 20.2)	15.9 (12.5, 21.0)	11.9 (9.0, 14.2)	11.8 (9.3, 14.8)	10.4 (8.2, 13.0)	8.7 (5.6, 10.9)	12.8 (9.6, 16.5)	14.3 (10.5, 16.0)
Vitamin C (mg)	342.4 (234.1, 463.9)	289.4 (213.6, 391.4)	139.2 (89.5, 211.5)	123.1 (104.1, 194.1)	297.8 (202.5, 369.8)	290.4 (164.6, 370.4)	97.6 (61.6, 158.0)	103.9 (66.5, 197.4)	183.8 (135.5, 289.9)	144.0 (98.4, 215.8)	139.1 (102.7, 191.9)	133.6 (69.1, 160.6)
Total Flavonoids (mg)	735.3 (387.7, 1,096.4)	642.8 (351.3, 999.2)	810.7 (725.1, 1,130.3)	806.4 (708.2, 1,347.3)	1,588.6 (1,063.9, 1,793.7)	1,533.9 (1,027.6, 1,795.0)	1,330.8 (726.8, 1,376.4)	1,340.7 (737.0, 1,382.3)	989.3 (563.2, 1,328.5)	801.7 (513.8, 932.5)	275.4 (201.8, 382.7)	242.1 (170.1, 329.0)
Anthocyanidins (mg)	61.4 (31.5, 92.8)	56.5 (24.7, 89.0)	15.4 (10.8, 26.0)	13.8 (10.7, 20.2)	55.4 (29.4, 95.3)	57.9 (24.6, 91.2)	17.3 (15.2, 30.4)	17.9 (15.0, 30.4)	35.5 (21.4, 60.1)	25.9 (17.6, 54.1)	29.8 (21.7, 47.4)	29.1 (20.3, 62.1)
Flavanol Monomers (mg)	364.9 (89.7, 510.0)	211.4 (103.6, 479.0)	157.9 (150.1, 295.7)	162.0 (148.2, 296.9)	323.0 (191.6, 349.1)	314.5 (194.8, 337.5)	296.9 (151.2, 302.4)	297.3 (152.7, 301.0)	193.4 (90.5, 290.0)	155.2 (73.3, 261.4)	20.5 (12.1, 41.0)	15.6 (9.9, 31.7)
Flavanol polymers (mg)	3.0 (0.0, 96.2)	3.0 (0.0, 48.0)	447.9 (447.9, 449.6)	447.9 (224.0, 785.4)	895.9 (447.9, 895.9)	895.9 (447.9, 895.9)	895.9 (447.9, 895.9)	895.9 (447.9, 895.9)	447.9 (180.2, 464.1)	447.9 (176.0, 447.9)	0.0 (0.0, 0.2)	0.0 (0.0, 0.0)
Total flavanols (mg)	393.1 (100.0, 716.0)	340.2 (117.9, 677.9)	605.9 (598.0, 806.8)	610.0 (596.2, 1,191.7)	1,213.7 (634.6, 1,238.3)	1,206.7 (631.6, 1,231.5)	1,192.5 (599.1, 1,197.7)	1,193.1 (600.5, 1,196.9)	631.2 (306.3, 832.6)	595.3 (243.7, 627.7)	21.3 (12.2, 55.5)	15.6 (9.9, 31.7)

Table 4.4 … Continued

Estimated daily food and nutrient intake	Morocco (Fes)		Pakistan (Karachi)		Kyrgyzstan (Chui)		Kyrgyzstan (Naryn)		UK (London)		Albania (Tirana)	
	NO	Yes	NO	Yes	NO	Yes	NO	Yes	NO	Yes	NO	Yes
	N = 681[1]	N = 72[1]	N = 80[1]	N = 26[1]	N = 790[1]	N = 87[1]	N = 781[1]	N = 57[1]	N = 70[1]	N = 37[1]	N = 525[1]	N = 43[1]
Flavanones (mg)	45.7 (29.8, 57.4)	44.6 (28.2, 52.3)	6.6 (4.8, 12.4)	6.5 (4.6, 10.1)	10.3 (3.5, 15.7)	6.4 (2.8, 11.7)	12.8 (7.4, 17.7)	12.8 (6.0, 17.8)	38.9 (15.5, 76.0)	18.1 (6.5, 59.8)	47.2 (37.9, 74.9)	38.8 (18.6, 65.7)
Flavones (mg)	7.4 (5.9, 9.9)	7.2 (5.5, 8.4)	4.5 (3.0, 6.4)	4.3 (3.2, 5.3)	5.3 (3.5, 7.0)	4.8 (3.2, 7.0)	1.7 (1.0, 2.8)	2.1 (1.1, 3.2)	3.5 (2.1, 5.9)	2.3 (1.5, 3.6)	2.0 (1.4, 3.0)	1.8 (1.2, 2.8)
Flavonols (mg)	82.0 (62.8, 107.7)	77.9 (60.2, 101.4)	74.8 (63.3, 112.3)	80.4 (63.3, 99.7)	87.3 (64.3, 98.0)	88.7 (56.0, 98.5)	50.5 (48.2, 59.6)	54.5 (48.7, 63.5)	63.1 (40.5, 84.5)	50.6 (32.2, 73.1)	45.6 (39.0, 53.6)	45.0 (38.0, 52.9)
Isoflavones (mg)	0.4 (0.3, 0.9)	0.4 (0.3, 0.7)	0.2 (0.1, 1.0)	0.3 (0.1, 1.8)	0.3 (0.2, 0.5)	0.2 (0.2, 0.4)	0.4 (0.2, 0.5)	0.3 (0.1, 0.4)	3.4 (0.3, 20.1)	2.8 (0.3, 15.6)	0.3 (0.3, 0.5)	0.3 (0.2, 0.4)
Proanthocyanidins (mg)	107.7 (68.4, 192.7)	96.2 (59.7, 154.9)	66.8 (43.7, 100.5)	68.0 (50.6, 75.6)	266.0 (177.4, 353.3)	223.9 (149.9, 349.1)	73.3 (59.8, 94.4)	75.9 (66.8, 97.7)	165.5 (109.3, 230.6)	97.0 (63.6, 172.7)	108.4 (66.4, 144.5)	78.5 (53.3, 128.8)
Chalcones (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)
Dihydrochalcones (mg)	3.2 (0.9, 6.0)	2.6 (0.9, 4.7)	0.9 (0.4, 2.6)	1.0 (0.4, 2.3)	6.0 (2.6, 6.0)	6.0 (4.7, 6.1)	0.9 (0.4, 1.1)	0.9 (0.6, 2.6)	2.6 (0.9, 5.5)	2.6 (0.4, 4.0)	4.7 (2.6, 6.0)	2.9 (2.6, 5.2)
Dihydroflavonols (mg)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.0 (0.0, 0.0)	0.3 (0.0, 1.8)	0.3 (0.0, 1.7)	0.0 (0.0, 0.6)	0.3 (0.0, 0.4)
Gallic Acid (mg)	34.7 (17.8, 103.5)	25.6 (17.4, 41.1)	0.1 (0.1, 0.2)	0.2 (0.1, 0.2)	0.5 (0.2, 1.0)	0.6 (0.2, 1.1)	0.1 (0.1, 0.4)	0.1 (0.1, 0.2)	2.4 (0.9, 14.8)	1.8 (0.7, 3.5)	0.5 (0.3, 2.6)	0.5 (0.1, 0.9)

[1]Median (IQR)

Table 4.5 summary of meta-analysis on the unadjusted and adjusted associations of daily intake of total flavonoids and subclasses with FVC, FEV1/FVC ratio (%) and Chronic Airflow Obstructions in adults participating in BOLD I dietary survey

Daily Dietary Flavonoid Intake	FVC (ML)				FEV_1/FVC ratio (%)				CHRONIC AIRFLOW OBSTRUCTIONS			
	Unadjusted		Adjusted		Unadjusted		Adjusted		Unadjusted		Adjusted	
	β (95%CI)	I^2	β (95%CI)	I^2	β (95%CI)	I^2	β (95%CI)	I^2	OR (95%CI)	I^2	OR (95%CI)	I^2
Total flavonoids, per 100mg increase	5.99 (-8.10, 20.09)	69.2%	-1.23 (-6.84, 4.38)	0%	0.06 (-0.00, 0.12)	0%	0.01 (-0.06, 0.08)	0%	0.99 (0.96, 1.01)	0%	1.02 (0.99, 1.06)	0%
Anthocyanidins, per 50mg increase	73.06 (-36.94, 183.06)	83.1%	-19.62 (-50.67, 11.42)	0%	-0.03 (-0.50, 0.44)	23.9 %	-0.12 (-0.53, 0.30)	0%	0.99 (0.88, 1.12)	0%	1.06 (0.88, 1.29)	0%
Flavanols, per 100mg increase	-1.61 (-14.11, 10.88)	43.4%	-1.28 (-7.49, 4.93)	0%	0.06 (-0.01, 0.13)	0%	0.03 (-0.04, 0.11)	0%	0.99 (0.96, 1.02)	0%	1.02 (0.98, 1.06)	0%
Flavanones, per 50mg increase	39.81 (-80.97, 160.58)	67.1%	10.30 (-46.19, 66.79)	0%	**0.89 (0.18, 1.60)**	19.2 %	-0.20 (-0.94, 0.53)		**0.74 (0.58, 0.94)**	0%	1.03 (0.69, 1.55)	0%
Flavones, per 10mg increase	83.96 (-196.96, 364.88)	74.6%	-19.62 (-186.72, 147.49)	0%	2.25 (-0.13, 4.62)	66.2 %	0.96 (-1.25, 3.16)	0%	**0.47 (0.26, 0.84)**	18.4%	**0.27 (0.09, 0.81)**	0%
Flavonols, per 50mg increase	7.54 (-132.84, 147.93)	79.8%	-32.67 (-99.20, 33.86)	22.1%	0.35 (-0.17, 0.87)	0%	0.31 (-0.39, 1.02)	0%	0.91 (0.72, 1.16)	10.4%	1.20 (0.85, 1.69)	0%
Isoflavones, per 50 mg increase	8.65 (-446.04, 463.34)	10.3%	739.96 (-529.51, 2009.42)	51.1%	0.33 (-7.32, 7.98)	40.3 %	-2.48 (-8.95, 3.99)	0%	0.06 (0.00, 12.79)	53.2%	0.04 (0.00, 4.90)	0%
Proanthocyanidins, per 50mg increase	19.21 (-9.39, 47.81)	68.0%	2.17 (-29.85, 34.19)	54.7%	0.125 (-0.08, 0.32)	46.9 %	-0.18 (-0.36, 0.01)	0%	0.92 (0.83, 1.02)	53.4%	1.06 (0.91, 1.23)	26.2%

Note: β is a regression coefficient (overall effect size); 95%CI – 95% of Confidence Interval; I^2 between-sites heterogeneity measure; BOLD in red – is with p<0.02

Conclusions

In this thesis, we presented the relationship between dietary flavonoid intake and respiratory outcome. To address this issue, we began by analysing the burden of COPD over the past three decades, which provides a clue to scan the burden in low- and middle-income countries by considering sub-Saharan African countries as a case study. This was followed by examining the extent to which the flavonoid content of selected food items varies based on the choice of FCTs, indicating that improving the flavonoid content estimate could contribute to population-level estimates of daily flavonoid intake. Daily intake of total flavonoids and ten other subclasses was estimated and studied for their associations with respiratory outcomes in adults participating in the BOLD I survey.

COPD remains a major public health burden in Sub-Saharan African (SSA) countries, with the number of cases steadily increasing over the past three decades. Observing the increasing trends of COPD change over the past three decades is important to improve understanding of the current status and progress being made in low- and middle-income countries, particularly in SSA. A heterogeneous distribution of COPD has been observed in sub-Saharan countries informing the importance of other environmental and socio-demographic factors with caution in interpretations where there are very few population-based studies.

After an exhaustive search for FCT with flavonoid data, a comparison of four international food composition tables was conducted and FCTs with flavonoid data from pre-existing tables were excluded. Comparisons were carried out on flavonoid contents of foods that were present between specific tables and the estimated level of agreement between FCTs varied by flavonoid class where some flavonoid subclasses showed moderate to excellent agreement levels among FCTs, while others, mainly total flavonoids had lower levels of agreement. The results inform the implication of a methodological approach that expands harmonization and measurement of flavonoid content of foods across tables in the improvement of flavonoid intake estimates in population-based surveys.

The USDA special databases for flavonoid were expanded for the purpose of improving dietary intake estimation in adults participating in BOLD I dietary survey. Daily dietary flavonoid intake was presented and approximately one-third

of the total variation in the distribution of total flavonoid intake was explained by the variation in between-site, which could suggest that a large portion was observed due to individual variability (within-sites variation). Of the flavonoid subclasses, the variation in the distribution of isoflavone intake was observed uniformly due to the variation between- and within- sites. This finding points to the implication of variation within and between BOLD sites in dietary flavonoid intake and gives an indication of subsequent influence in affecting respiratory outcomes in adults participating in the BOLD-I dietary survey. A meta-analysis with a two-stage approach was introduced and a 10 mg increase in daily flavone intake was inversely associated with chronic airflow obstruction while no relationship was observed with all other flavonoid intakes (total and subclasses). There is no statistical evidence to support the association between dietary flavonoid intake with FVC (ml) and FEV1 / FVC% among adults participating in the BOLD-I survey.

From these conclusions, we recommend further research on (i) comprehensive risk factor assessment, (ii) effect of choice of food composition tables (FCT) on the association between dietary flavonoids and respiratory outcomes, (iii) effect of dietary intake estimate categorization on the association between dietary flavonoids and respiratory outcomes and (iv) a population-based prospective study. Research that translates available evidence into policies and practices such as precision medicine is also highly recommended.

APPENDICES

Appendix A. Supplementary Files for Chapter 2

Appendix Table A.1 Age Standardized prevalence of COPD and YLD in 2019 and percentage change in age-standardized prevalence and YLDs by location and sex.

