Plasma Alkylresorcinol Metabolite, A Biomarker of Whole-Grain Wheat and Rye Intake, and Risk of Metabolic Syndrome: A Case-Control Study

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Abstract

Background: Whole-grain intake assessed through dietary recording methods has been suggested to be inversely associated with the metabolic syndrome (MetS) risk in several epidemiological studies. However, limited studies have evaluated the association between whole-grain intake and MetS risk when using objective biomarkers of whole-grain intake. The aim of this study was to examine the association between plasma 3-(3,5-dihydroxyphenyl)-1-propanoic acid (DHPPA), a biomarker of whole-grain wheat and rye intake, and MetS risk in a Chinese population.

Methods: A case-control study of 667 MetS cases and 667 matched controls was conducted based on baseline data of the Tongji-Ezhou Cohort study. Plasma DHPPA concentrations were assessed by high-performance liquid chromatography-tandem mass spectrometry. MetS was determined using definition of the Joint Interim Statement.

Results: Plasma DHPPA was inversely associated with MetS risk. After adjustment for age, sex, body mass index, smoking status, alcohol drinking status, physical activity and education level, the odds ratios (ORs) for MetS across increasing quartiles of plasma DHPPA concentrations were 1 (referent), 0.86 (0.58-1.26), 0.77 (0.52-1.15), and 0.59 (0.39-0.89), respectively. The inverse relation between plasma DHPPA and MetS persisted in stratified analyses according to confounding factors. In addition, the cubic spline analysis revealed a potential nonlinear association between plasma DHPPA and MetS, with a steep reduction in the risk at the lower range of plasma DHPPA concentration.

Conclusions: Our study revealed that higher plasma DHPPA concentrations were associated with lower odds of MetS. Our findings provided further evidence to support health benefits of whole grain consumption.

Background

Recent estimates indicate that the prevalence of metabolic syndrome (MetS) is increasing in China, with an estimated one third of Chinese adults affected (1). MetS is characterized by a cluster of cardiovascular disease risk factors, including central obesity, elevated blood pressure, dyslipidemia, and high blood glucose, and it carries an increased risk of type 2 diabetes and cardiovascular disease (2, 3). The pathogenesis of MetS is largely unknown, but probably represents a complex interaction between metabolic, genetic, and environmental factors, which include diet (4).

Whole grain is a good source of dietary fiber, phenolic compounds, phytoestrogens, vitamins, and minerals, which may confer protection on MetS (5). In previous epidemiological studies, whole-grain foods have been associated with lower risk of MetS (6, 7). Greater whole-grain intake also was favorably related to markers of MetS such as obesity and dyslipidemia (8, 9). However, most epidemiological studies estimated whole-grain intake with the use of dietary recording records (10–12). Given the diversity of whole-grain products in diets, assessing the intake accurately in free-living populations seems to be challenging, and the inaccurate identification of different whole-grain constituents might lead to

measurement errors (13, 14). A more objective estimation of whole-grain intake through use of a biomarker appears to be significant.

Alkylresorcinols are a cluster of phenolic lipids abundant in the outer layer of wheat and rye grain (15). Alkylresorcinols are absorbed through the small intestine, and plasma alkylresorcinols are suggested to be transported in lipoproteins (16). Intact alkylresorcinols and their 2 main end-products- 3,5-dihydroxybenozoic acid (DHBA) and 3-(3,5-dihydroxyphenyl)-1-propanoic acid (DHPPA)-are measurable in plasma (15, 17). Recently, alkylresorcinols and their metabolites have been suggested as biomarkers of whole-grain rye and wheat intake (18), and they have been used to assess whole-grain rye and wheat intake in several epidemiological studies (19, 20). Considering that the half-life of DHPPA (16.3 hours) is significantly longer than that of DHBA (10.1 hours) and alkylresorcinols (5 hours) and blood samples are usually taken after overnight fasting, plasma DHPPA appears to be a good and specific biomarker of whole-grain wheat and rye intake (21–23).

To our knowledge, no study has yet investigated the association of plasma biomarker concentrations of whole-grain wheat and rye intake with MetS risk in a Chinese population. We thus conducted this matched case-control study, which based on the baseline data of the Tongji-Ezhou Cohort (TJEZ) study, to examine the association of plasma DHPPA concentration with MetS.

