European Journal of Nutrition (2020) 59:801–812
https://doi.org/10.1007/s00394-019-01946-1

ORIGINAL CONTRIBUTION

Polyphenol intake and metabolic syndrome risk in European adolescents: the HELENA study

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Received: 17 September 2018 / Accepted: 10 March 2019 / Published online: 22 March 2019

Abstract

Purpose The role of polyphenol intake during adolescence to prevent metabolic syndrome (MetS) is little explored. This study aimed to evaluate the association between intake of total polyphenols, polyphenol classes and the 10 most consumed individual polyphenols with MetS risk in European adolescents.

Methods Of the cross-sectional HELENA study, 657 adolescents (54% girls; 14.8% overweight; 12.5–17.5 year) had a fasting blood sample and polyphenol intake data from two non-consecutive 24-h recalls matched with the Phenol-Explorer database. MetS was defined via the pediatric American Heart Association definition. Multilevel linear regressions examined the associations of polyphenol quartiles with MetS components, while logistic regression examined the associations with MetS risk.

Results After adjusting for all potential confounders (socio-demographics and nine nutrients), total polyphenol intake, polyphenol classes and individual polyphenols were not associated with MetS risk. From all MetS components, only BMI *z*-score was modestly inversely associated with total polyphenol intake. Further sub analyses on polyphenol classes revealed that flavonoid intake was significantly associated with higher diastolic blood pressure and lower BMI, and phenolic acid intake was associated with higher low-density cholesterol. For individual polyphenols, the above BMI findings were often confirmed (not independent from dietary intake) and a few associations were found with insulin resistance.

Conclusion Higher intakes of total polyphenols and flavonoids were inversely associated with BMI. No consistent associations were found for other MetS components.

Keywords Risk factor · Polyphenol · Flavonoid · Youth · Obesity · Cholesterol

Abbreviations

AHA	Pediatric American Heart Association
BMI	Body mass index
DBP	Diastolic blood pressure
HDL-c	High-density lipoprotein
HOMA-IR	Homeostasis model of assessment of insulin resistance
LDL-c	Low-density lipoprotein
Q	Quartile
SBP	Systolic blood pressure
TG	Triglycerides
WC	Waist circumference
WHR	Waist–hip ratio

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00394-019-01946-1) contains supplementary material, which is available to authorized users.

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Introduction

Metabolic syndrome (MetS) is a cluster of metabolic abnormalities, including obesity, dyslipidemia, hypertension, and insulin resistance [1], increasing the risk of cardiovascular disease and type 2 diabetes [2]. MetS is a major worldwide public health problem, also in children and adolescents [1]. Subclinical metabolic changes during childhood can track towards disease in adulthood [3]. Dietary behaviour, such as consumption of plant-based foods seems to help in the prevention and treatment of MetS clinical manifestations [4].

Within plant-based foods, several bioactive compounds have been considered as health-stimulating. According to their chemical structures, polyphenols can be divided into four main classes: flavonoids, phenolic acids, stilbenes, and lignans [5]. Dietary polyphenols may have a potentially beneficial effect on MetS components, by reducing body weight, blood pressure, and blood glucose and by improving lipid metabolism [6, 7]. For example, total polyphenol intake was negatively associated with MetS and some of its components (waist circumference, blood pressure, and lipid and glucose alterations) in Polish adults of the HAPIEE study [8] and a higher polyphenol intake was inversely associated with hypertension in the PEDIMED study [9]. Some polyphenol classes might drive these potential associations: a higher intake of flavanones, flavones and lignans were significantly associated with lower BMI over 6 years in a middle-aged general population [10]. However, inconsistent associations have been shown in different trials of polyphenol-rich foods and MetS [7]. Yet, such studies have not been undertaken in adolescents. Since polyphenol intake in adolescents seems to be very low [11] and since health factors track towards adulthood, studying the polyphenol-MetS relation in adolescents is needed to help early interventions in promoting healthy eating behaviour and preventing several chronic diseases.

Therefore, this study aimed to evaluate the association of polyphenol intake with MetS in European adolescents from the "Healthy Lifestyle in Europe by Nutrition in Adolescence" (HELENA) cross-sectional study. Due to the above mentioned variances depending on subtypes of polyphenols and MetS components in literature, several sub-analyses were undertaken. First, polyphenol intake was considered as total polyphenol, polyphenol classes and the ten most consumed individual polyphenols. Second, all individual components of MetS were also considered: BMI, waist circumference (WC), waist-hip ratio (WHR), systolic and diastolic blood pressure (SBP and DBP, respectively), triglycerides (TG), total cholesterol (TC), HDL cholesterol (HDL-c), LDL cholesterol (LDL-c), glucose and insulin resistance.