	Age-standardized Prevalence Rate per 100,000 in 2019 (95%UI)			Percentage Change in age standardized Prevalence rate, 1990–2019			Age-standardized YLDs Rate in 2019 (95%UI)			Percentage Change in age standardized YLDs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Sub-Saharan Africa	1705 (1599 to 1820)	1656 (1550 to 1771)	1769 (1665 to 1879)	-3.3	-5.0	-1.8	205 (171 to 231)	213 (178 to 245)	196 (162 to 225)	-3.3	-4.9	-2.0
Central Sub-Saharan Africa	1943 (1817 to 2076)	2009 (1866 to 2162)	1841 (1720 to 1968)	12.2	11.9	11.1	235 (197 to 269)	261 (215 to 305)	202 (167 to 233)	13.0	12.5	11.6
Eastern Sub-Saharan Africa	1503 (1408 to 1609)	1411 (1320 to 1513)	1616 (1509 to 1728)	-4.7	-6.6	-2.5	183 (153 to 209)	186 (155 to 216)	182 (152 to 208)	-4.2	-6.1	-1.6
Southern Sub-Saharan Africa	2244 (2090 to 2412)	1919 (1773 to 2076)	2771 (2580 to 2980)	-9.7	-11.5	-6.2	288 (239 to 329)	282 (234 to 329)	306 (253 to 353)	-10.6	-12.4	-7.0
Western Sub-Saharan Africa	1618 (1522 to 1721)	1665 (1559 to 1779)	1571 (1481 to 1665)	-4.5	-6.8	-3.3	191 (161 to 216)	202 (169 to 233)	179 (149 to 205)	-4.0	-6.5	-2.7
Angola	1758 (1645 to 1871)	1834 (1702 to 1975)	1656 (1549 to 1771)	1.9	-0.6	3.9	215 (177 to 244)	240 (197 to 282)	183 (149 to 213)	2.9	-0.4	4.0
Benin	1928 (1809 to 2049)	2003 (1868 to 2133)	1856 (1749 to 1974)	1.3	7.2	-4.9	229 (192 to 261)	246 (200 to 286)	211 (172 to 245)	1.8	7.4	-4.1
Botswana	2266 (2127 to 2409)	2113 (1965 to 2254)	2634 (2474 to 2818)	0.0	21.0	-12.6	291 (244 to 332)	306 (254 to 358)	290 (241 to 335)	0.7	18.6	-14.2
Burkina Faso	1452 (1372 to 1534)	1491 (1402 to 1580)	1412 (1327 to 1502)	8.0	4.1	13.2	174 (146 to 198)	185 (151 to 216)	162 (134 to 187)	8.8	4.5	14.9
Burundi	1758 (1653 to 1871)	1609 (1507 to 1718)	1917 (1797 to 2042)	-8.2	-5.7	-12.1	212 (177 to 242)	212 (174 to 247)	214 (176 to 249)	-8.6	-5.4	-11.9
CÃ´te d'Ivoire	1698 (1601 to 1805)	1680 (1576 to 1795)	1728 (1626 to 1836)	-4.5	-2.6	-5.9	201 (168 to 228)	207 (171 to 241)	196 (162 to 226)	-2.9	-1.4	-4.4
Cabo Verde	1514 (1437 to 1598)	1425 (1330 to 1518)	1614 (1525 to 1707)	-11.6	-5.4	-19.7	186 (155 to 210)	193 (158 to 224)	177 (144 to 205)	-12.3	-6.3	-19.9
Cameroon	2216 (2082 to 2360)	2283 (2129 to 2444)	2155 (2024 to 2291)	-1.7	-6.2	3.9	260 (219 to 297)	278 (230 to 326)	242 (199 to 281)	-1.5	-6.1	4.3
Central African Republic	1918 (1786 to 2054)	1846 (1700 to 1996)	1973 (1837 to 2110)	-0.1	-1.1	0.5	231 (192 to 264)	240 (200 to 280)	216 (177 to 253)	0.4	-0.8	0.9
Chad	1680 (1580 to 1784)	1732 (1616 to 1853)	1646 (1548 to 1749)	2.4	5.3	-0.2	198 (166 to 225)	212 (174 to 247)	186 (154 to 216)	1.5	4.4	-0.5
Comoros	1475 (1379 to 1569)	1364 (1274 to 1467)	1621 (1509 to 1728)	-3.0	-2.7	-2.1	181 (151 to 207)	181 (151 to 211)	183 (150 to 213)	-2.7	-2.7	-2.1

Appendix Table A.1 … Continued

	Age-standardized Prevalence Rate per 100,000 in 2019 (95%UI)			Percentage Change in age standardized Prevalence rate, 1990–2019			Age-standardized YLDs Rate in 2019 (95%UI)			Percentage Change in age standardized YLDs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Congo	2069 (1936 to 2209)	2430 (2259 to 2603)	1671 (1555 to 1799)	1.1	11.2	-9.9	253 (209 to 289)	315 (260 to 369)	184 (149 to 214)	1.2	10.9	-9.8
Democratic Republic of the Congo	1999 (1866 to 2146)	2052 (1896 to 2220)	1906 (1771 to 2049)	17.5	16.3	16.7	241 (202 to 276)	266 (219 to 312)	209 (172 to 243)	18.1	17.2	17.4
Equatorial Guinea	1850 (1711 to 1992)	2067 (1898 to 2253)	1546 (1428 to 1663)	8.7	21.4	-8.7	225 (188 to 258)	267 (220 to 313)	169 (138 to 197)	10.3	21.9	-8.2
Eritrea	1814 (1697 to 1940)	1551 (1447 to 1669)	2180 (2025 to 2342)	2.0	4.8	-2.0	219 (181 to 251)	204 (168 to 239)	242 (196 to 283)	2.3	4.6	-1.6
Eswatini	2477 (2348 to 2606)	1976 (1837 to 2122)	3333 (3163 to 3491)	-4.8	-8.3	0.8	314 (262 to 355)	287 (237 to 336)	368 (306 to 422)	-6.5	-9.7	-0.8
Ethiopia	1182 (1068 to 1303)	1136 (1030 to 1252)	1225 (1099 to 1361)	-27.5	-25.3	-30.6	145 (119 to 168)	151 (123 to 178)	139 (115 to 162)	-26.0	-24.1	-28.7
Gabon	1637 (1530 to 1752)	1478 (1372 to 1599)	1828 (1706 to 1953)	-0.6	-6.6	5.8	197 (164 to 224)	193 (159 to 225)	201 (164 to 234)	-1.0	-6.3	5.8
Gambia	2004 (1883 to 2133)	2119 (1976 to 2266)	1902 (1786 to 2022)	5.5	8.9	1.0	237 (197 to 271)	259 (213 to 301)	217 (177 to 251)	5.3	8.4	0.9
Ghana	1734 (1638 to 1833)	1607 (1509 to 1704)	1914 (1799 to 2025)	23.1	5.6	47.8	199 (165 to 224)	178 (147 to 206)	226 (186 to 260)	23.6	5.3	46.8
Guinea	1979 (1859 to 2108)	1981 (1844 to 2120)	1989 (1865 to 2117)	14.3	7.9	21.8	236 (197 to 271)	245 (202 to 287)	228 (187 to 267)	14.0	7.9	21.3
Guinea-Bissau	2032 (1908 to	1992 (1865 to	2092 (1956 to	-0.4	5.3	-5.9	241 (200 to	244 (203 to	237 (192	0.4	5.2	-5.2

Appendix Table A.1 … Continued

	Age-standardized Prevalence Rate per 100,000 in 2019 (95%UI)			Percentage Change in age standardized Prevalence rate, 1990–2019			Age-standardized YLDs Rate in 2019 (95%UI)			Percentage Change in age standardized YLDs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
	2165)	2132)	2234)				275)	284)	to 277)			
Kenya	1730 (1590 to 1893)	1651 (1521 to 1800)	1845 (1693 to 2017)	0.7	-7.6	11.9	211 (174 to 243)	217 (180 to 253)	206 (169 to 239)	0.5	-7.3	10.8
Lesotho	2815 (2671 to 2961)	2500 (2329 to 2670)	3369 (3204 to 3534)	11.2	20.8	3.2	361 (301 to 410)	361 (298 to 422)	374 (307 to 428)	10.7	18.0	1.6
Liberia	1520 (1431 to 1609)	1750 (1639 to 1864)	1306 (1212 to 1404)	18.5	20.9	14.8	179 (150 to 203)	212 (175 to 247)	147 (121 to 171)	18.5	20.5	14.0
Madagascar	2171 (2027 to 2319)	2121 (1968 to 2278)	2235 (2086 to 2386)	11.2	7.1	16.2	265 (218 to 302)	279 (229 to 327)	251 (203 to 293)	11.3	7.3	16.7
Malawi	1493 (1405 to 1587)	1262 (1171 to 1353)	1818 (1703 to 1933)	5.7	-4.6	19.6	181 (151 to 207)	167 (138 to 195)	204 (168 to 236)	5.2	-4.0	19.3
Mali	2327 (2176 to 2480)	2439 (2263 to 2615)	2224 (2077 to 2376)	9.7	11.2	8.3	275 (232 to 317)	299 (246 to 351)	253 (207 to 296)	10.0	11.6	9.1
Mauritania	1715 (1616 to 1824)	1928 (1806 to 2057)	1500 (1398 to 1605)	-6.1	-2.8	-10.0	205 (173 to 233)	238 (197 to 277)	172 (142 to 199)	-6.0	-2.5	-9.5
Mauritius	1985 (1882 to 2086)	1400 (1310 to 1492)	2717 (2563 to 2876)	-12.1	-17.3	-9.9	202 (164 to 232)	143 (116 to 168)	274 (220 to 320)	-12.6	-17.8	-10.7
Mozambique	1558 (1460 to 1651)	1269 (1180 to 1363)	1937 (1816 to 2054)	25.0	17.7	34.1	187 (156 to 214)	167 (139 to 195)	215 (177 to 248)	23.8	17.6	33.5
Namibia	2191 (2063 to 2330)	1670 (1543 to 1800)	2982 (2812 to 3164)	-7.5	-14.3	2.0	278 (232 to 316)	245 (201 to 286)	332 (275 to	-8.3	-14.6	1.2

Appendix Table A.1 … Continued

	Age-standardized Prevalence Rate per 100,000 in 2019 (95%UI)			Percentage Change in age standardized Prevalence rate, 1990–2019			Age-standardized YLDs Rate in 2019 (95%UI)			Percentage Change in age standardized YLDs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
									385)			
Niger	1719 (1607 to 1832)	1767 (1644 to 1895)	1670 (1565 to 1776)	5.2	5.3	3.1	205 (171 to 233)	218 (179 to 254)	191 (157 to 223)	5.7	5.3	3.2
Nigeria	1356 (1245 to 1478)	1456 (1334 to 1596)	1241 (1134 to 1344)	-17.6	-17.6	-20.5	161 (134 to 185)	178 (146 to 209)	142 (116 to 164)	-16.6	-16.8	-19.3
Rwanda	1806 (1693 to 1938)	1680 (1565 to 1810)	2018 (1892 to 2161)	-5.3	-2.5	-6.7	220 (183 to 252)	221 (184 to 259)	225 (184 to 261)	-4.8	-2.2	-6.3
Sao Tome and Principe	3392 (3222 to 3560)	3202 (3031 to 3388)	3626 (3437 to 3801)	33.8	26.4	39.7	395 (329 to 444)	389 (321 to 450)	404 (333 to 467)	32.1	25.1	38.4
Senegal	1759 (1655 to 1861)	1686 (1581 to 1798)	1845 (1729 to 1951)	1.6	4.1	-0.6	207 (173 to 235)	207 (169 to 240)	208 (170 to 241)	2.0	4.0	-0.5
Seychelles	2171 (2057 to 2291)	1557 (1455 to 1658)	2887 (2725 to 3064)	15.8	12.2	15.1	222 (181 to 255)	160 (130 to 188)	293 (236 to 342)	14.4	10.3	13.1
Sierra Leone	1875 (1767 to 1987)	2024 (1899 to 2155)	1737 (1638 to 1845)	12.1	22.7	2.1	222 (185 to 251)	249 (204 to 289)	197 (162 to 228)	12.1	22.1	2.1
Somalia	1518 (1409 to 1628)	1418 (1311 to 1537)	1686 (1565 to 1804)	-4.3	-1.7	-4.5	186 (153 to 214)	187 (155 to 219)	189 (155 to 221)	-3.6	-1.1	-5.0
South Africa	2256 (2088 to 2440)	1920 (1766 to 2089)	2803 (2591 to 3038)	-12.7	-15.5	-8.5	289 (240 to 331)	283 (233 to 333)	309 (255 to 359)	-13.7	-16.0	-9.1
South Sudan	1568 (1458 to 1684)	1471 (1362 to 1590)	1655 (1537 to 1775)	-3.9	-4.7	-3.8	187 (157 to 214)	190 (159 to 223)	184 (152 to 213)	-3.1	-4.5	-3.2

Appendix Table A.1 … Continued

	Age-standardized Prevalence Rate per 100,000 in 2019 (95%UI)			Percentage Change in age standardized Prevalence rate, 1990–2019			Age-standardized YLDs Rate in 2019 (95%UI)			Percentage Change in age standardized YLDs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Sudan	1863 (1748 to 1989)	1692 (1584 to 1812)	2003 (1872 to 2147)	18.4	9.9	24.9	172 (139 to 200)	168 (136 to 196)	175 (139 to 208)	17.0	9.8	24.1
Togo	1969 (1850 to 2095)	1853 (1736 to 1976)	2138 (1995 to 2274)	0.8	-3.8	7.0	234 (196 to 266)	229 (188 to 266)	242 (200 to 283)	1.3	-3.4	7.1
Uganda	1556 (1450 to 1662)	1396 (1287 to 1510)	1789 (1667 to 1908)	-0.4	-11.0	14.2	190 (157 to 216)	184 (154 to 215)	200 (163 to 233)	0.5	-9.8	14.9
United Republic of Tanzania	1299 (1208 to 1385)	1289 (1202 to 1377)	1321 (1221 to 1415)	5.4	4.3	6.5	160 (133 to 184)	171 (139 to 200)	150 (123 to 175)	6.0	5.6	7.1
Zambia	1650 (1551 to 1755)	1514 (1418 to 1617)	1816 (1701 to 1936)	8.4	0.9	17.8	200 (167 to 227)	199 (164 to 232)	203 (165 to 235)	8.1	0.5	17.3
Zimbabwe	1992 (1861 to 2134)	1779 (1642 to 1924)	2299 (2141 to 2454)	2.4	4.5	2.7	260 (214 to 296)	262 (213 to 306)	260 (213 to 301)	3.2	4.0	2.4

***Notes**: YLDs - years lived with disabilities. 95% UI - 95% uncertainty intervals. COPD - chronic obstructive pulmonary disease*

Appendix Table A.2 Age Standardized Death and YLL rate in 2019 and percentage change in age-standardized Death and YLLs by location and sex

