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Flavonoid intakes inversely associate with chronic obstructive pulmonary disease in smokers

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Take home message: While smoking cessation should remain the top priority for COPD prevention, the findings from this study suggest an importance of dietary flavonoids in partially mitigating the risk of COPD in persons who smoke or who used to smoke.

ABSTRACT

Introduction: Higher flavonoid intakes are beneficially associated with pulmonary function parameters, however, their association with chronic obstructive pulmonary disease (COPD) is unknown. This study aimed to examine associations between intakes of 1) total flavonoids, 2) flavonoid subclasses, and 3) major flavonoid compounds and incident COPD in participants from the Danish Diet, Cancer, and Health study.

Methods: This prospective cohort included 55,413 males and females without COPD, aged 50–65 years at recruitment. Habitual flavonoid intakes at baseline were estimated from a food frequency questionnaire using Phenol-Explorer. Danish nationwide registers were used to identify incident cases of COPD. Associations were modelled using restricted cubic splines within Cox proportional hazards models.

Results: During 23 years follow-up, 5557 participants were diagnosed with COPD. Of these, 4013 were current-, 1062 were former-, and 482 were never-smokers. After multivariable adjustments, participants with the highest, compared to the lowest, total flavonoid intakes had a 20% lower risk of COPD [Quintile 5 vs Quintile 1 HR (95% CI): 0.80 (0.74, 0.87)]; a 6-22% lower risk was observed for each flavonoid subclass. The inverse association between total flavonoid intake and COPD was present in both males and females but was only present in current [HR: 0.77 (0.70, 0.84)] and former [HR: 0.82 (0.69, 0.97)], but not never, smokers. Furthermore, higher flavonoid intakes appeared to lessen, but not negate, the higher risk of COPD associated with smoking intensity.

Conclusion: Dietary flavonoids may be important for partially mitigating the risk of smoking-related COPD. However, smoking cessation should remain highest priority.

Keywords: Epidemiology, diet, smoking, lung disease

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a common lung condition characterised by persistent respiratory symptoms and irreversible airflow limitations due to an abnormal inflammatory response of the lungs usually caused by significant exposure to noxious gases or particles [1, 2]. While smoking is the most common cause of COPD, other modifiable risk factors include air pollution, occupational exposure to dust, vapours and fumes, and respiratory infections in early life [3]; non-modifiable risk factors include age and genetic predisposition [4]. Given the high prevalence and burden of COPD worldwide, and that there is currently no cure [5], prevention strategies should be prioritised.

There is emerging evidence that diet impacts lung function and may play a protective role against COPD [6-8], likely through the modulation of inflammation and oxidative stress pathways which are implicated in the development of this chronic disease [9]. In a prospective cohort study of Swedish men, a strong inverse association between total fruit and vegetable consumption and COPD was observed in current and former smokers but not in never-smokers [10]. Fruit and vegetables, as well as tea, cocoa and other plant-based foods and beverages, are dietary sources of flavonoids – bioactive compounds that have been shown to reduce oxidative stress and systematic inflammation [11]. Flavonoids are a class of polyphenols, which can be further categorised into subclasses based on their chemical structure. Although epidemiological studies investigating the association between flavonoid intakes specifically and COPD are missing, there is some evidence that flavonoid intakes are favourably associated with pulmonary function parameters [12, 13] and less age-related decline in lung function [14].

Therefore, the primary aim of this study was to investigate the association between intakes of 1) total flavonoids, 2) flavonoid subclasses and 3) key flavonoid compounds within respective subclasses and incident COPD in the Danish Diet, Cancer, and Health cohort. In our previous work, a consistent finding is that associations between flavonoid intake and a range of chronic diseases (including cardiovascular disease, dementia, and diabetes [15, 16]) were stronger in current and former smokers. Given the importance of smoking as a risk factor for COPD, the purported anti-oxidant and anti-inflammatory properties of flavonoids, and that there is evidence of sex-related differences in COPD risk and outcomes [17], secondary aims were to explore interactions between flavonoid intake and risk factors for COPD, namely sex and smoking.

METHODS:

Study Population

The present study was conducted using data collected from participants of the Danish Diet, Cancer and Health study. A detailed description of the original study has been published previously [18]. In brief, 57,053 participants were recruited from of the cities of Copenhagen and Aarhus, in Denmark, between 1993 and 1997. Upon enrolment, 56,468 of these participants completed a food frequency questionnaire (FFQ) and had not been diagnosed with cancer. Data collected was cross-linked to the following nationwide registers, using the unique and permanent civil registration number assigned to all Danish residents: The Civil Registration System, The Integrated Database for Labor Market Research Database, and The Danish National Patient Register. The latter register [19] holds information on all hospital admissions and visits to outpatient clinics and urgent care centers in Denmark since 1978. It includes one primary diagnosis and one or more secondary diagnoses defined by the

International Classification of Diseases (ICD) [the 8th revision (ICD-8) until 1993 and the 10th revision (ICD-10) from 1994 to present]. In the present study, participants were excluded if they had a diagnosis of COPD, unspecified chronic bronchitis, or emphysema, prior to enrolment into the Danish Diet, Cancer and Health study (n=479; ICD-8: 491.00 – 492.09, ICD-10: J42 – J44), if they had reported improbable energy intakes [n=202; <2,092 kJ/day (<500 kcal/day) and >20,920 kJ/day (>5,000 kcal/day)], or if they had missing or extreme values for covariates (n=374; **Supplementary Figure E1**).

This study was approved by the Danish Data Protection Agency (Ref no 2012-58-0004 I-Suite nr: 6357, VD-2018-117).

Exposures

Primary exposures of interest in the present study were total flavonoid intakes (calculated by summing intakes of each of the 219 flavonoid compounds) and intakes of flavonoid subclasses and individual flavonoid compounds, with mean intakes >5 mg/day at baseline. A detailed description of how flavonoid intakes were estimated from the FFQ, using the Phenol-Explorer database [20], has been published previously [15]. In brief, flavonoid estimates (mg/100 g fresh food weight) for each food and beverage in the FFQ (n=174) were derived from the Phenol-Explorer database taking into consideration food processing using retention factors. These were then multiplied by intakes of respective foods and beverages (grams/day). In a post-hoc investigative analysis, smoking pack-years (lifetime average number of cigarettes smoked multiplied by the number of years smoked divided by 20) was modelled as the exposure of interest.

Study outcomes

The primary outcome was a first-time hospitalisation or outpatient visit with a primary or secondary diagnosis of COPD (ICD-10: J44), unspecified chronic bronchitis (ICD-10: J42) and emphysema (ICD-10: J43). The ICD-10 code J44 has previously been validated in the Danish National Patient Register and has a positive predictive value of 92% [95% confidence interval (CI): 91 – 93%] [21]. As patients with COPD may have been coded as having unspecified chronic bronchitis (ICD-10: J42) or emphysema (ICD-10: J43) these were also included. A first-time diagnosis of COPD is the only validated method to identify COPD in Danish registers; hereinafter this will be referred to as incident COPD. Most cases were identified by ICD-10 codes DJ449 (~69%), DJ441 (~12%), and DJ429 (~8%).

Covariates

A description of the covariates used is given in the Supplementary Material.

Statistical Analysis

Multivariable Cox proportional hazards models were used to investigate relationships between self-reported flavonoid intake and incident COPD. Each participants' time-to-event was calculated from the date of enrolment into the Danish Diet Cancer and Health study up until the date of a first-time diagnosis of COPD, death, emigration from Denmark, or the end of follow-up (August, 2017), whichever came first. Cox proportional hazards assumptions were tested by plotting Schoenfeld residuals, with no violation found. To allow the association between all continuous covariates, including the exposures of interest, and outcome to be non-linear, these variables were modelled with restricted cubic splines using the 'rms' R package with the rcs() function [22] in R. Quintiles of each flavonoid exposure

variable were generated, and the median value of each quintile was calculated. Hazard ratios (HRs), obtained from the Cox proportional hazards models described above, are relative to the median flavonoid intake in quintile 1 (reference value); these were plotted against the exposure variable, with 95% CI bands provided. In addition, HRs and 95% CIs were calculated from the fitted models, comparing the median of each quintile to the reference value of the median in quintile 1, and tabulated. For simpler visualisation, figures only include individuals with intakes ≤3 standard deviations above the mean. Three models of adjustment were used: 1) minimally adjusted: age (years) and sex; 1b) multivariable-adjusted: age, sex, BMI, smoking status (current/former/never), smoking pack-years, physical activity (total daily metabolic equivalent), pure alcohol intake (g/d), education (≤7 years/8 – 10 years/≥11 years), and socio-economic status (income); 2) multivariable-adjusted including potential dietary confounders: all variables in Model 1b plus energy intake (kJ/day) and intakes (g/d) of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids. Confounders were selected based on *a priori* knowledge [23-26]. A secondary aim was to investigate interactions with established risk factors for COPD [3] for which data had been collected at baseline (specifically, smoking status and sex). Firstly, analyses were stratified by sex and smoking status to examine the consistency of the associations. As there is potential for residual confounding by smoking intensity, when stratifying by smoking status, smoking pack-years was included as a covariate in the model. Interaction on the multiplicative scale was assessed by likelihood ratio tests of Cox proportional hazards models with and without the interaction terms. Secondly, standard logistic regression models were used to obtain the 20-year absolute risk estimates of a healthcare visit for COPD. These analyses used a binary outcome designating the occurrence of a COPD healthcare visit during the first 20 years of follow-up. Unless indicated by the relevant stratification variable, these estimates are for the ‘average’,

smoking cohort participant, i.e. a smoker, aged 56 years, with a BMI of 25.5 kg/m^2, a total daily metabolic equivalent score of 56, a mean household income of 394,701 – 570,930 DKK/year, and an alcohol intake of 13 g/day. In a post-hoc investigative analysis, we explored whether flavonoid intake modified the association between smoking intensity (represented by pack-years) and COPD, by plotting the predicted risk of COPD after 20 years of follow up against pack-years, separately for males and females in the highest and lowest flavonoid intake quintiles. For the aforementioned analysis, smoking pack-years was entered in the model as a restricted cubic spline. Finally, to avoid the potential for preclinical COPD leading to reverse causation, as a sensitivity analysis we omitted all cases that occurred within the first 5 years of follow-up. All analyses were undertaken using STATA/IC 14.2 (StataCorp LLC) and R statistics (R Core Team, 2021 [27]).

RESULTS

In this population of 55,413 Danish residents with a median age of 56 years, 5,557 incident cases of COPD were identified during a maximum of 23 years of follow-up (median [IQR] follow-up: 21 [19 – 22] years). Furthermore, 11,195 participants died without a prior hospital diagnosis of COPD and 276 (~0.5%) were lost to follow-up.

Baseline characteristics

Overall, the cohort reported a daily median [IQR] habitual flavonoid intake of 496 mg [287 – 805]. Participants with higher total flavonoid intakes tended to be female and were more likely to be non-smokers, have a lower BMI, exercise more, and have a higher education and income. Those consuming more flavonoids also ate, on average, more fish, wholegrains, fruits, and vegetables, and less red and processed meat (**Table 1**).

Associations of total and flavonoid subclass intakes with incident COPD

The inverse association between total flavonoid intake and incident COPD was non-linear ($p_{non\text{-}linearity}$<0.001); the steepness of the slope decreased as flavonoid intakes increased (**Figure 2**). Compared to participants in quintile 1, participants in quintile 5 had a 20% lower risk of COPD [HR (95% CI): 0.80 (0.74, 0.87)] after multivariable adjustments (Model 1b; **Table 2**). Non-linear associations were also observed for all flavonoid subclasses ($p_{non\text{-}linearity}$<0.001 for all; Figure 2). Comparing high (quintile 4 or 5) to low intakes (quintile 1), the risk of COPD was up to 18% lower for flavonols, 14% lower for flavanol monomers, 22% lower for flavanol oligo + polymers, 12% lower for anthocyanins, 9% lower for flavanones, and 15% lower for flavones, after multivariable adjustments (Model 1b; **Table 2**). Significant associations were apparent for total flavonoid intakes [Q5 vs Q1: 0.85 (0.78, 0.92)] and intakes of all flavonoid subclasses when potential dietary confounders were included as predictors in the model (Model 2; **Table 2**).