Materials and methods

Study population

This cross-sectional study is based on the HELENA study, a multicenter study on lifestyle and nutrition among 3528 adolescents aged 12.5–17.5 years from ten European cities: Athens and Heraklion (Greece), Dortmund (Germany), Ghent (Belgium), Lille (France), Pecs (Hungary), Rome (Italy), Stockholm (Sweden), Vienna (Austria), and Zaragoza (Spain). Data in the HELENA study were collected between 2006 and 2007, via random cluster sampling (all adolescents from a selection of classes) and stratified by geographical location, age and socio-economic status. Details on the recruitment methods, design and inclusion criteria have been reported elsewhere [12]. The study protocol was permitted by the ethics committee of each city involved and written informed consent was retrieved from all participants and their parents.

In the HELENA study, a total of 1089 blood samples were collected. Data on food intake (two 24-h dietary recalls) were not available from Heraklion and Pecs, so subjects from these cities ($n=211$) were excluded. Also, adolescents who took cardiovascular medication ($n=5$) or who had no valid data on 24-h dietary recalls and all MetS components ($n=216$) were excluded. For the present analysis, 657 adolescents were included (Supplemental Figure 1). Included and excluded participants did not differ according to age, sex, BMI and lifestyle, but those included were more from non-Mediterranean countries, had more often Tanner 3 stadium and more mid-category maternal education (data not shown).

Demographic and lifestyle measurements

Data on sex, age, city, and socio-economic status were recorded by a standardised self-reported questionnaire [13]. Socio-economic status was examined by parental education and the Family Affluence Scale (FAS). The parental education level of mother and father was defined as one of three levels (lower education, higher secondary education or university education). The FAS, which was previously validated [14], was used as an indicator of material wealth in the family. It was based on information about the number of cars in the family (0–3 depending on amount) and computers at home (0–3 depending on amount), internet availability at home (0 no, 1 yes), and having one's own bedroom (0 no, 1 yes). Scores range from 0 to 4 as low FAS score, and 5–8 as high-FAS score. Smoking status, physical activity (hour/week) and alcohol consumption were evaluated by questionnaire data. Pubertal status was based on the development of breast and pubic hair in females and the development of genital and pubic hair in males according to Tanner and Whitehouse [15]. The cities Athens in Greece, Rome in Italy, and Zaragoza in Spain were considered as Mediterranean.

Metabolic syndrome

Measurement of weight, height, and WC has been previously described [16]. BMI *z*-scores were calculated using the British Growth Reference Data from the Child Growth Foundation [17] and classified according to the International Obesity Task Force. SBP and DBP were measured twice in a sitting position with a 10 min interval in-between and the lowest reading was recorded [13], using the same type BP device approved by the European Hypertension Society. A

blood sample was collected at school between 8 and 10 A.M. after a 10-h overnight fast by venipuncture in a randomly selected one-third subset of the HELENA participants. Blood was collected in tubes for serum (blood lipid profile) and heparinized tubes for plasma (insulin), immediately placed on ice and centrifuged, aliquoted and transported at 4–7 °C (for a maximum of 14 h) to the central laboratory in IEL (Institut für Ernährungs- und Lebensmittelwissenschaften), Bonn University. Glucose, total cholesterol and HDL-c were assessed on fresh serum within 1 day of blood extraction by enzymatic methods (Dade Behring, Schwalbach, Germany). Heparin plasma was stored at − 80 °C until analysed for insulin concentrations using an Immulite 2000 analyser (DPC Bierman GmbH, Bad Nauheim, Germany). For insulin resistance, the homeostasis model assessment (HOMA-IR) was calculated [18].

In this study, MetS was defined as recommended by the pediatric American Heart Association (AHA) [19], i.e., three or more of the following risk factors: central obesity (WC ≥ 90th percentile for age, sex, and race/ethnicity), high TG concentrations (≥ 110 mg/dL), low HDL-c (≤ 10th percentile for race and sex), impaired fasting glucose (≥ 110 mg/dL), elevated blood pressure (≥ 90th percentile for age, sex, and height, both of SBP and DBP). The association of MetS according to different definitions with socio-demographic variables and diet can be found in Supplemental Table 1, but only the AHA definition was used for the current publication.

Dietary assessment

Using the HELENA-Dietary Assessment Tool, dietary data were assessed from a 24-h recall on 2 non-consecutive days, within a time-span of 2 weeks, but not on Fridays and Saturdays. Detailed quantitative information was compiled using household measurements or pictures of portion sizes for each item chosen. This tool has been validated in Flemish adolescents [20]. The nutrient composition of the diet (mean of 2 days) was calculated with the German Food Code and Nutrient Data Base (Bundeslebensmittelschlüssel, BLS, version II.3.1).

The intake of polyphenols was evaluated using the Phenol-Explorer database [21] accounting for cooking and processing of foods, as previously described [11]. Polyphenol content values detailed in the Phenol-Explorer database are obtained by different analytical methods but most often by 'chromatography'. Polyphenol intakes per person were estimated by multiplying the polyphenol content in a food by the amount of this food item eaten per day; then taking the sum over the day per individual; and then taking the mean over 2 days. Total polyphenol intake was calculated as the sum of individual polyphenols intake.

