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ABSTRACT

Background & Aims: Primary prevention of atrial fibrillation (AF) through behavioural and dietary modification is a critically important and unmet need. Flavonoids are bioactive dietary compounds with promising cardiovascular health benefits. Our aim was to investigate the association between flavonoid intake and clinically apparent AF.

Methods: Baseline data from 55 613 participants of the Danish Diet, Cancer and Health Study, without AF, recruited between 1993 and 1997, were cross-linked with Danish nationwide registries. Total flavonoid and flavonoid subclass intakes were calculated from validated food frequency questionnaires using the Phenol-Explorer database. Associations between flavonoid intake and incident AF (first-time hospitalization or outpatient visit) were examined using restricted cubic splines based on Cox proportional hazards models.

Results: During a median [IQR] follow-up of 21 [18 – 22] years, 7291 participants were diagnosed with AF. Total flavonoid intake was not statistically significantly associated with risk of incident AF in the whole cohort. However, compared to the lowest quintile, a total flavonoid intake of 1000 mg/day was associated with a lower risk of AF in smokers [0.86 (0.77, 0.96)] but not in non-smokers [0.96 (0.88, 1.06)], and a lower risk of AF in high alcohol consumers [>20 g/d: 0.84 (0.75, 0.95)] but not in low-to-moderate alcohol consumers [<20 g/d: 0.97 (0.89, 1.07].

Conclusion: Intake of flavonoids was not significantly associated with a lower risk of incident AF. However, higher intakes of flavonoids may be beneficial for those at a higher risk of developing AF.

23 Keywords: atrial fibrillation, flavonoids, prospective cohort study, primary
24 prevention, nutrition, cardiovascular disease.

25 Abstract word count: 240 words

INTRODUCTION

Atrial fibrillation (AF), the most common arrhythmia, is a growing public health problem with a higher risk of thromboembolic events, cognitive impairment, heart failure, and mortality [1]. With an increasing prevalence [2], the need for additional research of prevention methods is crucial. Development of AF relies on the progression of atrial structural remodelling that ultimately leads to anisotropic conduction and fibrillation. There is increasing evidence that inflammatory pathways contribute to both electrical and structural atrial remodelling as well as thrombogenesis [3]. The key role that inflammation plays in the pathophysiology of AF highlights this pathway as a potential preventive therapeutic target [3].

Flavonoids, bioactive compounds found in many fruits and vegetables as well as tea, red wine and chocolate, have antiatherogenic and antithrombotic effects, attributed in part to their capacity to attenuate inflammation [4]. Preclinical studies provide evidence that certain flavonoids have antiarrhythmic properties, which may inhibit atrial fibrillatory activity [5]. In the Danish Diet, Cancer, and Health Study, higher levels of chocolate intake were associated with a lower rate of clinically apparent AF [6], possibly due to the flavonoid content of chocolate [7].

To our knowledge, the relationship between flavonoid intake and incident AF has not been investigated in a large cohort setting. Therefore, the primary aim of this study was to investigate the association between flavonoid intake and clinically apparent AF incidence in a large cohort of Danish men and women. Secondary aims were to investigate whether these associations differed by known risk factors for AF such as presence of hypertension, diabetes mellitus, prevalent ischemic heart disease (IHD), smoking, BMI, and alcohol intake.

MATERIALS AND METHODS:

Study Population

Between December 1993 and May 1997, 56 468 men and women without cancer between the ages of 50-65 years, who were residing in Copenhagen or Aarhus, were recruited into the Danish Diet, Cancer, and Health study. Details of this cohort, which forms part of the European Prospective Investigation into Nutrition and Cancer, are published elsewhere [8].

All Danish citizens are assigned a unique personal identification number, which is used in all national registries. This allowed participants in the Danish Diet, Cancer, and Health study to be linked to the following registries on an individual level: The Civil Registration System [9] containing data on age, sex, emigration, and vital status, The Integrated Database for Labor Market Research Database [10] containing information on annual income since 1980, and The Danish National Patient Register [11] containing information on date of hospital admissions and outpatient visits since 1978, with 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 [11].

In the present study, participants were excluded if they had a prior diagnosis of AF or atrial flutter (n=437; ICD-8: 42793-42794, ICD-10: I48), if information regarding covariates was missing or if covariate values were extreme (n=214) or energy intakes implausible [<2 092 kJ/day (<500kcal/day) and >20 920 kJ/day (>5 000kcal/day)] (n=204). This left 55 613 participants from the original cohort in the current analysis (**Supplemental Figure 1)**.

This study was approved by the Danish Data Protection Agency (Ref no 2012-58-0004 I-Suite nr: 6357, VD-2018-117). Data were made available in an anonymized format to prevent the identification of specific individuals.

Public and Patient Involvement Statement

No patients or members of the public were involved in this research.

Flavonoid intake

Habitual intakes of total flavonoids and flavonoid subclasses were estimated from a validated food frequency questionnaire (FFQ). Participants were asked to complete the 192-item FFQ at baseline, indicating their usual frequency of intake of different food and beverage items over the past 12 months [12]. Using the Phenol-Explorer database [13], an estimate of the flavonoid content of each food and beverage in the food frequency questionnaire was derived [13, 14]. The intakes of 219 flavonoid aglycones were estimated and grouped into nine subclasses based on their chemical structure [flavonols, flavones, flavanols (flavanol monomers and flavanol oligo+polymers), flavanones, isoflavones, anthocyanins, chalcones, dihydrochalcones and dihydroflavonols]. Total flavonoid intake was calculated by summing each of the flavonoid subclasses. Flavonoid subclasses with average intakes less than 5 mg/d were not analysed individually.