Associations between major flavonoid compound intakes and incident COPD

Non-linear associations with incident COPD were observed for intakes of all major flavonoid compounds ($p_{non\text{-}linearity}$<0.001 for all; **Figure 2**). Clear plateaus in the association were seen for intakes of kaempferol, quercetin, epicatechin, hesperidin and apigenin. Associations appeared to be more linear for intakes of malvidin and both proanthocyanidin dimers and trimers and somewhat ‘u-shaped’ for intakes of cyanidin and delphinidin. The lowest hazard ratios observed were for participants with the highest intakes of malvidin [Q5 vs Q1: 0.63 (0.57, 0.70); Model 1b; **Supplementary Table 2**].

Association between total flavonoid intake and incident COPD stratified by sex and smoking

Of the 5557 participants who were diagnosed with COPD during follow-up, 2605 were male and 2952 were female. The association between total flavonoid intake and incident COPD was present in both males and females although the shapes of the associations differed; the association for females was initially steeper plateauing at a total flavonoid intake of approximately 500 mg/d ($p_{non\text{-}linearity}$=0.013) while the association for males was more linear ($p_{non\text{-}linearity}$=0.506; $p_{interaction}$<0.001; **Figure 3).** On an absolute scale, females had a higher risk of COPD than males irrespective of their smoking status or flavonoid intake (**Table 3**).

Of the 5557 COPD events, 4013 were in current smokers, 1062 were in former smokers, and 482 were in never-smokers. While a clear inverse association between total flavonoid intake and incident COPD was present in current/former (termed "ever") smokers, there was no inverse association in those who had never smoked ($p_{interaction}$=0.017; **Figure 3**). Current and former smokers with the highest total flavonoid intakes had a 23% and 18% lower risk of COPD, respectively, [current smokers Q5 vs Q1: 0.77 (0.70, 0.84); former smokers Q5 vs Q1: 0.82 (0.69, 0.97)] after multivariable adjustments (Model 1b; **Supplementary Tables 3 and 4**). Hazard ratios for other flavonoid subclasses and compounds among current and former smokers only are presented in **Supplementary Tables 3 – 6**. On an absolute scale, current and former smokers had a substantially higher risk of COPD than non-smokers irrespective of their flavonoid intake, although current smokers with a low flavonoid intake were at the highest risk (**Table 3**). For participants who were current smokers at baseline, the difference in the 20-year predicted risk of COPD between a participant in the highest versus the lowest flavonoid intake quintile was 5.21% for males and 6.20% for females (**Table 3**). Furthermore, for both males and females, flavonoid intakes appeared to modify the

association between smoking intensity (pack-years) and predicted risk of COPD at 20 years in that participants with the highest flavonoid intakes (quintile 5) had a lower predicted risk of COPD than their low flavonoid consuming (quintile 1) counterparts (**Figure 4**).

Sensitivity analysis

Excluding events within the first 5 years of follow-up did not materially alter the observed associations (Supplementary Table 7).

DISCUSSION

In this 23-year prospective cohort study of 55,413 Danish residents, we observed that baseline intakes of each flavonoid subclass, and all major flavonoid compounds investigated, were non-linearly inversely associated with incident COPD. The association between total flavonoid intake and incident COPD was only present in current and former smokers, who accounted for 91% of the COPD events observed. In the present study, the 'average' cohort participant who was both a current smoker and a low flavonoid consumer at baseline, had between a ~6% (females) and ~5% (males) higher risk of COPD than their high-flavonoid consuming counterparts. Furthermore, a high flavonoid intake appeared to lessen, but not negate, the risk of COPD associated with higher smoking intensity.

In 2001, the first study to examine the association between dietary flavonoid intake and lung function reported a beneficial inverse association between intakes of catechins, flavonols, and flavones (the only flavonoid subclasses for which food content data was available at the time) and forced expiratory volume in one second (FEV_1) [28]. Despite these findings, there have been very few studies since. A longitudinal analysis of participants of the Veterans Affairs Normative Aging Study [14] demonstrated inverse associations between anthocyanin intake and age-related decline in lung function, a risk factor for COPD [29], in current, former, and

never smokers. More recently, two cross-sectional studies report protective associations between various flavonoid subclasses and pulmonary function parameters [12, 13]. To our knowledge, the present study is the first to investigate associations between dietary flavonoid intakes and incident COPD. Our findings of clear inverse associations for all flavonoid subclasses, after multivariable adjustments for demographic, lifestyle and dietary confounders, highlights the need for further research in this important, yet sparsely investigated, area. Furthermore, that we see evidence of a plateau in the association, even in high-risk groups, points to optimal flavonoid intakes that are achievable with diet alone.

In the present study, the association between flavonoid intake and COPD was only present in current and former smokers and the absolute risk of COPD in both current and former smokers was lower for those with the highest flavonoids intakes; this aligns with the hypothesis that flavonoids may work to counteract, in part, the increase in systemic inflammation and oxidative stress, induced by smoking [30], that gives rise to COPD [31]. This hypothesis is supported by findings from our post-hoc exploratory analysis that the risk of COPD associated with a higher number of smoking pack-years is lower in participants who consume more flavonoid-rich foods. There is a substantial overlap between pathways involved in cigarette smoke-induced inflammation and oxidative stress [31, 32] and those identified as being modulated by flavonoids [33]. That flavonoids may protect against COPD by inhibiting oxidative stress and inflammation through these signalling pathways has been demonstrated in a cigarette smoke-induced COPD mouse model supplemented with flavonoids extracted from loquat leaves [34] and a cigarette smoke-induced COPD rat model where the animals were supplemented with the flavonoid, fisetin [35]. While human intervention studies are lacking, a 2-week supplementation with flavonoid-rich grape juice decreased smoking-induced inflammation in a randomised controlled trial conducted in healthy smokers [36]. In the present study, on the relative scale, the association between total

flavonoid intake and COPD was apparent in both males and females, although the shapes of the associations appeared to differ. The reasons underpinning this are difficult to determine given that, due to the complexity of interacting physiological, behavioral, and/or genetic factors, it is not yet fully understood why women have a higher risk of COPD than men [37].

In the present study, the 'average' cohort participant who was both a current smoker and a low flavonoid consumer at baseline, had a ~6% (for females) or ~5% (for males) higher risk of COPD than their high-flavonoid consuming counterparts. This risk difference was less for former smokers (~2% each for males and females) although their risk of COPD was approximately one third that of current smokers. Reducing COPD cases by ~2% in former smokers and ~5-6% in current smokers would have a huge public health impact and begs the question of whether dietary modifications should be of higher priority in current and former smokers. However, irrespective of flavonoid intake, both current and former smokers had a substantially higher risk of COPD (~8 and ~3 fold higher, respectively) than non-smokers reminding us that targeting smoking cessation is, and must continue to be, the top priority for reducing COPD risk.

The current study has numerous strengths including a large adult population followed for 23 years with a relatively large number of events, allowing us to examine associations in subpopulations, and a negligible loss to follow-up, allowing for the estimation of absolute risks. Although our hypothesis and subsequent findings are supported by mechanistic evidence, this study is observational in nature and thus we cannot confirm causality. We also acknowledge that persons in this cohort with a higher flavonoid intake tended to have healthier diet and lifestyle and we cannot rule out the possibility of residual or unmeasured confounding. Furthermore, there may have been misclassification in the exposures as diet was self-reported using an FFQ and may have changed over time. Likewise, smoking status

and intensity were only captured at baseline and thus changes during follow-up could not be accounted for. In the DNPR, COPD diagnoses are underreported and diagnosis in primary care only would not have been captured, which may have led to lower estimation of COPD events during follow-up [21]. However, these exposure and outcome misclassifications would likely bias examined associations toward the null. Moreover, clinical data on COPD severity such as spirometry data and symptom severity of COPD were not available.

We show that smoking and former-smoking persons consuming a flavonoid-rich diet have a lower risk of COPD than those with low flavonoid intakes. While the findings of this study suggest an importance of dietary flavonoids, in partially mitigating the risk of COPD in persons who smoke, both current and former smokers remained at a substantially higher risk of COPD compared to non-smokers indicating that dietary modifications should be secondary to smoking cessation.

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REFERENCES

1. Brusselle GG, Joos GF, Bracke KR. New insights into the immunology of chronic obstructive pulmonary disease. *Lancet* 2011: 378(9795): 1015-1026.
2. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the Diagnosis, Management, and Prevention of Chronic Obstructive Pulmonary Disease (2021 Report). 2021 [cited; Available from: https://goldcopd.org/wp-content/uploads/2020/11/GOLD-REPORT-2021-v1.1-25Nov20_WMV.pdf
3. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *Lancet* 2007: 370(9589): 765-773.
4. Australian Institute of Health and Welfare. COPD, associated comorbidities and risk factors. 2016 [cited 2019 13 February]; Available from: https://www.aihw.gov.au/reports/chronic-respiratory-conditions/copd-associated-comorbidities-risk-factors/contents/about-copd-and-associated-comorbidities
5. Calzetta L, Ritondo BL, Matera MG, et al. Investigational treatments in phase I and II clinical trials: a systematic review in chronic obstructive pulmonary disease (COPD). *Expert Opin Investig Drugs* 2020: 29(7): 723-738.
6. Vasankari T, Härkänen T, Kainu A, et al. Predictors of New Airway Obstruction–An 11 Year's Population-Based Follow-Up Study. *COPD* 2019: 16(1): 45-50.
7. Zheng P-F, Shu L, Si C-J, et al. Dietary patterns and chronic obstructive pulmonary disease: a meta-analysis. *COPD* 2016: 13(4): 515-522.
8. Whyand T, Hurst J, Beckles M, et al. Pollution and respiratory disease: can diet or supplements help? A review. *Respir Res* 2018: 19(1): 1-14.
9. Kirkham PA, Barnes PJ. Oxidative stress in COPD. *Chest* 2013: 144(1): 266-273.
10. Kaluza J, Larsson SC, Orsini N, et al. Fruit and vegetable consumption and risk of COPD: a prospective cohort study of men. *Thorax* 2017: 72(6): 500-509.
11. Wu M, Luo Q, Nie R, et al. Potential implications of polyphenols on aging considering oxidative stress, inflammation, autophagy, and gut microbiota. *Crit Rev Food Sci Nutr* 2020: 1-19.
12. Garcia-Larsen V, Thawer N, Charles D, et al. Dietary intake of flavonoids and ventilatory function in European adults: A GA2LEN study. *Nutrients* 2018: 10(1): 95.
13. Pounis G, Arcari A, Costanzo S, et al. Favorable association of polyphenol-rich diets with lung function: Cross-sectional findings from the Moli-sani study. *Respir Med* 2018: 136: 48-57.
14. Mehta AJ, Cassidy A, Litonjua AA, et al. Dietary anthocyanin intake and age-related decline in lung function: longitudinal findings from the VA Normative Aging Study–3. *Am J Clin Nutr* 2016: 103(2): 542-550.
15. Bondonno NP, Dalgaard F, Kyrø C, et al. Flavonoid intake is associated with lower mortality in the Danish Diet Cancer and Health Cohort. *Nat Commun* 2019: 10(1): 1-10.
16. Bondonno CP, Bondonno NP, Dalgaard F, et al. Flavonoid intake and incident dementia in the Danish Diet, Cancer, and Health cohort. 2021: 7(1): e12175.