Statistical analyses

The statistical analyses were conducted with the software package IBM SPSS statistics version 23 (IBM, New York, USA) and the level of significance was set at two-sided $p < 0.05$. Data were presented as mean ± standard deviation or as mean ± standard errors and percentages. The log or square root transformation was applied to fit normality when required (for outcomes in linear regression), but estimated means and standard errors were back-transformed for interpretation. Dietary polyphenol intakes were expressed as mg of polyphenols per 1000 kcal to correct for total energy intake (correlation between raw polyphenol intake and energy intake was $r = 0.381$; $p \leq 0.001$). Demographic and lifestyle parameters (as potential confounders) were evaluated depending on quartiles of total polyphenol intake and depending on association with MetS. These differences between total polyphenol intake quartiles were tested using ANOVA for continuous variables and Chi-squared test for categorical variables.

Multilevel regressions were chosen to adjust for the clustering within countries. Multiple linear regression was applied to assess the associations between polyphenol intake (as quartiles of energy-adjusted intake) and components of MetS. Confounder choice was based on significant associations with either polyphenol intake or MetS. Model 1 was adjusted for age, sex, European region, BMI z-score and Tanner stage. Model 2 was additionally adjusted for intakes of the following nutrients: mono- and disaccharides, polysaccharides, fibre, protein, monounsaturated fatty acids, cholesterol, and vitamin C. For all significant findings based on overall polyphenol quartile difference, the regression was repeated with the continuous polyphenol variable to verify linear, quadratic or cubic relations (data not shown in tables, just mentioned in text). Adjustment for BMI or not did not change the results for the other MetS components. Percentage of explained variance by polyphenols was reported as change in R^2 after including the polyphenol variable (ΔR^2).

A multilevel logistic regression analysis was performed to assess the relationship between polyphenol intake and having at least one of the MetS components at risk following the AHA definition. This classification was chosen since very few adolescents (< 5%) were classified as having MetS (thus being at risk for at least 3 MetS components). Again, these regressions were adjusted according to model 1 and 2.

Results

General characteristics of the subjects

The median and interquartile range of polyphenol intake was 347.2 mg/day (171.1; 569.5) and 162.2 mg/day/1000 kcal

(91.4; 566.5). Based on AHA, 3.7% or 24 adolescents (Q1 = 6 adolescents, Q2 = 5 adolescents, Q3 = 6 adolescents, and Q4 = 7 adolescents) had MetS and 43.1% had at least one risk factor, 9.7% had high glucose, 30.6% had high waist circumference, 9.6% had high triglyceride concentrations, 2.3% had low HDL, and 8.1% had high blood pressure. Overweight and obesity prevalence was 14.8% and 5.3%, respectively.

Baseline characteristics of the 657 participants (54% girls) are presented in Table 1. Participants with a higher polyphenol intake were older ($p = 0.019$), from Non-Mediterranean countries ($p < 0.001$), had lower BMI *z*-score ($p = 0.004$) and had higher pubertal status ($p = 0.008$). Moreover, a higher intake of total carbohydrates, mono- and disaccharides, fibre and vitamin C and a lower intake of polysaccharides, protein, monounsaturated fatty acids, and cholesterol were associated with a higher intake of polyphenols.

Association of demographic characteristics and nutrient composition of the diet with MetS can be found in Supplemental Table 1. Significant differences in MetS were found depending on the European region, education of mother, education of father, BMI *z*-score, mono- and disaccharides, monounsaturated fatty acids, cholesterol and energy intake. These differences were almost the same when using different MetS definitions (AHA, NCEP-ATP, IDF and WHO) and all following analyses gave the same results when using these different MetS definitions.

Metabolic syndrome and polyphenol intake

There was no difference in overall MetS depending on energy-adjusted quartiles of polyphenol intake (Table 2). From the MetS-related components, only BMI *z*-score had a significant association with energy-adjusted quartiles of polyphenol intake ($\Delta R^2 = 0.006$; linear relation was confirmed), a higher intake was reflected in a lower BMI *z*-score, independent from other nutrients.

Metabolic syndrome and polyphenol class intake

The metabolic variables according to quartiles of energy-adjusted intake of polyphenol classes are presented in Supplemental Table 2. Again, none of the polyphenol classes was related to overall MetS. Flavonoid consumption was significantly associated with lower BMI *z*-score (linear relation was confirmed). In addition, flavonoids had non-linear associations (respectively; quadratic instead of linear relation was confirmed) with systolic and diastolic blood pressure (raw or *z*-score) after adjusting for all potential confounders: only the lowest flavonoid quartile had low blood pressure. Phenolic acid consumption was only associated with higher LDL-c (linear relation was confirmed). Stilbenes did not show significant associations. Lignan consumption was significantly associated with BMI *z*-score (quadratic relation was confirmed), but only in model 1 (no adjustment for nutrients). Change in R^2 by polyphenols was around 1%.