	Age-standardized Deaths rate in 2019, (95%UI)			Percentage Change in Age-standardized Deaths rate, 1990–2019			Age-standardized YLLs rate in 2019, (95%UI)			Percentage Change in Age-standardized YLLs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Sub-Saharan Africa - WB	29 (25 to 33)	21 (15 to 27)	40 (33 to 45)	-21.6	-16.0	-21.6	510 (436 to 587)	364 (259 to 474)	684 (565 to 801)	-24.7	-23.8	-24.2
Central Sub-Saharan Africa	43 (30 to 67)	38 (19 to 75)	49 (33 to 65)	-17.3	-11.6	-22.2	729 (509 to 1078)	628 (319 to 1198)	859 (550 to 1161)	-21.9	-16.2	-24.9
Eastern Sub-Saharan Africa	29 (25 to 34)	20 (14 to 26)	42 (34 to 50)	-27.5	-23.1	-26.3	524 (444 to 617)	353 (249 to 476)	725 (582 to 890)	-31.4	-29.8	-30.4
Southern Sub-Saharan Africa	32 (29 to 35)	22 (19 to 26)	50 (45 to 54)	-17.9	-18.5	-13.8	550 (503 to 603)	358 (295 to 417)	842 (771 to 918)	-19.1	-21.0	-15.8
Western Sub-Saharan Africa	24 (21 to 28)	16 (12 to 20)	33 (27 to 40)	-17.2	-23.8	-19.5	428 (355 to 496)	300 (220 to 370)	569 (450 to 691)	-20.4	-24.2	-18.6
Angola	31 (23 to 39)	27 (15 to 41)	35 (27 to 43)	-35.4	-34.1	-36.4	515 (384 to 654)	449 (238 to 648)	598 (466 to 759)	-41.8	-40.1	-41.7
Benin	26 (20 to 33)	18 (13 to 25)	37 (27 to 48)	-31.6	-28.0	-28.8	464 (352 to 612)	334 (229 to 472)	628 (452 to 839)	-32.3	-29.8	-31.4
Botswana	39 (27 to 52)	25 (13 to 36)	64 (46 to 86)	-30.4	-28.6	-28.1	706 (477 to 947)	427 (214 to 625)	1125 (800 to 1547)	-30.5	-29.4	-29.1
Burkina Faso	19 (16 to 23)	13 (10 to 18)	27 (21 to 34)	-17.4	-18.8	-10.0	350 (282 to 434)	262 (180 to 345)	466 (357 to 606)	-14.8	-17.1	-10.0
Burundi	43 (32 to 55)	29 (19 to 42)	58 (41 to 78)	-28.3	-25.6	-34.1	784 (588 to 1033)	542 (336 to 815)	1025 (710 to 1455)	-34.0	-31.0	-39.1
CÃ´te d'Ivoire	25 (20 to 31)	16 (11 to 21)	36 (26 to 45)	-34.2	-27.3	-33.3	447 (335 to 574)	283 (192 to 393)	612 (440 to 793)	-34.7	-30.3	-35.2
Cabo Verde	18 (14 to 25)	13 (9 to 19)	25 (21 to 34)	-48.6	-48.0	-47.9	296 (243 to 403)	205 (144 to 303)	422 (352 to 581)	-53.6	-55.0	-52.8
Cameroon	25 (18 to 32)	17 (11 to 24)	35 (23 to 46)	-34.2	-34.6	-31.4	453 (307 to 599)	314 (196 to 441)	616 (379 to 824)	-32.9	-36.0	-29.9
Central African Republic	53 (35 to 79)	42 (22 to 81)	68 (44 to 92)	-14.5	-10.6	-16.0	1003 (669 to 1424)	748 (371 to 1361)	1334 (846 to 1818)	-15.7	-12.2	-16.6
Chad	31 (23 to 40)	22 (14 to 30)	40 (27 to 54)	-13.9	-15.4	-16.7	568 (417 to 741)	413 (271 to 590)	706 (476 to 985)	-15.4	-18.4	-17.3

Appendix Table A.2 … Continued

	Age-standardized Deaths rate in 2019, (95%UI)			Percentage Change in Age-standardized Deaths rate, 1990–2019			Age-standardized YLLs rate in 2019, (95%UI)			Percentage Change in Age-standardized YLLs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Comoros	26 (20 to 33)	17 (11 to 26)	38 (29 to 48)	-33.3	-26.1	-35.6	451 (347 to 588)	313 (195 to 484)	626 (474 to 811)	-35.1	-25.5	-37.4
Congo	35 (26 to 44)	30 (15 to 47)	41 (21 to 51)	-35.2	-30.2	-42.3	579 (420 to 748)	488 (248 to 722)	684 (349 to 885)	-41.7	-34.3	-48.3
Democratic Republic of the Congo	47 (30 to 77)	42 (21 to 88)	54 (31 to 74)	-11.3	-4.5	-15.6	801 (520 to 1251)	696 (341 to 1412)	938 (527 to 1320)	-14.3	-8.1	-17.1
Equatorial Guinea	30 (20 to 51)	25 (12 to 64)	38 (20 to 52)	-42.3	-34.2	-47.9	474 (303 to 771)	380 (179 to 930)	611 (314 to 845)	-52.1	-44.4	-56.3
Eritrea	33 (23 to 42)	24 (12 to 36)	49 (32 to 65)	-19.5	-11.1	-29.0	621 (435 to 799)	452 (211 to 677)	893 (585 to 1204)	-26.5	-16.5	-33.9
Eswatini	42 (31 to 55)	25 (14 to 37)	78 (62 to 95)	-27.6	-28.6	-22.0	779 (572 to 1026)	403 (216 to 621)	1420 (1110 to 1797)	-27.1	-32.7	-20.0
Ethiopia	28 (23 to 33)	19 (13 to 25)	37 (27 to 47)	-39.1	-36.7	-41.3	484 (386 to 573)	338 (231 to 447)	623 (452 to 803)	-48.7	-46.8	-49.7
Gabon	26 (18 to 33)	19 (9 to 27)	35 (21 to 49)	-35.0	-36.7	-36.4	427 (295 to 560)	295 (132 to 411)	593 (348 to 844)	-39.7	-40.4	-40.3
Gambia	30 (23 to 38)	22 (15 to 32)	42 (31 to 54)	-11.8	-4.3	-14.3	542 (405 to 697)	391 (257 to 584)	717 (515 to 942)	-12.4	-8.4	-13.4
Ghana	26 (16 to 32)	11 (8 to 14)	48 (24 to 60)	-10.3	-31.3	6.7	471 (281 to 592)	203 (136 to 262)	839 (438 to 1067)	-10.5	-34.9	7.8
Guinea	31 (24 to 39)	23 (16 to 32)	40 (28 to 52)	-16.2	-20.7	-11.1	574 (432 to 733)	439 (293 to 631)	713 (498 to 944)	-14.6	-24.0	-7.3
Guinea-Bissau	34	23	51	-32.0	-20.7	-31.1	671	446	964	-33.1	-24.7	-33.6

Appendix Table A.2 … Continued

	Age-standardized Deaths rate in 2019, (95%UI)			Percentage Change in Age-standardized Deaths rate, 1990–2019			Age-standardized YLLs rate in 2019, (95%UI)			Percentage Change in Age-standardized YLLs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
	(26 to 44)	(16 to 32)	(35 to 67)				(491 to 872)	(297 to 633)	(637 to 1295)			
Kenya	31 (24 to 41)	22 (14 to 37)	44 (31 to 60)	-6.1	-8.3	4.8	542 (422 to 713)	381 (241 to 642)	748 (521 to 1027)	-4.4	-13.6	6.7
Lesotho	71 (50 to 95)	52 (28 to 79)	104 (73 to 140)	-4.1	-1.9	-8.0	1315 (921 to 1803)	918 (467 to 1435)	1956 (1353 to 2673)	-2.6	-0.8	-2.4
Liberia	18 (14 to 25)	16 (11 to 24)	21 (14 to 28)	-18.2	-15.8	-12.5	325 (236 to 453)	301 (199 to 447)	348 (220 to 495)	-19.2	-20.6	-17.3
Madagascar	43 (31 to 56)	30 (19 to 45)	59 (42 to 79)	-8.5	0.0	-9.2	775 (557 to 1037)	569 (354 to 854)	1011 (711 to 1393)	-12.2	-5.3	-11.9
Malawi	25 (20 to 30)	16 (10 to 21)	40 (32 to 51)	-19.4	-23.8	-9.1	449 (352 to 550)	275 (182 to 385)	697 (537 to 912)	-21.4	-30.6	-10.8
Mali	34 (26 to 42)	25 (14 to 36)	42 (32 to 55)	-10.5	-13.8	-12.5	667 (482 to 866)	512 (273 to 758)	813 (593 to 1093)	-14.6	-17.0	-14.7
Mauritania	19 (15 to 23)	15 (10 to 20)	22 (17 to 28)	-38.7	-34.8	-45.0	308 (231 to 401)	269 (179 to 368)	346 (258 to 459)	-45.7	-40.9	-51.1
Mauritius	19 (15 to 25)	11 (8 to 17)	31 (25 to 38)	-38.7	-35.3	-40.4	298 (234 to 385)	161 (116 to 260)	479 (377 to 599)	-41.3	-36.9	-44.0
Mozambique	25 (20 to 33)	14 (9 to 21)	43 (33 to 60)	-7.4	-12.5	7.5	471 (355 to 632)	237 (147 to 357)	792 (593 to 1111)	-2.9	-17.1	10.2
Namibia	45 (34 to 58)	27 (16 to 43)	75 (59 to 89)	-28.6	-27.0	-25.0	777 (585 to 1008)	430 (255 to 696)	1289 (1012 to 1567)	-30.4	-32.1	-25.9
Niger	31 (22 to 43)	24 (16 to 34)	38 (25 to 61)	-18.4	-11.1	-25.5	547 (389 to	446 (283 to	655 (418 to	-23.6	-17.1	-27.4

Appendix Table A.2 … Continued

	Age-standardized Deaths rate in 2019, (95%UI)			Percentage Change in Age-standardized Deaths rate, 1990–2019			Age-standardized YLLs rate in 2019, (95%UI)			Percentage Change in Age-standardized YLLs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
							790)	645)	1087)			
Nigeria	22 (17 to 27)	15 (10 to 19)	29 (20 to 39)	-12.0	-16.7	-17.1	362 (274 to 456)	267 (178 to 357)	464 (319 to 640)	-19.0	-21.0	-20.0
Rwanda	36 (28 to 46)	26 (17 to 42)	53 (38 to 70)	-41.9	-36.6	-41.1	629 (490 to 816)	458 (302 to 765)	899 (643 to 1194)	-48.5	-45.9	-47.4
Sao Tome and Principe	58 (44 to 72)	41 (22 to 57)	79 (57 to 106)	0.0	-2.4	-4.8	1014 (761 to 1261)	720 (402 to 1009)	1346 (952 to 1823)	0.1	-6.7	0.7
Senegal	26 (20 to 31)	18 (13 to 23)	35 (27 to 45)	-27.8	-21.7	-30.0	451 (350 to 567)	322 (227 to 420)	595 (445 to 794)	-29.8	-25.1	-30.7
Seychelles	25 (21 to 29)	16 (12 to 20)	38 (30 to 46)	-24.2	-11.1	-33.3	411 (335 to 479)	241 (169 to 301)	618 (487 to 749)	-28.3	-18.6	-35.8
Sierra Leone	27 (20 to 35)	21 (14 to 30)	35 (24 to 46)	-25.0	-8.7	-27.1	494 (359 to 658)	396 (258 to 580)	599 (404 to 842)	-23.2	-9.8	-28.6
Somalia	40 (26 to 63)	27 (14 to 50)	62 (39 to 119)	-23.1	-10.0	-22.5	771 (491 to 1219)	517 (269 to 967)	1161 (699 to 2241)	-24.5	-15.9	-22.9
South Africa	32 (29 to 36)	22 (19 to 27)	49 (45 to 54)	-15.8	-15.4	-14.0	536 (490 to 605)	350 (304 to 437)	819 (746 to 908)	-19.3	-21.9	-16.2
South Sudan	27 (18 to 36)	13 (8 to 21)	38 (26 to 54)	-25.0	-31.6	-29.6	456 (305 to 638)	243 (141 to 403)	644 (417 to 921)	-31.4	-32.1	-31.0
Sudan	29 (19 to 40)	19 (12 to 31)	37 (21 to 53)	-21.6	-20.8	-24.5	510 (332 to 725)	331 (201 to 537)	661 (369 to 956)	-27.4	-30.2	-27.6
Togo	26 (20 to 34)	19 (13 to 27)	40 (27 to 52)	-25.7	-26.9	-14.9	479 (350 to 633)	339 (233 to 489)	696 (466 to 957)	-25.0	-32.2	-13.8

Appendix Table A.2 … Continued

	Age-standardized Deaths rate in 2019, (95%UI)			Percentage Change in Age-standardized Deaths rate, 1990–2019			Age-standardized YLLs rate in 2019, (95%UI)			Percentage Change in Age-standardized YLLs rate, 1990–2019		
	Both	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**	**Both**	**Female**	**Male**
Uganda	30 (22 to 39)	18 (12 to 29)	50 (33 to 65)	-31.8	-28.0	-25.4	537 (390 to 704)	313 (201 to 500)	856 (563 to 1137)	-32.5	-29.0	-28.0
United Republic of Tanzania	21 (17 to 25)	15 (10 to 20)	29 (23 to 37)	-19.2	-16.7	-21.6	381 (300 to 458)	275 (187 to 381)	506 (382 to 647)	-21.1	-16.2	-23.1
Zambia	29 (23 to 35)	18 (12 to 25)	43 (34 to 52)	-19.4	-21.7	-10.4	520 (407 to 638)	329 (215 to 463)	747 (571 to 930)	-21.1	-26.2	-11.6
Zimbabwe	24 (17 to 31)	18 (8 to 26)	34 (25 to 44)	-7.7	-5.3	-10.5	404 (279 to 525)	276 (125 to 415)	594 (406 to 780)	-7.8	-6.1	-3.4

Notes: YLLs - years life lost. 95% UI - 95% uncertainty intervals. COPD - chronic obstructive pulmonary disease

Appendix Table A.3 Age Standardized DALY due to COPD in 2019 and percentage change in age standardized DALYs by location and sex

	Age-standardized DALYs rate in 2019, (95%UI)			Percentage Change in Age-standardized DALYs rate, 1990–2019		
	Both	Female	Male	Both	Female	Male
Sub-Saharan Africa - WB	715 (634 to 798)	577 (461 to 697)	880 (759 to 997)	-19.6	-17.9	-20.1
Central Sub-Saharan Africa	965 (744 to 1321)	889 (580 to 1466)	1062 (754 to 1362)	-15.5	-9.4	-19.8
Eastern Sub-Saharan Africa	708 (622 to 802)	539 (431 to 669)	907 (763 to 1077)	-25.9	-23.1	-26.0
Southern Sub-Saharan Africa	839 (773 to 908)	640 (561 to 716)	1149 (1060 to 1234)	-16.3	-17.3	-13.5
Western Sub-Saharan Africa	619 (543 to 693)	503 (412 to 583)	749 (634 to 875)	-16.0	-17.8	-15.2
Angola	729 (597 to 874)	689 (477 to 896)	781 (646 to 943)	-33.4	-30.5	-35.0
Benin	693 (581 to 842)	580 (463 to 725)	839 (659 to 1051)	-23.8	-17.7	-26.1
Botswana	998 (761 to 1236)	733 (518 to 935)	1415 (1089 to 1842)	-23.5	-15.1	-26.5
Burkina Faso	524 (448 to 610)	447 (358 to 537)	627 (510 to 767)	-8.2	-9.1	-5.0
Burundi	996 (797 to 1259)	754 (542 to 1028)	1239 (915 to 1666)	-29.8	-25.3	-35.7
CÃ´te d'Ivoire	647 (537 to 779)	490 (389 to 602)	808 (638 to 988)	-27.5	-20.5	-29.7
Cabo Verde	482 (417 to 586)	399 (328 to 497)	598 (518 to 759)	-43.3	-39.8	-46.4
Cameroon	714 (564 to 866)	592 (468 to 727)	858 (625 to 1073)	-24.0	-24.7	-22.8
Central African Republic	1234 (902 to 1652)	988 (610 to 1603)	1550 (1062 to 2038)	-13.1	-9.7	-14.5
Chad	766 (617 to 947)	625 (473 to 807)	892 (660 to 1174)	-11.5	-11.8	-14.3
Comoros	631 (521 to 769)	495 (372 to 665)	809 (654 to 1001)	-28.4	-18.3	-31.8
Congo	832 (668 to 998)	803 (559 to 1050)	869 (538 to 1078)	-33.1	-21.8	-43.1
Democratic Republic of the Congo	1042 (758 to 1493)	962 (604 to 1682)	1147 (740 to 1521)	-8.4	-2.1	-12.4
Equatorial Guinea	700 (522 to 994)	647 (437 to 1201)	781 (488 to 1020)	-41.4	-28.3	-50.6
Eritrea	841 (652 to 1022)	656 (411 to 896)	1134 (827 to 1456)	-20.6	-10.9	-29.0
Eswatini	1093 (882 to 1348)	689 (496 to 914)	1788 (1474 to 2174)	-22.2	-24.8	-16.6
Ethiopia	629 (525 to 724)	489 (380 to 596)	761 (584 to 939)	-44.8	-41.4	-46.9
Gabon	624 (488 to 758)	488 (328 to 610)	794 (551 to 1043)	-31.2	-30.4	-32.9
Gambia	779 (638 to 944)	649 (501 to 856)	934 (727 to 1165)	-7.8	-2.4	-10.5
Ghana	670 (473 to 793)	381 (309 to 448)	1065 (651 to 1290)	-2.5	-20.6	14.1
Guinea	810 (660 to 977)	684 (534 to 880)	942 (722 to 1177)	-8.0	-15.0	-1.7