17. Perez TA, Castillo EG, Ancochea J, et al. Sex differences between women and men with COPD: A new analysis of the 3CIA study. *Respiratory Medicine* 2020: 171: 106105.
18. Tjønneland A, Olsen A, Boll K, et al. Study design, exposure variables, and socioeconomic determinants of participation in Diet, Cancer and Health: a population-based prospective cohort study of 57,053 men and women in Denmark. *Scand J Public Health* 2007: 35(4): 432-441.
19. Lynge E, Sandegaard JL, Rebolj M. The Danish national patient register. *Scand J Public Health* 2011: 39(7_suppl): 30-33.
20. Neveu V, Perez-Jiménez J, Vos F, et al. Phenol-Explorer: an online comprehensive database on polyphenol contents in foods. *Database* 2010: 2010.
21. Thomsen RW, Lange P, Hellquist B, et al. Validity and underrecording of diagnosis of COPD in the Danish National Patient Registry. *Respir Med* 2011: 105(7): 1063-1068.
22. Gauthier J, Wu Q, Gooley T. Cubic splines to model relationships between continuous variables and outcomes: a guide for clinicians. Nature Publishing Group, 2019.
23. Mannino DM, Buist AS. Global burden of COPD: risk factors, prevalence, and future trends. *The Lancet* 2007: 370(9589): 765-773.
24. Hanson C, Rutten EP, Wouters EF, et al. Influence of diet and obesity on COPD development and outcomes. *Int J Chron Obstruct Pulmon Dis* 2014: 9: 723.
25. Scoditti E, Massaro M, Garbarino S, et al. Role of diet in chronic obstructive pulmonary disease prevention and treatment. *Nutrients* 2019: 11(6): 1357.
26. Tabak C, Smit H, Heederik D, et al. Diet and chronic obstructive pulmonary disease: independent beneficial effects of fruits, whole grains, and alcohol (the MORGEN study). *Clin Exp Allergy* 2001: 31(5): 747-755.
27. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/. 2019.
28. Tabak C, ARTS IC, Smit HA, et al. Chronic obstructive pulmonary disease and intake of catechins, flavonols, and flavones: the MORGEN Study. *Am J Respir Crit Care Med* 2001: 164(1): 61-64.
29. Mannino DM, Davis KJ. Lung function decline and outcomes in an elderly population. *Thorax* 2006: 61(6): 472-477.
30. Yanbaeva DG, Dentener MA, Creutzberg EC, et al. Systemic effects of smoking. *Chest* 2007: 131(5): 1557-1566.
31. Boutten A, Goven D, Artaud-Macari E, et al. NRF2 targeting: a promising therapeutic strategy in chronic obstructive pulmonary disease. *Trends Mol Med* 2011: 17(7): 363-371.
32. van der Vaart H, Postma DS, Timens W, et al. Acute effects of cigarette smoke on inflammation and oxidative stress: a review. *Thorax* 2004: 59(8): 713-721.
33. Chen L, Teng H, Jia Z, et al. Intracellular signaling pathways of inflammation modulated by dietary flavonoids: The most recent evidence. *Crit Rev Food Sci Nutr* 2018: 58(17): 2908-2924.
34. Jian T, Chen J, Ding X, et al. Flavonoids isolated from loquat (Eriobotrya japonica) leaves inhibit oxidative stress and inflammation induced by cigarette smoke in COPD mice: the role of TRPV1 signaling pathways. *Food Funct* 2020: 11(4): 3516-3526.
35. Hussain T, Al-Attas OS, Alamery S, et al. The plant flavonoid, fisetin alleviates cigarette smoke-induced oxidative stress, and inflammation in Wistar rat lungs. *J Food Biochem* 2019: 43(8): e12962.
36. Kokkou E, Siasos G, Georgiopoulos G, et al. The impact of dietary flavonoid supplementation on smoking-induced inflammatory process and fibrinolytic impairment. *Atherosclerosis* 2016: 251: 266-272.
37. DeMeo DL, Ramagopalan S, Kavati A, et al. Women manifest more severe COPD symptoms across the life course. *Int J Chron Obstruct Pulmon Dis* 2018: 13: 3021.

FIGURES

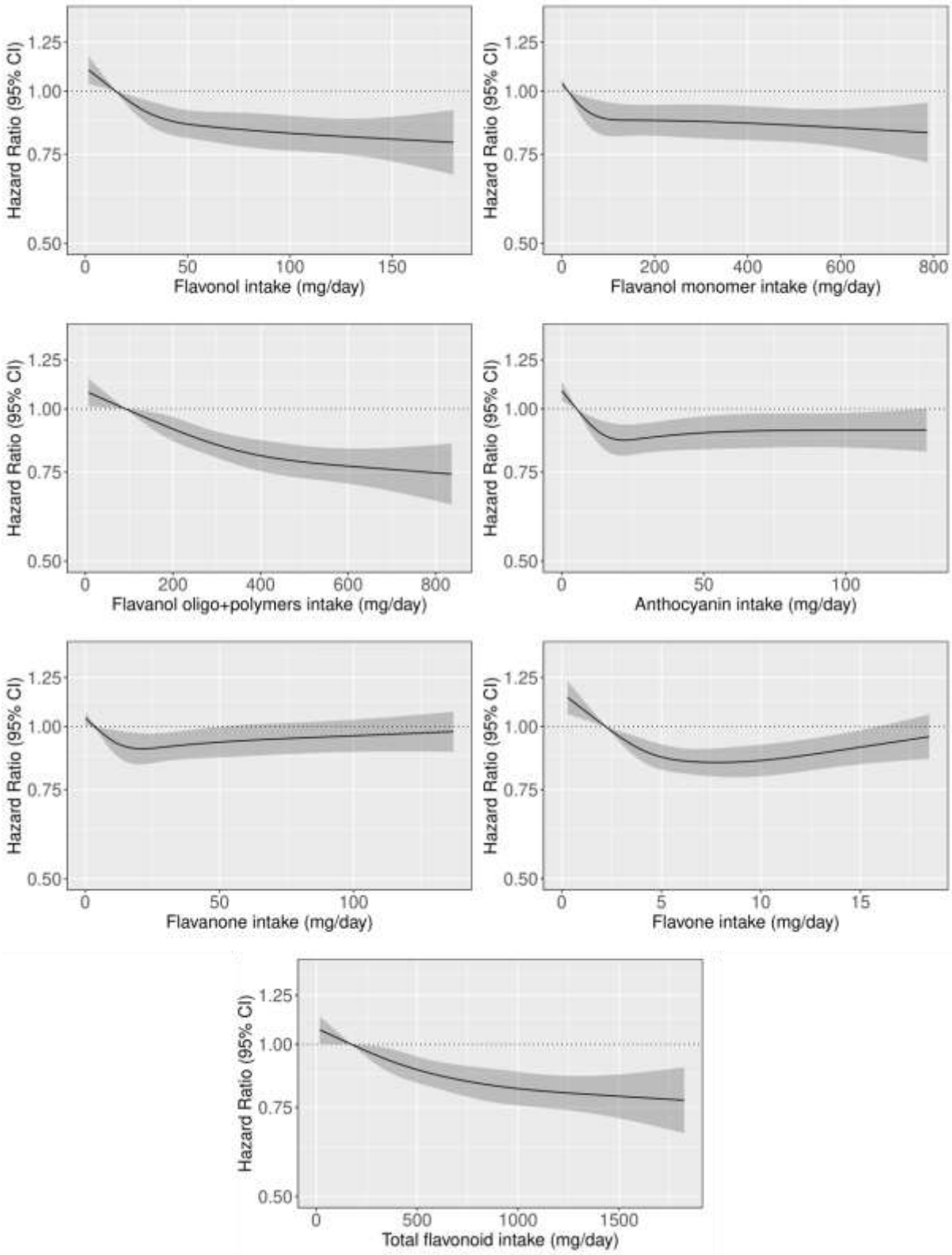

Hazard Ratio (95% CI)
1.25
1.00
0.75
0.50
0
50
100
150
Flavonol intake (mg/day)
0
200
400
600
800
Flavanol monomer intake (mg/day)
Flavanol oligo+polymers intake (mg/day)
Anthocyanin intake (mg/day)
Flavanone intake (mg/day)
0
5
10
15
Flavone intake (mg/day)
500
1000
1500
Total flavonoid intake (mg/day)

Figure 1. Cubic spline curves describing the association between total flavonoid and flavonoid subclass intakes and chronic obstructive pulmonary disease (COPD) related healthcare visits in participants of the Danish Diet Cancer and Health cohort (n=55,413). Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, smoking pack-years, physical activity, education, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile.

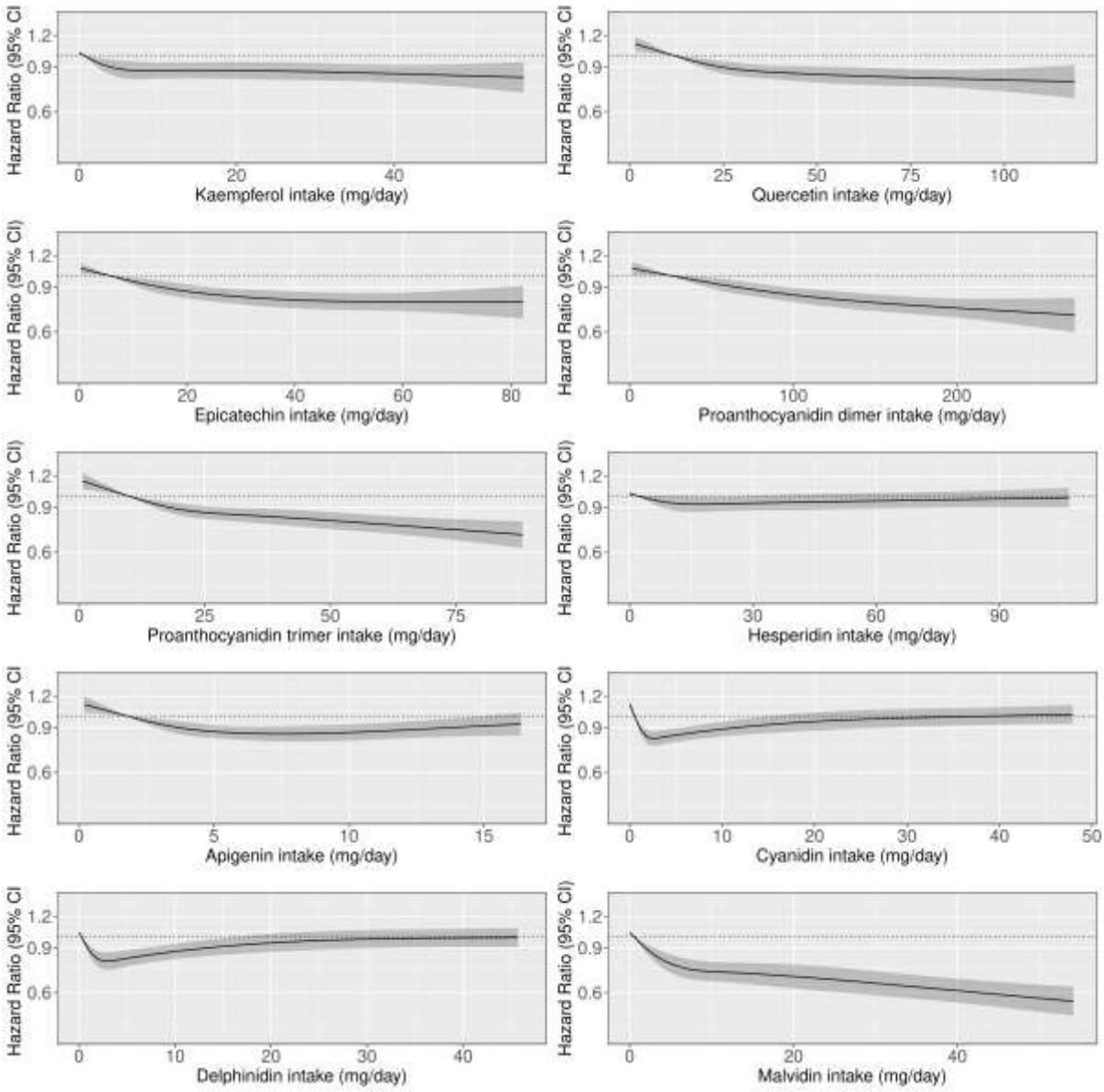


Figure 2. Cubic spline curves describing the association between major flavonoid compound intake and chronic obstructive pulmonary disease (COPD) related healthcare visits in participants of the Danish Diet Cancer and Health cohort (n=55,413). Hazard ratios and 95% CI's are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, smoking pack-years, physical activity, social economic status (income), and alcohol intake (Model 1b) and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile.