Metabolic syndrome and individual polyphenols

The 10 most consumed individual polyphenols were not associated with overall MetS (Supplemental Table 3). A lower BMI *z*-score was found for higher consumers of proanthocyanidin polymers (> 10mers), proanthocyanidin 4–6 oligomers, proanthocyanidin 7–10 oligomers, proanthocyanidin trimers, (−)-epicatechin, and (+)-catechin, but not after adjustment for nutrients (only in model 1; linear relation was confirmed). For 5-caffeoylquinic acid, the opposite direction was found for BMI *z*-score (linear relation was confirmed) and Procyanidin dimer B2 had a quadratic association with BMI *z*-score, but again only in model 1. Ferulic acid intake was associated with WC (only a linear trend $p = 0.077$ was confirmed) in model 2: quartile 2 and 3 were higher WC than quartile 4 (highest quartile). (+)-Catechin intake was associated with lower WC *z*-score in model 1 (linear relation was confirmed). HOMA-IR was in a non-linear way (quadratic instead of linear relation confirmed) significantly different in model 1 depending on (−)-epicatechin and procyanidin dimer B2 intake: lowest for quartile 1 and other quartiles higher. Change in R^2 by polyphenols was around 1%.

Food sources

To translate these findings into foods consumed, the main food sources of total polyphenols, polyphenol classes and individual polyphenols are shown in Supplemental Table 4. Chocolate products (19%), apples and pears (16%), and fruit and vegetables juices were the main sources of total polyphenol intake and flavonoid intake, while coffee (28%), apples and pears (11%), and savoury snacks (9%) were the top three major food sources of phenolic acids.

Discussion

To our knowledge, this is the first observational study that examined associations of polyphenol intake (total, classes and the ten most consumed) with MetS and its components in adolescents. Because of the cross-sectional study design, we cannot exclude the possibility of reverse causation. The most consistent finding was a significant inverse association between polyphenol intake (total and flavonoid in specific) and BMI *z*-score. The effect size was 0.3 standard deviation difference in BMI *z*-score for lowest vs highest polyphenol quartile, which is larger than those reported by previous studies [8, 22, 23]. Nevertheless, we could not confirm the main hypothesis of polyphenol intake (total, classes or

Table 1 General characteristics of the HELENA participants according to energy-adjusted quartiles of polyphenol intake

	Q1 ($n=148$)	Q2 ($n=173$)	Q3 ($n=178$)	Q4 ($n=158$)	p^a
Total polyphenols (mg/1000 kcal)	51.8 ± 22.4	121.8 ± 22.1	213.9 ± 32.6	458.9 ± 281.8	
Flavonoids (mg/1000 kcal)	48.4 ± 33.7	106.5 ± 41.5	176.7 ± 56.8	352.3 ± 238.1	
Phenolic acids (mg/1000 kcal)	15.1 ± 15.7	28.6 ± 27.5	47.7 ± 48.2	105.8 ± 110.8	
Stilbenes (mg/1000 kcal)	0.04 ± 0.15	0.03 ± 0.12	0.04 ± 0.14	0.14 ± 0.60	
Lignans (mg/1000 kcal)	0.97 ± 3.5	1.25 ± 4.04	1.21 ± 4.51	0.87 ± 3.30	
Other polyphenols (mg/1000 kcal)	7.3 ± 7.6	10.6 ± 10.8	13.9 ± 14.0	14.9 ± 14.6	
Gender—girls (%)	47	51	55	61	0.09
Age (years)	14.6 (1.2)[b]	14.6 (1.3)[b]	14.7 (1.2)	14.9 (1.2)	**0.019**
European region (%)					**< 0.001**
Mediterranean countries	39	39	24	8	
Non-Mediterranean countries	61	61	76	92	
Education of mother (%)					0.23
Lower (secondary) education	40	27	29	34	
Higher secondary education	32	35	37	34	
Higher education or university degree	28	38	34	32	
Education of father (%)					0.48
Lower (secondary) education	42	33	31	33	
Higher secondary education	26	30	35	28	
Higher education or university degree	32	37	34	38	
Family affluence scale (FAS) (%)					0.54
Low-FAS score	46	45	39	41	
High-FAS score	54	55	61	59	
Smoking status (%)					0.15
Never	57	62	71	58	
Former smoker	22	17	14	22	
Current smoker	21	21	15	20	
Alcohol use (%)					0.06
No	82	79	74	70	
Yes	18	21	26	30	
Physical activity (min/day)	701 ± 616	737 ± 562	737 ± 587	766 ± 561	0.82
BMI *z*-score	0.64 ± 1.09[b]	0.50 ± 1.13[b]	0.29 ± 1.07	0.23 ± 1.06	**0.004**
Tanner stage (%)					**0.008**
Tanner stage 1	11	14	10	7	
Tanner stage 2	25	30	29	15	
Tanner stage 3	48	39	46	51	
Tanner stage 4	16	17	15	27	
Carbohydrates (g/day)	118.7 ± 13.6[b]	122.9 ± 14.9[b]	123.3 ± 13.8	126.5 ± 14.2	**0.001**
Monosaccharides and disaccharides (g/day)	50.3 ± 15[b]	56.8 ± 17.4[b]	60.5 ± 16.1[b]	66.6 ± 14.5	**< 0.001**
Polysaccharides (g/day)	65.2 ± 10.8[b]	63.5 ± 12.7[b]	61.4 ± 10.7	58.9 ± 9.8	**< 0.001**
Fibre (g/day)	7.6 ± 1.6[b]	8.2 ± 1.8[b]	8.7 ± 1.9	9.2 ± 2.2	**< 0.001**
Proteins (g/day)	42.2 ± 7.1[b]	39.5 ± 6.7[b]	38.7 ± 6.6[b]	37.0 ± 5.4	**< 0.001**
Lipids (g/day)	37.8 ± 4.8	37.2 ± 5.1	37.5 ± 4.9	36.8 ± 5.4	0.54
Saturated fatty acids (g/day)	15.7 ± 2.3	15.6 ± 2.6	15.6 ± 2.6	15.8 ± 2.9	0.96
Monounsaturated fatty acids (g/day)	14.0 ± 2.2[b]	13.5 ± 2.2[b]	13.7 ± 2[b]	12.9 ± 2	**0.004**
Polyunsaturated fatty acids (g/day)	5.2 ± 1.4	5.2 ± 1.5	5.3 ± 1.3	5.3 ± 1.3	0.92
Cholesterol (mg/day)	159.6 ± 41.9[b]	147.0 ± 36.5	146.8 ± 36	139.7 ± 33.6	**0.001**
Minerals (g/day)	17.4 ± 4.8	17.4 ± 5	16.7 ± 3.7	16.9 ± 4.7	0.77
Vitamins					
Vitamin B (mg/day)	26.4 ± 9.5	26.3 ± 8.2	24.8 ± 6.1	25.4 ± 7.4	0.83
Vitamin C (mg/day)	88.7 ± 44.2[b]	114 ± 65.8[b]	120 ± 67.2	133.2 ± 76.8	**< 0.001**

