Nutrition, Metabolism & Cardiovascular Diseases (2023) **33**, 1167–1178

Available online at www.sciencedirect.com

Nutrition, Metabolism & Cardiovascular Diseases

journal homepage: www.elsevier.com/locate/nmcd

Dietary polyphenols, metabolic syndrome and cardiometabolic risk factors: An observational study based on the DCH-NG subcohort

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Received 14 November 2022; received in revised form 17 February 2023; accepted 27 February 2023
Handling Editor: A. Siani
Available online 2 March 2023

KEYWORDS
Metabolic syndromes;
Heart disease risk factors;
Diet surveys;
Food;
Polyphenol;
Phenolic acid;
Cohort

Abstract *Background and aims:* Polyphenol-rich foods have beneficial properties that may lower cardiometabolic risk. We aimed to prospectively investigate the relationship between intakes of dietary polyphenols, and metabolic syndrome (MetS) and its components, in 676 Danish residents from the MAX study, a subcohort of the Danish Diet, Cancer and Health–Next Generations (DCH-NG) cohort.
Methods and results: Dietary data were collected using web-based 24-h dietary recalls over one year (at baseline, and at 6 and 12 months). The Phenol-Explorer database was used to estimate dietary polyphenol intake. Clinical variables were also collected at the same time point. Generalized linear mixed models were used to investigate relationships between polyphenol intake and MetS. Participants had a mean age of 43.9y, a mean total polyphenol intake of 1368 mg/day, and 75 (11.6%) had MetS at baseline. Compared to individuals with MetS in Q1 and after adjusting for age, sex, lifestyle and dietary confounders, those in Q4 – for total polyphenols, flavonoids and phenolic acids–had a 50% [OR (95% CI): 0.50 (0.27, 0.91)], 51% [0.49 (0.26, 0.91)] and 45% [0.55 (0.30, 1.00)] lower odds of MetS, respectively. Higher total polyphenols, flavonoids and phenolic acids intakes as continuous variable were associated with lower risk for elevated systolic blood pressure (SBP) and low high-density lipoprotein cholesterol (HDL-c) ($p < 0.05$).
Conclusions: Total polyphenol, flavonoid and phenolic acid intakes were associated with lower odds of MetS. These intakes were also consistently and significantly associated with a lower risk for higher SBP and lower HDL-c concentrations.

Abbreviations: DCH-NG, Diet Cancer and Health - Next Generations; DBP, diastolic blood pressure; HbA1c, glycosilated hemoglobin; HDL-c, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; MetS, metabolic syndrome; PE, Phenol-Explorer; SBP, systolic blood pressure; TG, triglyceride; WC, waist circumference; WG, whole grain; 24-HDRs, 24-h dietary recalls.

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https://doi.org/10.1016/j.numecd.2023.02.022

1. Introduction

Metabolic syndrome (MetS) is a cluster of metabolic disorders that increases the risk of developing chronic diseases [1]. Cardiometabolic risk factors include high waist circumference (WC), insulin resistance, hypertension, dysglycemia, dyslipidemia, and altered inflammatory markers such as C-reactive protein and cytokines, among others [1].

Following a healthy diet is one of the most important modifiable lifestyle factors for preventing obesity, MetS and cardiometabolic diseases [2,3]. Controlled clinical trials have shown that healthy lifestyles, such as a higher adherence to a Mediterranean diet, may have a positive impact on individuals with MetS [4,5]. This is partially attributed to polyphenolic compounds, a large family of phytochemicals ubiquitously distributed in plant-based food such as fruits, vegetables, beverages, cocoa products and whole grain (WG) products [6]. Multiple mechanisms explaining the health benefits of polyphenols on MetS have been proposed, including improvements in endothelial function, positive effects on inflammatory and metabolic pathways, and, most recently, their impact on the gut microbiota [7,8].

Evidence of the potential cardiometabolic protective effects of polyphenols comes from several epidemiological studies and randomized clinical trials [9,10]. Most of the studies have focused on flavonoids and their subclasses, namely, flavan-3-ols, flavonols and anthocyanins [11]. Despite the fact that polyphenols are one of the most researched dietary factors in relation to MetS through bibliometric analysis [12], few studies have examined associations between habitual intakes of polyphenols (total and main classes) and MetS [13,14]. A cross-sectional study showed that individuals consuming higher intakes of polyphenols were less likely to have MetS (highest vs. lowest quartile) and a high WC, blood pressure, triglyceride (TG) and low high-density lipoprotein cholesterol (HDL-c) in women, and high fasting glucose in both genders [15]. Recently, the PREDIMED-Plus study reported positive associations between HDL-c and total polyphenol intake and also with most of the polyphenol subclasses [16]. However, no association was found between total polyphenols intake and other MetS components.

The aim of the present study was to investigate the associations between intakes of polyphenols (total polyphenols and their main classes) and the prevalence of MetS and cardiometabolic risk factors in 676 participants of the MAX study from the Danish Diet, Cancer and Health – Next Generation (DCH-NG) cohort. Our hypothesis was that a higher intake of polyphenols would be inversely associated with MetS and cardiometabolic risk factors. Secondary analyses were to examine whether associations differed according to lifestyle factors (e.g. smoking status, age, and sex), timepoints or presence of previously diagnosed clinical conditions.

2. Methods

2.1. Study population and design

The current analysis is based on the DCH-NG MAX study, a validation subsample study within the DCH-NG cohort. This large population-based family study, established in Denmark between August 2015 and April 2019, is an extension of the Diet, Cancer and Health (DCH) cohort [17]. The DCH-NG cohort includes 39,554 adult participants with complete data collection and incorporates biological children (Generation 1), their spouses (Generation 1-Parent) and the grandchildren (Generation 2) of the participants in the DCH cohort (Generation 0) [18]. From August 2017 to January 2018, 720 participants of the DCH-NG MAX study (Fig. 1), aged 18 or older, were enrolled and both questionnaire data and biological samples (i.e. blood) were collected at baseline, and at 6 and 12 months.

The DCH-NG research project was approved by the Danish Data Protection Agency ((journal number 2013–41-2043/2014–231-0094) and by the Committee on Health Research Ethics for the Capital Region of Denmark (journal number H-15001257). The participants provided their written informed consent to participate in the study.

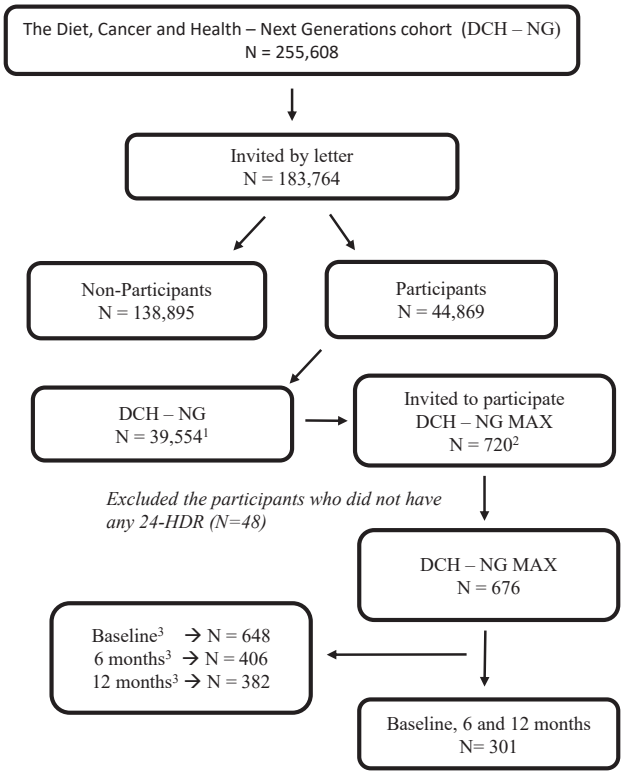

Figure 1 Flow chart of participants from DCH cohort and subcohort MAX [18].[1] completed FFQ, lifestyle questionnaire and the study center assessment.[2] validation sub-study that included 24 HDRs and re-visit the center at 6 and 12 months after the baseline.[3]14 participants had only twelve months of dietary data, 8 participants had six months of dietary data and 6 participants with both days (six and twelve months).