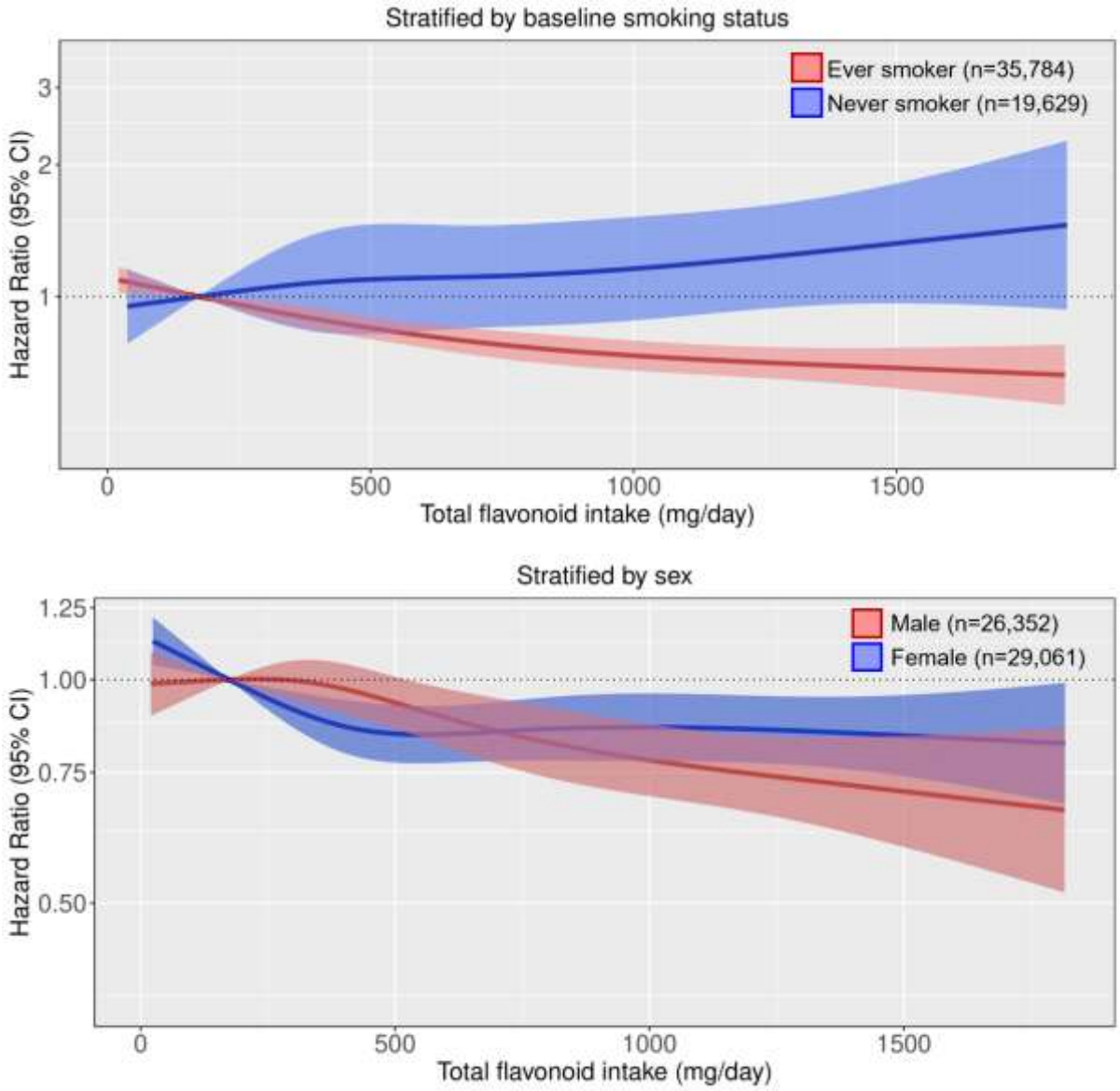


Figure 3. Multivariable-adjusted association between total flavonoid intake and chronic obstructive pulmonary disease (COPD) related healthcare visits stratified by baseline smoking status and sex. Hazard ratios and 95% CI's are based on Cox proportional hazards models and are comparing the specific level of flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile (174 mg/day). All analyses were standardized for age, sex, BMI, smoking status, smoking pack-years, physical activity, social economic status (income), education, and alcohol intake (Model 1b).

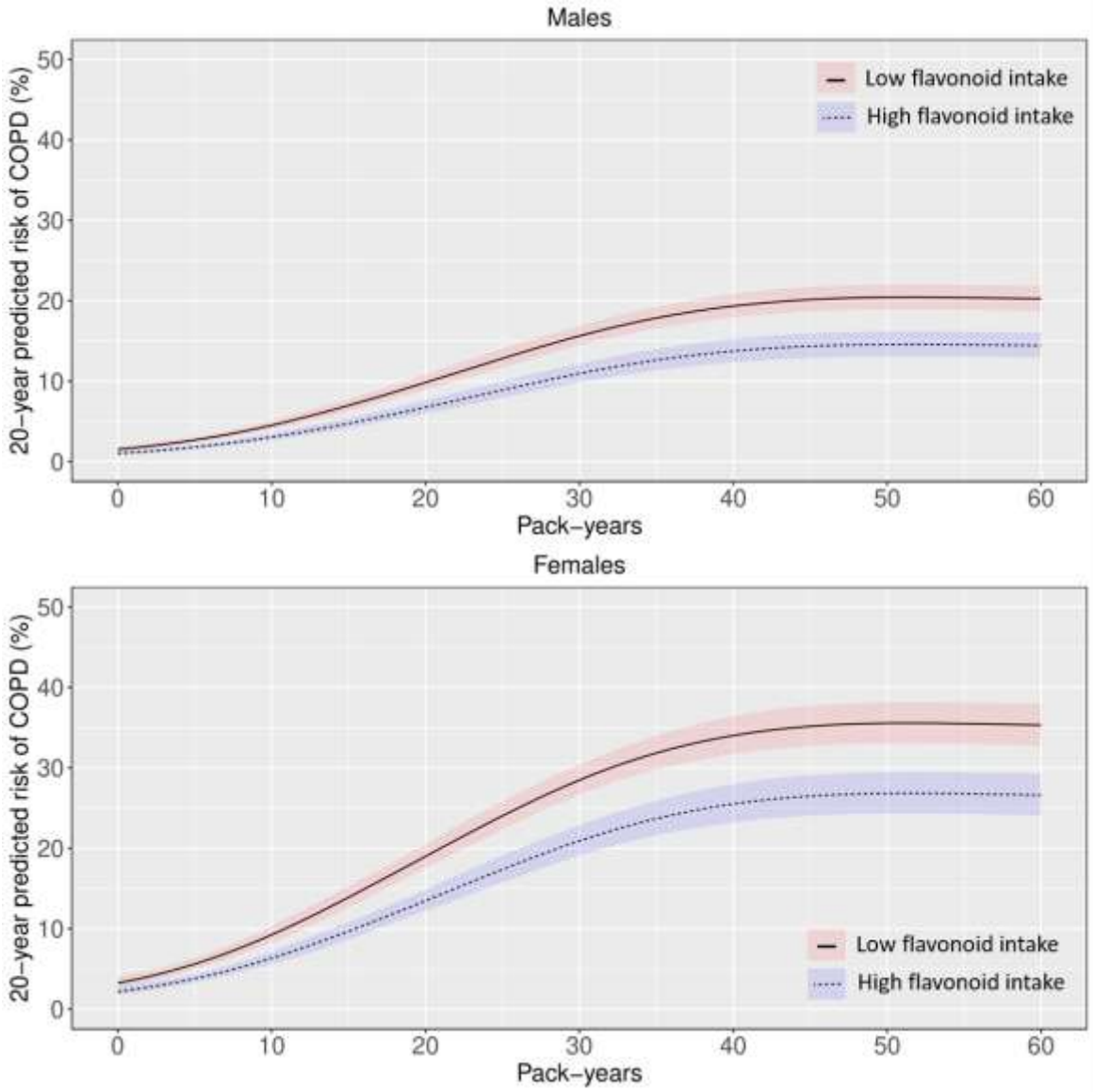


Figure 4. The 20-year predicted risks (%) and 95% confidence bands of chronic obstructive pulmonary disease (COPD by smoking pack-years for high (quintile 5) versus low (quintile 1) total flavonoid intakes, presented separately for males and females. The predicted risks are calculated from logistic regression models and are for a participant aged 56 years, with a BMI of 25.5, a total daily metabolic equivalent score of 56, with a mean household income of 394,701 – 570,930 DKK/year, and an alcohol intake of 13 g/day.

Table 1. Baseline characteristics of study population

	Total population n = 55,413	Total flavonoid intake quintiles				
		Q1 n = 11,083	Q2 n = 11,083	Q3 n = 11,082	Q4 n = 11,083	Q5 n = 11,082
Total flavonoid intake (mg/d)	496 [287 – 805]	174 [127 – 213]	321 [287 – 357]	496 [442 – 549]	727 [660 – 805]	1203 [1025 – 1436]
Sex (male)	26,352 (47.6)	6410 (57.8)	5669 (51.2)	5279 (47.6)	4923 (44.4)	4071 (36.7)
Age (years)	56 [52 – 60]	56 [52 – 60]	56 [52 – 60]	56 [52 – 60]	56 [52 – 60]	55 [52 – 60]
BMI (kg/m^2)	25.5 [23.3, 28.2]	26.1 [23.8, 28.9]	25.9 [23.6, 28.5]	25.6 [23.3, 28.3]	25.3 [23.2, 27.9]	24.9 [22.7, 27.4]
MET score	56.5 [37.0, 84.8]	51.0 [32.3, 78.0]	55.5 [36.3, 84.0]	57.4 [38.0, 85.0]	58.5 [38.5, 87.0]	60.0 [39.8, 88.5]
Smoking status						
Never	19,629 (35.4)	2737 (24.7)	3743 (33.8)	3982 (35.9)	4442 (40.1)	4725 (42.6)
Former	15,862 (28.6)	2659 (24.0)	2969 (26.8)	3203 (28.9)	3527 (31.8)	3504 (31.6)
Current	19,922 (36.0)	5692 (51.3)	4364 (39.4)	3895 (35.2)	3112 (28.1)	2859 (25.8)
Education						
≤7 years	18,143 (32.7)	5051 (45.6)	4191 (37.8)	3539 (31.9)	2972 (26.8)	2390 (21.6)
8–10 years	25,558 (46.1)	4847 (43.7)	5211 (47.0)	5298 (47.8)	5250 (47.4)	4952 (44.7)
≥11 years	11,684 (21.1)	1184 (10.7)	1670 (15.1)	2239 (20.2)	2852 (25.7)	3739 (33.7)
Mean household income						
≤394,700 DKK/year	13,634 (24.6)	3270 (29.5)	2694 (24.3)	2658 (24.0)	2535 (22.9)	2477 (22.3)
394,701 – 570,930 DKK/year	13,842 (25.0)	3238 (29.2)	2959 (26.7)	2683 (24.2)	2565 (23.1)	2397 (21.6)
570,931 – 758,297 DKK/year	13,953 (25.2)	2909 (26.2)	3011 (27.2)	2870 (25.9)	2598 (23.4)	2565 (23.1)
> 758,297 DKK/year	13,984 (25.2)	1671 (15.1)	2412 (21.8)	2869 (25.9)	3383 (30.5)	3649 (32.9)
Hypertensive	9,288 (16.8)	1839 (16.6)	1891 (17.1)	1888 (17.0)	1846 (16.7)	1824 (16.5)
Hypercholesterolemic	4,138 (7.5)	902 (8.1)	820 (7.4)	845 (7.6)	848 (7.7)	723 (6.5)
Comorbidities						
Diabetes	1158 (2.1)	275 (2.5)	215 (1.9)	249 (2.2)	211 (1.9)	208 (1.9)
Ischemic heart disease	2116 (3.8)	561 (5.1)	403 (3.6)	424 (3.8)	383 (3.5)	345 (3.1)
Ischemic stroke	769 (1.4)	214 (1.9)	145 (1.3)	145 (1.3)	130 (1.2)	135 (1.2)
CKD	200 (0.4)	42 (0.4)	33 (0.3)	43 (0.4)	42 (0.4)	40 (0.4)
Medication use						
Insulin treated	683 (1.2)	158 (1.4)	121 (1.1)	152 (1.4)	129 (1.2)	123 (1.1)
Antihypertensive	6797 (12.3)	1337 (12.1)	1398 (12.6)	1379 (12.4)	1348 (12.2)	1335 (12.0)
Statin	1085 (2.0)	265 (2.4)	214 (1.9)	222 (2.0)	213 (1.9)	171 (1.5)