Table 1 (continued)

	Q1 ($n=148$)	Q2 ($n=173$)	Q3 ($n=178$)	Q4 ($n=158$)	p^a
Vitamin A (mg/day)	1.2 ± 0.53	1.1 ± 0.44	1.1 ± 0.35	1.0 ± 0.38	0.18
Vitamin D (µg/day)	2.2 ± 0.86	2.1 ± 0.94	2.0 ± 0.75	2.0 ± 0.94	0.29
Vitamin E (mg/day)	10.1 ± 4	10.4 ± 3.7	10.6 ± 2.9	10.8 ± 3.5	0.45
Vitamin K (µg/day)	239.4 ± 90.3	248.0 ± 92.3	236.9 ± 73.4	238.0 ± 86.2	0.71
Energy intake (kcal/day)	2331 ± 1046	2403 ± 1135	2197 ± 873	2122 ± 1041	0.08

Data are presented as means ± standard deviation and frequencies. Bold: statistical significance when $p<0.05$

Q quartile

[a]ANOVA-one factor was used for continuous variables and X^2 test for categorical variables

[b]$p < 0.05$ vs quartile 4, post hoc test for multiple comparisons (Bonferroni test)

individual) and lower overall MetS. This is probably because of the low prevalence of MetS in the HELENA participants (1.6–3.8% depending on the definition used [24]).

In addition, a few contradictory findings were found like higher LDL-c by phenolic acid intake and some non-linear associations for certain polyphenols. A biological rationale for non-linear associations is that a beneficial effect might only be seen in extreme values of polyphenol intake (quadratic) or in a moderate consumption (U-shaped relation). For example, one meta-analysis showed mostly non-linear associations with type 2 diabetes [25]. Especially as polyphenol intake in our adolescent population is low, the advantageous effects might only be visible in the highest quartile. Unless other studies confirm these findings, we cannot rule out that our findings were due to multiple testing.

Metabolic syndrome and total polyphenol intake

In the HELENA study, total polyphenol intake was not associated with the risk of MetS, which is in agreement with the results from a Tehranian healthy adult population [26]. It should be considered that the prevalence of MetS in the HELENA study was low and that not all MetS components might be influenced by polyphenol intake. Interestingly, only lower BMI *z*-score was significantly associated with polyphenols in the HELENA population. In fact, adipose tissue quality for which BMI is a parameter, can stimulate over time the other MetS factors, such as increasing blood pressure, dyslipidemia, insulin resistance, inflammation, etc. [27]. As mechanistic pathway, polyphenols have been associated with gut microbiota that affect obesity [28], but can also modulate neuropeptides involved in food intake. Indeed, some studies have shown that polyphenol intake increases energy expenditure [29, 30]. Nevertheless, a recent systematic review indicates that weight loss by polyphenols is not clinically relevant in overweight and obese individuals [31], but many interventional studies have a duration of less than 3 months and it might still be relevant for prevention.