2.2. Dietary data

Participants (n = 676) of the DCH-NG MAX study completed at least one 24-h dietary recall (24-HDR). The participants by each time point were: baseline (n = 648), 6 months (n = 406) and 12 months (n = 382). It is important to mention that only 301 participants completed the three timepoints for all yesterday's 24-HDR. The participants used the web-based tool myfood24 (www.myfood24.org/) from Leeds University [19], which has been mainly linked with the Danish national food database and now contains approximately 1600 Danish food items, including a recipe maker. Also, we included food sources from other food databases to expand the table such as Swedish Food Agency (https://www.livsmedelsverket.se/en), McCance and Widdowson's Food Composition Table versions 6 and 7, and specific brands from the myfood24, among others. The 24-HDRs were used to estimate intakes of individual foods, energy, macronutrients, and micronutrients.

2.3. Polyphenol dietary intake

A specific protocol was used to estimate the dietary intake of polyphenols from DCH-NG MAX 24 HDRs using an "in-house" software developed by the University of Barcelona, the Bellvitge Biomedical Research Institute (IDIBELL) and the *Centro de Investigación Biomédica en Red* (CIBER) [20]. The total polyphenol content was calculated as the sum of all individual compounds expressed as they are found in nature (i.e. glycosides, aglycones and esters) [21]. In addition, the dietary intake of polyphenols was estimated by classes: flavonoids, phenolic acids, lignans, stilbenes, alkylphenol and tyrosol. The data used in the present study were mainly acquired by chromatography without previous hydrolysis of the food extracts, except for lignans and proanthocyanidins [21]. The estimated intake of dietary polyphenols of the DCH-NG MAX study has been previously described elsewhere [22]. The percentage contribution of classes of dietary polyphenols, and the top five most consumed foods or individual polyphenols for each polyphenol class is presented in Supplementary Table 1.

2.4. Biological, anthropometrical and clinical data

All participants visited Copenhagen study center three times (baseline, 6 months and 12 months) for the physical examination and collection of biological samples. The anthropometric measures for height and weight were performed using Seca 264 and Seca 515/514, respectively. The WC was measured midway between the lowest rib margin and the iliac crest and to the nearest 0.1 cm, using a measuring tape. Blood pressure was measured on the left arm, three times after at least 5 min of rest, using an Omron M−10 IT[a] and Omron HB-1300 (arm circumferences <22 cm and >42 cm). Blood samples were collected in a non-fasting status (from 1 to more than 9 h since last meal). Biochemical analysis was performed to determine HDL-c, TG and high-sensitivity C-reactive protein (hs-CRP) using tubes with lithium heparin and the hemoglobin A1c using tubes with K_2EDTA. A complete description of the physical examination and biological samples is presented elsewhere [18].

2.5. Metabolic syndrome and cardiometabolic risk factors

MetS was defined as the presence of three or more of its five components according to the International Diabetes Federation (IDF) definition [23], including: WC (>88 cm in women and >102 cm in men); high serum TG concentration ≥1.7 mmol/L; reduced serum HDL-c (<1.3 mmol/L in women and <1.0 mmol/L in men); high blood pressure, high systolic blood pressure (SBP) (>130 mmHg) and/or high diastolic blood pressure (DBP) (>85 mmHg); and high HbA1c (>42 mmol/mol) as a biomarker for long-term glycemic control, replacing fasting plasma glucose [24,25]. Drug use (lipid or blood pressure treatment) were included as an alternative indicator. Furthermore, we included high hs-CRP as a cardiovascular risk factor (≥2.0 mg/L) [26,27]. Most of the cutoffs of lower cardiometabolic risk were in line with the recommendations of the European Guidelines on cardiovascular disease prevention in clinical practice [28]. Cardiometabolic risk factors were used as categorical variables; they were scored and categorized as 1 = risk and 0 = protective, following the metabolic risk classification. We remark that HDL-c as a categorical variable was risk scored 1 in presence of low HDL-c.

2.6. Statistical analysis

Data were analyzed using generalized linear mixed models (GLMMs) for both descriptive and inferential statistics. The baseline characteristic data are presented as means or percentages (95% confidence interval: CI; in parentheses); models were adjusted for sex (male or female), age (years), time point (baseline, 6 and 12 months), and total energy intake (as appropriate) (Table 1).

Intakes of polyphenols and their classes were modelled as continuous variables, after log2 transformation (Table 2), and as categorical variables, using quartiles of total and/or classes of polyphenols (Table 3 or Supplementary Tables 2−8). P for trend was calculated by modelling quartiles of polyphenols as a continuous variable.

Associations between dietary polyphenol intake (as continuous or quartiles of intake) and the prevalence of MetS and cardiometabolic risk factors (as categorical variables) were assessed using GLMMs including the measurements at 0, and at 6 and 12 months in a random intercepts model (number of participant). Results are presented as odds ratios (OR) and 95% CI. Model 1 was adjusted for age, sex and time point; Model 2 was adjusted for all covariates in Model 1 plus physical activity (regular vs. no regular exercise), smoking (never, former and current smoker), alcohol intake and body mass index (BMI, excluded in MetS and WC models for

Table 1 Characteristics of study population by total and quartiles of polyphenol intake[1].