HRT						
Never	15,810 (54.4)	2584 (55.2)	3014 (55.7)	3241 (55.9)	3233 (52.5)	3738 (53.3)
Current	8742 (30.1)	1282 (27.4)	1551 (28.7)	1682 (29.0)	1996 (32.4)	2231 (31.8)
Former	4478 (15.4)	803 (17.2)	838 (15.5)	871 (15.0)	923 (15.0)	1043 (14.9)
NSAID	17,934 (32.6)	3493 (31.7)	3493 (31.8)	3594 (32.6)	3589 (32.5)	3765 (34.2)
Aspirin	6983 (12.6)	1362 (12.3)	1345 (12.1)	1420 (12.8)	1370 (12.4)	1486 (13.4)
Dietary characteristics						
Energy (kcal)	2,271 [1878 – 2717]	2,060 [1680 – 2484]	2,214 [1844 – 2629]	2,330 [1944 – 2768]	2,375 [1988 – 2824]	2,373 [1976 – 2842]
Total fish intake (g/d)	38 [25 – 55]	33 [22 – 49]	38 [25 – 54]	40 [27 – 57]	41 [28 – 59]	40 [27 – 57]
Red meat intake (g/d)	78 [56 – 107]	80 [58 – 108]	81 [59 – 110]	80 [58 – 110]	78 [57 – 107]	72 [52 – 99]
Processed meat intake (g/d)	25 [14 – 40]	28 [17 – 45]	26 [15 – 42]	25 [14 – 40]	23 [14 – 38]	20 [11 – 34]
Refined grain intake (g/d)	46 [29 – 72]	45 [27 – 80]	46 [29 – 73]	47 [30 – 72]	46 [30 – 70]	45 [30 – 68]
Wholegrain intake (g/d)	128 [86 – 175]	116 [72 – 165]	123 [84 – 171]	126 [86 – 173]	135 [97 – 181]	144 [103 – 193]
Dietary fibre intake (g/d)	20 [16 – 25]	16 [13 – 20]	19 [16 – 23]	21 [17 – 25]	22 [18 – 27]	23 [19 – 29]
Saturated FA (g/d)	31 [24–39]	29 [23–37]	31 [24–39]	32 [24–40]	32 [25–41]	32 [24–41]
Polyunsaturated FA (g/d)	13 [10–17]	12 [9–16]	13 [10–17]	14 [10–18]	14 [11–18]	14 [10–18]
Monounsaturated FA (g/d)	27 [21–35]	26 [20–34]	27 [21–35]	28 [22–35]	28 [22–35]	27 [21–34]
Fruit intake (g/d)	171 [95 – 281]	87 [44 – 141]	161 [98 – 238]	193 [114 – 301]	224 [140 – 360]	240 [141 – 390]
Vegetable intake (g/d)	162 [105 – 231]	114 [71 – 170]	150 [100 – 212]	168 [114 – 235]	185 [127 – 254]	196 [135 – 272]
Alcohol intake (g/d)	13 [6 – 31]	11 [3 – 23]	13 [6 – 25]	15 [6 – 34]	14 [7 – 32]	13 [6 – 32]

Data expressed as median [IQR] or n (%), unless otherwise stated.

BMI, body mass index; CKD, chronic kidney disease; DKK, Danish Krone; FA, fatty acids; HRT, hormone replacement therapy, MET, metabolic equivalent; NSAID, Nonsteroidal anti-inflammatory drug.

Table 2. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid intake

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 11,083	**n = 11,083**	**n = 11,082**	**n = 11,083**	**n = 11,082**
Total Flavonoids					
No. events	1621	1222	1085	861	768
Intake (mg/d)[1]	174 (6–251)	321 (251–395)	496 (395–602)	727 (602–910)	1203 (910–3552)
HR (95% CI)					
Model 1	ref.	0.71 (0.68, 0.75)	0.55 (0.52, 0.59)	0.48 (0.45, 0.51)	0.43 (0.40, 0.46)
Model 1b	ref.	0.94 (0.90, 0.99)	0.89 (0.84, 0.95)	0.85 (0.79, 0.91)	0.80 (0.74, 0.87)
Model 2	ref.	0.96 (0.91, 1.01)	0.92 (0.86, 0.98)	0.88 (0.82, 0.95)	0.85 (0.78, 0.92)
Flavonols					
No. events	1665	1286	989	869	748
Intake (mg/d)[1]	15 (0–21)	26 (21–32)	39 (32–50)	66 (50–83)	116 (83–251)
HR (95% CI)					
Model 1	ref.	0.73 (0.70, 0.76)	0.57 (0.53, 0.60)	0.45 (0.42, 0.49)	0.42 (0.39, 0.45)
Model 1b	ref.	0.93 (0.89, 0.97)	0.88 (0.83, 0.94)	0.85 (0.79, 0.91)	0.82 (0.76, 0.89)
Model 2	ref.	0.95 (0.91, 1.00)	0.92 (0.86, 0.98)	0.89 (0.83, 0.96)	0.88 (0.81, 0.95)
Flavanol monomers					
No. events	1636	1217	1086	861	757
Intake (mg/d)[1]	14 (0–21)	30 (21–46)	67 (46–115)	261 (115–282)	474 (282–916)
HR (95% CI)					
Model 1	ref.	0.81 (0.79, 0.84)	0.59 (0.55, 0.63)	0.45 (0.42, 0.49)	0.45 (0.41, 0.48)
Model 1b	ref.	0.96 (0.93, 0.99)	0.90 (0.84, 0.97)	0.87 (0.81, 0.94)	0.86 (0.80, 0.93)
Model 2	ref.	0.97 (0.94, 1.00)	0.94 (0.87, 1.01)	0.92 (0.85, 0.99)	0.91 (0.84, 0.98)
Flavanol oligo+polymers					
No. events	1642	1230	1016	898	771
Intake (mg/d)[1]	92 (1–136)	179 (136–217)	256 (217–303)	360 (303–434)	537 (434–2254)
HR (95% CI)					
Model 1	ref.	0.67 (0.64, 0.70)	0.54 (0.51, 0.57)	0.48 (0.45, 0.51)	0.44 (0.41, 0.47)
Model 1b	ref.	0.93 (0.88, 0.98)	0.87 (0.83, 0.93)	0.82 (0.77, 0.88)	0.78 (0.72, 0.84)
Model 2	ref.	0.94 (0.90, 0.99)	0.90 (0.84, 0.95)	0.85 (0.79, 0.91)	0.81 (0.74, 0.87)
Anthocyanins					
No. events	1525	998	904	1035	1095
Intake (mg/d)[1]	5 (0–10)	13 (10–17)	20 (17–24)	36 (24–53)	70 (53–397)
HR (95% CI)					
Model 1	ref.	0.64 (0.61, 0.67)	0.53 (0.50, 0.57)	0.59 (0.55, 0.63)	0.72 (0.67, 0.77)
Model 1b	ref.	0.91 (0.86, 0.95)	0.87 (0.81, 0.93)	0.88 (0.83, 0.95)	0.91 (0.84, 0.98)
Model 2	ref.	0.91 (0.86, 0.96)	0.88 (0.82, 0.95)	0.90 (0.84, 0.97)	0.93 (0.86, 1.01)
Flavanones					
No. events	1462	1075	996	1005	1019
Intake (mg/d)[1]	3 (0–6)	9 (6–13)	17 (13–26)	32 (26–49)	70 (49–564)
HR (95% CI)					
Model 1	ref.	0.78 (0.75, 0.82)	0.65 (0.60, 0.70)	0.64 (0.60, 0.68)	0.69 (0.64, 0.74)
Model 1b	ref.	0.94 (0.90, 0.99)	0.91 (0.84, 0.97)	0.91 (0.86, 0.97)	0.94 (0.88, 1.01)

Model 2	ref.	0.94 (0.90, 0.99)	0.91 (0.84, 0.97)	0.91 (0.85, 0.97)	0.94 (0.87, 1.01)
Flavones					
No. events	1501	1179	944	922	1011
Intake (mg/d)[1]	2 (0–3)	4 (3–4)	5 (4–6)	7 (6–9)	11 (9–51)
HR (95% CI)					
Model 1	ref.	0.70 (0.67, 0.74)	0.59 (0.55, 0.62)	0.55 (0.52, 0.59)	0.58 (0.54, 0.63)
Model 1b	ref.	0.91 (0.87, 0.96)	0.87 (0.82, 0.92)	0.85 (0.8, 0.90)	0.87 (0.81, 0.93)
Model 2	ref.	0.92 (0.87, 0.97)	0.88 (0.82, 0.93)	0.86 (0.8, 0.92)	0.88 (0.81, 0.95)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking status, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

[1]Median; range in parentheses (all such values).

Table 3. 20-year predicted risk of chronic obstructive pulmonary disease (COPD)

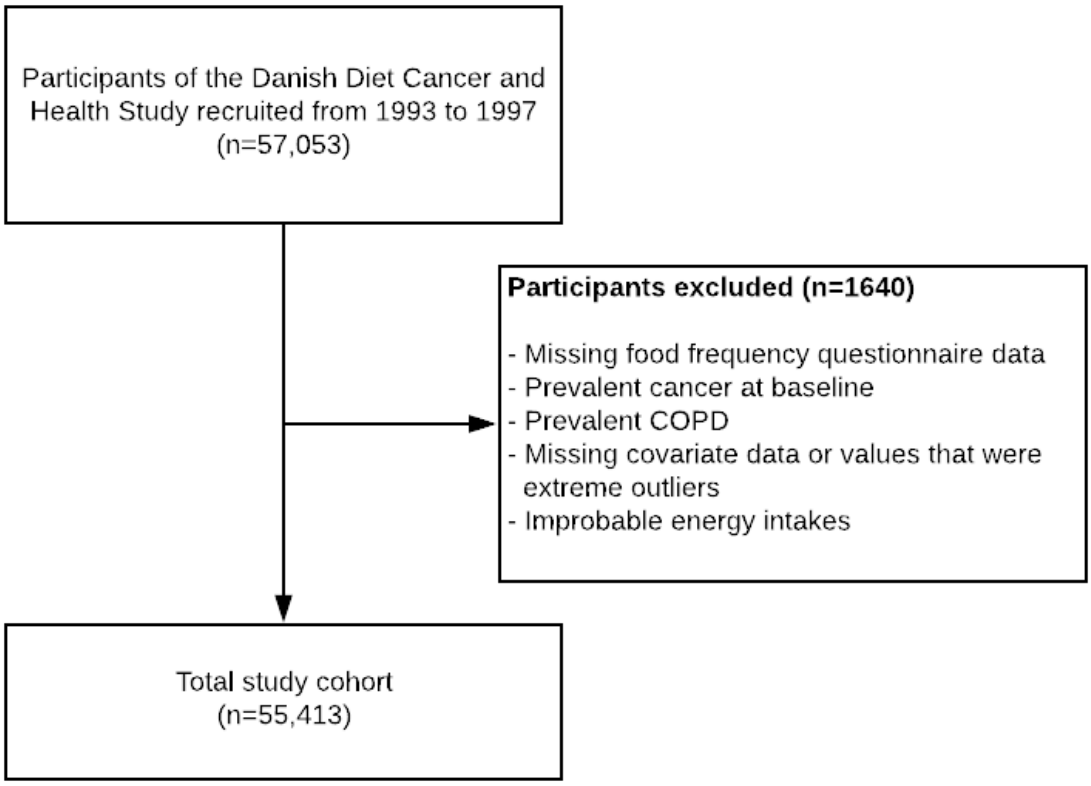
	Total flavonoid intake		Risk difference (%)
	Q1 Risk (95% CI)	Q5 Risk (95% CI)	
Male			
Non-smoker	2.35 (2.07, 2.66)	1.60 (1.39, 1.84)	0.75
Former smoker	6.26 (5.68, 6.89)	4.32 (3.85, 4.84)	1.94
Current smoker	18.53 (17.31, 19.82)	13.32 (12.10, 14.65)	5.21
Female			
Non-smoker	3.06 (2.71, 3.45)	2.09 (1.84, 2.37)	0.97
Former smoker	8.06 (7.31, 8.87)	5.59 (5.02, 6.22)	2.47
Current smoker	22.99 (21.53, 24.52)	16.79 (15.41, 18.26)	6.20

The 20-year predicted risks (%) of COPD calculated from logistic regression models. Unless indicated by the stratification variable, these estimates are for a smoking participant, aged 56 years, with a BMI of 25.5, a total daily metabolic equivalent score of 56, with a mean household income of 394,701 – 570,930 DKK/year, and an alcohol intake of 13 g/day.