In contrast with the HELENA study, total polyphenol intake was inversely associated with MetS and some of its components (BMI, WC, blood pressure, and lipid alterations) in Polish adults of the HAPIEE study [8]. Nevertheless, these findings were not adjusted for the nutrient composition of the diet and a linear association was found only for BMI and WC. A higher dietary intake of polyphenols decreased systolic and diastolic BP in a high cardiovascular risk group [32], reduced cardiovascular events and cardiovascular mortality [33], increased HDL-c and decreased LDL-c, triglycerides, systolic and diastolic BP in a population with type 2 diabetes [23], and reduced WC, BP, high lipoprotein cholesterol, and triglycerides in women, and fasting plasma glucose in both gender in Polish older adults [8]. All these previous studies are not in adolescents, but in an adult population with higher MetS risk and higher polyphenol intake.

Metabolic syndrome and intake of polyphenol classes

Polyphenol subclasses may have their own specific impact on cardiometabolic risk factors, due to their different chemical structures and metabolism [34]. Flavonoids were the most consumed polyphenol group in the HELENA study, but again not associated with MetS. High flavonoid intake was associated with lower BMI, even after adjustment for nutrients. In agreement, a cohort study found that a higher intake of some of flavonoids was significantly associated with lower BMI over 6 years in a middle-aged general population [10]. Investigation of the mechanisms of action of flavonoids has mainly focused on glucose homeostasis: increasing insulin secretion and reducing insulin resistance, reducing apoptosis, promoting pancreatic β-cell proliferation, inflammation and oxidative stress in the muscle; all aspects that are also involved in obesity [35, 36]. Indeed, another study found that a higher flavonoid intake from fruit and vegetables during adolescence was associated with lower LDL-c levels [22] and higher HOMA2-%S among

Table 2 Metabolic syndrome and its individual components according to energy-adjusted quartiles of polyphenol intake

	Q1 ($n=148$)	Q2 ($n=173$)	Q3 ($n=178$)	Q4 ($n=158$)	p value[a]
Metabolic syndrome[b]					
Model 1	0.58 ± 0.07	0.61 ± 0.07	0.67 ± 0.06	0.66 ± 0.07	0.57
Model 2	0.62 ± 0.09	0.67 ± 0.08	0.68 ± 0.08	0.64 ± 0.09	0.89
BMI *z*-score					
Model 1	0.51 ± 0.11[c,d,e]	0.38 ± 0.11	0.32 ± 0.11	0.37 ± 0.11	**0.023**
Model 2	0.37 ± 0.11[c,d]	0.23 ± 0.10	0.17 ± 0.10	0.08 ± 0.11	**0.010**
WC (cm)					
Model 1	72.1 ± 0.56	72.0 ± 0.55	72.1 ± 0.55	71.7 ± 0.55	0.27
Model 2	71.0 ± 0.57	70.6 ± 0.56	70.8 ± 0.56	70.6 ± 0.58	0.67
WC *z*-score					
Model 1	0.75 ± 0.09	0.74 ± 0.09	0.70 ± 0.09	0.68 ± 0.09	0.31
Model 2	0.63 ± 0.09	0.58 ± 0.09	0.55 ± 0.09	0.55 ± 0.09	0.46
WHR					
Model 1	0.79 ± 0.004	0.79 ± 0.004	0.79 ± 0.004	0.79 ± 0.004	0.39
Model 2	0.79 ± 0.01	0.79 ± 0.004	0.79 ± 0.004	0.79 ± 0.01	0.75
HOMA-IR					
Model 1	1.8 ± 1.1	1.9 ± 1.1	1.8 ± 1.1	1.8 ± 1.1	0.84
Model 2	1.7 ± 1.1	1.8 ± 1.1	1.9 ± 1.1	1.8 ± 1.1	0.50
Glucose (mg/dL)					
Model 1	90.4 ± 0.81	90.9 ± 0.79	90.5 ± 0.79	90.8 ± 0.86	0.83
Model 2	90.0 ± 0.97	90.4 ± 0.89	90.8 ± 0.89	90.9 ± 1	0.81
SBP (mmHg)					
Model 1	114.7 ± 1.8	115.0 ± 1.8	115.3 ± 1.8	115.0 ± 1.8	0.83
Model 2	113.3 ± 1.8	113.9 ± 1.7	115.3 ± 1.7	114.8 ± 1.8	0.11
SBP *z*-score					
Model 1	− 0.28 ± 0.17	− 0.26 ± 0.17	− 0.23 ± 0.17	− 0.26 ± 0.17	0.88
Model 2	− 0.40 ± 0.17	− 0.35 ± 0.17	− 0.23 ± 0.17	− 0.28 ± 0.17	0.15
DBP (mmHg)					
Model 1	63.7 ± 1	64.4 ± 1	64.0 ± 1	64.8 ± 1	0.18
Model 2	63.1 ± 1.1	63.7 ± 1.1	64.5 ± 1.1	64.7 ± 1.1	0.07
DBP *z*-score					
Model 1	0.70 ± 0.11	0.78 ± 0.11	0.74 ± 0.11	0.82 ± 0.11	0.21
Model 2	0.63 ± 0.12	0.71 ± 0.12	0.79 ± 0.12	0.82 ± 0.13	0.07
HDL-c (mg/dL)					
Model 1	56.7 ± 0.01	55.1 ± 0.01	54.6 ± 0.01	55.0 ± 0.01	0.20
Model 2	56.4 ± 0.01	55.7 ± 0.01	54.2 ± 0.01	55.4 ± 0.01	0.39
LDL-c (mg/dL)					
Model 1	91.3 ± 0.01	93.0 ± 0.01	93.9 ± 0.01	94.4 ± 0.01	0.69
Model 2	88.6 ± 0.02	92.3 ± 0.01	93.0 ± 0.01	95.0 ± 0.02	0.38
TG (mg/dL)					
Model 1	62.8 ± 1	61.9 ± 1	59.7 ± 1	60.1 ± 1	0.65
Model 2	64.1 ± 1.1	61.4 ± 1	59.8 ± 1	59.3 ± 1.1	0.62