Atrial fibrillation

The primary outcome was a hospital admission or an outpatient visit with a primary or secondary diagnosis of AF or atrial flutter. These ICD codes have previously been validated in this cohort with a positive predictive value of 92.6% [15]. From here on in, the combined diagnosis of AF and/or atrial flutter is referred to as AF.

Baseline Covariates

Information on lifestyle factors and demographics were obtained from self-administered questionnaires completed by participants at baseline. Measurements such as BMI, blood pressure and total cholesterol were taken at the study centers at baseline. Average annual income, defined as household income after taxation and interest over 5-years, was used as a proxy for socio-economic status. Comorbidities were defined using ICD-8 and ICD-10 primary or secondary diagnosis codes any time prior to baseline. These consisted of chronic kidney disease (ICD-8: 580-584, ICD-10: N02-N08, N11-N12, N14, N18-N19, N26, N158-N160, N162-N164, N168, Q61, E102, E112, E132, E142, I120, M321B), chronic obstructive pulmonary disease (COPD) (ICD-8: 491-493, ICD-10: J42-J44), heart failure (ICD-8: 4270-4271, ICD-10: I42, I50, I110, J81), hyperthyroidism (ICD-8: 242, ICD-10: E05), and cancers (ICD-8: 140-209, ICD-10: C00-C99). For ischemic stroke and IHD a combination of ICD-codes and self-reported data of ischemic stroke and myocardial infarction, respectively, were used. The codes used were stroke: ICD-8 433-434; ICD-10 I63, and IHD: ICD-8: 410-414; ICD-10: I20-I25. For hypertension and diabetes, only self-reported data was used due to the underreporting of these ICD codes in The Danish National Patient Register [16].

Statistical Analysis

Participants were followed from the date of enrollment until development of AF, death, emigration, or end of follow-up (August, 2017). Nonlinear relationships were examined with restricted cubic splines; hazard ratios (HR) were based on Cox proportional hazards models. Individuals with intakes greater than 4 standard deviations above the mean were excluded in the spline analysis and HR with 95%

confidence intervals (CI) were plotted for each unit of the exposure with the median intake in quintile 1 as the reference. Analysis of variance was used to compare the model with only the linear term to the model that included both the linear and the cubic spline terms. The exposure variables were categorized by quintiles of intake. HR and 95% CI for the median intakes in each quintile of the exposure variables were obtained from the splines. Cox proportional hazards assumptions were tested using log-log plots of the survival function versus time and assessed for parallel appearance. All deaths were censored rather than treated as a competing risk [17]. Five models of adjustment were used: 1) minimal-adjusted; 2) multivariable-adjusted; 3) multivariable-adjusted including covariates potentially on the causal pathway that may therefore introduce collider stratification bias; 4) multivariable-adjusted including potential dietary confounders; 5) multivariable-adjusted including potential dietary confounders that are also a source of flavonoids (**Supplemental Table 1**). Covariates were chosen *a priori* to the best of our knowledge of potential confounders of flavonoid intake and AF. We did not include total energy intake as a covariate in any model as we believe, given the underlying biology, that crude values of flavonoid intake are more relevant.

We stratified our analyses by baseline smoking status, alcohol intake, BMI, diabetes status, IHD status, and hypertension status in order to examine the impacts of flavonoids in different subgroups. When stratifying by alcohol intake and BMI, we excluded all participants with an alcohol intake of zero (n=1 283) and all participants with a BMI<18.5 (n=451), respectively, as these were not the subgroups of interest. We chose stratification cut-off points of 20 g pure alcohol per day and 30 kg/m^2 for BMI as the risk of mortality is highest beyond these levels [18, 19]. As there is the potential for residual confounding, when stratifying by alcohol intake and BMI the

corresponding continuous variables, alcohol intake and BMI, respectively, were included in the model. Analyses were undertaken using STATA/IC 14.2 (StataCorp LLC) and R statistics (R Core Team (2018)) [18]. Statistical significance was set at $p \leq 0.05$ (two-tailed) for all tests.

RESULTS

In this population of 55 613 Danish citizens, followed for a median [IQR] of 21 [18 - 22] years, 7 291 participants had incident AF and 6286 participants were hospitalized for AF. Furthermore, 11 415 participants died without AF.

Baseline Characteristics

The cohort had a median [IQR] age of 56 [52 - 60] years at baseline and 26 344 (47.4%) were male. Compared to participants in the lowest quintile of total flavonoid intake, those in the highest quintile were more likely to be female, have a lower BMI, be more physically active, have received a higher degree of education, receive a higher income and take hormone replacement therapy, aspirin, and other nonsteroidal anti-inflammatory drugs (**Table 1**). These participants were also less likely to be current smokers, have hypercholesterolemia, COPD, IHD, heart failure or diabetes, or have had a stroke. Participants with a higher flavonoid intake tended to consume more fish, fibre, fatty acids, fruit and vegetables, and less red or processed meat.