Methods

Study population and design

The TJEZ cohort study is an ongoing prospective cohort study investigating the associations of lifestyle, dietary factors, and genetic markers with chronic diseases. The study was set in Echeng Steel, the largest construction steel production base in Hubei Province, China. All working employees and retired employees from Echeng steel were invited to participate. Participants who were permanent residence in Ezhou and aged above 20 years at the time of recruitment were recruited. Individuals were not recruited if they had cancer or were pregnant. Between 2013 and 2014, 5533 adult residents were recruited, with a response rate of 96.6%. Data allowing the determination of the status of MetS was available for 4137 of the baseline individuals, and the prevalence of MetS was 33.6%. Among them, we excluded 1966 individuals without plasma DHPPA data, and 97 individuals with severe psychological disorders, physical disabilities, cardiovascular disease, Alzheimer's disease, dementia, tuberculosis, AIDS, or other communicable diseases. Finally, 667 members classified as MetS were included in the analyses. Each MetS case was matched with 1 control individual. Control individuals were randomly selected among participants without MetS in the TJEZ study at baseline, and matching variables including sex and age (±3 years). The flow chart of participant recruitment and case-control selection is shown in Additional file 1: Figure S1. Ethics approval was granted by the Ethics and Human Subject Committee of Tongji Medical College. All enrolled participants gave written informed consent.

Data collection

Demographic characteristics and medical history were collected at baseline using standardized, self-administered questionnaires. Lifestyle factors including smoking habits, alcohol drinking status, and physical activity were also obtained via questionnaires. Individuals who reported smoking ≥ 1 cigarette/day over the past 6 months were considered as smokers, otherwise, they were defined as nonsmokers. Alcohol drinking status was classified as current drinking (≥ 1 time/week over the previous 6 months) and nondrinking. Physical activity was defined as regular exercise for at least 60 min per week over the previous 6 months. Education level was grouped into three categories: none or elementary school, middle school, and high school or college. Physical examinations including anthropometric measurements were performed by trained nurses. Body weight and standing height were measured in light indoor clothing and without shoes. Waist circumference were measured at the narrowest level over light clothing, using an upstretched tape meter, and measurements were recorded to the nearest 0.1 cm. Body mass index (BMI) was calculated by dividing the weight in kilograms by the square of the height in meters. Resting blood pressure were measured in a seated position after 5 minutes of seated rest. A standard mercury sphygmomanometer was used for obtaining measurements.

After overnight fasting, venous blood samples were collected from all participants at enrollment. All samples were separated for plasma within 1 hour and stored in -80℃ freezers until laboratory analysis. Fasting plasma triglycerides, total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), and glucose were obtained with automated bioassays.

MetS case definition

MetS was characterized according to the harmonized criteria as the presence of at least three of the following risk factors (24): (1) central obesity: waist circumference ≥ 90 cm in men or ≥ 80 cm in women (following Chinese-specific cutoffs for abdominal obesity defined by the International Diabetes Federation) (25); (2) Hypertriglyceridemia: triglycerides ≥ 1.70 mmol/L; (3) Low levels of HDL-C: HDL-C < 1.03 mmol/L in men or < 1.30 mmol/L in women; (4) High blood pressure: blood pressure ≥ 130/85 mmHg or use of antihypertensive medication; (5) High fasting glucose: ≥ 5.56 mmol/L or current use of antidiabetic medication or self-reported history of diabetes.

Measurement of plasma DHPPA concentrations

Plasma DHPPA was measured by high-performance liquid chromatography-tandem mass spectroscopy (LC-MS/MS) (AB Sciex QTRAP 4500, Applied Biosystems, Foster City, CA). Samples from cases and controls were randomly assayed. Prior to analysis, all samples were thawed, mixed thoroughly by vortex. Then, 50 μL of plasma sample was spiked with the internal standard (1 ng of syringic acid). The sample was hydrolyzed overnight at 37℃ with β-glucuronidase/sulfatase and then extracted with acetonitrile. After centrifugation, we collected the supernatant and repeated the procedure once. The combined supernatants were evaporated to dryness under vacuum at 35℃ and reconstituted with 50 μL solvent (acetonitrile/water, 1:1, vol/vol). After centrifugation 20,238 ´ *g* at 4℃ for 5 min, 5 μL of the supernatant was analyzed with LC-MS/MS. Four replicate quality control samples were analyzed in each batch (n = 48). Both the intra- and interassay coefficients of variation were < 10%.