	Age-standardized DALYs rate in 2019, (95%UI)			Percentage Change in Age-standardized DALYs rate, 1990–2019		
	Both	Female	Male	Both	Female	Male
Guinea-Bissau	911 (728 to 1115)	690 (537 to 881)	1201 (869 to 1527)	-26.7	-16.3	-29.5
Kenya	753 (625 to 933)	598 (440 to 860)	954 (726 to 1235)	-3.1	-11.4	7.6
Lesotho	1677 (1289 to 2156)	1279 (825 to 1809)	2330 (1726 to 3037)	0.0	4.0	-1.8
Liberia	503 (409 to 635)	514 (405 to 667)	496 (365 to 643)	-9.0	-7.4	-9.8
Madagascar	1039 (818 to 1299)	848 (624 to 1140)	1262 (949 to 1631)	-7.2	-1.5	-7.4
Malawi	630 (535 to 731)	442 (342 to 557)	900 (740 to 1125)	-15.2	-22.5	-5.5
Mali	942 (750 to 1150)	811 (553 to 1057)	1066 (834 to 1364)	-8.6	-8.4	-10.1
Mauritania	513 (428 to 608)	508 (407 to 605)	517 (417 to 633)	-34.6	-27.3	-42.4
Mauritius	500 (426 to 596)	304 (252 to 402)	753 (638 to 881)	-32.3	-29.1	-35.3
Mozambique	659 (534 to 804)	403 (306 to 524)	1007 (805 to 1323)	3.6	-5.8	14.4
Namibia	1055 (846 to 1284)	675 (488 to 938)	1621 (1341 to 1905)	-25.7	-26.6	-21.6
Niger	752 (594 to 991)	664 (504 to 870)	846 (605 to 1278)	-17.4	-11.0	-22.2
Nigeria	523 (431 to 623)	444 (350 to 535)	605 (455 to 779)	-18.3	-19.4	-20.0
Rwanda	850 (704 to 1038)	679 (509 to 985)	1123 (860 to 1420)	-41.5	-36.7	-42.4
Sao Tome and Principe	1409 (1149 to 1657)	1109 (781 to 1409)	1750 (1350 to 2227)	7.3	2.4	7.5
Senegal	657 (549 to 779)	528 (429 to 634)	803 (647 to 998)	-22.3	-16.1	-24.7
Seychelles	633 (546 to 714)	401 (324 to 466)	911 (775 to 1055)	-17.5	-9.1	-25.4
Sierra Leone	716 (578 to 879)	645 (498 to 830)	796 (598 to 1039)	-14.9	0.2	-22.9
Somalia	957 (669 to 1413)	704 (454 to 1154)	1350 (887 to 2426)	-21.2	-12.4	-20.8
South Africa	826 (759 to 898)	633 (560 to 722)	1128 (1041 to 1232)	-17.3	-19.4	-14.4
South Sudan	644 (493 to 821)	434 (325 to 593)	828 (603 to 1092)	-24.9	-22.1	-26.3
Sudan	682 (500 to 898)	499 (363 to 712)	836 (540 to 1139)	-19.7	-20.5	-20.7
Togo	713 (584 to 876)	567 (455 to 728)	939 (704 to 1194)	-18.1	-23.1	-9.1
Uganda	727 (577 to 899)	497 (377 to 690)	1056 (758 to 1337)	-26.1	-22.9	-22.5
United Republic of Tanzania	541 (461 to 625)	446 (352 to 551)	656 (534 to 797)	-14.8	-9.0	-17.8
Zambia	720 (600 to 842)	528 (411 to 671)	950 (772 to 1138)	-14.7	-18.0	-6.8
Zimbabwe	664 (532 to 787)	537 (386 to 689)	854 (662 to 1040)	-3.8	-1.6	-1.8

Appendix Table A.4 Percentage of COPD related YLDs attributable to risk factors by sex and location in 2019

	Female					Male				
	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Sub-Saharan Africa - WB	12.5	37.7	12.5	5.3	9.6	14.4	31.8	16.9	4.1	35.2
Central Sub-Saharan Africa	9.9	44.7	12.7	3.4	5.8	11.9	36.9	15.7	2.5	33.8
Eastern Sub-Saharan Africa	6.6	51.1	15.2	4.4	8.7	8.3	44.3	18.5	3.1	33.0
Southern Sub-Saharan Africa	15.3	8.6	7.5	8.1	22.9	16.1	6.1	13.9	5.2	51.3
Western Sub-Saharan Africa	16.2	39.4	13.1	5.1	5.2	18.4	33.4	17.3	4.2	27.9
Angola	12.5	23.7	10.4	6.5	9.9	14.0	17.5	14.9	3.9	42.1
Benin	10.2	52.4	15.4	5.1	6.6	12.9	43.1	19.0	3.9	30.6
Botswana	14.0	11.5	7.5	10.0	19.3	15.0	8.2	14.4	7.4	54.8
Burkina Faso	7.3	64.1	14.6	5.8	2.6	9.8	55.9	19.6	3.8	25.6
Burundi	5.1	64.8	19.1	3.2	8.3	6.9	57.6	19.5	2.5	33.2
CÃ´te d'Ivoire	14.5	41.9	13.3	8.4	11.3	17.5	33.3	17.2	6.3	38.7
Cabo Verde	24.3	9.3	10.1	5.4	7.9	25.6	6.4	14.1	4.3	27.9
Cameroon	21.0	29.7	16.6	5.0	3.9	24.0	22.2	19.0	2.8	34.2
Central African Republic	7.0	64.0	11.3	4.2	5.6	9.3	55.9	16.0	3.2	32.8
Chad	7.5	66.3	12.2	5.9	6.9	10.0	57.9	17.5	3.5	33.4
Comoros	5.7	41.4	12.0	7.5	6.2	7.2	33.8	18.6	5.7	43.1
Congo	17.9	19.5	8.3	4.8	5.0	19.3	13.8	12.0	3.5	38.3
Democratic Republic of the Congo	8.3	53.1	14.0	2.3	4.8	10.5	44.1	16.4	2.0	31.2
Equatorial Guinea	23.8	5.8	11.0	4.7	4.8	24.3	3.9	13.6	3.7	38.1
Eritrea	12.0	42.1	14.3	4.2	1.3	14.9	34.2	18.8	4.1	32.6
Eswatini	11.7	20.4	8.8	4.4	11.1	13.2	15.1	14.7	3.0	29.9
Ethiopia	6.7	56.3	11.7	2.2	1.8	8.4	50.3	17.5	2.0	18.4

Appendix Table A.4 …Continued

	Female					Male				
	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Gabon	21.0	2.2	6.1	5.2	5.9	21.6	1.4	10.9	3.9	34.7
Gambia	13.0	49.0	9.9	9.3	3.7	16.1	39.6	15.8	6.2	42.5
Ghana	20.8	22.3	17.0	3.4	5.4	23.3	16.4	19.6	2.8	23.7
Guinea	8.8	60.1	12.1	6.5	6.6	11.5	51.3	17.3	4.5	45.2
Guinea-Bissau	10.0	56.6	12.5	6.3	3.4	12.9	47.6	17.6	4.6	23.1
Kenya	7.6	36.5	14.7	4.5	7.9	9.0	29.5	18.8	3.1	36.8
Lesotho	11.8	28.2	9.7	11.3	11.3	13.6	21.4	17.1	6.0	58.7
Liberia	10.5	52.8	12.7	4.4	6.1	13.1	43.1	16.4	3.0	28.4
Madagascar	4.6	54.0	19.5	4.8	5.0	5.9	45.5	21.7	3.4	32.2
Malawi	4.8	55.8	15.4	4.6	8.2	6.4	48.8	15.6	3.2	41.5
Mali	8.2	66.3	13.2	5.5	5.8	10.8	57.6	18.0	3.9	35.2
Mauritania	23.4	23.6	9.0	5.8	10.2	25.8	17.0	13.0	4.0	39.6
Mauritius	9.1	0.3	7.5	12.3	9.6	9.4	0.2	16.1	6.8	54.9
Mozambique	3.7	61.6	17.2	4.4	9.2	5.0	55.2	17.4	3.1	36.3
Namibia	12.8	15.6	7.1	5.8	25.8	14.2	11.4	13.2	4.5	42.5
Niger	6.9	72.9	12.3	5.4	2.8	9.4	65.6	19.5	3.9	22.9
Nigeria	20.3	27.5	12.0	4.1	4.0	22.1	23.5	15.5	4.3	19.1
Rwanda	9.3	47.8	18.7	5.0	24.6	11.8	39.6	20.1	3.7	47.8
Sao Tome and Principe	13.2	27.8	5.6	2.6	7.3	15.1	20.9	14.2	2.1	29.9
Senegal	14.0	45.7	8.8	9.6	3.8	17.3	37.0	17.9	7.2	35.9
Seychelles	9.6	0.1	9.9	11.0	14.2	9.9	0.1	14.9	6.6	61.2
Sierra Leone	9.4	57.5	13.1	7.5	10.9	12.0	48.1	15.8	4.7	41.0
Somalia	1.9	80.4	13.4	5.0	6.3	2.7	77.1	19.9	3.7	36.4
South Africa	16.7	3.3	6.2	7.9	24.9	17.2	2.4	13.1	5.4	51.2
South Sudan	8.0	53.4	15.1	5.2	6.2	10.4	45.3	17.1	3.8	35.8

Appendix Table A.4 …Continued

	Female					Male				
	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient particulate matter pollution	HAP from solid fuels	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Sudan	22.1	18.7	5.3	10.7	8.8	24.5	13.6	16.3	9.0	54.4
Togo	11.9	45.4	16.1	6.2	11.0	14.8	36.9	18.4	4.7	41.0
Uganda	8.4	50.3	15.9	3.9	9.4	10.8	42.4	18.6	3.1	30.7
United Republic of Tanzania	6.4	49.0	16.0	6.8	16.5	8.3	41.0	19.3	4.1	42.4
Zambia	9.6	35.0	12.8	5.7	13.1	11.5	27.6	16.9	3.5	37.7
Zimbabwe	7.8	36.2	15.2	8.7	14.7	9.4	28.6	19.4	3.9	55.1

Notes: YLDs - years lived with disabilities; COPD - chronic obstructive pulmonary disease; HAP – household air pollution

Appendix Table A.5 Percentage of COPD related Deaths attributable to risk factors by sex and location in 2019

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Sub-Saharan Africa	7.5	12.6	42.2	4.9	14.3	4.3	12.1	7.6	15.0	35.9	4.6	19.3	3.9	39.1
Central Sub-Saharan Africa	8.6	10.0	50.0	3.1	14.6	2.5	6.0	8.6	12.4	40.5	3.1	18.1	2.0	37.7
Eastern Sub-Saharan Africa	5.8	7.1	56.4	5.6	17.4	3.3	12.8	5.9	8.8	48.7	5.5	20.8	2.7	39.5
Southern Sub-Saharan Africa	5.3	16.4	8.7	12.4	8.1	7.3	28.2	5.2	16.9	6.0	12.3	15.0	5.5	55.2
Western Sub-Saharan Africa	9.8	16.8	43.7	1.4	15.2	4.4	6.5	9.9	19.7	36.7	1.3	20.1	4.2	30.1
Angola	6.8	13.3	25.3	3.9	12.4	5.0	10.7	6.8	14.9	18.6	3.9	17.4	3.2	48.8
Benin	11.5	10.8	55.3	0.7	17.5	4.0	7.0	11.6	13.7	45.8	0.7	21.6	3.3	37.8
Botswana	5.9	14.8	12.2	4.6	8.9	9.8	26.9	5.9	15.6	8.5	4.6	15.7	7.9	61.2
Burkina Faso	8.5	7.8	68.4	1.6	16.2	5.1	3.1	8.6	10.6	60.4	1.6	22.1	3.9	26.0
Burundi	8.0	5.4	69.5	7.3	21.7	2.2	8.8	8.0	7.3	61.0	7.3	21.9	2.0	40.1
CÃ´te d'Ivoire	7.1	15.5	44.8	0.5	15.2	7.6	16.7	7.1	18.7	35.6	0.5	19.5	6.5	38.0
Cabo Verde	4.6	26.2	10.0	3.9	11.6	4.4	9.3	4.6	27.5	6.9	3.9	16.2	4.1	32.0
Cameroon	10.2	22.1	31.2	2.0	18.5	3.9	5.8	10.2	25.3	23.4	2.0	21.1	2.5	34.3
Central African Republic	12.1	7.4	68.1	0.9	13.2	3.4	6.8	12.2	9.8	59.2	0.9	18.2	2.9	38.3
Chad	8.7	8.0	70.6	3.8	13.9	4.9	9.9	8.8	10.7	62.1	3.8	19.6	3.4	40.6
Comoros	1.8	6.2	44.9	0.8	13.7	6.3	9.6	1.8	7.6	35.9	0.8	20.9	5.4	56.6
Congo	7.7	18.8	20.5	1.1	9.5	3.9	5.0	7.7	20.5	14.7	1.1	13.9	3.1	46.7
Democratic Republic of the Congo	9.0	8.8	56.2	3.3	15.5	1.8	5.2	9.0	11.1	46.6	3.3	18.7	1.6	34.9
Equatorial Guinea	6.4	25.2	6.1	1.6	12.8	4.0	5.4	6.4	25.8	4.1	1.6	16.0	3.2	42.5
Eritrea	7.0	12.9	45.3	2.5	16.2	3.3	1.8	7.0	15.7	36.1	2.5	21.0	3.9	32.5
Eswatini	5.0	12.4	21.7	9.6	10.2	3.6	23.1	5.0	13.6	15.6	9.6	16.2	3.0	34.2
Ethiopia	7.7	7.0	63.2	7.4	14.2	1.5	2.1	7.6	8.8	55.3	7.1	20.2	1.5	23.9