Associations between total flavonoid and flavonoid subclass intakes and AF

Total flavonoid intakes beyond quintile 1 were associated with a 3-5% lower risk of incident AF, although this was not statistically significant after adjusting for potential

lifestyle confounders (**Table 2 and Figure 2**). For AF hospitalizations, after adjusting for potential lifestyle confounders and compared to participants in Q1, participants in Q3 and Q4 had a statistically significant 7% and 8% lower risk of an AF hospitalization, with HRs (95% CI) of 0.93 (0.87, 0.99) and 0.92 (0.86, 0.98), respectively (**Supplemental Table 2 and Supplemental Figure 2**). Similar patterns were seen for the associations between flavonoid subclasses and both incident AF and AF hospitalizations. HRs for alternative models of adjustment (3 and 5) are presented in **Supplemental Table 3** but do not differ substantively

Stratified analyses

The inverse association between total flavonoid intake and incident AF was apparent in smokers but not in non-smokers (**Figure 3**). A total flavonoid intake of 1000 mg/d was associated with a significant 11% lower risk of AF in smokers [HR: 0.89 (0.80, 0.99)], whereas no association was observed in non-smokers [HR: 0.98 (0.90, 1.07)], compared to those consuming 173 mg/d. Similarly, an association was only apparent in participants who consumed >20 g/d of alcohol; a total flavonoid intake of 1000 mg/d was associated with a statistically significant 12% lower risk of incident AF [HR: 0.88 (0.79, 0.98)] whereas no association was observed in those who consumed ≤20 g/d of alcohol [HR: 0.99 (0.91, 1.08)]. There was some evidence for an association in participants with diabetes at baseline where 1000 mg/d total flavonoid intake was associated with a non-significant 24% lower risk of incident AF, [HR: 0.76 (0.51, 1.14)] (Figure 2). However, the number of participants with diabetes (n=1 162) at baseline was modest and the associated confidence interval in this subgroup was wide. No clear effect modification by baseline hypertension status, IHD status, or BMI was observed (Figure 3).

DISCUSSION

The growing epidemic of AF exerts a significant and growing burden on public health. Accordingly, primary prevention of AF through behavioural and dietary modification is a critically important and unmet need. In this cohort of 55 613 Danish participants, a higher habitual intake of total flavonoids was not associated with a lower risk of incident AF. However, total flavonoid intake was associated with a lower risk of incident AF in smokers and in heavy alcohol consumers.

Increasing evidence highlights the role of inflammation and oxidative stress in the pathophysiology of AF, suggesting that these processes could be key therapeutic targets for primary prevention [3, 19]. Studies relating diet to AF incidence have primarily focused on fish derived n-3 polyunsaturated fatty acids (PUFAs), alcohol intake, caffeine, ascorbic acid, and, more recently, chocolate [20]. While heavy alcohol intake is invariably associated with a higher risk of AF, other, more beneficial, dietary components are not consistently favourable for AF prevention. Supplementation with a combination of PUFAs, vitamin C, and vitamin E has been shown to reduce the incidence of post-operative AF and attenuate oxidative stress and inflammation, attributed to their antioxidant capacity [21]. In a previous study of participants in the Danish Diet, Cancer and Health cohort, those with a higher level of chocolate intake had a lower rate of AF hospitalization, possibly due to the high flavanol content of cocoa [6]. However, in a recent meta-analysis of 5 cohort studies, the hazard ratio of AF was 0.96 (95% CI 0.90-1.03) for the highest versus lowest category of chocolate consumption [22].

Preclinical and clinical studies on flavonoids suggest that they can ameliorate early markers of cardiovascular disease [4], while observational studies demonstrate an

214 inverse association between flavonoid intake and cardiovascular disease incidence
215 and mortality [5, 23]. In the present cohort, we have shown that higher flavonoid intakes
216 are associated with a lower risk of atherosclerotic cardiovascular disease [24][in press].
217 A number of *in vitro* studies demonstrate that flavonoids can activate potassium
218 channels or inhibit calcium channels [4, 5], in particular $Ca_v1.2$ channels which are
219 critical regulators of vascular tone and cardiac activity [25]. However, flavonoids are
220 readily metabolised upon ingestion [4], an important consideration that was not
221 accounted for in most of these studies. While flavonoids were initially considered as
222 antioxidants, they, and their *in vivo* metabolites, are now seen as signalling molecules,
223 resulting in the downstream upregulation of enzymes that protect against oxidant
224 damage [26]. It is more likely that the cardiovascular protective effects of flavonoids lie
225 in their anti-inflammatory and anti-thrombogenic properties [4].

226 Our finding that flavonoid intake was only modestly associated with AF
227 hospitalizations, and not with overall incident AF, may be due to their beneficial
228 effects on comorbidities, such as cardiovascular disease [27] and diabetes [3], which
229 increase the likelihood of hospitalization. In this study we were unable to determine
230 whether the patients were admitted due to AF or whether AF was incidentally
231 diagnosed. Due to the potential for selection bias, caution should be taken in
232 interpreting results from studies using only AF hospitalizations as an outcome.
233 Overall, this study shows that total flavonoid intake or any flavonoid subclass intake
234 do not seem to be associated with incident AF.

235 Inflammation is a contributor to AF both direct and indirectly mediated by other
236 inflammatory cardiovascular diseases [3]. Higher levels of oxidative stress and
237 inflammation are associated with smoking, high alcohol intake, obesity, diabetes,

IHD, and hypertension [27]. In the present study there was a significant association between flavonoid intake and incident AF in participants who smoked or consumed high levels of alcohol. This finding supports the hypothesis that any risk reduction in AF afforded by flavonoids is likely through inflammatory and oxidative stress pathways, rather than antiarrhythmic properties.