	Quartile 1 k = 358	Quartile 2 k = 360	Quartile 3 k = 360	Quartile 4 k = 358	All n = 676, k = 1436
Demographic characteristics					
Sex, female (%)	49.8 (40.1–59.4)	37.4 (29.0–46.6)	40.3 (31.7–49.7)	47.7 (38.0–57.6)	56.3 (50.7–61.7)
Age (y)	43.9 (42.9–44.8)	43.9 (42.9–44.8)	43.9 (42.9–44.9)	43.9 (43.0–44.9)	43.9 (43.0–44.9)
BMI (kg/m2)	25.3 (24.9–25.6)	25.3 (25.0–25.6)	25.3 (25.0–25.6)	25.2 (24.9–25.5)	25.3 (25.0–25.5)
WC (cm)	88.4 (87.1–89.4)	88.5 (87.5–89.4)	88.0 (87.1–88.9)	87.7 (86.8–88.7)	88.2 (87.3–89.0)
Physical activity (%)					
Regular	88.5 (83.1–92.4)	91.8 (0.87–94.7)	90.0 (85.1–93.4)	88.2 (82.6–92.2)	89.7 (87.1–91.9)
Not regular	11.5 (7.6–16.9)	8.2 (5.3–12.6)	10.0 (6.6–14.9)	11.8 (7.8–17.4)	10.3 (8.1–12.9)
Smoking status (%)					
Never	58.7 (49.0–67.8)	55.0 (45.6–64.1)	54.7 (45.3–63.8)	51.6 (41.8–61.4)	55.0 (49.4–60.6)
Former	18.2 (12.6–25.7)	17.2 (11.9–24.2)	19.6 (13.8–27.0)	18.5 (12.8–26.0)	18.4 (14.8–22.5)
Current	15.4 (10.5–21.9)	13.9 (9.6–19.7)	11.7 (7.9–17.1)	10.6 (7.0–15.7)	12.8 (10.2–15.8)
Risk factors					
SBP (mmHg)	117.8 (116.4–119.1)	117.2 (115.9–118.5)	116.6 (115.4–117.9)	117.0 (115.6–118.3)	117.1 (116.2–118.1)
DBP (mmHg)	80.1 (79.0–81.1)	80.1 (79.1–81.1)	79.9 (78.9–80.9)	79.7 (78.7–80.7)	79.9 (79.3–80.6)
HbA1c (mmol/mol)	34.5 (34.0–35.0)	34.2 (33.7–34.6)	34.1 (33.6–34.5)	34.3 (33.7–34.8)	34.2 (33.8–34.6)
TG (mmol/L)	1.42 (1.34–1.51)	1.38 (1.30–1.47)	1.32 (1.23–1.40)	1.35 (1.26–1.44)	1.37 (1.31–1.43)
HDL (mmol/L)	1.50 (1.46–1.53)	1.52 (1.48–1.55)	1.54 (1.51–1.58)	1.54 (1.50–1.57)	1.52 (1.49–1.55)
LDL (mmol/L)	3.06 (2.99–3.14)	3.05 (2.98–3.13)	3.04 (2.97–3.11)	3.06 (2.98–3.13)	3.05 (2.99–3.11)
hsCRP (mg/L)	1.59 (1.33–1.85)	1.37 (1.12–1.62)	1.32 (1.06–1.57)	1.33 (1.07–1.60)	1.40 (1.25–1.55)
Dietary characteristics					
Energy (kcal)	1802 (1699–1904)	2104 (2004–2203)	2283 (2184–2383)	2386 (2281–2491)	2144 (2078–2209)
Saturated FA (g/d)	26.2 (24.9–27.5)	26.5 (25.2–27.7)	27.2 (25.9–28.5)	28.4 (27.1–29.8)	27.1 (26.3–27.8)
Monounsaturated FA (g/d)	29.5 (28.2–30.8)	28.8 (27.5–30.1)	29.2 (27.9–30.5)	30.2 (28.9–31.6)	29.4 (28.7–30.1)
Polyunsaturated FA (g/d)	13.9 (13.1–14.6)	14.0 (13.5–14.7)	13.9 (13.3–14.6)	14.6 (13.9–15.4)	14.1 (13.7–14.5)
Total sugars (g/d)	62.5 (57.8–67.2)	70.2 (65.6–74.7)	69.7 (65.1–74.3)	67.7 (62.9–72.5)	67.5 (64.8–70.2)
Sucrose (g/d)	29.1 (25.5–32.7)	38.7 (35.3–42.2)	39.1 (35.7–42.6)	28.7 (25.0–32.3)	33.9 (31.8–36.0)
Dietary fiber AOAC (g/d)	19.7 (18.7–20.8)	21.4 (20.4–22.5)	22.9 (21.9–24.0)	22.9 (21.8–24.0)	21.7 (21.1–22.4)
Alcohol intake (g/d)	8.5 (6.1–10.8)	10.4 (8.1–12.6)	11.1 (8.8–13.3)	11.9 (9.5–14.2)	10.4 (9.2–11.7)
Sodium (mg/d)	3119 (2961–3276)	2997 (2845–3150)	3041 (2889–3194)	3018 (2859–3177)	3044 (2958–3130)
Food intake					
Red meat intake (g/d)	158 (141–175)	111 (95–128)	107 (91–124)	91 (74–108)	117 (108–126)
Processed meat intake (g/d)	25 (19–31)	22 (17–28)	31 (25–37)	32 (26–38)	28 (24–31)
Total fish intake (g/d)	47 (37–57)	42 (32–53)	50 (40–61)	43 (32–53)	46 (40–51)
Fruit intake (g/d)	93 (75–111)	129.4 (112–146)	134 (117–152)	161 (143–179)	129 (119–140)
Vegetable intake (g/d)	219 (207–232)	236 (214–259)	241 (218–263)	239 (215–262)	162 (139–185)
Cereal whole grain (g/d)	109 (96–122)	140 (128–153)	147 (135–160)	154 (141–167)	138 (130–145)
Coffee (ml/d)	148 (102–194)	346 (302–390)	495 (451–540)	820 (773–867)	452 (425–479)
Tea (ml/d)	42 (8–76)	126 (93–159)	191 (159–224)	201 (166–235)	140 (118–163)
Normal soft drink (ml/d)	118 (94–141)	86 (63–108)	67 (44–90)	57 (32–81)	82 (68–96)
Light soft drink (ml/d)	77 (52–102)	71 (48–95)	50 (26–74)	60 (35–86)	65 (48–82)
Salt (g/d)	0.5 (0.2–0.7)	0.6 (0.3–0.9)	0.6 (0.3–0.8)	0.5 (0.2–0.8)	0.5 (0.4–0.7)

[1]All values are means or percentages, 95 CI in parentheses. n, subjects. k, measures. BMI, body mass index. WC, waist circumference. SBP, systolic blood pressure. DBP, diastolic blood pressure. HbA1c, glycosilated hemoglobin. TG, triglycerides. HDL, high-density lipoprotein. HsCRP, high-sensitivity C-reactive protein. Models were computed using generalized mixed linear models adjusted for sex, age, time points and total energy intake (as appropriate). P for trend used the continuous variable of quartiles of polyphenols.

potential collider bias); Model 3 was adjusted for all covariates in Model 2 plus intakes of saturated FA, polyunsaturated FA, monounsaturated FA, total sugars, fiber, sodium and total energy; Model 4 was adjusted for all covariates in Model 2 plus consumption of red meat, processed meat, fish, soft drinks, salt and energy intake.

We also conducted sensitivity analyses to test the robustness of our results, in the MetS outcome specifically using model (model 3) because it includes nutrients instead of model 4 which includes food items. We re-ran the analyses after exclusion of 12-month record data (n = 662, k = 1054), or 6-month record data (n = 669, k = 1030). Further sensitivity analyses were done after excluding, separately, participants with BMI >25.0 kg/m^2 (n = 305, k = 639), former and current tobacco status (n = 539, k = 1168), no regular physical activity (n = 562, k = 1203), with any level of alcohol consumption (n = 546, k = 926), ever diagnosed with heart attack, stroke/brain hemorrhage, diabetes, high blood pressure and cholesterol levels (n = 632, k = 1313), and gastrointestinal disorders such as irritable bowel syndrome, Crohn's disease, ulcerative colitis or celiac/gluten intolerance (n = 636, k = 1327A p-value <0.05 was considered statistically significant in two-tailed test.). IBM SPSS 27.0 was used for statistical analysis.

3. Results

Baseline characteristics of the study population (n, subjects = 676, k, measures = 1436) by total and quartiles of polyphenols are shown in Table 1. Across the three timepoints, females comprised 56% (50–61) of the participants and the mean age was 43.9 y (43.0–44.9). Participants with a higher quartile of total polyphenol intake had a lower WC and were less likely to be current smokers. Compared with participants with the lowest total polyphenol intakes, those with the highest intakes were more likely to have a lower concentration of TG and hs-CRP and have higher HDL-c levels. They also tended to consume more fruit, vegetables, WG products and beverages such as coffee and tea, while eating less red meat and consuming fewer soft drinks. Moreover, the participants with higher intakes of total polyphenol consumed significantly more energy, and had a higher intake of saturated fatty acid, fiber, and alcohol (after adjusting for total energy) than those with lower polyphenol intakes (Table 1).