Appendix Table A.5 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
Gabon	3.5	22.6	2.3	1.0	7.1	4.0	6.5	3.5	22.8	1.5	1.0	12.9	3.5	38.8
Gambia	6.9	13.8	51.8	1.0	11.4	9.0	5.2	6.9	17.1	42.1	1.0	17.7	6.5	46.5
Ghana	10.0	22.3	23.9	0.4	21.0	2.5	7.6	10.0	24.8	17.4	0.4	23.1	2.1	30.7
Guinea	7.9	9.3	63.5	0.9	13.5	5.6	9.0	7.9	12.1	54.3	0.9	18.9	4.3	49.2
Guinea-Bissau	7.0	10.6	59.9	0.8	14.1	5.4	4.0	7.1	13.6	50.3	0.8	19.4	4.4	24.3
Kenya	5.1	8.4	39.4	7.3	17.0	3.6	12.9	4.8	9.5	31.9	7.2	21.1	3.1	44.8
Lesotho	6.4	12.4	29.6	20.9	11.0	9.4	21.3	6.4	14.1	22.2	20.9	18.7	6.3	63.7
Liberia	5.7	11.1	56.2	0.6	14.8	3.8	7.3	5.7	14.2	46.7	0.6	19.1	2.8	32.7
Madagascar	3.0	4.8	56.9	5.0	20.9	3.9	6.4	3.1	6.2	47.8	5.0	23.3	3.1	36.3
Malawi	4.7	5.2	60.9	5.3	18.5	3.1	12.1	4.7	6.8	51.7	5.3	17.0	2.7	56.4
Mali	7.2	8.5	69.5	4.2	14.4	4.8	6.9	7.2	11.4	60.6	4.2	19.5	3.8	42.3
Mauritania	5.3	24.8	25.0	4.8	11.4	5.0	7.9	5.3	27.7	18.3	4.8	13.9	3.8	40.7
Mauritius	0.0	9.8	0.3	2.3	7.4	11.8	12.1	0.0	9.8	0.2	2.3	16.4	7.6	62.6
Mozambique	3.6	4.0	67.1	2.9	19.9	3.5	12.7	3.6	5.3	58.5	2.9	19.9	2.7	46.5
Namibia	7.0	13.7	16.7	5.9	8.4	5.1	43.6	7.0	14.7	11.8	5.9	14.6	4.6	52.0
Niger	9.0	7.3	77.4	4.1	12.7	4.5	3.0	9.1	10.1	70.2	4.1	21.1	3.4	27.7
Nigeria	11.9	21.7	30.8	0.6	15.0	3.3	5.1	11.8	23.4	29.1	0.7	19.4	4.5	21.3
Rwanda	8.9	10.0	51.1	9.7	20.9	3.3	42.5	8.9	12.4	41.7	9.7	21.9	3.4	61.5
Sao Tome and Principe	5.6	13.7	28.9	0.5	6.6	1.9	8.3	5.6	15.6	21.6	0.5	15.7	1.6	30.5
Senegal	6.3	15.0	48.9	1.3	10.1	9.3	3.9	6.3	18.4	39.3	1.3	19.9	7.6	35.1
Seychelles	1.7	10.3	0.1	0.3	10.7	9.7	18.3	1.7	10.3	0.1	0.3	15.6	7.5	70.3
Sierra Leone	6.2	9.9	60.7	0.6	14.9	7.5	9.9	6.2	12.8	51.4	0.6	18.6	5.3	46.7
Somalia	4.2	2.0	86.8	1.4	15.1	4.2	10.3	4.2	2.9	82.1	1.4	22.2	3.8	45.7
South Africa	5.0	17.7	3.8	13.1	6.9	7.2	28.6	5.0	17.9	2.5	13.0	14.2	5.6	54.3

Appendix Table A.5 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
South Sudan	6.8	8.7	57.6	0.7	17.3	4.8	10.3	6.8	11.1	48.3	0.7	19.4	4.0	45.3
Sudan	8.6	23.4	19.9	3.7	5.7	9.7	9.7	8.7	25.7	14.3	3.7	17.9	9.5	58.9
Togo	11.3	12.7	48.3	0.5	18.1	4.5	14.7	11.3	15.6	38.9	0.5	20.3	4.0	47.6
Uganda	6.8	9.0	54.4	3.1	18.1	2.8	16.6	6.8	11.4	44.9	3.1	20.9	2.8	37.3
United Republic of Tanzania	4.3	7.0	53.2	4.6	18.8	5.4	23.1	4.3	8.9	44.0	4.6	22.0	4.0	53.0
Zambia	6.9	10.3	37.7	4.6	14.6	4.7	26.2	6.9	12.2	29.2	4.6	18.9	3.4	47.4
Zimbabwe	6.0	8.4	38.8	5.7	17.6	6.7	26.8	6.0	9.9	30.0	5.7	21.2	3.9	64.5

Notes: COPD - chronic obstructive pulmonary disease; HAP – household air pollution

Appendix Table A.6 Percentage of COPD related YLLs attributable to risk factors by sex and location in 2019

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Sub-Saharan Africa	7.5	12.2	42.6	4.7	14.3	4.6	11.4	7.5	14.5	36.4	4.6	19.4	4.0	39.9
Central Sub-Saharan Africa	8.6	9.9	49.5	3.1	14.6	2.7	6.6	8.6	12.2	40.5	3.1	18.0	2.2	39.0
Eastern Sub-Saharan Africa	5.7	6.9	55.3	5.6	17.2	3.7	11.6	5.8	8.7	48.3	5.4	20.9	2.9	39.1
Southern Sub-Saharan Africa	5.3	16.5	8.7	12.4	8.3	7.7	28.2	5.3	16.9	6.3	12.2	15.2	5.5	56.2
Western Sub-Saharan Africa	9.6	16.3	43.6	1.4	14.8	4.6	6.5	9.7	19.2	37.5	1.4	20.1	4.3	32.1
Angola	6.7	13.1	25.0	3.9	12.1	5.5	11.6	6.7	14.8	18.5	3.9	17.3	3.5	50.0
Benin	11.2	10.5	53.8	0.7	17.0	4.4	7.8	11.4	13.5	45.3	0.7	21.5	3.6	37.5
Botswana	5.8	14.7	12.1	4.6	8.7	10.0	25.2	5.8	15.5	8.4	4.6	15.6	7.7	59.8
Burkina Faso	8.0	7.4	64.7	1.6	15.6	5.1	3.0	8.5	10.5	59.8	1.6	22.2	4.0	29.0
Burundi	7.8	5.3	67.8	7.3	21.3	2.5	9.2	8.0	7.2	60.4	7.3	21.9	2.2	40.0
CÃ´te d'Ivoire	6.9	15.1	43.8	0.5	15.0	7.9	15.9	7.0	18.5	35.2	0.5	19.5	6.5	41.8
Cabo Verde	4.6	25.8	9.9	3.9	11.8	4.7	10.5	4.6	27.3	6.9	3.9	16.4	4.3	34.5
Cameroon	10.0	21.6	30.6	2.0	18.1	4.3	4.6	10.1	25.1	23.2	2.0	21.0	2.7	37.6
Central African Republic	12.0	7.3	67.1	0.9	12.9	3.7	6.9	12.1	9.8	58.7	0.9	18.1	3.1	38.6
Chad	8.5	7.8	68.9	3.8	13.7	5.2	8.9	8.6	10.6	61.3	3.8	19.7	3.5	39.7
Comoros	1.8	6.1	44.1	0.8	13.6	6.8	8.8	1.8	7.6	35.7	0.8	21.0	5.6	53.5
Congo	7.6	18.7	20.4	1.1	9.4	4.2	5.7	7.6	20.4	14.6	1.1	13.9	3.3	45.6
Democratic Republic of the Congo	8.9	8.7	55.7	3.3	15.5	2.0	5.6	8.9	11.0	46.3	3.3	18.6	1.8	36.4
Equatorial Guinea	6.3	25.0	6.0	1.6	12.8	4.2	5.6	6.3	25.7	4.1	1.6	16.0	3.5	44.4
Eritrea	6.9	12.7	44.4	2.5	16.0	3.6	1.7	6.9	15.6	35.7	2.5	20.9	4.1	34.8
Eswatini	4.9	12.3	21.6	9.6	10.2	3.9	18.6	4.9	13.6	15.6	9.6	16.1	3.0	33.5
Ethiopia	7.5	6.9	61.9	7.3	14.1	1.7	2.2	7.5	8.8	54.7	7.1	20.3	1.7	23.6

Appendix Table A.6 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
Gabon	3.4	22.5	2.3	1.0	7.2	4.4	7.0	3.4	22.7	1.5	1.0	12.8	3.7	40.2
Gambia	6.8	13.6	51.1	1.0	11.2	9.1	4.9	6.8	16.9	41.6	1.0	17.7	6.5	48.1
Ghana	9.8	21.9	23.4	0.4	20.2	2.8	6.8	9.9	24.5	17.2	0.4	22.6	2.5	29.2
Guinea	7.7	9.0	61.7	0.9	13.2	5.9	8.5	7.8	12.0	53.6	0.9	18.9	4.5	50.5
Guinea-Bissau	6.9	10.4	58.9	0.8	13.8	5.8	4.1	7.0	13.4	49.7	0.8	19.4	4.5	25.8
Kenya	5.0	8.3	38.6	7.3	16.8	4.0	11.4	4.8	9.4	31.7	7.2	21.1	3.1	44.2
Lesotho	6.4	12.3	29.4	20.9	10.9	10.3	16.6	6.4	14.0	22.0	20.9	18.5	6.2	63.4
Liberia	5.6	10.9	54.8	0.6	14.3	4.0	7.7	5.7	14.0	46.3	0.6	19.0	2.9	35.2
Madagascar	3.0	4.7	55.4	5.0	20.7	4.2	5.8	3.0	6.1	47.1	5.0	23.3	3.3	35.6
Malawi	4.6	5.1	59.5	5.3	18.0	3.6	12.7	4.6	6.7	51.3	5.3	17.2	3.0	52.3
Mali	7.1	8.4	68.5	4.2	14.3	5.1	7.2	7.2	11.3	60.1	4.2	19.5	3.9	40.3
Mauritania	5.3	24.6	24.7	4.8	10.9	5.3	9.4	5.3	27.4	18.1	4.8	14.4	4.0	43.7
Mauritius	0.0	9.5	0.3	2.3	7.8	12.0	11.5	0.0	9.7	0.2	2.3	17.0	7.3	60.7
Mozambique	3.5	3.9	65.4	2.9	19.6	3.7	12.6	3.6	5.3	58.1	2.9	19.8	2.9	44.7
Namibia	7.0	13.7	16.6	5.9	8.4	5.4	38.7	7.0	14.7	11.7	5.9	14.5	4.6	48.1
Niger	8.7	7.1	75.1	4.1	12.8	4.7	3.2	9.0	10.0	69.4	4.1	21.4	3.7	25.8
Nigeria	11.6	21.2	31.2	0.6	14.5	3.5	5.3	11.6	23.0	30.6	0.7	19.5	4.7	23.5
Rwanda	8.6	9.7	49.7	9.7	20.6	3.9	36.7	8.8	12.3	41.3	9.7	22.1	3.5	58.2
Sao Tome and Principe	5.6	13.5	28.6	0.5	6.3	2.2	9.0	5.6	15.4	21.4	0.5	15.5	1.8	32.8
Senegal	6.2	14.7	48.1	1.3	10.0	9.4	4.6	6.2	18.2	38.9	1.3	19.9	7.5	39.5
Seychelles	1.7	10.2	0.1	0.3	11.0	10.3	17.7	1.7	10.3	0.1	0.3	16.0	7.2	67.8
Sierra Leone	6.0	9.6	59.0	0.6	14.5	7.4	11.6	6.1	12.6	50.7	0.6	18.3	5.1	47.9
Somalia	4.1	2.0	84.8	1.4	15.0	4.5	9.2	4.2	2.9	81.3	1.4	22.2	3.7	44.6
South Africa	5.1	17.9	3.3	13.1	7.1	7.6	29.6	5.1	18.1	2.4	13.0	14.4	5.6	55.7

Appendix Table A.6 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
South Sudan	6.6	8.4	55.7	0.7	16.9	4.8	9.3	6.8	11.0	47.9	0.7	19.5	3.9	44.6
Sudan	8.4	22.6	19.2	3.7	5.7	10.1	9.9	8.4	25.0	13.9	3.7	17.6	9.3	57.7
Togo	11.1	12.5	47.4	0.5	17.8	5.1	14.8	11.2	15.5	38.5	0.5	20.3	4.4	47.5
Uganda	6.6	8.8	53.2	3.1	17.9	3.1	14.5	6.7	11.3	44.5	3.1	20.8	3.0	36.8
United Republic of Tanzania	4.2	6.8	51.4	4.6	18.2	5.9	21.6	4.3	8.8	43.6	4.6	21.9	4.0	52.3
Zambia	6.8	10.1	37.1	4.6	14.4	5.1	21.0	6.8	12.1	29.0	4.6	19.0	3.4	46.4
Zimbabwe	6.0	8.3	38.6	5.7	17.6	7.2	24.1	6.0	9.9	29.8	5.7	21.2	3.9	63.8

Notes: YLLs - years life lost; COPD - chronic obstructive pulmonary disease; HAP – household air pollution

Appendix Table A.7 Percentage of COPD related DALYs attributable to risk factors by sex and location in 2019