Strengths of the present study include a large adult population followed for 23 years with limited loss to follow-up; all deaths and emigrations are captured in the Danish registries. However, as this is an observational study, we are not able to conclude causality. Although the data allowed us to adjust for many potential dietary and lifestyle confounders, unmeasured confounders, such as sleep apnoea (due to the lack of a specific ICD-8 code), could not be taken into consideration. Confounding by unobserved and potentially protective dietary factors cannot be discounted, although, adjusting for other major indicators of a healthy diet in this study did not substantially alter the risk estimates. Dietary intake and clinical data were only captured at baseline and may have changed over the 23 years of follow-up and it is unclear how changes in the trajectories of dietary intake and confounders may have impacted the observed associations. This limitation may have attenuated the power to detect an association. Common FFQ limitations apply in that not all flavonoid-rich foods were captured (for example, berries) meaning that intakes of some flavonoid subclasses (anthocyanins in particular) were likely underestimated. Although race and ethnicity were not considered, participants would most likely have been Caucasian; caution should be taken when extrapolating these findings to other populations.

Our findings suggest that higher flavonoid intakes are not associated with a lower risk of AF incidence. However, flavonoid-rich foods may be beneficial for those at a

higher risk of developing AF. The association between flavonoid intake and lower AF incidence in smokers and in heavy alcohol consumers needs replication in other studies.

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Author contributions

NB, FD, KM, CK, GG, JH, KO, contributed to the conception or design of the work. NP, FD, KM, CB, LJ, KC, CK, GG, AT, AS, JP, JH, KO, CA contributed to the acquisition, analysis, or interpretation of data for the work. NB drafted the manuscript. FD, KM, CB, LJ, KC, CK, GG, AT, AS, JP, JH, KO, CA critically revised the manuscript. All gave final approval and agree to be accountable for all aspects of work ensuring integrity and accuracy.

Conflicts of interest:

The authors declare no conflicts of interest.

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285 **Disclaimer:**

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289 views of the International Agency for Research on Cancer / World Health
290 Organization.

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Table 1. Baseline characteristics of study population

		Total flavonoid intake quintiles				
	Total population	**Q1**	**Q2**	**Q3**	**Q4**	**Q5**
	n = 55 613	**n = 11 123**	**n = 11 123**	**n = 11 122**	**n = 11 123**	**n = 11 122**
Total flavonoid intake (g/d)	494 [287, 804]	173 [127, 213]	320 [287, 356]	494 [441, 548]	726 [659, 804]	1 201 [1 024, 1 435]
Sex (male)	26 344 (47.4)	6411 (57.6)	5669 (51.0)	5277 (47.4)	4935 (44.4)	4052 (36.4)
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 [23.7, 28.8]	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	66.6 (44.1)	61.5 (43.5)	66.0 (44.3)	67.4 (44.0)	68.8 (44.6)	69.4 (43.6)
Smoking status						
Never	19 532 (35.1)	2701 (24.3)	3720 (33.4)	3970 (35.7)	4429 (39.8)	4712 (42.4)
Former	15 985 (28.7)	2663 (23.9)	3008 (27.0)	3229 (29.0)	3562 (32.0)	3523 (31.7)
Current	20 096 (36.1)	5759 (51.8)	4394 (39.5)	3924 (35.3)	3131 (28.2)	2888 (26.0)
Education						
≤7 years	18 300 (32.9)	5091 (45.8)	4220 (37.9)	3578 (32.2)	3009 (27.1)	2402 (21.6)
8 – 10 years	25 640 (46.1)	4855 (43.6)	5229 (47.0)	5301 (47.7)	5273 (47.4)	4982 (44.8)
≥11 years	11 645 (20.9)	1171 (10.5)	1669 (15.0)	2240 (20.1)	2833 (25.5)	3732 (33.6)
Mean household income						
≤394 700 DKK/year	13 809 (24.8)	3324 (29.9)	2728 (24.5)	2700 (24.3)	2561 (23.0)	2496 (22.4)
394 701 – 570 930 DKK/year	13 906 (25.0)	3246 (29.2)	2979 (26.8)	2692 (24.2)	2579 (23.2)	2410 (21.7)
570 931 – 758 297 DKK/year	13 946 (25.1)	2889 (26.0)	3005 (27.0)	2878 (25.9)	2604 (23.4)	2570 (23.1)
> 758 297 DKK/year	13 952 (25.1)	1664 (15.0)	2410 (21.7)	2853 (25.6)	3378 (30.4)	3647 (32.8)
Hypertensive	8 997 (16.2)	1 781 (16.0)	1 839 (16.5)	1 834 (16.5)	1 798 (16.2)	1 755 (15.8)
Hypercholesterolemic	4 097 (7.4)	891 (8.0)	812 (7.3)	834 (7.5)	847 (7.6)	721 (6.5)
Comorbidities						
Diabetes	1 162 (2.1)	277 (2.5)	215 (1.9)	248 (2.2)	213 (1.9)	209 (1.9)
Heart failure	182 (0.3)	49 (0.4)	43 (0.4)	33 (0.3)	33 (0.3)	24 (0.2)