3.1. Associations between polyphenol intake and MetS

The baseline prevalence of MetS was 11.6%, 8.6%, 11.8% at baseline, 6 and 12 months (p value = 0.191), and ranged from 6.4 to 15.4% in quartiles of total polyphenol and their classes. Over the three timepoints, individuals consuming higher quantities of polyphenols were less likely to have MetS [($OR_{Q4vs.Q1}$ (95%CI): 0.50 (0.27, 0.91); Model 3, Table 2)] compared to those in the lowest quartile of intake. The association analysis of individual classes of polyphenol intake revealed differences in associations with MetS. The flavonoid class showed an inverse association in all models [$OR_{Q4vs.Q1}$: 0.49 (0.27, 0.91); Model 3, Table 2)]. Similarly, the phenolic acid class intake showed an inverse associations in all models and higher quartiles of comparison [$OR_{Q4vs.Q1}$: 0.55 (0.30, 1.00); Model 3, Table 2)]. No associations were observed with the intake of stilbenes, lignans, alkylphenols, and tyrosol. In sensitivity analysis, exclusion of participants with unhealthy lifestyle habits or preclinical conditions did not alter the overall results. Nevertheless, the significant associations for total polyphenols and the phenolic acid class were only present in nonsmokers (never/former smokers), although the OR was comparable to that seen for current smokers (Fig. 2).

3.2. Associations between polyphenol intake and cardiometabolic risk factors

Intakes of total polyphenol, and some classes, were inversely associated with high WC, high SBP, low HDL-c and high hs-CRP (Table 3 and Supplementary Tables 2–8). Intakes of flavonoids [$OR_{\text{per log2 unit increment}}$: 0.90 (0.81, 1.00)], stilbenes, and tyrosols were inversely associated with high WC (Table 3). Intake of total polyphenols [$OR_{\text{per log2}}$: 0.81 (0.68, 0.97)] and [$OR_{\text{per log2}}$: 0.87 (0.76, 1.00)], were inversely associated with high SBP and DBP, respectively (Table 3). The most consistent results were observed between the intake of total polyphenols [$OR_{\text{per log2}}$: 0.77 (0.64, 0.91)], flavonoids and phenolic acids and the odds of having low HDL-c; however, positive association was found between alkylphenols and odds of low HDL-c [$OR_{\text{per log2}}$: 1.14 (1.02, 1.28]. Only phenolic acid intake was associated with high hs-CRP [$OR_{\text{per log2}}$: 0.89 (0.80, 0.99)]. No significant associations were found between high TG, and high HbA1c and total polyphenols, and their classes, in the fully adjusted models (Table 3 and Supplementary Tables 2–8). Overall, the associations between cardiometabolic risk factors and polyphenols, and their classes, remained significant mainly in the highest quartiles (Quartile 4, Fig. 3 and Supplementary Tables). Finally, no significant interactions between polyphenols and confounding variables such as sex, BMI, physical activity and smoking status were observed in secondary analysis.

4. Discussion

In parallel with the global ongoing pandemic of overweight and obesity, MetS prevalence has been increasing worldwide [4,29]. In this observational subcohort of 676 Danish participants, individuals with higher total polyphenol and phenolic acid intakes, were less likely to have MetS, after adjusting for age, sex, lifestyle and dietary confounders. The magnitude of the reduction of the prevalence of MetS observed in association with an increased polyphenol intake is quite high (more than 50% by moving from the first to the third quartile of intake) and, therefore, potentially relevant for public health.

When comparing our estimated total mean polyphenols (1368 mg) in MAX-study with other similar studies, a higher mean intake was found compared to what has been reported in studies from European or American countries [9]. The main polyphenol class contributor were phenolic acids (62.6%) and flavonoids (31.8%), and the most consumed polyphenol subclasses were hydroxycinnamic acids and proanthocyanidins [22]. Phenolic acids are by far the largest contributors to the total polyphenol intake due to the high coffee consumption and the most consumed flavonoid-rich foods sources among these participants were tea, cocoa products and fruits [22,30]. The food consumption between Mediterranean and non-Mediterranean countries, highlights large differences in nonalcoholic beverages, varieties of fruits, type of vegetables, WG product and cocoa products [31], which can be explained by population and regional characteristics, such as food availability and food consumption culture.

Evidence from a Polish study showed a similar trend that total polyphenol and phenolic acid intakes, and also higher quartiles of stilbenes, were inversely associated with MetS prevalence [15]. However, these results were not adjusted for other dietary factors. Furthermore, this population was older, and used FFQs to estimate polyphenol intakes. In part, this may be explained by the fact that coffee was the main contributor to the intake of total polyphenols in both populations [15,22], similarly to our study in which the main food source of phenolic acid was coffee (approximately 75.0%). Another study, within Iranian adults, also using the FFQ and PE in combination,

Table 2 MetS associations by total and quartiles of total polyphenol intake and class of polyphenol[1].

MetS Prevalence	Quartile 1 k = 358	Quartile 2 k = 360	Quartile 3 k = 360	Quartile 4 k = 358	P trend	Continuous (log2) n = 676, k = 1436
Polyphenols						
Cutoff	<651	652–1053	1053–1798	>1799		1368 (19)*
Model 1	1 Ref.	0.51 (0.28–0.91)	0.43 (0.24–0.78)	0.57 (0.33–0.99)	0.126	0.84 (0.71–0.98)
Model 2	1 Ref.	0.53 (0.29–0.96)	0.41 (0.22–0.74)	0.53 (0.30–0.93)	0.063	0.81 (0.68–0.97)
Model 3	1 Ref.	0.52 (0.28–0.96)	0.40 (0.21–0.75)	0.50 (0.27–0.91)	0.059	0.83 (0.69–0.99)
Model 4	1 Ref.	0.56 (0.30–1.03)	0.43 (0.22–0.80)	0.58 (0.32–1.05)	0.155	0.86 (0.51–1.46)
Flavonoids						
Cutoff	<135	136–291	292–552	>553		426 (6.7)*
Model 1	1 Ref.	0.60 (0.35–1.04)	0.44 (0.24–0.79)	0.55 (0.31–0.96)	0.062	0.88 (0.81–0.99)
Model 2	1 Ref.	0.60 (0.35–1.05)	0.47 (0.25–0.85)	0.54 (0.31–0.97)	0.068	0.90 (0.82–1.00)
Model 3	1 Ref.	0.61 (0.34–1.07)	0.44 (0.23–0.83)	0.49 (0.26–0.91)	0.046	0.88 (0.79–0.99)
Model 4	1 Ref.	0.61 (0.35–1.08)	0.51 (0.27–0.95)	0.55 (0.30–1.01)	0.096	0.90 (0.81–1.00)
Phenolic acids						
Cutoff	<234	235–552	553–1151	>1152		867 (18.9)*
Model 1	1 Ref.	0.61 (0.35–1.08)	0.36 (0.19–0.68)	0.60 (0.34–1.06)	0.225	0.87 (0.77–0.98)
Model 2	1 Ref.	0.64 (0.36–1.13)	0.36 (0.19–0.69)	0.55 (0.30–0.98)	0.108	0.86 (0.76–0.97)
Model 3	1 Ref.	0.63 (0.35–1.13)	0.38 (0.19–0.73)	0.55 (0.30–1.00)	0.134	0.86 (0.75–0.97)
Model 4	1 Ref.	0.67 (0.37–1.20)	0.40 (0.21–0.78)	0.61 (0.33–1.11)	0.250	0.88 (0.77–1.00)
Stilbenes[2]						
Cutoff	<0.00	0.00–0.01	0.01-0.31	>0.32		1.4 (0.1)*
Model 1	1 Ref.	1.10 (0.63–1.92)	0.80 (0.44–1.46)	0.95 (0.54–1.67)	0.950	0.98 (0.95–1.02)
Model 2	1 Ref.	1.19 (0.67–2.09)	0.82 (0.44–1.50)	1.02 (0.54–1.94)	0.925	0.98 (0.94–1.02)
Model 3	1 Ref.	1.17 (0.65–2.09)	0.77 (0.41–1.45)	0.97 (0.50–1.88)	0.987	0.98 (0.94–1.01)
Model 4	1 Ref.	1.10 (0.62–1.97)	0.79 (0.42–1.47)	1.03 (0.54–1.99)	0.787	0.98 (0.95–1.02)
Lignans						
Cutoff	<0.6	0.6-2.2	2.2–16.5	>16.5		11.7 (0.3)*
Model 1	1 Ref.	0.60 (0.34–1.06)	0.62 (0.35–1.10)	0.65 (0.37–1.14)	0.544	0.93 (0.86–1.01)
Model 2	1 Ref.	0.65 (0.36–1.16)	0.65 (0.36–1.17)	0.64 (0.36–1.14)	0.412	0.93 (0.86–1.01)
Model 3	1 Ref.	0.67 (0.37–1.23)	0.69 (0.37–1.27)	0.71 (0.37–1.34)	0.692	0.94 (0.86–1.02)
Model 4	1 Ref.	0.64 (0.35–1.17)	0.67 (0.37–1.22)	0.66 (0.36–1.20)	0.511	0.93 (0.86–1.01)
Alkylphenols						
Cutoff	<8.8	8.9–26.6	26.7–51.6	>51.7		39.1 (0.5)*
Model 1	1 Ref.	1.16 (0.64–2.08)	1.23 (0.69–2.18)	0.81 (0.44–1.48)	0.335	0.96 (0.88–1.05)
Model 2	1 Ref.	1.16 (0.64–2.11)	1.33 (0.74–2.39)	0.78 (0.42–1.45)	0.289	0.96 (0.88–1.05)
Model 3	1 Ref.	1.19 (0.64–2.19)	1.49 (0.80–2.78)	0.96 (0.46–1.98)	0.781	0.99 (0.89–1.10)
Model 4	1 Ref.	1.17 (0.64–2.15)	1.40 (0.76–2.56)	0.81 (0.42–1.57)	0.391	0.97 (0.88–1.06)
Tyrosol[2]						
Cutoff	<1.6	1.7-5.5	5.6–13.7	>13.7		10.8 (0.3)*
Model 1	1 Ref.	1.71 (0.96–3.02)	1.26 (0.69–2.28)	0.15 (0.64–2.06)	0.757	0.99 (0.91–1.07)
Model 2	1 Ref.	1.85 (1.03–3.33)	1.34 (0.73–2.47)	1.19 (0.64–2.21)	0.764	0.99 (0.91–1.08)
Model 3	1 Ref.	1.71 (0.94–3.11)	1.24 (0.67–2.32)	1.03 (0.53–2.00)	0.478	0.98 (0.89–1.07)
Model 4	1 Ref.	1.73 (0.96–3.12)	1.20 (0.64–2.25)	0.99 (0.51–1.92)	0.396	0.97 (0.88–1.06)