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from Low solid temperature fuels		Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from Low solid temperature fuels		Occupational particulate matter, gases, and fumes	Secondhand smoke	Smoking
Sub-Saharan Africa	4.7	12.3	40.9	3.0	13.6	4.8	10.7	5.8	14.5	35.4	3.5	18.8	4.0	38.8
Central Sub-Saharan Africa	5.9	9.9	48.1	2.2	14.0	2.9	6.3	6.9	12.2	39.9	2.5	17.6	2.3	38.0
Eastern Sub-Saharan Africa	3.7	6.8	53.9	3.6	16.5	3.9	10.6	4.6	8.6	47.5	4.3	20.4	2.9	37.9
Southern Sub-Saharan Africa	3.0	16.0	8.7	7.0	8.0	7.9	25.9	3.9	16.7	6.2	8.9	14.8	5.4	54.9
Western Sub-Saharan Africa	5.7	16.2	41.9	0.8	14.1	4.8	6.0	7.4	19.0	36.5	1.1	19.4	4.3	31.0
Angola	4.3	12.9	24.5	2.5	11.5	5.9	11.0	5.1	14.6	18.3	3.0	16.7	3.6	48.1
Benin	6.4	10.4	53.2	0.4	16.3	4.7	7.3	8.5	13.4	44.7	0.5	20.8	3.7	35.8
Botswana	3.3	14.4	11.9	2.7	8.2	10.0	22.7	4.6	15.4	8.3	3.7	15.3	7.6	58.8
Burkina Faso	4.7	7.4	64.4	0.9	15.2	5.4	2.8	6.3	10.3	58.8	1.1	21.5	3.9	28.1
Burundi	5.6	5.2	66.9	5.2	20.6	2.7	9.0	6.6	7.1	59.9	6.0	21.4	2.3	38.8
CÃ´te d'Ivoire	4.0	14.8	43.0	0.3	14.3	8.1	13.9	5.3	18.3	34.7	0.4	18.9	6.5	41.0
Cabo Verde	2.3	25.1	9.6	2.0	11.0	5.0	9.2	3.2	26.8	6.7	2.8	15.7	4.3	32.5
Cameroon	5.2	21.4	30.2	1.0	17.4	4.6	4.3	7.2	24.7	22.9	1.4	20.4	2.7	36.7
Central African Republic	8.9	7.2	66.3	0.7	12.5	3.8	6.5	10.3	9.7	58.3	0.8	17.8	3.1	37.8
Chad	5.6	7.7	68.0	2.5	13.2	5.4	8.2	6.8	10.4	60.6	2.9	19.2	3.5	38.4
Comoros	1.1	6.0	43.1	0.5	13.0	7.1	7.9	1.4	7.5	35.2	0.6	20.5	5.6	51.1
Congo	4.6	18.4	20.0	0.6	9.0	4.5	5.4	6.0	20.2	14.4	0.8	13.5	3.4	44.0
Democratic Republic of the Congo	6.3	8.6	54.9	2.3	15.1	2.1	5.3	7.2	10.9	45.9	2.6	18.2	1.8	35.4
Equatorial Guinea	3.6	24.5	5.9	0.9	12.0	4.4	5.3	4.9	25.4	4.0	1.3	15.4	3.5	43.0
Eritrea	4.6	12.5	43.7	1.7	15.5	3.8	1.6	5.4	15.4	35.4	2.0	20.4	4.1	34.3
Eswatini	2.8	12.1	21.1	5.5	9.6	4.1	15.4	3.9	13.5	15.5	7.6	15.8	3.0	32.8
Ethiopia	5.2	6.8	60.2	5.0	13.3	1.8	2.1	6.1	8.7	53.9	5.8	19.8	1.8	22.7

Appendix Table A.7 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
Gabon	2.0	21.9	2.2	0.6	6.7	4.7	6.5	2.6	22.4	1.5	0.7	12.3	3.7	38.8
Gambia	4.0	13.4	50.3	0.6	10.7	9.2	4.4	5.2	16.7	41.2	0.8	17.2	6.4	46.8
Ghana	5.2	21.4	22.9	0.2	18.7	3.1	6.1	7.7	24.3	17.0	0.3	21.9	2.5	28.0
Guinea	4.9	8.9	61.1	0.6	12.8	6.1	7.8	5.9	11.8	53.0	0.7	18.5	4.5	49.2
Guinea-Bissau	4.4	10.3	58.0	0.5	13.4	5.9	3.9	5.6	13.3	49.3	0.7	19.0	4.5	25.3
Kenya	3.1	8.0	37.9	4.6	16.0	4.2	10.1	3.7	9.3	31.2	5.6	20.6	3.1	42.5
Lesotho	4.5	12.1	29.0	14.8	10.6	10.6	15.0	5.3	14.0	21.9	17.5	18.3	6.2	62.6
Liberia	3.2	10.7	53.9	0.4	13.6	4.1	7.0	4.0	13.8	45.3	0.4	18.2	3.0	33.2
Madagascar	2.0	4.6	54.9	3.3	20.3	4.4	5.5	2.4	6.1	46.7	4.0	23.0	3.3	34.9
Malawi	2.8	5.0	58.1	3.3	17.0	4.0	11.0	3.6	6.7	50.7	4.1	16.8	3.0	49.8
Mali	4.5	8.3	67.7	2.6	13.9	5.3	6.6	5.5	11.1	59.5	3.2	19.2	3.9	39.1
Mauritania	2.8	24.0	24.1	2.5	10.0	5.5	9.8	3.5	26.9	17.8	3.2	14.0	4.0	42.3
Mauritius	0.0	9.3	0.3	1.2	7.6	12.2	10.6	0.0	9.6	0.2	1.4	16.7	7.1	58.6
Mozambique	2.0	3.8	63.8	1.7	18.6	4.0	11.2	2.8	5.2	57.5	2.3	19.3	2.9	42.9
Namibia	4.4	13.4	16.2	3.7	7.9	5.6	33.9	5.6	14.6	11.6	4.6	14.2	4.6	47.0
Niger	5.8	7.0	74.3	2.7	12.6	5.0	3.0	6.9	9.8	68.5	3.1	21.0	3.8	25.1
Nigeria	6.9	20.8	29.7	0.4	13.5	3.7	4.8	8.9	22.8	28.9	0.6	18.5	4.6	22.4
Rwanda	5.8	9.6	49.0	6.4	19.9	4.3	32.7	7.0	12.2	41.0	7.7	21.7	3.5	56.1
Sao Tome and Principe	3.6	13.4	28.3	0.3	6.1	2.3	8.4	4.3	15.4	21.2	0.4	15.2	1.9	32.1
Senegal	3.7	14.4	47.1	0.8	9.5	9.5	4.3	4.6	17.9	38.4	0.9	19.4	7.4	38.5
Seychelles	1.0	10.0	0.1	0.2	10.6	10.6	16.3	1.2	10.2	0.1	0.2	15.6	7.0	65.6
Sierra Leone	3.7	9.5	58.4	0.3	13.9	7.5	11.3	4.6	12.5	50.1	0.4	17.7	5.0	46.1
Somalia	2.9	1.9	83.5	1.0	14.5	4.7	8.4	3.6	2.9	80.7	1.2	21.9	3.7	43.4
South Africa	2.8	17.4	3.3	7.3	6.7	7.7	27.5	3.7	17.8	2.4	9.4	14.0	5.5	54.5

Appendix Table A.7 … Continued

	Female							Male						
	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking	Ambient ozone pollution	Ambient particulate matter pollution	HAP from solid fuels	Low temperature	Occupational particulate matter, gases, and fumes	Second hand smoke	Smoking
South Sudan	3.6	8.2	54.6	0.4	16.1	5.0	7.9	5.2	10.9	47.3	0.6	18.9	3.9	42.6
Sudan	5.5	22.5	19.0	2.4	5.6	10.3	9.5	6.6	24.9	13.8	2.9	17.3	9.3	57.0
Togo	6.5	12.2	46.6	0.3	17.1	5.6	13.3	8.3	15.3	38.1	0.4	19.8	4.5	45.8
Uganda	4.1	8.7	52.1	1.9	17.1	3.4	12.5	5.4	11.2	44.1	2.5	20.4	3.0	35.6
United Republic of Tanzania	2.5	6.6	50.5	2.8	17.4	6.2	19.6	3.3	8.7	43.0	3.5	21.3	4.1	50.0
Zambia	4.2	9.9	36.3	2.9	13.8	5.3	18.0	5.4	11.9	28.7	3.6	18.5	3.4	44.5
Zimbabwe	3.0	8.1	37.4	2.9	16.4	7.9	19.4	4.1	9.7	29.4	4.0	20.6	3.9	61.2

Notes: Disability-adjusted life year; COPD - chronic obstructive pulmonary disease; HAP – household air pollution

Appendix B. Supplementary Files for Chapter 3

Appendix Table B.1 List of flavonoid subclasses and compounds by food composition tables under study.

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
Anthocyanins	Cyanidin Delphinidin Pelargonidin Malvidin Cyanidin-3-galactoside Idaein Peonidin cyanidin-3-glucoside Cyanidin-3-rutinoside cyanidin 3-(3"malonyl)glucoside Cyanidin 3-glucoside malonate Cyanidin 3-O-di-hexoside cyanidin-3-(6"-acetoyl)glucoside Cyanidin-3-arabinoside Cyanidin-3-glucoside-succinate Cyanidin-3-sambubioside Delphinidin-3-(6"-acetoyl)glucoside Delphinidin-3-arabinoside delphinidin-3-galactoside Delphinidin-3-glucoside malvidin-3-(6"-acetoyl)galactoside malvidin-3-(6"-acetoyl)glucoside Malvidin-3-arabinoside Malvidin-3-galactoside Malvidin-3-glucoside Pelargonidin 3-glucoside malonate Pelargonidin-3-acetyl-glucoside pelargonidin-3-arabinoside pelargonidin-3-galactoside Pelargonidin-3-glucoside Pelargonidin-3-glucoside-succinate Pelargonidin-3-o-glucoside-acetate pelargonidin-3-O-	NA	Delphinidin 3-O-feruloyl-glucoside Delphinidin 3-O-glucoside Delphinidin 3,5-O-diglucoside Malvidin 3-O-glucoside Petunidin 3-O-glucoside Petunidin 3-O-rhamnoside Petunidin 3,5-O-diglucoside Cyanidin Cyanidin 3-O-glucoside Cyanidin 3,5-O-diglucoside Pelargonidin Pelargonidin 3-O-glucoside Pelargonidin 3,5-O-diglucoside Peonidin Cyanidin 3-O-(6"-malonyl-glucoside) Cyanidin 3-O-(6"-malonyl-3"-glucosyl-glucoside) Delphinidin 3-O-glucosyl-glucoside Cyanidin 3-O-arabinoside Cyanidin 3-O-galactoside Cyanidin 3-O-xyloside Cyanidin 3-O-rutinoside Malvidin 3,5-O-diglucoside Anthocyanins, total Peonidin 3-O-glucoside Peonidin 3-O-rutinoside Pelargonidin 3-O-rutinoside Cyanidin 3-O-(6"-acetyl-galactoside) Cyanidin 3-O-(6"-acetyl-glucoside) Cyanidin 3-O-(6"-dioxalyl-glucoside) Cyanidin 3-O-(6"-p-coumaroyl-glucoside) Cyanidin 3-O-(6"-succinyl-glucoside) Cyanidin 3-O-glucosyl-rutinoside Cyanidin 3-O-sophoroside Delphinidin 3-O-(6"-acetyl-galactoside)	Cyanidin Delphinidin Malvidin Pelargonidin Peonidin Petunidin

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
	malonyl-glucoside pelargonidin-3-rutinoside Peonidin-3-arabinoside Peonidin-3-galactoside peonidin-3-glucoside Petunidin Petunidin 3-O-rutinoside petunidin-3-(6"-acetoyl)glucoside Petunidin-3-arabinoside Petunidin-3-galactoside Petunidin-3-glucoside Cyanidin-3-(6-p-coumaroylglucoside) Delphinidin-3-(p-coumaroylglucoside)-5-glucoside Malvidin-3-(6-p-coumaroylglucoside) Malvidin-3-(p-coumaroylglucoside)-5-glucoside Petunidin-3-(6-p-coumaroylglucoside) Petunidin-3-(p-coumaroylglucoside)-5-glucoside carboxypyrano-cyanidin 3-rutinoside cyanidin 3-malonylglucoside cyanidin 3-malonylglycosyl-5-glucoside Cyanidin-3-rutinoside dimer Cyanidin-3,5-diglucoside peonidin-3-rutinoside Delphinidin-3,5-diglucoside Pelargonidin-3,5-diglucoside		Delphinidin 3-O-(6"-acetyl-glucoside) Delphinidin 3-O-(6"-p-coumaroyl-glucoside) Delphinidin 3-O-arabinoside Delphinidin 3-O-galactoside Malvidin 3-O-(6"-acetyl-galactoside) Malvidin 3-O-(6"-acetyl-glucoside) Malvidin 3-O-(6"-p-coumaroyl-glucoside) Malvidin 3-O-arabinoside Malvidin 3-O-galactoside Pelargonidin 3-O-(6"-malonyl-glucoside) Pelargonidin 3-O-(6"-succinyl-glucoside) Pelargonidin 3-O-arabinoside Peonidin 3-O-(6"-acetyl-galactoside) Peonidin 3-O-(6"-acetyl-glucoside) Peonidin 3-O-arabinoside Peonidin 3-O-galactoside Petunidin 3-O-(6"-acetyl-galactoside) Petunidin 3-O-(6"-acetyl-glucoside) Petunidin 3-O-(6"-p-coumaroyl-glucoside) Petunidin 3-O-arabinoside Petunidin 3-O-galactoside Peonidin 3-O-(6"-p-coumaroyl-glucoside) Malvidin 3-O-(6"-caffeoyl-glucoside) Pigment A Pinotin A Vitisin A Delphinidin 3-O-rutinoside	
Flavanols	(-)-Epicatechin Epicatechin-gallate Catechin Epigallocatechin Gallocatechin gallate Epigallocatechin gallate Gallocatechin catechin gallate Pinocembrin	(-)-Epicatechin (-)-Epigallocatechin (-)-Epigallocatechin 3-gallate (+)-Catechin (-)Gallocatechin Gallocatechin 3-gallate	(-)-Epicatechin (-)-Epicatechin 3-O-gallate (-)-Epigallocatechin (-)-Epigallocatechin 3-O-gallate (+)-Catechin (+)-Gallocatechin (+)-Catechin 3-O-gallate (+)-Gallocatechin 3-O-gallate (+)-Catechin 3-O-glucose	(-)-Epicatechin (-)-Epicatechin 3-gallate (-)-Epigallocatechin (-)-Epigallocatechin 3-gallate (+)-Catechin (+)-Gallocatechin Theaflavin

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
			Theaflavin Theaflavin 3-O-gallate Theaflavin 3,3'-O-digallate Theaflavin 3'-O-gallate (-)-Epicatechin-(2a-7)(4a-8)-epicatechin 3-O-galactoside	Theaflavin-3,3'-digallate Theaflavin-3'-gallate Thearubigins
Flavanones	Naringenin chalcone Naringenin R-Naringenin aglycone R-Naringenin glycoside S-Naringenin aglycone S-Naringenin glycoside Hesperetin Hesperidin Naringin Narirutin Neohesperidin Sinensetin	Hesperetin Hesperidin Naringenin	Eriodictyol Naringenin Naringenin 7-O-glucoside Hesperetin Didymin Eriocitrin Hesperidin Naringin Narirutin Neoeriocitrin Neohesperidin Poncirin 6-Geranylnaringenin 6-Prenylnaringenin 8-Prenylnaringenin Isoxanthohumol	Eriodictyol Hesperetin Naringenin
Flavones	Apigenin Luteolin Chrysin Isovitexin Vitexin	Apigenin Apigenin 6-C-glucoside apigenin-7-O-neohesperidoside Luteolin	Apigenin Apigenin 7-O-glucoside Luteolin Luteolin 7-O-glucoside Apigenin 7-O-apiosyl-glucoside 7,3',4'-Trihydroxyflavone 7,4'-Dihydroxyflavone Geraldone Luteolin 7-O-glucuronide Luteolin 7-O-(2-apiosyl-6-malonyl)-glucoside Apigenin 7-O-glucuronide Luteolin 7-O-malonyl-glucoside Luteolin 7-O-rutinoside Apigenin 7-O-(6"-malonyl-apiosyl-glucoside) Chrysoeriol 7-O-(6"-malonyl-apiosyl-glucoside) Chrysoeriol 7-O-(6"-malonyl-glucoside) Chrysoeriol 7-O-apiosyl-glucoside Chrysoeriol 7-O-glucoside Luteolin 7-O-(2-apiosyl-glucoside) Tangeretin Isorhoifolin Luteolin 6-C-glucoside Apigenin 6,8-di-C-glucoside	Apigenin Luteolin