IHD	2 082 (3.7)	558 (5.0)	397 (3.6)	415 (3.7)	381 (3.4)	331 (3.0)
Stroke	702 (1.4)	192 (1.9)	141 (1.3)	128 (1.2)	120 (1.2)	121 (1.2)
COPD	838 (1.5)	219 (2.0)	184 (1.7)	155 (1.4)	148 (1.3)	132 (1.2)
CKD	200 (0.4)	43 (0.4)	30 (0.3)	44 (0.4)	42 (0.4)	41 (0.4)
Cancer	244 (0.4)	53 (0.5)	42 (0.4)	60 (0.5)	33 (0.3)	56 (0.5)
Hyperthyroidism	396 (0.7)	82 (0.7)	71 (0.6)	85 (0.8)	72 (0.6)	86 (0.8)
Medication use						
Insulin	378 (0.7)	78 (0.7)	63 (0.6)	86 (0.8)	80 (0.7)	71 (0.6)
Antihypertensive medication	6 770 (12.2)	1328 (11.9)	1404 (12.6)	1375 (12.4)	1342 (12.1)	1321 (11.9)
Statin	1 037 (1.9)	248 (2.2)	207 (1.9)	213 (1.9)	207 (1.9)	162 (1.5)
HRT						
Never	15 916 (28.6)	2594 (23.3)	3042 (27.4)	3256 (29.3)	3260 (29.3)	3764 (33.8)
Current	8 790 (15.8)	1289 (11.6)	1565 (14.1)	1692 (15.2)	1989 (17.9)	2255 (20.3)
Former	4 531 (8.1)	820 (7.4)	842 (7.6)	891 (8.0)	932 (8.4)	1046 (9.4)
NSAID	18 008 (32.6)	3510 (31.8)	3495 (31.6)	3613 (32.7)	3615 (32.7)	3775 (34.2)
Aspirin	7 015 (12.6)	1371 (12.3)	1351 (12.1)	1421 (12.8)	1381 (12.4)	1491 (13.4)
Dietary characteristics						
Energy (kj)	9 497 [7 855, 11 365]	8 610 [7 027, 10 387]	9 260 [7 713, 10 997]	9 748 [8 135, 11 583]	9 934 [8 321, 11 817]	9 922 [8 252, 11 881]
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]
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 [11, 18]
Monounsaturated FA (g/d)	27 [21, 35]	25 [21, 34]	28 [22, 35]	28 [22, 36]	28 [22, 36]	27 [21, 34]
Fruit intake (g/d)	171 [95, 281]	89 [44, 141]	161 [98, 237]	193 [114, 300]	224 [139, 360]	240 [141, 390]
Vegetable intake (g/d)	161 [105, 231]	114 [71, 170]	150 [99, 211]	168 [113, 235]	184 [127, 253]	196 [135, 272]
Alcohol intake (g/d)	13 [6, 31]	11 [3, 23]	13 [6, 24]	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; COPD, common obstructive pulmonary disease; DKK, Danish Krone; FA, fatty acids; HRT, hormone replacement therapy; IHD, ischemic heart disease; MET, metabolic equivalent; NSAID, Nonsteroidal anti-inflammatory drug.

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Table 2. Hazard ratios of incident atrial fibrillation by quintiles of flavonoid intake

	Flavonoid intake quintiles				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
	(n=11 123)	**(n=11 123)**	**(n=11 122)**	**(n=11 123)**	**(n=11 122)**
Total Flavonoids					
No. events	1 398	1 301	1 265	1 179	1 143
Intake (mg/d)*	173 (6 – 251)	320 (251 – 394)	494 (394 – 601)	726 (601 – 908)	1201 (908 – 3552)
HR (95% CI)					
Model 1	ref.	**0.94 (0.90, 0.99)**	**0.91 (0.85, 0.96)**	**0.88 (0.83, 0.94)**	**0.87 (0.82, 0.93)**
Model 2	ref.	0.97 (0.92, 1.01)	0.95 (0.89, 1.00)	0.94 (0.89, 1.00)	0.95 (0.89, 1.02)
Model 4	ref.	0.97 (0.92, 1.01)	0.95 (0.89, 1.01)	0.95 (0.89, 1.01)	0.96 (0.90, 1.03)
Flavonols					
No. events	1 345	1 359	1 231	1 251	1 100
Intake (mg/d)*	15 (0 – 20)	26 (20 – 32)	38 (32 – 50)	66 (50 – 82)	116 (82 – 251)
HR (95% CI)					
Model 1	ref.	0.97 (0.93, 1.01)	**0.94 (0.89, 1.00)**	**0.89 (0.84, 0.95)**	0.88 (0.83, 0.94)
Model 2	ref.	0.97 (0.93, 1.01)	0.96 (0.90, 1.02)	0.95 (0.89, 1.01)	0.97 (0.91, 1.03)
Model 4	ref.	0.97 (0.93, 1.01)	0.95 (0.89, 1.01)	0.95 (0.89, 1.01)	0.96 (0.90, 1.03)
Flavanol monomers					
No. events	1 398	1 295	1 306	1 172	1 115
Intake (mg/d)*	14 (0 – 21)	30 (21 – 45)	66 (45 – 115)	260 (115 – 281)	473 (281 – 916)
HR (95% CI)					
Model 1	ref.	0.98 (0.96, 1.01)	**0.95 (0.89, 1.01)**	**0.88 (0.82, 0.93)**	**0.87 (0.82, 0.93)**
Model 2	ref.	0.98 (0.95, 1.01)	0.96 (0.90, 1.02)	0.96 (0.90, 1.02)	0.97 (0.91, 1.03)
Model 4	ref.	0.98 (0.96, 1.01)	0.96 (0.90, 1.02)	0.96 (0.90, 1.02)	0.97 (0.91, 1.04)
Flavanol oligo+polymers					