[1]All data were computed using generalized linear mixed models. *All polyphenol values are mean and standard error (s.e.) adjusted for age, sex, time origin and energy intake. The data models represent the OR (odds ratios) and CI (confidence interval). n: subjects, k: measures. MetS, metabolic syndrome. Model 1 adjusted for age, sex and time origin; Model 2 adjusted for all covariates in Model 1 plus physical activity, smoking and alcohol intake Model 3 adjusted for all covariates in Model 2 plus intakes of saturated FA, polyunsaturated FA, monounsaturated FA, total sugars, fiber, sodium and total energy; Model 4 adjusted for all covariates in Model 2 plus consumption of red meat, processed meat, fish, soft drinks, salt and energy intake. P for trend used the continuous variable of quartiles of polyphenols. [2]Stilbenes and tyrosol present n = 676: Q1 (k: 359); Q2 (k: 359); Q3 (k: 360); Q4 (k: 358).

showed that total polyphenol intakes was not associated with MetS, but flavonoid intakes were inversely associated with MetS [14]. In this case, the major food sources of total polyphenols were fruit and vegetables. Moreover, a recent prospective study in Chinese adults showed that a higher flavonoid intake was associated with a lower risk of MetS and central obesity [32]. However, a European study of adolescents showed no association with total polyphenols, classes or individual polyphenols, which may be related to the low intake of total polyphenols and the lower prevalence of MetS at this age. Apparently, population characteristics such as previous cardiometabolic risk profile, dietary polyphenol intakes and their classes as well as food sources are important aspects to consider in this analysis.

For cardiovascular risk factors, intakes of total polyphenols, flavonoids and phenolic acids were associated with a lower risk of higher SBP and lower HDL-c. There is growing evidence from studies that higher intakes of polyphenols decrease blood pressure [33], which is partially attributed to the flavon-3-ols effect [11]. The potential molecular mechanisms that could impact vascular health include the role of nitric oxide and anti-inflammatory effects, among others [33]. However, gut

Table 3 Cardiometabolic risk factor associations by total and classes of polyphenols.