Model 1, adjusted for age, sex, European region, education of mother, education of father, puberty status, BMI *z*-score. Model 2 was additionally adjusted for monosaccharides and disaccharides, polysaccharides, fibre, monounsaturated fatty acids, saturated fatty acids, cholesterol, protein, vitamin C, and energy intake

Q quartile, *BMI* body mass index, *WC* waist circumference, *HOMA-IR* Homeostasis Model of Assessment of insulin resistance, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *HDL-c* high-density lipoprotein, *LDL-c* low-density lipoprotein, *TG* triglycerides, *WHR* waist–hip ratio

Data are presented as means ± standard error. Bold values indicate statistical significance when $p < 0.05$

[a]Differences between quartiles of polyphenol intake using multiple linear regression, except for MetS, which were observed using multiple logistic regression. Values of HOMA-IR and TG were derived by back transformation of $\log_e$, and values of HDL-c and LDL-c were obtained by back transformation of square

Table 2 (continued)

root

[b]Metabolic syndrome (MetS) based on the AHA definition and predicted probability to have at least one MetS risk factor based on logistic regression

[c]$p < 0.05$ vs quartiles 4, post hoc test for multiple comparisons (Bonferroni test) if total p value was significant

[d]$p < 0.05$ vs quartiles 3, post hoc test for multiple comparisons (Bonferroni test) if total p value was significant

[e]$p < 0.05$ vs quartiles 2, post hoc test for multiple comparisons (Bonferroni test) if total p value was significant

females [37]. Nevertheless, fruit and vegetables only had 45% contribution to flavonoid intake in the HELENA study. Non-linear alteration might indicate U-shaped associations in which extremes are not beneficial and thus the need for good Dietary Reference Intake (DRI), but the detected non-linear associations with blood pressure seem not that relevant as the adolescents had normal levels (less than 90th percentile or 120 and 80 mmHg) [38].

In contrast, phenolic acid consumption (for which coffee was the major contributor) was associated with higher (thus less beneficial) LDL-c. Non-significant results have most often been reported: no association of coffee consumption with LDL-c in a Brazilian study [39], no effect of coffee consumption on blood lipids in Colombian healthy adults [40] and in Turkish adults [41]. It should be considered that our HELENA population are healthy adolescents with low LDL-c levels (< 130 mg/dL) [42] and low polyphenol intake. Consequently, these data might indicate the beginning of the J-shaped curve between coffee consumption and cardiovascular risk [43], thus missing the steep slope towards increased risk. In line with our HELENA study, phenolic acid intake was not associated with WC, hypertriglyceridemia, low serum HDL-c, hyperglycemia, hypertension, and MetS in Tehranian adults [26] or for cardiovascular disease in the PREDIMED study [9].

The intake of stilbenes, lignans and other polyphenols were not associated with MetS and its components in model 2. In agreement, the same findings were found in Tehranian adults [26] and no effect on bone mineral density or content, body composition, lipoproteins, glucose, or inflammation after flaxseed lignan complex supplementation [44]. In contrast, lignan and stilbenes were found to be inversely associated with WC in Polish adults [8]. The intake of lignans and stilbenes in the HELENA study was below 1 mg/day, and the intake of other polyphenols was 21–22 mg/day, which were lower than the aforementioned studies.

Metabolic syndrome and individual polyphenols

As different groups of phenolic compounds are digested and absorbed through various pathways and to different extents [45], certain polyphenols might show significant associations with health outcomes and others not. Almost all findings disappeared after adjusting for nutrients in model 2. The inclusion of dietary nutrient composition in the model attenuated the association of individual polyphenols and BMI, probably due to larger effects of other non-polyphenol nutrients.

Only for ferulic acid consumption and WC the association was present in model 2, but the highest WC in the study (in quartile 3) was still a healthy level (less than 75th percentile reference [46]), thus without clinical relevance. A mechanistic animal study suggests that ferulic acid intake could reduce obesity via modulation of enzymatic (amylase and lipase) activities, hormonal (insulin, ghrelin, and leptin) and inflammatory responses [47].