No. events	1 397	1 325	1 208	1 217	1 139
Intake (mg/d)*	91 (0 – 136)	179 (136 – 217)	255 (217 – 302)	359 (302 – 434)	536 (434 – 2254)
HR (95% CI)					
Model 1	ref.	**0.92 (0.88, 0.97)**	**0.89 (0.84, 0.94)**	**0.87 (0.82, 0.92)**	**0.86 (0.81, 0.92)**
Model 2	ref.	0.96 (0.92, 1.02)	0.94 (0.89, 1.00)	**0.92 (0.87, 0.98)**	0.93 (0.87, 1.00)
Model 4	ref.	0.96 (0.92, 1.02)	0.94 (0.89, 1.00)	**0.93 (0.87, 0.99)**	0.94 (0.88, 1.01)
Anthocyanins					
No. events	1 241	1 190	1 274	1 223	1 358
Intake (mg/d)*	5 (0 – 10)	13 (10 – 17)	20 (17 – 24)	36 (24 – 53)	71 (53 – 397)
HR (95% CI)					
Model 1	ref.	**0.93 (0.88, 0.98)**	**0.92 (0.86, 0.98)**	0.98 (0.92, 1.04)	1.06 (0.99, 1.13)
Model 2	ref.	0.99 (0.93, 1.04)	0.99 (0.92, 1.06)	1.01 (0.95, 1.08)	1.04 (0.97, 1.11)
Model 4	ref.	0.99 (0.94, 1.04)	0.99 (0.93, 1.06)	1.02 (0.95, 1.09)	1.04 (0.97, 1.12)
Flavanones					
No. events	1 301	1 294	1 231	1 212	1 248
Intake (mg/d)*	3 (0 – 6)	9 (6 – 13)	17 (13 – 26)	32 (26 – 49)	70 (49 – 564)
HR (95% CI)					
Model 1	ref.	0.97 (0.93, 1.02)	0.95 (0.88, 1.01)	**0.93 (0.87, 0.99)**	**0.95 (0.90, 1.02)**
Model 2	ref.	0.97 (0.93, 1.02)	0.95 (0.89, 1.02)	0.94 (0.88, 1.00)	0.96 (0.90, 1.02)
Model 4	ref.	0.98 (0.93, 1.02)	0.96 (0.89, 1.03)	0.94 (0.88, 1.00)	0.96 (0.90, 1.03)
Flavones					
No. events	1 327	1 249	1 259	1 186	1 265
Intake (mg/d)*	2 (0 – 3)	4 (3 – 4)	5 (4 – 6)	7 (6 – 9)	11 (9 – 51)
HR (95% CI)					
Model 1	ref.	**0.92 (0.86, 0.97)**	**0.89 (0.84, 0.95)**	**0.87 (0.82, 0.93)**	**0.89 (0.83, 0.95)**
Model 2	ref.	0.97 (0.91, 1.03)	0.95 (0.89, 1.01)	**0.93 (0.87, 0.99)**	**0.93 (0.87, 1.00)**

Model 4	ref.	0.97 (0.91, 1.03)	0.96 (0.89, 1.02)	0.94 (0.88, 1.00)	0.95 (0.88, 1.02)

Hazard ratios (95% CI) for incident atrial fibrillation (first-time hospitalization or outpatient visit) 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 2 adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, social economic status (income), and hyperthyroidism; Model 4 adjusted for all covariates in Model 2 plus intakes of fish, red meat, processed food, polyunsaturated fatty acids, monounsaturated fatty acids, and saturated fatty acids.

*Median; range in parentheses (all such values). **Bold** indicates $p<0.05$.

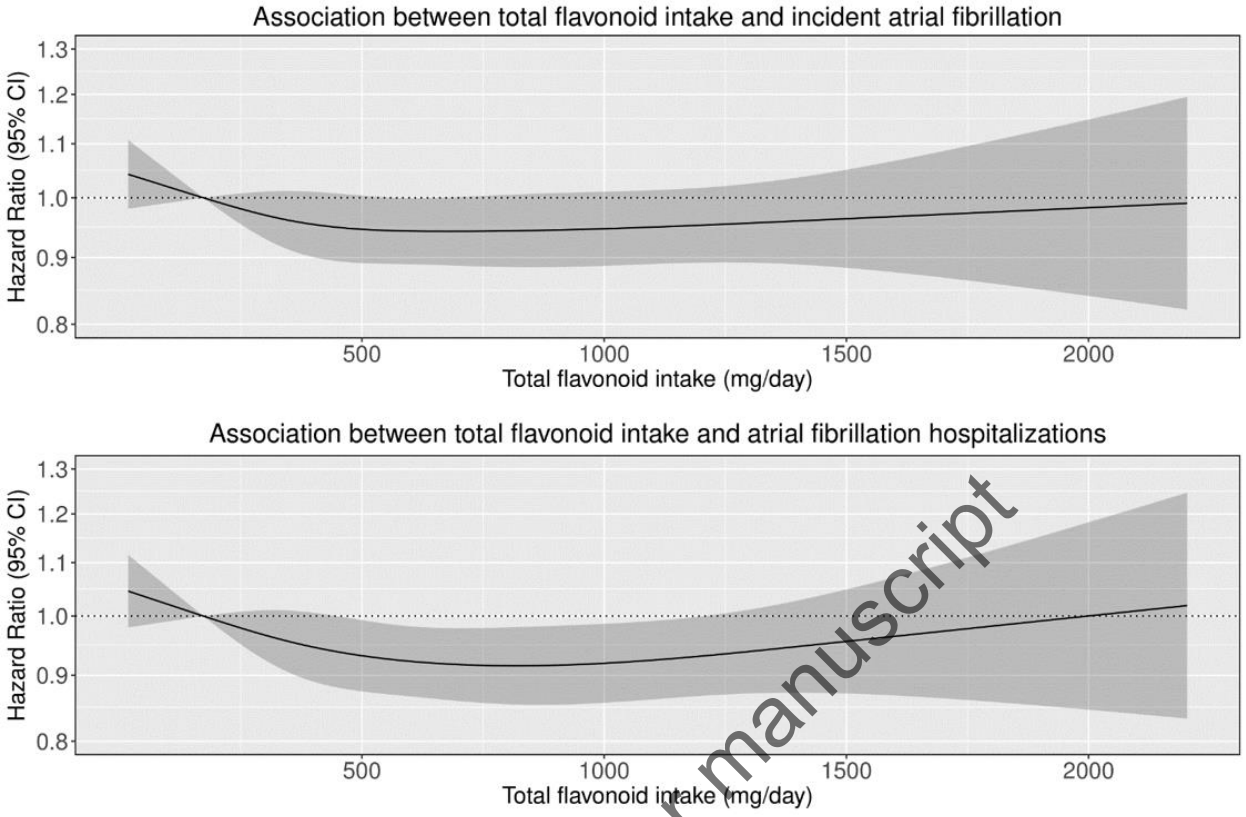
FIGURE LEGENDS:

Figure 1. Associations between total flavonoid intake and incident atrial fibrillation (AF; first-time hospitalization or outpatient visit; n=7 291) and AF hospitalizations (n=6 286), in participants of the Danish Diet, Cancer and Health cohort. Hazard ratios for cubic splines are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, social economic status (income), and hyperthyroidism and are comparing the specific level of total flavonoid intake (horizontal axis) to the median intake for participants in the lowest intake quintile (173 mg/d).

Figure 2. Hazard ratios based on cubic spline curves to describe the association between flavonoid subclass intakes (mg/day) and incident atrial fibrillation (first-time hospitalization or outpatient visit) among participants of the Danish Diet, Cancer and Health cohort. Hazard ratios are based on Cox proportional hazards models adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, social economic status (income), and hyperthyroidism 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 associations between total flavonoid intake and incident atrial fibrillation (first-time hospitalization or outpatient visit), stratified by baseline smoking status (smoker n=20 096; non-smoker n=35 517), alcohol intake (<20 g/day n=35 458; (>20 g/day n=18 872), BMI (<30 kg/m^2 n=46 991; >30 kg/m^2 n=8 171), ischemic heart disease (IHD) status (IHD n=2 082; no IHD n=53 531), diabetes status (diabetic n=1 162; non-diabetic n=54 451), and hypertension status (hypertensive n=8 997; non-hypertensive n=46 616). Hazard ratios are based on Cox proportional hazards models and are comparing the specific level of total flavonoid intake

(horizontal axis) to the median intake for participants in the lowest intake quintile (173 mg/day). All analyses were adjusted for age, sex, BMI, smoking status, physical activity, alcohol intake, social economic status (income), and hyperthyroidism, not including the stratification variable for each subgroup if that variable was discrete.



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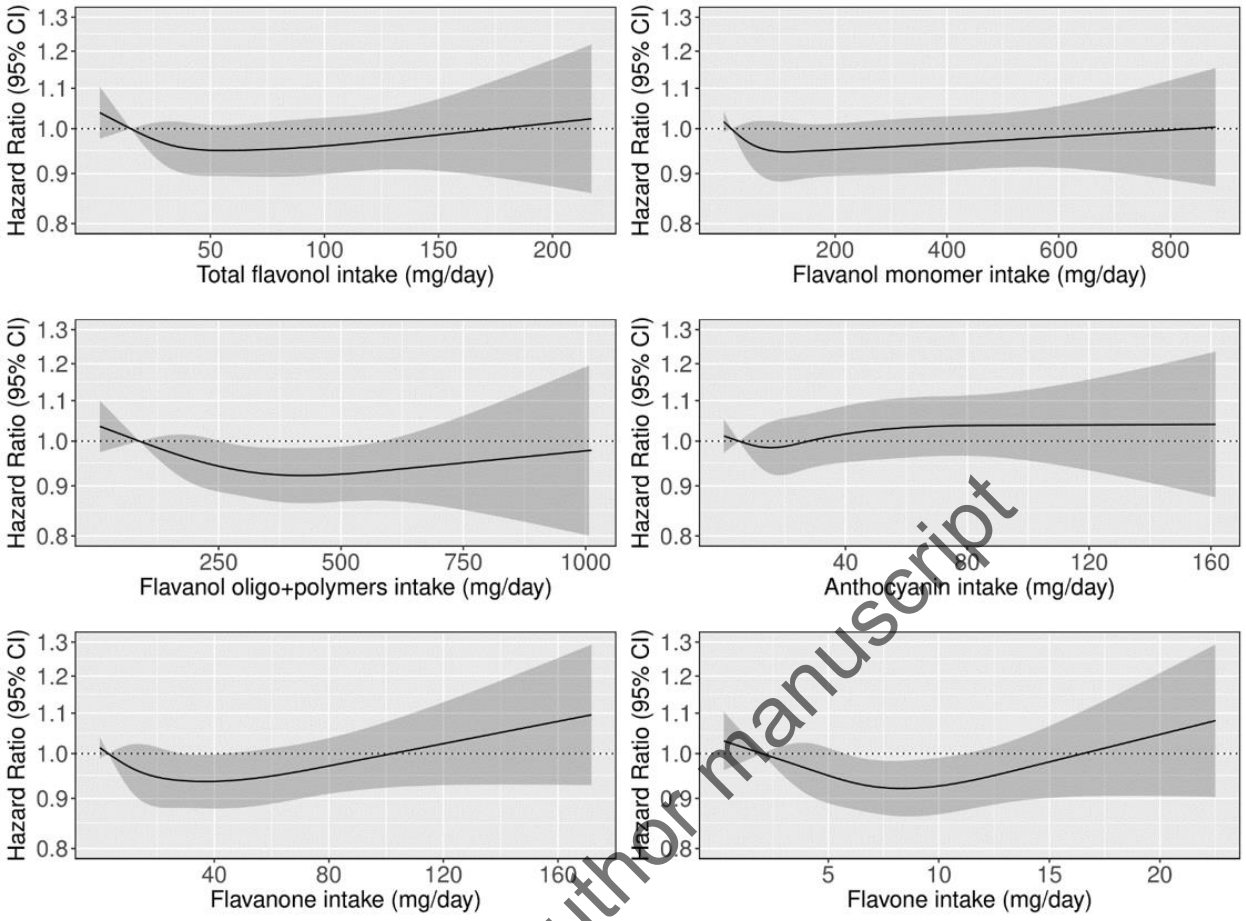