Cardiometabolic risk factors (prevalence)	Polyphenols n = 676, k = 1436	Flavonoids n = 676, k = 1436	Phenolic acids n = 676, k = 1436	Stilbenes n = 676, k = 1436	Lignans n = 676, k = 1436	Alkyphenols n = 676, k = 1436	Tyrosols n = 676, k = 1436
WC (22.6%)							
Model 1	0.92 (0.79–1.08)	0.92 (0.84–1.01)	0.93 (0.83–1.04)	0.97 (0.94–1.00)	0.94 (0.88–1.01)	0.93 (0.86–1.01)	0.95 (0.88–1.02)
Model 2	0.91 (0.78–1.06)	0.93 (0.84–1.02)	0.92 (0.82–1.03)	0.96 (0.93–1.00)	0.94 (0.88–1.01)	0.93 (0.86–1.01)	0.94 (0.88–1.02)
Model 3	0.91 (0.77–1.08)	0.90 (0.81–1.00)	0.93 (0.82–1.05)	0.96 (0.93–0.99)	0.96 (0.89–1.04)	0.94 (0.86–1.03)	0.92 (0.85–1.00)
Model 4	0.93 (0.79–1.10)	0.92 (0.83–1.02)	0.94 (0.83–1.07)	0.97 (0.93–1.00)	0.94 (0.88–1.01)	0.93 (0.85–1.00)	0.92 (0.85–0.99)
SBP (18.1%)							
Model 1	0.88 (0.75–1.03)	0.92 (0.84–1.01)	0.90 (0.80–1.00)	1.02 (0.99–1.05)	0.98 (0.92–1.05)	1.01 (0.93–1.10)	0.96 (0.90–1.04)
Model 2	0.84 (0.72–0.99)	0.91 (0.83–1.01)	0.88 (0.78–0.99)	1.01 (0.97–1.04)	1.00 (0.93–1.07)	1.04 (0.95–1.13)	0.93 (0.86–1.01)
Model 3	0.81 (0.68–0.97)	0.90 (0.81–1.00)	0.86 (0.76–0.98)	1.01 (0.97–1.05)	0.97 (0.90–1.05)	1.02 (0.93–1.13)	0.95 (0.88–1.03)
Model 4	0.86 (0.72–1.02)	0.92 (0.83–1.02)	0.89 (0.79–1.01)	1.01 (0.97–1.04)	1.01 (0.94–1.08)	1.05 (0.96–1.15)	0.94 (0.86–1.01)
DBP (29.1%)							
Model 1	1.01 (0.90–1.1)	0.98 (0.91–1.06)	1.03 (0.94–1.13)	1.01 (0.98–1.04)	1.00 (0.95–1.05)	1.02 (0.96–1.08)	0.98 (0.93–1.04)
Model 2	0.91 (0.80–1.03)	0.98 (0.90–1.06)	0.95 (0.86–1.05)	1.01 (0.98–1.03)	1.00 (0.94–1.06)	1.01 (0.95–1.09)	0.97 (0.92–1.03)
Model 3	0.87 (0.76–1.00)	0.96 (0.88–1.05)	0.94 (0.85–1.04)	1.01 (0.98–1.04)	0.98 (0.92–1.04)	1.00 (0.93–1.08)	0.98 (0.92–1.04)
Model 4	0.91 (0.80–1.05)	0.98 (0.90–1.07)	0.96 (0.87–1.06)	1.06 (0.98–1.04)	1.00 (0.95–1.06)	1.02 (0.95–1.09)	0.97 (0.91–1.03)
HbA1c (4.5%)							
Model 1	0.93 (0.78–1.11)	0.98 (0.87–1.11)	0.89 (0.68–1.16)	0.99 (0.96–1.03)	0.94 (0.86–1.03)	0.92 (0.85–0.99)	1.00 (0.91–1.09)
Model 2	0.93 (0.74–1.19)	1.01 (0.90–1.14)	0.87 (0.67–1.14)	0.99 (0.95–1.04)	0.96 (0.89–1.05)	0.94 (0.86–1.02)	1.00 (0.91–1.09)
Model 3	0.94 (0.78–1.14)	1.03 (0.90–1.17)	0.91 (0.80–1.05)	1.00 (0.96–1.04)	0.97 (0.88–1.07)	0.94 (0.86–1.04)	0.98 (0.89–1.08)
Model 4	0.92 (0.77–1.11)	1.01 (0.90–1.15)	0.91 (0.79–1.04)	0.99 (0.95–1.04)	0.96 (0.88–1.05)	0.93 (0.85–1.01)	1.00 (0.91–1.11)
TG (22.0%)							
Model 1	0.92 (0.81–1.05)	0.93 (0.86–1.01)	0.94 (0.86–1.04)	0.99 (0.97–1.02)	0.97 (0.92–1.03)	1.03 (0.96–1.10)	0.98 (0.92–1.04)
Model 2	0.91 (0.80–1.04)	0.96 (0.88–1.04)	0.94 (0.85–1.04)	0.99 (0.96–1.02)	1.00 (0.94–1.06)	1.07 (0.99–1.15)	0.98 (0.91–1.04)
Model 3	0.89 (0.77–1.02)	0.95 (0.87–1.04)	0.93 (0.83–1.03)	0.99 (0.96–1.02)	0.99 (0.92–1.06)	1.06 (0.98–1.15)	0.97 (0.90–1.04)
Model 4	0.90 (0.79–1.04)	0.96 (0.88–1.04)	0.94 (0.84–1.04)	0.99 (0.96–1.02)	1.00 (0.94–1.06)	1.07 (0.99–1.16)	0.97 (0.90–1.04)
HDL (11.0%)							
Model 1	0.79 (0.67–0.92)	0.87 (0.79–0.96)	0.86 (0.76–0.97)	0.98 (0.94–1.01)	0.94 (0.87–1.01)	1.04 (0.95–1.14)	0.92 (0.85–1.00)
Model 2	0.79 (0.68–0.93)	0.90 (0.82–1.00)	0.87 (0.77–0.98)	0.99 (0.95–1.03)	0.97 (0.90–1.05)	1.09 (0.99–1.21)	0.94 (0.86–1.02)
Model 3	0.77 (0.64–0.91)	0.88 (0.78–0.98)	0.86 (0.76–0.98)	0.98 (0.95–1.02)	0.98 (0.90–1.07)	1.14 (1.02–1.28)	0.94 (0.86–1.02)
Model 4	0.79 (0.67–0.93)	0.90 (0.80–1.00)	0.87 (0.76–0.99)	0.99 (0.95–1.03)	0.97 (0.90–1.05)	1.10 (0.99–1.22)	0.93 (0.85–1.02)
hsCRP (18.8%)							
Model 1	0.91 (0.80–1.04)	0.96 (0.88–1.04)	0.90 (0.82–1.00)	1.00 (0.98–1.03)	0.93 (0.88–0.99)	0.99 (0.93–1.06)	0.96 (0.90–1.02)
Model 2	0.90 (0.79–1.03)	0.99 (0.91–1.08)	0.90 (0.81–0.99)	1.01 (0.98–1.04)	0.96 (0.90–1.02)	1.03 (0.96–1.11)	0.96 (0.90–1.03)
Model 3	0.88 (0.76–1.02)	0.98 (0.89–1.07)	0.89 (0.80–0.99)	1.01 (0.97–1.04)	0.96 (0.90–1.03)	1.05 (0.96–1.14)	0.95 (0.88–1.02)
Model 4	0.90 (0.78–1.04)	0.98 (0.90–1.07)	0.90 (0.81–1.00)	1.01 (0.98–1.04)	0.97 (0.91–1.03)	1.05 (0.97–1.13)	0.94 (0.88–1.01)

Total mean polyphenol and class intakes were used as a continuous variable, after log2 transformation. The data represent the OR (odds ratios) and confidence interval (CI). n, subjects. k, measures. WC, waist circumference. SBP, systolic blood pressure. DBP, diastolic blood pressure. HbA1c, glycosilated hemoglobin. TG, triglycerides. HDL, high-density lipoprotein. HsCRP, high-sensitivity C-reactive protein. Model 1 adjusted for age, sex and time point; Model 2 adjusted for all covariates in Model 1 plus physical activity, smoking, alcohol intake and body mass index (excluded for WC models). Model 3 adjusted for all covariates in Model 2 plus intakes of saturated FA, polyunsaturated FA, monounsaturated FA, total sugars, fiber, sodium and total energy; Model 4 adjusted for all covariates in Model 2 plus consumption of red meat, processed meat, fish, soft drinks, salt and energy intake. HbA1c (k = 1428), TG (k = 1431), HDL (k = 1431), LDL (k = 1431), hsCRP (k = 1431).