Flavonoid intakes associate with a lower risk of chronic obstructive pulmonary disease in smokers

Nicola P. Bondonno, Benjamin H. Parmenter, Frederik Dalgaard, Kevin Murray, Daniel Bech Rasmussen, Cecilie Kyrø, Aedin Cassidy, Catherine P. Bondonno, Joshua R. Lewis, Kevin D. Croft, Gunnar Gislason, Augustin Scalbert, Anne Tjønneland, Kim Overvad, Anja Olsen, Jonathan M. Hodgson.

Online Data Supplement



Supplementary Figure 1. Participant flow diagram in the Danish Diet, Cancer, and Health study.

Supplementary Table 1. Definitions of prevalent comorbidities at baseline

Prevalent disease	Definition
Ischemic heart disease	Self-reported myocardial infarction, ICD-8 diagnosis [410-414] or ICD-10 diagnosis [I20-I25] prior to enrolment
Ischemic stroke	Self-reported stroke, ICD-8 diagnosis [433-434] or ICD-10 diagnosis [I63] prior to enrolment
Diabetes	Self-reported diabetes or use of insulin and other glucose-lowering medications [ATC; A10A, A10B] prior to enrolment
Chronic kidney disease	ICD-8 diagnosis [580-584] or ICD-10 diagnosis [N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, Q61, E102, E112, E132, E142, I120, M321B] prior to enrolment

ATC; Anatomical Therapeutic Chemical Classification, ICD; International Classification of Diseases [the 8th revision (ICD-8) until 1993 and the 10th revision (ICD-10) from 1994 to present].

METHODS

Covariates:

Participants completed several questionnaires upon enrolment in the Danish Diet, Cancer and Health study, from which we obtained data on their sex, age, education, smoking habits, alcohol consumption, daily physical activity, and diet. In the present study, participants were defined as "current smokers" at baseline if they reported that they were currently smoking daily, "previous smokers" if they indicated that, at any stage in their life, they smoked daily for at least one year, or "never smokers" if they were neither of the above. Anthropometry was measured during a clinical visit at the study centers. Socio-economic status was represented using each participant's average annual income over the five years prior to study enrolment (defined as household income after taxation and interest, using the value of the Danish currency in 2015). Prevalent diabetes, chronic kidney disease, ischemic heart disease, and ischemic stroke were determined by self-reported data in combination with ICD-8, ICD-10, and Anatomical Therapeutic Chemical (ATC) Classification codes (Supplementary Table 1).

Supplementary Table 2. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid compound intakes

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 11,083	**n = 11,083**	**n = 11,082**	**n = 11,083**	**n = 11,082**
Flavonols					
Kaempferol					
No. events	1722	1160	1074	846	755
Intake (mg/d)[1]	1 (0–1)	2 (1–3)	4 (3–8)	18 (8–20)	33 (20–68)
HR (95% CI)					
Model 1	ref.	0.84 (0.81, 0.86)	0.59 (0.55, 0.63)	0.45 (0.42, 0.49)	0.45 (0.42, 0.48)
Model 2	ref.	0.96 (0.94, 0.99)	0.89 (0.83, 0.96)	0.87 (0.81, 0.94)	0.86 (0.79, 0.93)
Model 3	ref.	0.98 (0.95, 1.01)	0.94 (0.88, 1.01)	0.92 (0.86, 1.00)	0.91 (0.84, 0.99)
Quercetin					
No. events	1653	1280	1002	874	748
Intake (mg/d)[1]	12 (0–16)	20 (16–24)	29 (24–37)	46 (37–58)	78 (58–168)
HR (95% CI)					
Model 1	ref.	0.73 (0.70, 0.76)	0.57 (0.54, 0.61)	0.47 (0.44, 0.50)	0.42 (0.39, 0.45)
Model 2	ref.	0.93 (0.89, 0.97)	0.88 (0.83, 0.93)	0.85 (0.79, 0.91)	0.82 (0.75, 0.88)
Model 3	ref.	0.94 (0.90, 0.99)	0.91 (0.85, 0.97)	0.89 (0.83, 0.96)	0.87 (0.80, 0.95)
Flavanol monomers					
Epicatechin					
No. events	1626	1293	1036	847	755
Intake (mg/d)[1]	6 (0–9)	12 (9–15)	19 (15–25)	31 (25–39)	53 (39–155)
HR (95% CI)					
Model 1	ref.	0.71 (0.67, 0.74)	0.54 (0.51, 0.58)	0.45 (0.42, 0.48)	0.41 (0.38, 0.44)
Model 2	ref.	0.93 (0.89, 0.97)	0.87 (0.82, 0.93)	0.82 (0.77, 0.88)	0.79 (0.73, 0.85)
Model 3	ref.	0.94 (0.90, 0.99)	0.90 (0.84, 0.96)	0.86 (0.80, 0.92)	0.83 (0.77, 0.90)
Flavanol oligo+polymers					
Proanthocyanidin dimers					
No. events	1671	1204	1069	833	780
Intake (mg/d) [1]	25 (0–38)	49 (38–62)	78 (62–94)	113 (94–138)	177 (138–510)
HR (95% CI)					
Model 1	ref.	0.69 (0.66, 0.72)	0.53 (0.50, 0.56)	0.47 (0.44, 0.50)	0.43 (0.40, 0.47)
Model 2	ref.	0.94 (0.89, 0.98)	0.88 (0.83, 0.93)	0.82 (0.77, 0.88)	0.76 (0.70, 0.82)
Model 3	ref.	0.95 (0.91, 1.00)	0.90 (0.85, 0.96)	0.85 (0.80, 0.92)	0.80 (0.74, 0.87)
Proanthocyanidin trimers					
No. events	1667	1178	878	992	842
Intake (mg/d)[1]	10 (0–14)	17 (14–20)	23 (20–29)	35 (29–42)	54 (42–320)
HR (95% CI)					
Model 1	ref.	0.65 (0.62, 0.67)	0.53 (0.50, 0.56)	0.51 (0.48, 0.54)	0.52 (0.48, 0.56)
Model 2	ref.	0.91 (0.87, 0.95)	0.87 (0.82, 0.92)	0.83 (0.78, 0.89)	0.79 (0.73, 0.85)
Model 3	ref.	0.92 (0.88, 0.97)	0.88 (0.83, 0.94)	0.85 (0.80, 0.91)	0.80 (0.74, 0.87)
Flavanones					
Hesperidin					
No. events	1451	1069	1009	998	1030
Intake (mg/d)[1]	2 (0–4)	6 (4–9)	12 (9–18)	24 (18–38)	54 (38–449)
HR (95% CI)					
Model 1	ref.	0.79 (0.76, 0.83)	0.66 (0.62, 0.71)	0.64 (0.60, 0.69)	0.70 (0.65, 0.75)
Model 2	ref.	0.96 (0.92, 1.00)	0.93 (0.87, 1.00)	0.93 (0.87, 0.99)	0.95 (0.89, 1.02)
Model 3	ref.	0.96 (0.92, 1.00)	0.93 (0.86, 1.00)	0.93 (0.87, 0.99)	0.95 (0.88, 1.02)
Flavones					
Apigenin					
No. events	1495	1131	1022	920	989
Intake (mg/d)[1]	2 (0–2)	3 (2–4)	5 (4–5)	6 (5–8)	10 (8–46)

HR (95% CI)					
Model 1	ref.	0.73 (0.70, 0.77)	0.61 (0.58, 0.65)	0.56 (0.53, 0.60)	0.57 (0.53, 0.62)
Model 2	ref.	0.92 (0.88, 0.97)	0.88 (0.83, 0.93)	0.86 (0.80, 0.91)	0.86 (0.80, 0.93)
Model 3	ref.	0.93 (0.88, 0.98)	0.88 (0.83, 0.94)	0.86 (0.80, 0.92)	0.87 (0.80, 0.95)
Anthocyanins					
Cyanidin					
No. events	1438	1048	918	940	1213
Intake (mg/d)[1]	1 (0–1)	1 (1–1)	2 (1–3)	4 (3–8)	17 (8–203)
HR (95% CI)					
Model 1	ref.	0.70 (0.68, 0.73)	0.56 (0.53, 0.60)	0.56 (0.52, 0.60)	0.77 (0.71, 0.83)
Model 2	ref.	0.89 (0.86, 0.93)	0.83 (0.78, 0.88)	0.83 (0.78, 0.89)	0.93 (0.86, 1.01)
Model 3	ref.	0.91 (0.87, 0.95)	0.86 (0.80, 0.91)	0.86 (0.80, 0.92)	0.95 (0.87, 1.03)
Delphinidin					
No. events	1536	885	1015	923	1198
Intake (mg/d)[1]	0 (0–1)	1 (1–1)	2 (1–4)	5 (4–8)	18 (8–188)
HR (95% CI)					
Model 1	ref.	0.70 (0.66, 0.73)	0.59 (0.55, 0.63)	0.61 (0.57, 0.65)	0.86 (0.79, 0.93)
Model 2	ref.	0.87 (0.83, 0.91)	0.81 (0.75, 0.87)	0.82 (0.76, 0.88)	0.93 (0.86, 1.01)
Model 3	ref.	0.88 (0.84, 0.93)	0.83 (0.77, 0.89)	0.84 (0.78, 0.90)	0.95 (0.87, 1.03)
Malvidin					
No. events	1819	1457	613	803	865
Intake (mg/d)[1]	0 (0–1)	2 (1–6)	6 (6–6)	11 (6–14)	35 (14–114)
HR (95% CI)					
Model 1	ref.	0.75 (0.72, 0.78)	0.50 (0.47, 0.54)	0.47 (0.44, 0.50)	0.55 (0.51, 0.59)
Model 2	ref.	0.89 (0.86, 0.93)	0.76 (0.69, 0.83)	0.72 (0.66, 0.79)	0.63 (0.57, 0.70)
Model 3	ref.	0.91 (0.87, 0.94)	0.78 (0.72, 0.86)	0.76 (0.69, 0.83)	0.67 (0.60, 0.75)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking status, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

[1]Median; range in parentheses (all such values).