Without adjustment for nutrients, proanthocyanidins (the most frequent polyphenol subclass in our population) were associated with lower BMI z-score; (−)-Epicatechin intake with HOMA-IR in a quadratic way and with lower BMI z-score; and (+)-Catechin intake with lower BMI and WC. For these three polyphenols previous experimental research has suggested such biologic activity. Proanthocyanidins might increase energy expenditure, suppression of food intake and inhibiting digestive enzymes like lipase and amylase resulting in lower fat and glucose absorption from the gut [48]. Epicatechin might prevent the adipose tissue inflammation and insulin resistance, at least by marked suppression of CCL-19 expression [49] and to mitigate obesity-associated insulin resistance [50]. Catechin might reduce weight by modifying gut microbiota and gene expression in colonic epithelial cells, thus changing fat digestion, fat absorption, and lipolysis in adipocytes [51].

Food sources

Regional and age differences in food consumption can influence the intake of specific polyphenols and thus also the observed effect on MetS. Interestingly, chocolate products were the major contributors of polyphenols in our adolescent population, followed by fruit (juices). Chocolate products are often no major contributor in other (mainly adult population) studies [9, 23]. Epidemiological studies have suggested that cocoa polyphenol intake may lower cardiovascular risk [52], although this might be patient-dependent [53] e.g., only in the elderly [54]. Health benefits of total flavanols and epicatechin

are often only seen at rather high doses [53], much higher than the mean intake of flavanols (148.33 mg/day) and epicatechin (7.13 mg/day) in the HELENA study, but higher chocolate consumption was associated with lower BMI, WC, and body fat in the HELENA study [55].

Strengths and limitations

To the best of our knowledge, this is the first study investigating detailed associations of polyphenols with MetS in adolescents. As the adolescents had lower polyphenol intake and better metabolic health than adults, testing agreement with adult studies is relevant. Also the observed differential effects depending on polyphenol class and MetS component confirmed the importance of studying these details. Secondly, this study has a large and heterogeneous population sample, which gives an approximation of the average situation in European cities [12]. Thirdly, high quality data collection has been strived for via the standardised collection of data, the centralised measurements of biochemical variables and the consideration of relevant confounders. Fourthly, the most comprehensive polyphenol database (Phenol-Explorer) was used.

Nevertheless, our study has limitations. An important limitation was that the prevalence of metabolic syndrome was very low in healthy adolescents and, therefore, statistical power was reduced. Given the low magnitude of detected associations, further corroboration in larger studies is required. Additionally, the cross-sectional design does not allow causal relations and the analyses are rather exploratory without adjustment for multiple testing (by next to main hypothesis also testing separate metabolic syndrome factors, separate polyphenol classes and non-linear trends). Other limitations are linked to the estimation of polyphenol intake due to the missing dietary data of Friday and Saturday, some missing details in the 24-h recalls like herbs and specific oil types, food items for which composition was not available in the Phenol-Explorer database, and some individual polyphenols within the same subclass which could have opposing effects. Consequently, the measurement of polyphenol biomarkers like in biofluids could have added value in examining health effects [56], especially since a lot of metabolization happens before reaching the bio-active substances. Using the same methodology as in our study, i.e., 24-h recalls and the phenol-explorer database, reported polyphenol intake was significantly associated with polyphenol biomarkers in urine [57].

Conclusion

In conclusion, a dietary pattern high in total polyphenols and flavonoids may help to prevent overweight as it was consistently related to BMI independent of socio-demographic status or other nutrient parameters and showed a small but clinically relevant effect size (BMI z-score 0.4 vs 0.1 in lowest and highest polyphenol intake quartile). Nevertheless, no consistent associations with other MetS parameters could be found: there were only a few additional non-linear associations with certain polyphenols or findings became non-significant after statistical adjustment for nutrients. These findings suggest the importance of investigating specific mechanisms of individual polyphenols and determining which dose of specific polyphenols should be consumed for maximal benefit. Future studies using longitudinal data and using polyphenol biomarkers are needed to determine health effects in more detail.

Acknowledgements We would like to thank all fieldworkers and all participating adolescents. We acknowledge the work of Mieke De Maeyer and the Phenol explorer team for the support of polyphenol' estimation.

Author contributions RWW formulated the research question, has analysed the data, prepared the estimation of polyphenols, and wrote a draft of the paper. NM helped in refining the research question, setting up the database, analyzing the data and did editing of the first draft. NM, SDH and LAM are PhD supervisors of RWW; LAM was the coordinator of the HELENA project. From the International Agency for Research on Cancer, we received help from AS, VK, JAR and IH in the linking to their Phenol-Explorer database containing the polyphenol concentrations in food items. All other authors were involved in the HELENA project (coordinator or data collection in their country). All authors have read the draft and agreed on the final version.

Funding The HELENA Study was carried out with the financial support of the European Community Sixth RTD Framework Programme (Contract FOODCT-2005-007034). The writing group takes sole responsibility for the content of this article. The European Community is not liable for any use that may be made of the information contained therein. The first author was sponsored as PhD student by Indonesia Endowment Fund for Education (LPDP, Indonesia).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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