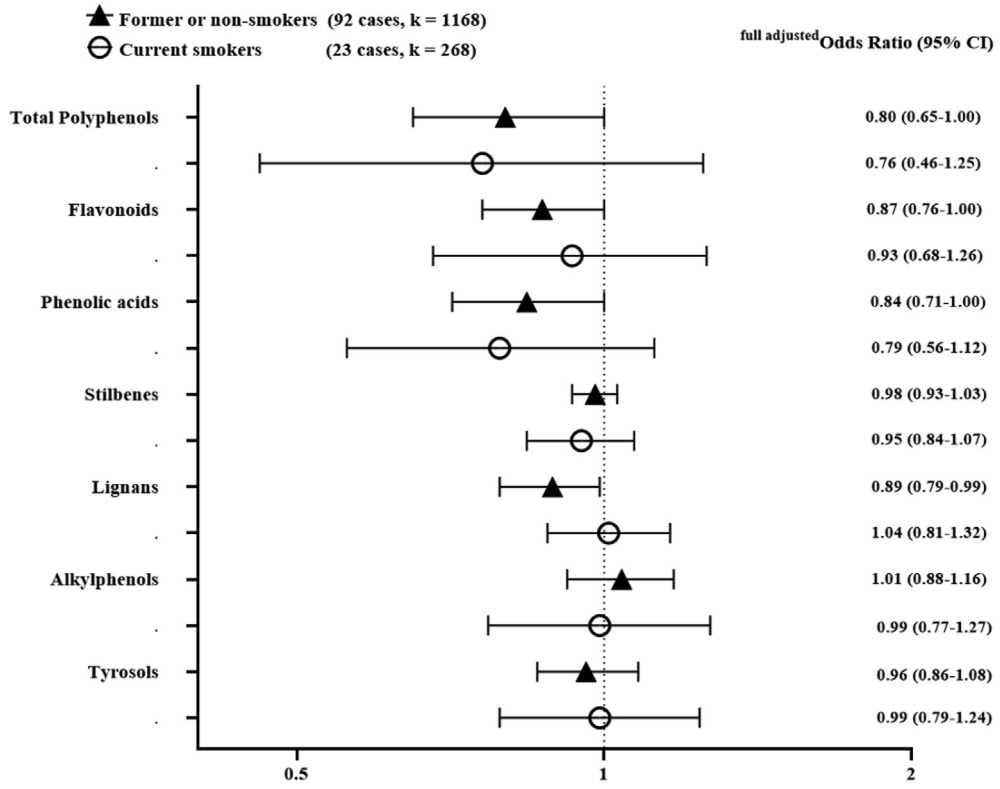

Figure 2 Forest plot showing the odds ratio associations between total polyphenols and their classes (mg/day), and metabolic syndrome (n = 676, k: 1436) among participants of the MAX study from the Danish Diet, Cancer and Health – Next Generations cohort, stratified by smoking status. Generalized linear mixed models were performed. Model 3 was adjusted for age, sex, time point, physical activity, alcohol intake, intakes of saturated FA, polyunsaturated FA, monounsaturated FA, total sugars, fiber, sodium and total energy.

microbiome-derived metabolites may also play an important role in vascular-protective effects [11].

In this respect it is worth underlining that coffee, which is the major contributor of polyphenols and, in particular, phenolic acid in our study population, is also a source of caffeine which is associated to an increased risk for hypertension. Therefore, for a moderate coffee consumption the beneficial effects of polyphenols on blood pressure may prevail over the detrimental ones due to caffeine; conversely, for a very high coffee consumption the caffeine intake would hamper the benefits of polyphenols on blood pressure [34].

With regards to HDL-c component, a study from Spain showed a positive association between total polyphenol intake and HDL-c levels, but contrary to our results, they found that low phenolic acid intake was associated with a lower WC and not with HDL-c [16]. Nevertheless, both studies showing that high flavonoid intake was inversely associated with high WC [16]. There were large differences between populations when comparing the dietary pattern (e.g. higher fruit consumption), total polyphenols (i.e. lower intake) and the main contributor to total polyphenol intake (e.g. flavonoids). The implications of improving HDL functionality via dietary polyphenols in both studies are various due to its key role in cholesterol transport, antioxidative and anti-inflammatory functions, and the endothelial vasoprotective properties of this particle [35].

Several reports on cardiovascular risk factors and dietary polyphenols were mostly focused on the flavonoid class [36]. Flavonoids have been significantly associated with MetS, and WC, SBP and HDL-c components. In contrast, HbA1c and TG components were not associated with flavonoid intakes in the fully adjusted model. However, the previously mentioned Polish study showed an inverse association between fasting plasma glucose, and no associations with SBP and HDL-c for flavonoid intakes [15]. Indeed, another study shows that participants with the highest tertiles of flavonoids had a lower risk of hypertriglyceridemia but not of MetS and its components [14]. Thus, the effects of total flavonoid intakes on MetS components are still unclear. Differences in health outcomes between studies can be explained by several factors, such as main food sources and the flavonoid subclass distribution, from dietary assessment and the design of the study to lifestyle habits and sociodemographic characteristics [33]. For example, a population-based study in Brazil showed an inverse association between hypertension and the highest tertiles of tyrosol, alkylphenols, lignans and stilbenes; however, flavonoids were not significantly associated [37].

Some cardiovascular risk factors show significant associations but without consistency of total polyphenols or all classes. For instance, intakes of flavonoids, stilbenes and tyrosols were only inversely associated with WC, which

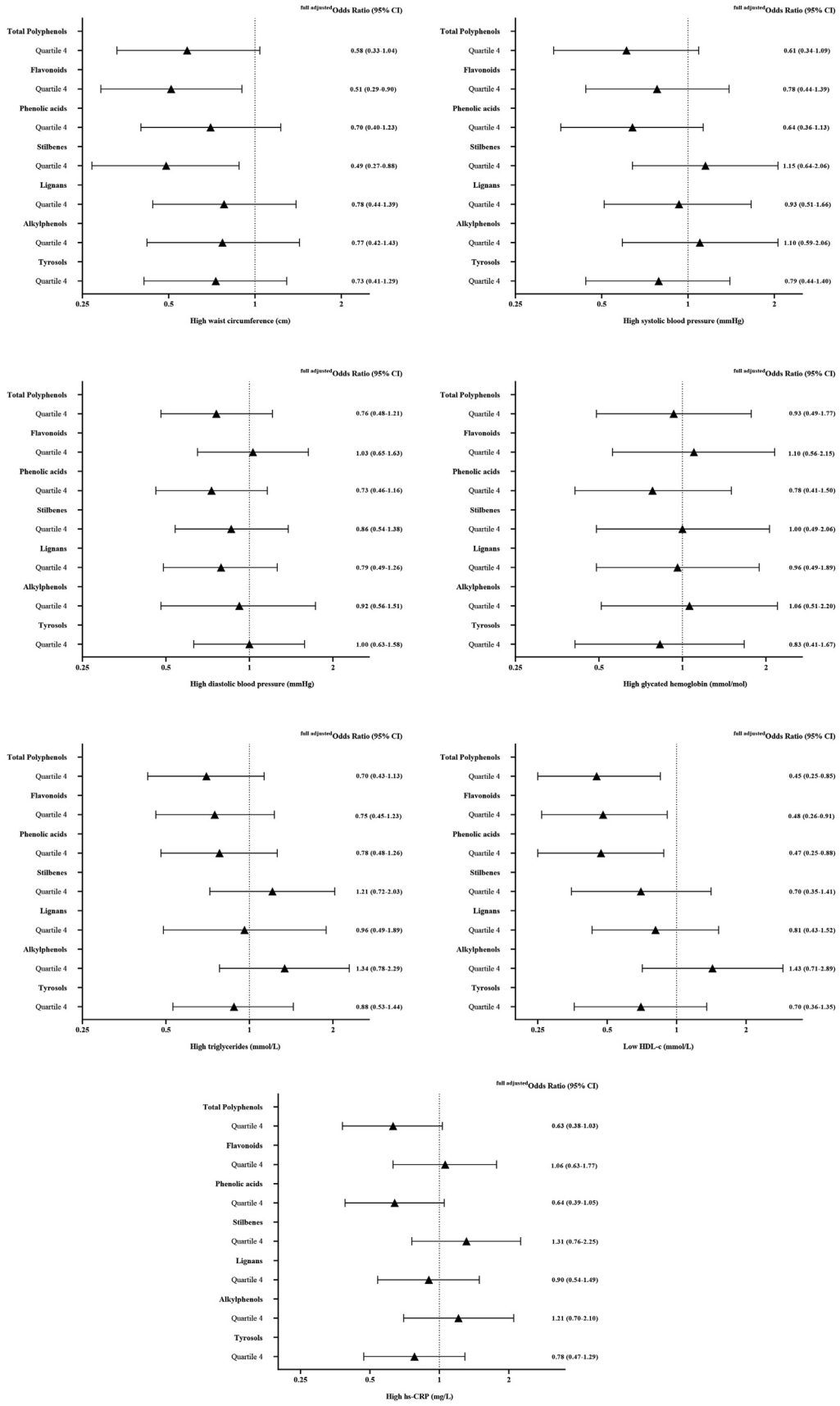

Figure 3 Forest plot showing the odds ratio associations between total polyphenols and their classes (mg/day), and cardiometabolic risk factors (n = 676, k: 1436) among participants of the MAX study from the Danish Diet, Cancer and Health – Next Generations cohort. Generalized linear mixed models were performed. Model 3 (quartile 4) was adjusted for age, sex, time point, physical activity, smoking, alcohol intake, body mass index

was also found in other studies [15]. The highest food contributor to these classes are berries, wine, grapes and olive products, and some specific compounds of them (e.g. resveratrol) would be acting in mechanistic pathways that have potential anti-inflammatory/obesogenic effects [38]. Interestingly, the intake of phenolic acids was inversely associated with hs-CRP. This is relevant because long-term elevated hs-CRP is associated with increased cardiovascular risk, incident heart failure and all-cause death even when all atherogenic lipids are more favorable [27]. Moreover, the EPIC study observed an inverse association between plasma concentrations of phenolic acids and hs-CRP [39]. However, a meta-analysis of RCT found no differences between flavan-3ols and hs-CRP or other inflammatory biomarkers [11].