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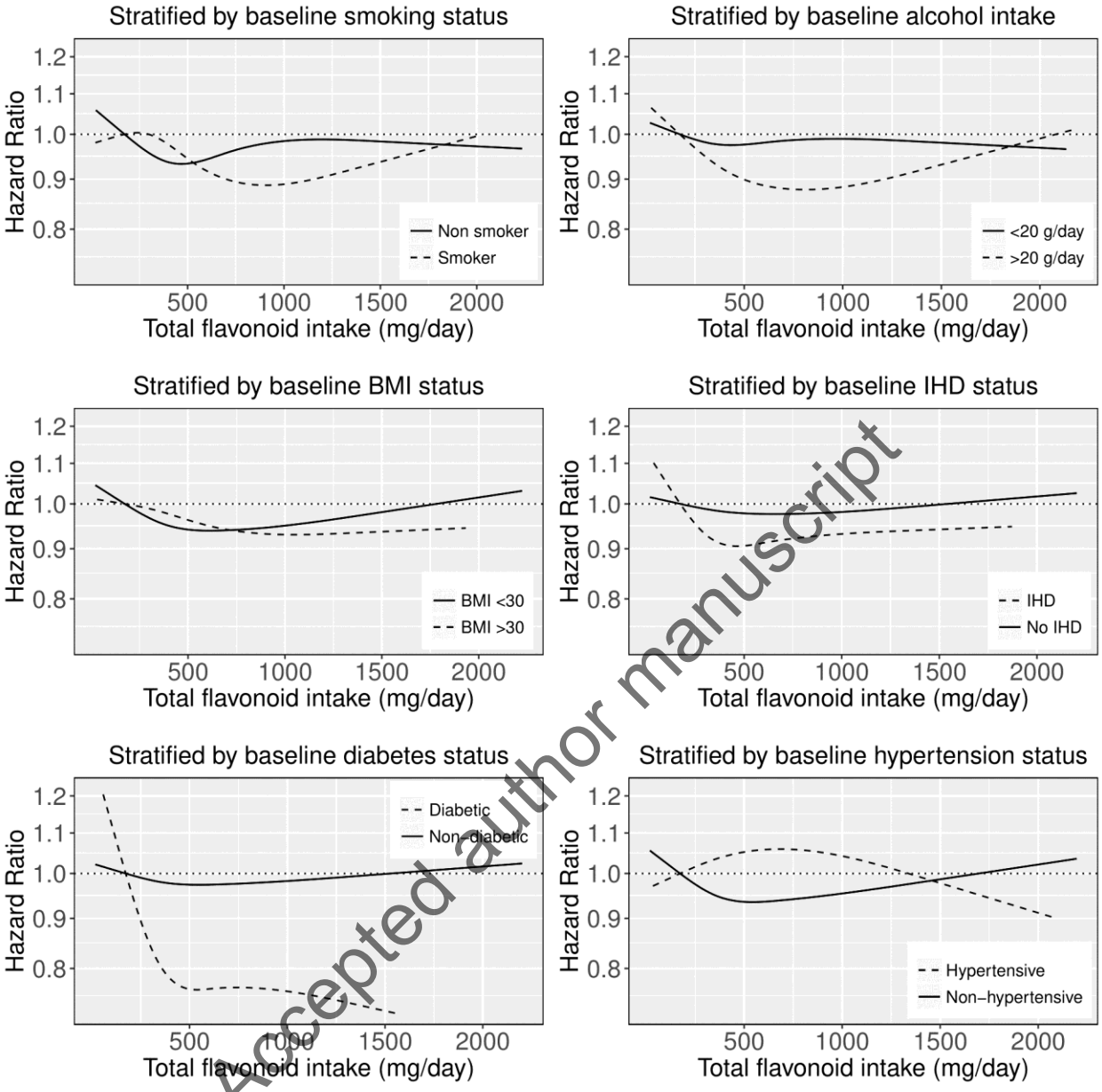

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