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
			Chrysin Diosmin Nobiletin Sinensetin Tetramethylscutellarein	
Flavonols	Kaempferol Myricetin Quercetin Isorhamnetin Fisetin Quercetin-3-rutinoside quercetin 3-xyloside Quercetin-3-arabinoside Quercetin-3-galactoside Quercetin-3-glucoside Quercetin-3-rhamnoside Kaempferol-3-glucoside Kaempferol-3-rutinoside Fisetin aglycone Fisetin glycoside Galangin Kaempferol acetyl-glucoside Kaempferol aglycone Kaempferol-3-glucoside-malonate Kaempferol-3-glucuronide Kaempferol-3-malonyl-glucoside Kaempferol-3(p-coumaroylglucoside) Morin myricetin-3-glucoside Myricetin-O-rhamnoside Quercetin 3-O-acetyl-rhamnoside Quercetin aglycone Quercetin glucoside Quercetin glycoside Quercetin-3-glucuronide	Isorhamnetin Kaempferol Myricetin Quercetin Quercetin 3-β-galactoside Quercetin 3-β-D-glucoside Quercetin 3-O-rutinoside	Quercetin 3-O-rutinoside Kaempferol Myricetin Quercetin 6,8-Dihydroxykaempferol Isorhamnetin Isorhamnetin 3-O-galactoside Kaempferol 3-O-galactoside Kaempferol 3-O-glucoside Kaempferol 3-O-rutinoside Quercetin 3-O-galactoside Quercetin 3-O-glucoside Kaempferol 3-O-acetyl-glucoside Kaempferol 3-O-xylosyl-glucoside Myricetin 3-O-rhamnoside Kaempferol 3-O-glucuronide Kaempferol 3-O-xylosyl-rutinoside Quercetin 3-O-glucuronide Quercetin 3-O-rhamnoside Quercetin 3-O-xylosyl-rutinoside Kaempferol 3-O-(2"-rhamnosyl-6"-acetyl-galactoside) 7-O-rhamnoside Kaempferol 3-O-(2"-rhamnosyl-galactoside) 7-O-rhamnoside Kaempferol 3-O-(6"-acetyl-galactoside) 7-O-rhamnoside Kaempferol 3-O-galactoside 7-O-rhamnoside Kaempferol 7-O-glucoside Quercetin 3-O-(6"-acetyl-galactoside) 7-O-rhamnoside Quercetin 3-O-galactoside 7-O-rhamnoside Kaempferol 3-O-(6"-malonyl-glucoside) Kaempferol 3-O-rhamnoside Quercetin 3-O-(6"-malonyl-glucoside)	Isorhamnetin Kaempferol Myricetin Quercetin

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
			Quercetin 3-O-(6"-malonyl-glucoside) 7-O-glucoside 5,3',4'-Trihydroxy-3-methoxy-6:7-methylenedioxyflavone 4'-O-glucuronide 5,4'-Dihydroxy-3,3'-dimethoxy-6:7-methylenedioxyflavone 4'-O-glucuronide Jaceidin 4'-O-glucuronide Patuletin 3-O-(2"-feruloylglucosyl)(1->6)-[apiosyl(1->2)]-glucoside Patuletin 3-O-glucosyl-(1->6)-[apiosyl(1->2)]-glucoside Spinacetin 3-O-(2"-feruloylglucosyl)(1->6)-[apiosyl(1->2)]-glucoside Spinacetin 3-O-(2"-p-coumaroylglucosyl)(1->6)-[apiosyl(1->2)]-glucoside Spinacetin 3-O-glucosyl-(1->6)-[apiosyl(1->2)]-glucoside Spinacetin 3-O-glucosyl-(1->6)-glucoside Galangin Isorhamnetin 4'-O-glucoside Quercetin 3,4'-O-diglucoside Quercetin 4'-O-glucoside Quercetin 7,4'-O-diglucoside Rhamnetin Kaempferol 3-O-sophoroside Kaempferol 3,7-O-diglucoside Quercetin 3-O-sophoroside Quercetin 3-O-arabinoside Quercetin 3-O-xyloside Isorhamnetin 3-O-glucoside Isorhamnetin 3-O-glucuronide Morin Myricetin 3-O-arabinoside Quercetin 3-O-acetyl-rhamnoside Quercetin 3-O-glucosyl-xyloside Quercetin 3-O-xylosyl-glucuronide	

Flavonoid subclasses	eBASIS	IFCT	Phenol Explorer	USDA
			3-Methoxynobiletin 3-Methoxysinensetin Kaempferide Kaempferol 3-O-glucosyl-rhamnosyl-galactoside Kaempferol 3-O-glucosyl-rhamnosyl-glucoside Myricetin 3-O-galactoside Myricetin 3-O-glucoside Myricetin 3-O-rutinoside Quercetin 3-O-glucosyl-rhamnosyl-galactoside Quercetin 3-O-glucosyl-rhamnosyl-glucoside Quercetin 3-O-rhamnosyl-galactoside 3,7-Dimethylquercetin	
Isoflavones	Biochanin A Daidzein Formononetin Genistein Glycitein Genistin	Daidzein Genistein	6"-O-Acetyldaidzin 6"-O-Acetylgenistin 6"-O-Acetylglycitin 6"-O-Malonyldaidzin 6"-O-Malonylgenistin 6"-O-Malonylglycitin Daidzein Daidzin Formononetin Genistein Genistin Glycitein Glycitin Biochanin A	Daidzein Genistein Glycitein Total isoflavones Coumestrol Formononetin Biochanin A
Proanthocyanidins	Procyanidin B2 Procyanidin B1 Procyanidin Procyanidin B3	NA	02 mers 03 mers 04-06 mers 07-10 mers Polymers (>10 mers) Procyanidin dimer B1 Procyanidin dimer B2 Procyanidin dimer B3 Procyanidin dimer B4 Procyanidin dimer B5 Procyanidin dimer B7 Procyanidin trimer C1 Procyanidin trimer EEC Prodelphinidin dimer B3 Procyanidin trimer C2 Prodelphinidin trimer C-GC-C Prodelphinidin trimer GC-C-C Prodelphinidin trimer GC-GC-C Procyanidin trimer T2 Cinnamtannin A2	Proanthocyanidin 4-6mers Proanthocyanidin 7-10mers Proanthocyanidin dimers Proanthocyanidin polymers (>10mers) Proanthocyanidin trimers

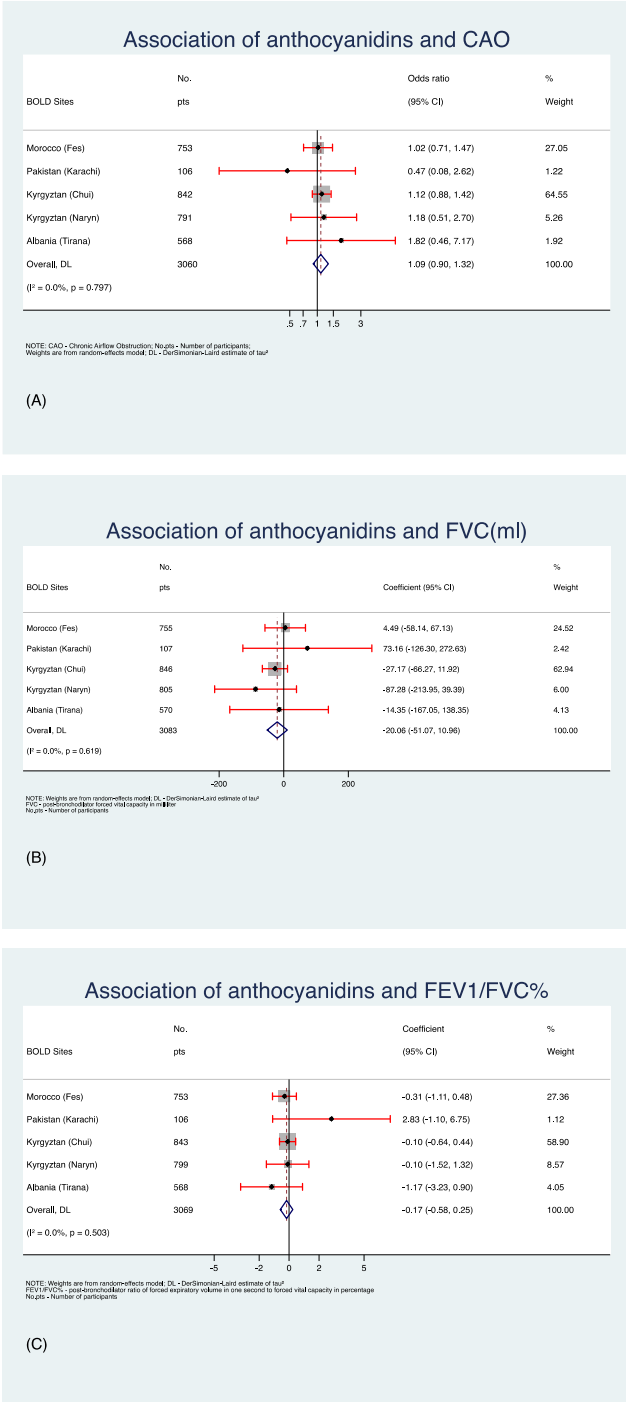
Appendix Table B.2 List of flavonoid-containing foods included in the BOLD study that were common to the food composition tables under study

Nuts	Vegetables	Fruits	Legumes
Almonds	Aubergine	Apple	Chickpeas
Cashew	Beetroot	Avocado	Fava beans
Peanuts	Brussels sprouts	Banana	Lentils
Pistachios	Cabbage (white, green, or red)	Berries (blueberries, strawberries, or blackberries)	Peas
	Carrot	Cherries	
	Cauliflower	Fig	
	Celery	Grapes	
	Courgette	Juice of lemon or orange	
	Cucumber	Pomegranate	
	Green leaves, small (purslane, watercress)	Mango	
	Ginger	Melon, watermelon	
	Herbs (fennel, basil, dill, coriander, parsley)	Orange	
	Lettuce	Peach	
	Onion	Pear	
	Potatoes	Pineapple	
	Radish	Plum	
	Spinach		
	Tomato		

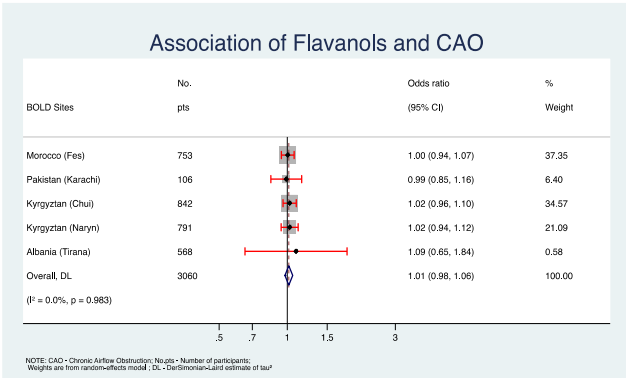
Appendix C. Supplementary Files for Chapter 4

Appendix Table C.1 Mean Daily Dietary Flavonoid Intake of participants in the BOLD I Survey, by Sites (N = 3925)

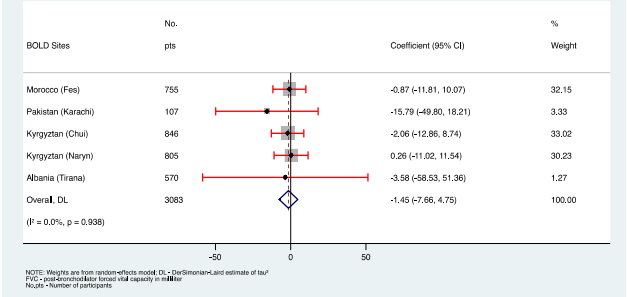
ESTIMATED DAILY FOOD AND NUTRIENT INTAKE	OVERALL N = 3,925	MOROCCO (FES) N = 917	PAKISTAN (KARACHI) N = 155	KYRGYZSTAN (CHUI) N = 1,004	KYRGYZSTAN (NARYN) N = 1,036	UK (LONDON) N = 107	INDIA (MYSORE) N = 111	ALBANIA (TIRANA) N = 595
Total Flavonoids (mg)	989.1 (599.4)	836.3 (559.6)	897.0 (398.9)	1,506.4 (539.5)	1,052.6 (410.7)	943.9 (579.1)	809.7 (212.2)	306.8 (159.4)
Anthocyanidins (mg)	50.6 (52.6)	66.4 (42.8)	23.5 (35.4)	77.2 (78.9)	26.0 (19.6)	43.3 (37.1)	26.7 (17.7)	37.3 (23.4)
Flavanol Monomers (mg)	265.0 (253.9)	384.4 (344.3)	224.3 (196.1)	349.3 (247.6)	229.4 (119.9)	221.4 (242.6)	140.6 (42.8)	42.2 (64.2)
Flavanol polymers (mg)	402.5 (368.9)	92.7 (165.9)	467.1 (269.7)	672.5 (281.5)	631.6 (307.4)	388.1 (316.2)	395.5 (134.9)	12.2 (39.6)
Total flavanols (mg)	667.5 (497.0)	477.1 (447.9)	691.4 (376.7)	1,021.8 (364.0)	861.1 (407.7)	609.5 (496.2)	536.0 (177.4)	54.5 (91.1)
Flavanones (mg)	29.4 (32.1)	50.3 (37.4)	12.5 (18.3)	13.8 (19.8)	14.1 (12.0)	47.7 (49.8)	12.5 (6.5)	54.8 (29.2)
Flavones (mg)	4.6 (3.5)	8.0 (3.1)	5.0 (2.9)	5.8 (3.5)	2.0 (1.4)	3.8 (2.7)	4.0 (2.0)	2.3 (1.2)
Flavonols (mg)	69.9 (31.3)	86.9 (30.8)	84.7 (29.8)	84.4 (31.8)	52.4 (18.0)	61.0 (31.6)	82.2 (27.1)	45.4 (12.7)
Isoflavones (mg)	1.2 (5.0)	1.8 (4.1)	1.1 (2.0)	0.5 (0.6)	0.3 (0.3)	14.1 (23.8)	2.1 (1.2)	0.5 (2.0)
Proanthocyanidins (mg)	162.2 (158.1)	142.0 (126.5)	77.0 (53.1)	297.5 (221.0)	95.0 (60.8)	159.7 (105.2)	145.5 (97.1)	107.6 (53.0)
Chalcones (mg)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)	0.0 (0.0)
Dihydrochalcones (mg)	3.5 (3.4)	3.8 (3.7)	1.9 (2.4)	5.5 (3.9)	1.7 (2.1)	3.3 (3.5)	0.7 (0.6)	4.1 (1.9)
Dihydroflavonols (mg)	0.1 (0.5)	0.0 (0.1)	0.0 (0.0)	0.0 (0.1)	0.0 (0.0)	1.5 (2.6)	0.0 (0.1)	0.3 (0.5)
Gallic Acid (mg)	13.5 (30.5)	49.4 (44.4)	0.2 (0.3)	1.6 (9.9)	0.9 (3.8)	12.2 (33.0)	13.8 (9.5)	3.8 (7.3)



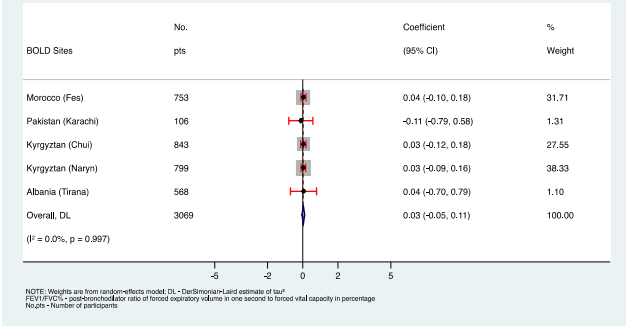
Appendix Figure C.1 Association of daily anthocyanidins intake (per 50 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 50 mg increase in daily anthocyanidins intake.]