Statistical analysis

General characteristics were presented as means ± standard deviations for parametrically distributed variables, medians (interquartile ranges) for nonparametrically distributed variables, and percentage for categorical variables. Differences in descriptive characteristics between the case and control groups were explored using Student *t* test (normal distribution) or Mann-Whitney U test (non-normal distribution) for continuous variables; for categorical variables, the chi-square test was used. Plasma DHPPA concentrations were considered as continuous variable and categorized into quartiles according to their distribution among the controls (quartile 1, < 7.74 nmol/L, quartile 2, 7.75-12.30 nmol/L, quartile 3, 12.31-20.97 nmol/L, quartile 4, ≥ 20.98 nmol/L). Logistic regression models were used to estimate odds ratios (ORs) and 95% standard deviations (CIs) of MetS in relation to plasma DHPPA concentrations. The regression models were adjusted for age, sex, BMI, current smoking, current alcohol drinking, physical activity and education level. Linear trend *P*-values were estimated by modeling the median value of each plasma DHPPA category as a continuous variable. To further examined the the potential nonlinear relation between plasma DHPPA and MetS, we used a cubic spline regression model with 4 knots at the 20th, 40th, 60th, and 80th percentiles of plasma DHPPA concentrations.

Given that plasma alkylresorcinols-precursor of DHPPA-are transported in lipoprotein (16), the variations in carrier lipoprotein concentrations might result in their difference in plasma DHPPA concentrations. Hence, a new variable-plasma DHPPA / (total cholesterol + triglycerides) index-was generated to adjust for variations in the concentrations of carrier lipoproteins. Similar to plasma DHPPA concentrations, plasma DHPPA / (total cholesterol + triglycerides) index was considered as a continuous variable and categorized into quartiles according to its distribution among the controls (quartile 1, < 1.27 nmol/mmol, quartile 2, 1.28-2.14 nmol/mmol, quartile 3, 2.15-3.62 nmol/mmol, quartile 4, ≥ 3.63 nmol/mmol). Logistic regression models were fit to estimate odds ratios (ORs) and 95% standard deviations (CIs) of MetS in relation to plasma DHPPA / (total cholesterol + triglycerides). The regression models were adjusted for age, sex, BMI, current smoking status, current alcohol drinking status, physical activity and education level. Linear trend P-values were estimated by modeling the median value of each plasma DHPPA / (total cholesterol + triglycerides) category as a continuous variable. To further examined the potential nonlinear relation between plasma DHPPA / (total cholesterol + triglycerides) and MetS, we used a cubic spline regression model with 4 knots at the 20th, 40th, 60th, and 80th percentiles of plasma DHPPA / (total cholesterol + triglycerides) index.

To estimate the consistency of the DHPPA-MetS association according to participant characteristics, we conducted stratified analyses by sex, age (<50 and ≥50 years), BMI (<24 and ≥24 kg/m^2), current smoking status (yes or no), current drinking status (yes or no) and physical activity (yes or no). Interactions between plasma DHPPA categories and these confounding factors on ORs of MetS were tested using likelihood ratio tests, comparing models with and without multiplicative interaction terms. Statistical analyses were performed with SPSS 23.0 software (SPSS, Inc.) and Stata/SE 12.0 software (StataCorp LP). $P < 0.05$ was considered significant.

Results

The general characteristics of the study groups are shown in Table 1. Demographic characteristics, lifestyle factors and education level were comparable between the MetS case and control groups. As expected, individuals with MetS had higher waist circumference and blood pressure, higher levels of fasting plasma glucose, and more adverse lipid profiles (lower HDL-C and higher triglycerides levels) than those without MetS. Plasma DHPPA concentrations were lower in MetS cases than in controls (10.43 nmol/L [6.70-17.24] vs. 12.35 nmol/L [7.74–20.97], $P < 0.001$). Similarly, plasma DHPPA / (total cholesterol + triglyceride) indexes were significantly lower in MetS cases than in controls (1.54 nmol/mmol [0.92–2.48] vs. 2.13 nmol/mmol [1.28–3.62], $P < 0.001$).

Table 1

Characteristics of MetS cases and controls [a]