Supplementary Table 3. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid intake in current smokers (n = 19,922)

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 3985	**n = 3984**	**n = 3984**	**n = 3984**	**n = 3985**
Total Flavonoids					
HR (95% CI)					
Model 1	ref.	0.83 (0.79, 0.88)	0.73 (0.67, 0.78)	0.64 (0.59, 0.69)	0.58 (0.53, 0.63)
Model 1b	ref.	0.95 (0.89, 1.01)	0.90 (0.83, 0.97)	0.83 (0.77, 0.90)	0.77 (0.70, 0.84)
Model 2	ref.	0.97 (0.91, 1.03)	0.93 (0.86, 1.01)	0.88 (0.80, 0.96)	0.82 (0.74, 0.90)
Flavonols					
HR (95% CI)					
Model 1	ref.	0.86 (0.81, 0.90)	0.75 (0.70, 0.81)	0.65 (0.61, 0.70)	0.57 (0.52, 0.63)
Model 1b	ref.	0.96 (0.90, 1.01)	0.92 (0.85, 0.99)	0.85 (0.79, 0.93)	0.78 (0.71, 0.86)
Model 2	ref.	0.98 (0.93, 1.05)	0.96 (0.88, 1.05)	0.91 (0.84, 1.00)	0.85 (0.77, 0.94)
Flavanol monomers					
HR (95% CI)					
Model 1	ref.	0.89 (0.86, 0.92)	0.76 (0.7, 0.82)	0.67 (0.62, 0.73)	0.61 (0.56, 0.67)
Model 1b	ref.	0.95 (0.92, 0.99)	0.90 (0.83, 0.97)	0.86 (0.80, 0.94)	0.82 (0.74, 0.90)
Model 2	ref.	0.97 (0.94, 1.01)	0.94 (0.87, 1.02)	0.92 (0.84, 1.00)	0.88 (0.79, 0.96)
Flavanol oligo+polymers					
HR (95% CI)					
Model 1	ref.	0.81 (0.76, 0.86)	0.69 (0.64, 0.74)	0.63 (0.58, 0.68)	0.58 (0.53, 0.63)
Model 1b	ref.	0.93 (0.88, 0.99)	0.87 (0.81, 0.94)	0.81 (0.75, 0.88)	0.75 (0.69, 0.82)
Model 2	ref.	0.95 (0.89, 1.01)	0.90 (0.83, 0.97)	0.85 (0.78, 0.93)	0.79 (0.72, 0.87)
Anthocyanins					
HR (95% CI)					
Model 1	ref.	0.73 (0.69, 0.77)	0.62 (0.57, 0.67)	0.65 (0.60, 0.70)	0.72 (0.67, 0.79)
Model 1b	ref.	0.89 (0.83, 0.94)	0.83 (0.76, 0.91)	0.86 (0.79, 0.93)	0.87 (0.79, 0.95)
Model 2	ref.	0.90 (0.84, 0.95)	0.85 (0.78, 0.93)	0.88 (0.81, 0.96)	0.90 (0.82, 0.99)
Flavanones					
HR (95% CI)					
Model 1	ref.	0.88 (0.84, 0.92)	0.78 (0.71, 0.85)	0.75 (0.69, 0.81)	0.77 (0.71, 0.84)
Model 1b	ref.	0.95 (0.91, 1.00)	0.92 (0.84, 1.00)	0.92 (0.85, 1.00)	0.94 (0.86, 1.03)
Model 2	ref.	0.96 (0.91, 1.01)	0.93 (0.85, 1.01)	0.93 (0.86, 1.01)	0.95 (0.87, 1.04)
Flavones					
HR (95% CI)					
Model 1	ref.	0.83 (0.78, 0.88)	0.74 (0.68, 0.79)	0.68 (0.63, 0.73)	0.68 (0.62, 0.74)
Model 1b	ref.	0.93 (0.88, 0.99)	0.88 (0.82, 0.95)	0.84 (0.78, 0.91)	0.83 (0.76, 0.91)
Model 2	ref.	0.95 (0.89, 1.01)	0.91 (0.84, 0.99)	0.87 (0.80, 0.94)	0.85 (0.77, 0.94)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

Supplementary Table 4. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid intake in former smokers (n = 15,862)

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 3173	**n = 3172**	**n = 3172**	**n = 3172**	**n = 3173**
Total Flavonoids					
HR (95% CI)					
Model 1	ref.	0.82 (0.73, 0.92)	0.73 (0.63, 0.84)	0.70 (0.60, 0.82)	0.63 (0.53, 0.74)
Model 1b	ref.	0.94 (0.84, 1.06)	0.92 (0.80, 1.06)	0.92 (0.78, 1.07)	0.82 (0.69, 0.97)
Model 2	ref.	0.96 (0.86, 1.08)	0.96 (0.82, 1.11)	0.96 (0.82, 1.14)	0.88 (0.73, 1.05)
Flavonols					
HR (95% CI)					
Model 1	ref.	0.77 (0.69, 0.85)	0.66 (0.57, 0.77)	0.67 (0.58, 0.78)	0.62 (0.52, 0.73)
Model 1b	ref.	0.87 (0.78, 0.97)	0.82 (0.71, 0.96)	0.89 (0.76, 1.04)	0.82 (0.69, 0.98)
Model 2	ref.	0.90 (0.80, 1.00)	0.87 (0.74, 1.02)	0.95 (0.80, 1.12)	0.89 (0.74, 1.06)
Flavanol monomers					
HR (95% CI)					
Model 1	ref.	0.91 (0.85, 0.96)	0.74 (0.63, 0.88)	0.67 (0.57, 0.78)	0.67 (0.57, 0.79)
Model 1b	ref.	0.97 (0.92, 1.03)	0.91 (0.78, 1.08)	0.89 (0.76, 1.05)	0.86 (0.73, 1.02)
Model 2	ref.	0.98 (0.93, 1.05)	0.95 (0.81, 1.13)	0.94 (0.80, 1.11)	0.91 (0.77, 1.08)
Flavanol oligo+polymers					
HR (95% CI)					
Model 1	ref.	0.77 (0.68, 0.87)	0.71 (0.62, 0.81)	0.70 (0.60, 0.81)	0.63 (0.53, 0.74)
Model 1b	ref.	0.91 (0.81, 1.02)	0.88 (0.77, 1.01)	0.88 (0.75, 1.02)	0.79 (0.67, 0.94)
Model 2	ref.	0.93 (0.82, 1.04)	0.91 (0.79, 1.04)	0.91 (0.77, 1.06)	0.83 (0.69, 1.00)
Anthocyanins					
HR (95% CI)					
Model 1	ref.	0.74 (0.66, 0.83)	0.65 (0.56, 0.76)	0.69 (0.59, 0.79)	0.79 (0.67, 0.93)
Model 1b	ref.	0.91 (0.80, 1.03)	0.87 (0.74, 1.03)	0.89 (0.75, 1.04)	0.94 (0.78, 1.13)
Model 2	ref.	0.92 (0.81, 1.04)	0.89 (0.75, 1.06)	0.91 (0.76, 1.07)	0.97 (0.80, 1.16)
Flavanones					
HR (95% CI)					
Model 1	ref.	0.79 (0.71, 0.88)	0.68 (0.58, 0.8)	0.70 (0.61, 0.81)	0.79 (0.67, 0.93)
Model 1b	ref.	0.88 (0.79, 0.98)	0.82 (0.70, 0.97)	0.88 (0.76, 1.02)	0.99 (0.84, 1.16)
Model 2	ref.	0.88 (0.79, 0.98)	0.82 (0.69, 0.97)	0.88 (0.76, 1.03)	0.99 (0.84, 1.18)
Flavones					
HR (95% CI)					
Model 1	ref.	0.71 (0.63, 0.79)	0.63 (0.55, 0.72)	0.68 (0.59, 0.78)	0.77 (0.66, 0.91)
Model 1b	ref.	0.81 (0.73, 0.90)	0.77 (0.68, 0.88)	0.84 (0.73, 0.97)	0.94 (0.80, 1.10)
Model 2	ref.	0.83 (0.74, 0.93)	0.80 (0.69, 0.93)	0.87 (0.75, 1.03)	0.99 (0.82, 1.19)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

Supplementary Table 5. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid compound intakes in current smokers (n = 19,922)

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 3985	**n = 3984**	**n = 3984**	**n = 3984**	**n = 3985**
Flavonols					
Kaempferol					
HR (95% CI)					
Model 1	ref.	0.90 (0.87, 0.93)	0.75 (0.69, 0.81)	0.67 (0.61, 0.72)	0.61 (0.56, 0.67)
Model 2	ref.	0.96 (0.93, 1.00)	0.90 (0.83, 0.98)	0.87 (0.80, 0.95)	0.82 (0.74, 0.90)
Model 3	ref.	0.99 (0.95, 1.02)	0.96 (0.88, 1.05)	0.94 (0.86, 1.03)	0.88 (0.80, 0.97)
Quercetin					
HR (95% CI)					
Model 1	ref.	0.86 (0.81, 0.91)	0.76 (0.70, 0.81)	0.65 (0.61, 0.70)	0.58 (0.53, 0.63)
Model 2	ref.	0.95 (0.90, 1.01)	0.91 (0.84, 0.98)	0.85 (0.78, 0.92)	0.78 (0.71, 0.86)
Model 3	ref.	0.98 (0.92, 1.04)	0.95 (0.87, 1.03)	0.90 (0.83, 0.98)	0.84 (0.76, 0.93)
Flavanol monomers					
Epicatechin					
HR (95% CI)					
Model 1	ref.	0.82 (0.77, 0.87)	0.71 (0.66, 0.77)	0.62 (0.58, 0.67)	0.57 (0.52, 0.62)
Model 2	ref.	0.93 (0.88, 0.99)	0.88 (0.81, 0.95)	0.81 (0.75, 0.88)	0.75 (0.69, 0.83)
Model 3	ref.	0.95 (0.89, 1.01)	0.91 (0.84, 0.99)	0.86 (0.78, 0.93)	0.80 (0.73, 0.88)
Flavanol oligo+polymers					
Proanthocyanidin dimers					
HR (95% CI)					
Model 1	ref.	0.82 (0.77, 0.87)	0.70 (0.64, 0.75)	0.62 (0.57, 0.67)	0.57 (0.52, 0.62)
Model 2	ref.	0.94 (0.88, 0.99)	0.88 (0.81, 0.95)	0.81 (0.75, 0.88)	0.73 (0.67, 0.80)
Model 3	ref.	0.96 (0.90, 1.02)	0.91 (0.84, 0.99)	0.85 (0.78, 0.93)	0.78 (0.71, 0.86)
Proanthocyanidin trimers					
HR (95% CI)					
Model 1	ref.	0.77 (0.73, 0.81)	0.66 (0.62, 0.71)	0.62 (0.58, 0.67)	0.60 (0.55, 0.65)
Model 2	ref.	0.90 (0.85, 0.95)	0.85 (0.79, 0.92)	0.83 (0.76, 0.90)	0.77 (0.70, 0.85)
Model 3	ref.	0.92 (0.87, 0.97)	0.88 (0.81, 0.95)	0.86 (0.79, 0.93)	0.79 (0.72, 0.88)
Flavanones					
Hesperidin					
HR (95% CI)					
Model 1	ref.	0.89 (0.85, 0.94)	0.80 (0.73, 0.87)	0.77 (0.71, 0.83)	0.78 (0.72, 0.85)
Model 2	ref.	0.97 (0.92, 1.02)	0.94 (0.86, 1.02)	0.94 (0.87, 1.02)	0.95 (0.87, 1.04)
Model 3	ref.	0.97 (0.92, 1.02)	0.94 (0.87, 1.03)	0.94 (0.87, 1.03)	0.96 (0.87, 1.05)
Flavones					
Apigenin					
HR (95% CI)					
Model 1	ref.	0.86 (0.81, 0.91)	0.76 (0.71, 0.82)	0.70 (0.65, 0.76)	0.68 (0.62, 0.74)
Model 2	ref.	0.94 (0.89, 1.00)	0.90 (0.83, 0.97)	0.86 (0.79, 0.92)	0.83 (0.76, 0.91)
Model 3	ref.	0.96 (0.90, 1.02)	0.92 (0.84, 0.99)	0.88 (0.80, 0.95)	0.86 (0.77, 0.95)
Anthocyanins					
Cyanidin					
HR (95% CI)					
Model 1	ref.	0.80 (0.76, 0.83)	0.68 (0.63, 0.74)	0.68 (0.62, 0.73)	0.85 (0.77, 0.93)
Model 2	ref.	0.89 (0.85, 0.94)	0.83 (0.76, 0.89)	0.82 (0.76, 0.89)	0.92 (0.84, 1.02)
Model 3	ref.	0.92 (0.87, 0.96)	0.86 (0.80, 0.93)	0.86 (0.79, 0.94)	0.95 (0.86, 1.05)
Delphinidin					
HR (95% CI)					
Model 1	ref.	0.78 (0.74, 0.81)	0.64 (0.59, 0.69)	0.65 (0.60, 0.71)	0.84 (0.77, 0.92)
Model 2	ref.	0.88 (0.84, 0.93)	0.80 (0.73, 0.88)	0.81 (0.74, 0.89)	0.91 (0.82, 1.00)