(A)

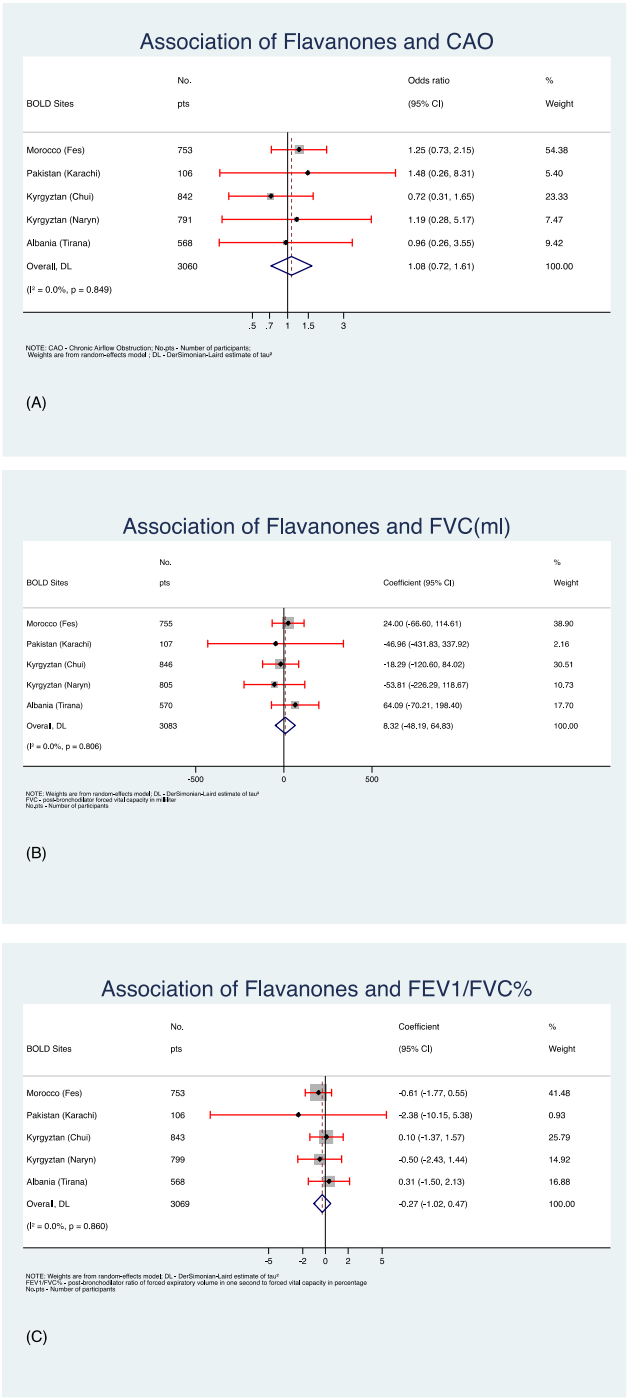


(B)

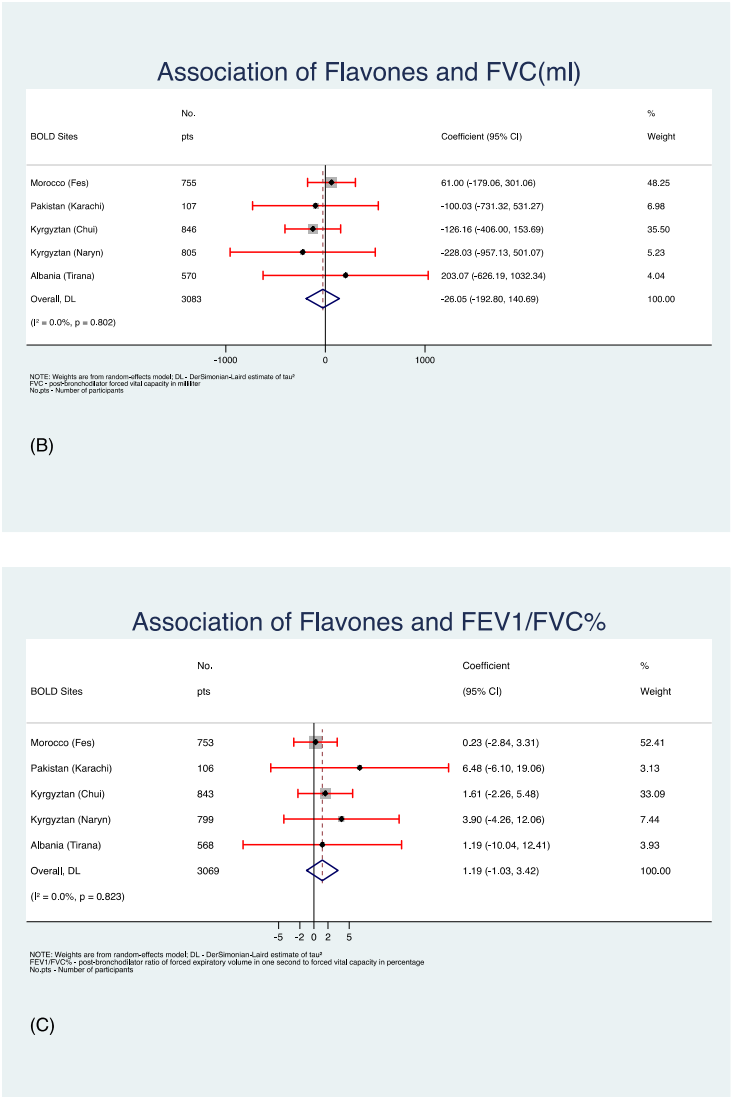


(C)

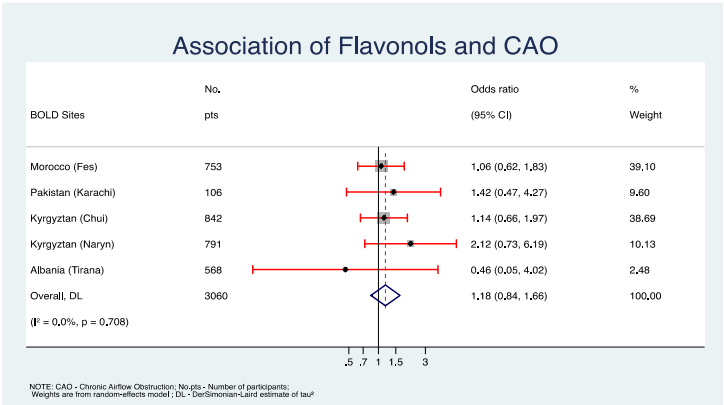
Appendix Figure C.2 Association of daily flavanols intake (per 100 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 100 mg increase in daily flavanols intake.]



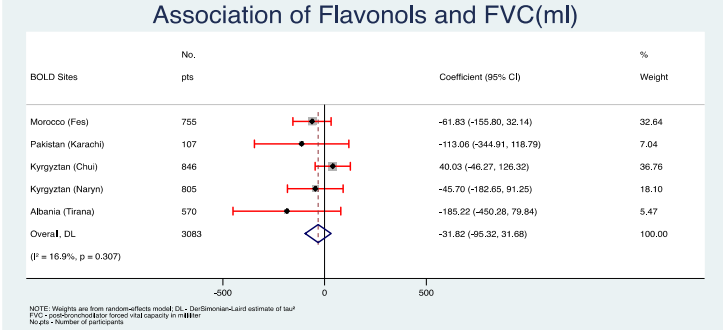
Appendix Figure C.3 Association of daily flavanones intake (per 50 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 50 mg increase in daily flavanones intake.]



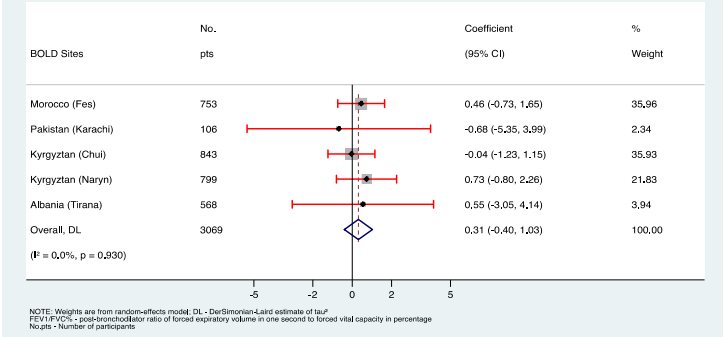
Appendix Figure C.4 Association of daily flavones intake (per 10 mg increase) with (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 10 mg increase in daily flavones intake.]



(A)

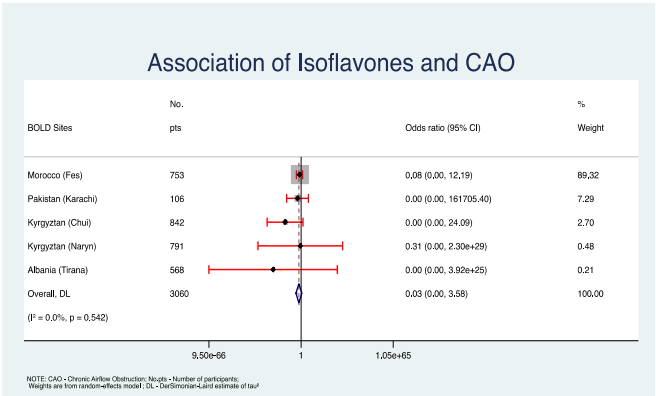


(B)

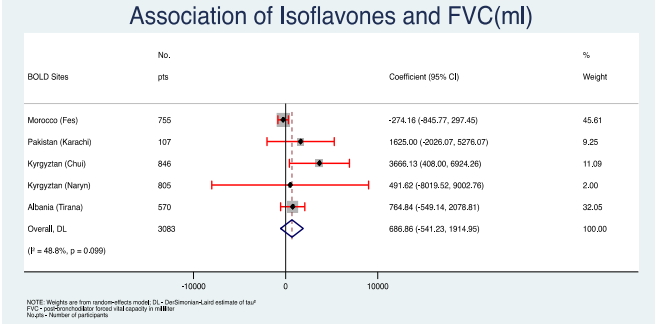


(C)

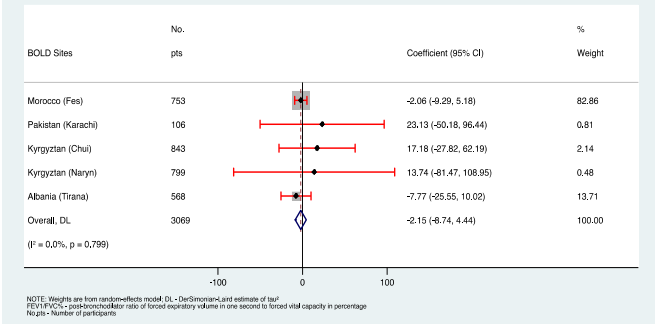
Appendix Figure C.5 Association of daily flavonols intake (per 50 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 50 mg increase in daily flavonols intake.]



(A)

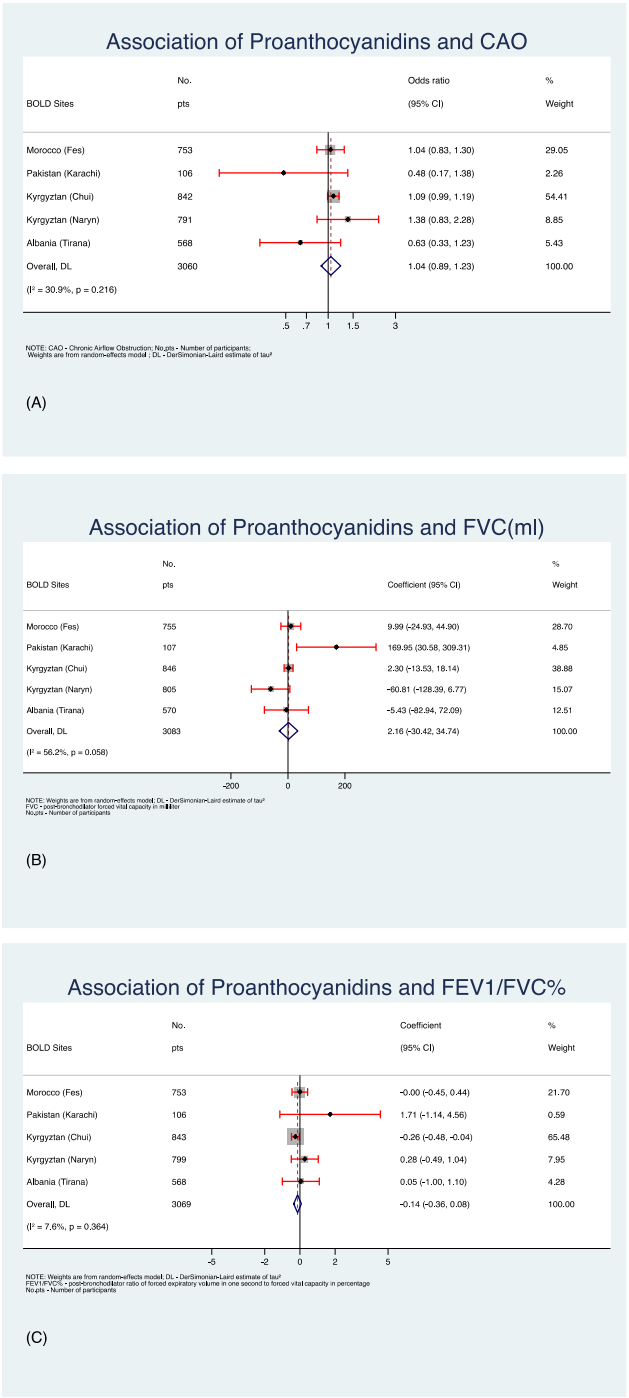


(B)



(C)

Appendix Figure C.6 Association of daily isoflavones intake (per 50 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 50 mg increase in daily isoflavones intake.]



Appendix Figure C.7 Association of daily proanthocyanidins intake (per 50 mg increase) with (A) CAO, (B) FVC, (ml) (C) FEV1/FVC% across sites participating in BOLD I dietary survey. [adjusted for sex, age, educational level, smoking status, BMI, wealth index, hypertension, diabetes, total energy intake, Omega-3 fatty acids, β-Carotene, vitamin C, vegetable diversity score, and fruit diversity score. The regression coefficient indicates the increase in (B) FVC (ml) (C) FEV_1/FVC% per 50 mg increase in daily proanthocyanidins intake.]