The literature suggests that HbA1c could be considered a useful component of MetS albeit still not a massive criterion in research studies [24]. Extensive evidence supports the notion that polyphenol-rich diets, especially in terms of flavonoids and phenolic acids, may prevent type 2 diabetes risk [40]. Despite the different clinical approaches to dysglycemia, there was no significant association between HbA1c and dietary polyphenols, which could be related to the previously mentioned population characteristics, polyphenol dietary intakes and also the relationships between variables in the study. In addition, HbA1c is an imprecise marker of glucose control for values below 5.5% (37 mmol/mol), which is the range in which most of our participants were included [41].

Surprisingly, the total alkylphenol intake was positively associated with low HDL-c. In the Nordic diet, alkylresorcinols (resorcinolic lipids) are the main alkylphenols in the diet. Alkylresorcinols are present in high contents in whole grain wheat and rye. WG consumption has increased in Denmark over the last decade and alkylresorcinols are valid food biomarkers of whole grain wheat and rye intake [42]. WG consumption seems to be cardioprotective and reduces MetS components [43]. More prospective studies and well-designed trials are necessary to evaluate the lipid-lowering properties obtained from consumption/types of whole-grain-rich foods and in different large populations.

No significant interaction was observed in any of the adjustment variables and the associations remained statistically significant even when performing the sensitivity analyses. Nonetheless, we stratified by smoking status because in a previous study associations were stronger in smokers than in nonsmokers [44]. In nonsmokers (92 cases, k= 1168), we observed a protective association between total polyphenol intake and MetS, while in smokers such association was statistically non-significant. One reason for these differences may be is the lower statistical power in current smokers. Another reason could be the younger age of the population and the prevalence/time of the cardiovascular risk factor under exposure to smoking. Indeed, cardiovascular diseases increase as populations age (especially in males) [45].

The present study has three main strengths. First, we based on a prospective observational analysis of the variables, including data collection by each time point for biochemical parameters. The second is the use of the most updated food composition database, which supports approaches related to formal analysis as well as cardiometabolic risk factors that have been extensively used in the literature. Also, to the best of our knowledge, there are no prior studies to analyze all main classes of polyphenols in relation to MetS and cardiometabolic risk factors. Lastly, the MAX study is a subcohort of the DCH-NG cohort that is based on participants of the DCH study, whom they have followed for more than 20 years. However, this study has weaknesses related to the limitations of the PE database in terms of incompleteness (missing both foods and specific polyphenols) and the potential measurement error of self-reported variables, such as dietary data (24-HDR) and physical activity, which may underestimate the overall dietary intake. Besides, one to three days of 24-HDR may not be representative of a habitual diet [46]. In addition, the short follow up (1 year) does not allow us to see remarkably changes in the prevalence of MetS and cardiovascular risk factors over time. Furthermore, the repeated samples were available for 301 study participants, the cohort profile and MAX sample are not representative of the general population [18]. Finally, the observational design of our study does not allow to establish cause effect relationships.

Based on our results, we suggest that intervention studies should be undertaken to establish whether a polyphenol-rich diet can improve some cardiometabolic risk factors such as high SBP, high WC and low HDL-c and can reduce or delay, the onset of cardiometabolic diseases in free-living populations. However, for the time being our study supports the promotion of healthy diets associated with clear cardiometabolic benefits like the Mediterranean Diet and the Healthy Nordic Diet also in view of their high content of polyphenols.

Funding

This work was accomplished as part of the DiGuMet project “Diet × gut microbiome-based metabotypes to determine cardio-metabolic risk and tailor intervention strategies for improved health” supported within the European Joint Programming Initiative “A Healthy Diet for a Healthy Life” (http://www.healthydietforhealthylife.eu/), granted by MINECO Spain, PCIN-2017-076. Further support came from the grants PID2020-114921RB-C21 and PID2021-128542OA-I00 funded by MCIN/AEI/10.13039/501100011033, CIBERFES, CB16/10/00269, from the Instituto de Salud Carlos III all of them by “ERDF A way of making Europe”, and the Generalitat de Catalunya’s

(excluded for WC models), intakes of saturated FA, polyunsaturated FA, monounsaturated FA, total sugars, fiber, sodium and total energy. High waist circumference (k: 324), high systolic blood pressure (k: 260), high diastolic blood pressure (k: 418), high glycated hemoglobin (k: 64), high triglycerides (k: 311), low HDL-c (k: 158), high hs-CRP (k: 270).

Agency AGAUR 2021SGR00687. The DCH-NG cohort was supported by the Danish Cancer Society, Knæk Cancer 2012 and Den A.P. Møllerske Støttefond (grant nº 10619). The establishment of the MAX study was partly funded by FORMAS (DNR 2016-00314). FL receives support from the Chilean government for doing his PhD through the National Agency for Research and Development (ANID)/Food and Nutrition Doctoral Program/DOCTORADO BECAS CHILE/2019 – 72200061. RZ-R was supported by the "Miguel Servet" program (CPII20/00009) from the Institute of Health Carlos III (co-funded by the European Social Fund (ESF) – ESF investing in your future). C.A-L. is grateful for the ICREA Academia Award 2018.

Conflict of interest

Fabian Lanuza, Raul Zamora-Ros, Nicola P. Bondonno, Tomas Meroño, Agnetha Linn Rostgaard-Hansen, Anne Tjønneland, Rikard Landberg, Jytte Halkjær and Cristina Andres-Lacueva have no conflicts of interest.

Statement of authors' contributions to manuscript

F.L., R.Z-R., N-P.B., A.T., J.H. and CA-L. contributed the conceptualization and methodology of the current analysis. R.L., J.H., and A.T. conceived and conceptualized the MAX-study. A.R-H., J.H and A.T. collected the data of the DCH-NG cohort and the MAX-study. F.L. and A.R-H. computed the polyphenol dietary intake. F.L. performed the formal analysis and wrote the first draft of the manuscript. T.M supervised the statistical analysis. RZ-R. and C.A-L supervised the first draft of the manuscript. F.L., R.Z-R, T.M., N-P.B., A.R-H., J.H, A.T., R.L. and C.A-L reviewed, edited and contributed to the final version of the manuscript. All authors have read and agreed to the published version of the manuscript.

Acknowledgment

Myfood24 was developed through Medical Research Council Funding grant G110235. Myfood24 is now being supported by spin-out company Dietary Assessment Ltd. Requests to use myfood24 should be made to enquiries@myfood24.org. INSA has been recognized as a Maria de Maeztu Unit of Excellence grant (CEX2021-001234-M) funded by (MICIN/AEI/FEDER, UE).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.02.022.

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