Model 3	ref.	0.90 (0.85, 0.94)	0.82 (0.75, 0.90)	0.83 (0.76, 0.91)	0.93 (0.85, 1.02)
Malvidin					
HR (95% CI)					
Model 1	ref.	0.87 (0.84, 0.89)	0.58 (0.53, 0.63)	0.55 (0.50, 0.59)	0.56 (0.51, 0.61)
Model 2	ref.	0.92 (0.89, 0.95)	0.72 (0.64, 0.80)	0.69 (0.62, 0.77)	0.62 (0.54, 0.70)
Model 3	ref.	0.93 (0.89, 0.96)	0.74 (0.67, 0.83)	0.72 (0.65, 0.80)	0.66 (0.58, 0.75)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

Supplementary Table 6. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid compound intakes in former smokers (n = 15,862)

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 3173	**n = 3172**	**n = 3172**	**n = 3172**	**n = 3173**
Flavonols					
Kaempferol					
HR (95% CI)					
Model 1	ref.	0.90 (0.85, 0.95)	0.70 (0.59, 0.82)	0.65 (0.55, 0.76)	0.66 (0.56, 0.78)
Model 2	ref.	0.97 (0.91, 1.02)	0.89 (0.75, 1.05)	0.88 (0.75, 1.03)	0.86 (0.73, 1.01)
Model 3	ref.	0.98 (0.93, 1.03)	0.93 (0.79, 1.11)	0.93 (0.79, 1.10)	0.91 (0.77, 1.07)
Quercetin					
HR (95% CI)					
Model 1	ref.	0.77 (0.69, 0.86)	0.68 (0.59, 0.78)	0.70 (0.60, 0.81)	0.62 (0.53, 0.74)
Model 2	ref.	0.86 (0.78, 0.96)	0.83 (0.72, 0.96)	0.90 (0.77, 1.05)	0.82 (0.69, 0.97)
Model 3	ref.	0.89 (0.79, 0.99)	0.87 (0.75, 1.01)	0.96 (0.82, 1.13)	0.89 (0.74, 1.06)
Flavanol monomers					
Epicatechin					
HR (95% CI)					
Model 1	ref.	0.82 (0.73, 0.93)	0.72 (0.62, 0.84)	0.69 (0.59, 0.8)	0.62 (0.52, 0.73)
Model 2	ref.	0.95 (0.84, 1.06)	0.91 (0.78, 1.06)	0.89 (0.76, 1.03)	0.8 (0.67, 0.95)
Model 3	ref.	0.96 (0.86, 1.08)	0.94 (0.81, 1.1)	0.93 (0.79, 1.09)	0.85 (0.71, 1.02)
Flavanol oligo+polymers					
Proanthocyanidin dimers					
HR (95% CI)					
Model 1	ref.	0.80 (0.71, 0.90)	0.71 (0.62, 0.82)	0.69 (0.59, 0.80)	0.60 (0.51, 0.71)
Model 2	ref.	0.93 (0.83, 1.04)	0.90 (0.79, 1.04)	0.89 (0.76, 1.04)	0.77 (0.64, 0.91)
Model 3	ref.	0.95 (0.84, 1.06)	0.93 (0.81, 1.08)	0.92 (0.79, 1.09)	0.82 (0.68, 0.98)
Proanthocyanidin trimers					
HR (95% CI)					
Model 1	ref.	0.76 (0.69, 0.84)	0.66 (0.59, 0.75)	0.63 (0.55, 0.73)	0.61 (0.52, 0.72)
Model 2	ref.	0.90 (0.81, 0.99)	0.84 (0.74, 0.96)	0.81 (0.69, 0.94)	0.76 (0.64, 0.91)
Model 3	ref.	0.91 (0.82, 1.01)	0.86 (0.75, 0.98)	0.83 (0.70, 0.97)	0.79 (0.65, 0.95)
Flavanones					
Hesperidin					
HR (95% CI)					
Model 1	ref.	0.83 (0.74, 0.92)	0.73 (0.62, 0.85)	0.73 (0.63, 0.84)	0.80 (0.68, 0.94)
Model 2	ref.	0.91 (0.82, 1.01)	0.87 (0.74, 1.02)	0.91 (0.78, 1.05)	0.99 (0.85, 1.17)
Model 3	ref.	0.91 (0.82, 1.01)	0.86 (0.73, 1.02)	0.91 (0.78, 1.06)	1.00 (0.85, 1.19)
Flavones					
Apigenin					
HR (95% CI)					
Model 1	ref.	0.74 (0.66, 0.83)	0.65 (0.57, 0.75)	0.68 (0.59, 0.78)	0.76 (0.65, 0.90)
Model 2	ref.	0.83 (0.74, 0.93)	0.79 (0.69, 0.91)	0.83 (0.72, 0.96)	0.91 (0.78, 1.07)
Model 3	ref.	0.85 (0.75, 0.96)	0.81 (0.70, 0.94)	0.86 (0.73, 1.01)	0.96 (0.80, 1.15)
Anthocyanins					
Cyanidin					
HR (95% CI)					
Model 1	ref.	0.79 (0.72, 0.86)	0.69 (0.59, 0.79)	0.69 (0.59, 0.8)	0.92 (0.77, 1.10)
Model 2	ref.	0.85 (0.78, 0.93)	0.77 (0.67, 0.89)	0.77 (0.67, 0.9)	0.93 (0.77, 1.11)
Model 3	ref.	0.87 (0.79, 0.96)	0.80 (0.69, 0.93)	0.8 (0.68, 0.94)	0.94 (0.78, 1.14)
Delphinidin					
HR (95% CI)					
Model 1	ref.	0.72 (0.64, 0.80)	0.61 (0.52, 0.71)	0.62 (0.53, 0.73)	0.94 (0.78, 1.12)
Model 2	ref.	0.84 (0.75, 0.95)	0.78 (0.65, 0.92)	0.79 (0.66, 0.93)	0.97 (0.81, 1.16)

Model 3	ref.	0.85 (0.76, 0.95)	0.78 (0.66, 0.93)	0.79 (0.67, 0.94)	0.98 (0.82, 1.18)
Malvidin					
HR (95% CI)					
Model 1	ref.	0.67 (0.58, 0.76)	0.66 (0.58, 0.76)	0.58 (0.50, 0.66)	0.57 (0.48, 0.68)
Model 2	ref.	0.81 (0.69, 0.96)	0.81 (0.69, 0.96)	0.73 (0.61, 0.88)	0.60 (0.47, 0.76)
Model 3	ref.	0.83 (0.70, 0.99)	0.83 (0.70, 0.98)	0.76 (0.63, 0.92)	0.63 (0.49, 0.80)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease during 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and intakes of fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.

Supplementary Table 7. Hazard ratios of chronic obstructive pulmonary disease by quintiles of flavonoid intake excluding cases within the first 5 years of follow-up

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	n = 11,083	**n = 11,083**	**n = 11,082**	**n = 11,083**	**n = 11,082**
Total Flavonoids					
Model 1	ref.	0.72 (0.68, 0.76)	0.56 (0.52, 0.59)	0.48 (0.44, 0.51)	0.44 (0.40, 0.47)
Model 1b	ref.	0.94 (0.90, 0.99)	0.89 (0.83, 0.95)	0.84 (0.78, 0.91)	0.81 (0.74, 0.88)
Model 2	ref.	0.96 (0.91, 1.01)	0.92 (0.86, 0.99)	0.88 (0.81, 0.95)	0.85 (0.78, 0.93)
Flavonols					
Model 1	ref.	0.74 (0.70, 0.77)	0.58 (0.54, 0.62)	0.46 (0.43, 0.50)	0.43 (0.39, 0.46)
Model 1b	ref.	0.94 (0.89, 0.98)	0.89 (0.83, 0.95)	0.85 (0.79, 0.92)	0.83 (0.76, 0.90)
Model 2	ref.	0.96 (0.91, 1.01)	0.93 (0.87, 1.00)	0.91 (0.84, 0.98)	0.89 (0.82, 0.97)
Flavanol monomers					
Model 1	ref.	0.82 (0.79, 0.84)	0.60 (0.55, 0.65)	0.45 (0.42, 0.49)	0.45 (0.42, 0.49)
Model 1b	ref.	0.96 (0.93, 0.99)	0.90 (0.84, 0.98)	0.87 (0.81, 0.95)	0.87 (0.80, 0.94)
Model 2	ref.	0.98 (0.94, 1.01)	0.94 (0.87, 1.02)	0.92 (0.85, 1.00)	0.92 (0.84, 1.00)
Flavanol oligo+polymers					
Model 1	ref.	0.67 (0.64, 0.71)	0.54 (0.51, 0.58)	0.48 (0.45, 0.51)	0.44 (0.41, 0.48)
Model 1b	ref.	0.93 (0.88, 0.98)	0.87 (0.82, 0.93)	0.82 (0.76, 0.88)	0.78 (0.72, 0.85)
Model 2	ref.	0.94 (0.89, 1.00)	0.90 (0.84, 0.96)	0.85 (0.78, 0.91)	0.81 (0.74, 0.89)
Anthocyanins					
Model 1	ref.	0.65 (0.62, 0.69)	0.55 (0.51, 0.59)	0.61 (0.57, 0.65)	0.73 (0.68, 0.79)
Model 1b	ref.	0.92 (0.87, 0.97)	0.88 (0.82, 0.96)	0.90 (0.83, 0.96)	0.91 (0.84, 0.99)
Model 2	ref.	0.93 (0.87, 0.98)	0.90 (0.83, 0.97)	0.92 (0.85, 0.99)	0.93 (0.86, 1.02)
Flavanones					
Model 1	ref.	0.78 (0.74, 0.82)	0.65 (0.61, 0.71)	0.65 (0.61, 0.70)	0.71 (0.66, 0.76)
Model 1b	ref.	0.94 (0.89, 0.98)	0.90 (0.83, 0.97)	0.92 (0.86, 0.99)	0.96 (0.88, 1.03)
Model 2	ref.	0.94 (0.89, 0.99)	0.90 (0.83, 0.98)	0.92 (0.86, 0.99)	0.96 (0.88, 1.04)
Flavones					
Model 1	ref.	0.71 (0.67, 0.75)	0.60 (0.56, 0.63)	0.56 (0.53, 0.6)	0.59 (0.55, 0.64)
Model 1b	ref.	0.91 (0.87, 0.96)	0.87 (0.82, 0.93)	0.85 (0.8, 0.91)	0.87 (0.80, 0.94)
Model 2	ref.	0.92 (0.87, 0.97)	0.88 (0.82, 0.94)	0.87 (0.8, 0.93)	0.88 (0.81, 0.96)

Hazard ratios (95% CI) for chronic obstructive pulmonary disease between 5 and 23 years of follow up, obtained from restricted cubic splines based on Cox proportional hazards models. Model 1 adjusted for age and sex; Model 1b adjusted for age, sex, BMI, smoking status, smoking pack-years, physical activity, alcohol intake, education and socio-economic status (income); Model 2 adjusted for all covariates in Model 1b plus energy intake and fish, red meat, processed meat, wholegrains, refined grains, polyunsaturated fatty acids, monounsaturated fatty acids and saturated fatty acids.