Parameters	Cases (n = 667)	Controls (n = 667)	*P* value
Male, n (%)	411 (61.6)	411 (61.6)	1.000
Age (years)	56.74 (9.80)	56.36 (10.04)	0.475
Body mass index (kg/m^2)	25.79 (2.97)	22.80 (2.73)	< 0.001
SBP (mmHg)	145.23 (21.38)	133.72 (18.88)	< 0.001
DBP (mmHg)	83.20 (11.93)	77.36 (10.48)	< 0.001
Waist circumference (cm)	90.02 (7.87)	80.47 (7.85)	< 0.001
Triglycerides (mmol/L)	1.87 (1.40–2.48)	1.13 (0.81–1.47)	< 0.001
Total cholesterol (mmol/L)	4.94 (4.29–5.63)	4.69 (4.10–5.39)	< 0.001
HDL-C (mmol/L)	1.12 (0.93–1.33)	1.42 (1.18–1.68)	< 0.001
LDL-C (mmol/L)	2.82 (2.30–3.36)	2.63 (2.15–3.19)	< 0.001
Fasting plasma glucose (mmol/L)	6.36 (1.62)	5.65 (0.89)	< 0.001
Current smoker, n (%)	193 (28.9)	220 (33.0)	0.110
Current drinker, n (%)	195 (29.2)	211 (31.6)	0.341
Vigorous activity, n (%)	265 (39.7)	278 (41.7)	0.469
Educational level, n (%)			0.175
None or elementary school	186 (27.9)	162 (24.3)	
Middle school	294 (44.1)	291 (43.6)	
High school or college	187 (28.0)	214 (32.1)	

[a] Data are presented as n (%) for categorical data, means (standard deviations) for parametrically distributed data, or medians (interquartile ranges) for nonparametrically distributed data.
Abbreviations: DBP, diastolic blood pressure; DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure.

Parameters	Cases (n = 667)	Controls (n = 667)	*P* value
DHPPA (nmol/L)	10.43 (6.70-17.24)	12.35 (7.74–20.97)	< 0.001
DHPPA / (total cholesterol + triglycerides) nmol/mmol	1.54 (0.92–2.48)	2.14 (1.28–3.62)	< 0.001

[a] Data are presented as n (%) for categorical data, means (standard deviations) for parametrically distributed data, or medians (interquartile ranges) for nonparametrically distributed data. Abbreviations: DBP, diastolic blood pressure; DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; SBP, systolic blood pressure.

Higher plasma DHPPA concentrations were associated with lower odds of MetS (Table 2). After adjustment for age, sex and BMI, the ORs (95% CIs) for quartiles 1 through 4, respectively, of plasma DHPPA concentrations were 1 (referent), 0.86 (0.58–1.27), 0.78 (0.53–1.15), and 0.60 (0.40–0.90) for MetS. Further adjustment for lifestyle factors and education level did not change the association substantially. After further adjustments for smoking, drinking, physical activity and education level, the ORs (95% CIs) of MetS across increasing quartiles of plasma DHPPA concentrations were 1 (referent), 0.86 (0.58–1.26), 0.77 (0.52–1.15), and 0.59 (0.39–0.89), respectively. Similarly, plasma DHPPA / (cholesterol + triglycerides) indexes also were inversely associated with odds of MetS (see Additional file 2. Table S1). In addition, we further conducted analyses stratified by sex, age, BMI, smoking status, alcohol drinking status and physical activity (Table 3). The inverse relationship between plasma DHPPA and MetS was consistently observed in all subgroups, and tests for multiplicative interaction were not statistically significant in this study ($P > 0.05$).

Table 2

Associations of plasma DHPPA concentration with MetS [a]

Variables	Quartile of plasma DHPPA concentrations (nmol/L)				*P* for trend [b]
	Q1(referent), < 7.74	Q2, 7.75–12.30	Q3, 12.31–20.97	Q4, ≥ 20.98	
MetS					
No. of cases/controls, n/n	213/169	176/164	152/169	126/165	
Crude OR	1	0.84 (0.63–1.13)	0.71 (0.53–0.96)	0.60 (0.44–0.82)	0.001
Model 1 [c]	1	0.86 (0.58–1.27)	0.78 (0.53–1.15)	0.60 (0.40–0.90)	0.013
Model 2 [d]	1	0.86 (0.58–1.26)	0.77 (0.52–1.15)	0.59 (0.39–0.89)	0.012

[a] Data are odds ratios (95% confidence intervals). Odds ratios (95% confidence intervals) for MetS were estimated by conditional logistic regression. Abbreviations: DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; MetS, metabolic syndrome; OR, odds ratio; Q, quartile.

[b] Tests for linear trend were conducted by using the median value for each quartile and treating it as a continuous variable in the logistic regression.

[c] Adjusted for sex, age (years) and body mass index (kg/m^2).

[d] Additionally adjusted for smoking (current, former, and never), drinking (current, former, and never), physical activity (yes or no) and educational level (none or elementary school, middle school, and high school or college).

Table 3
Stratified analyses of MetS risk and plasma DHPPA concentrations by sex, age, body mass index, current smoking status, current alcohol consumption, and physical activity [a]

Groups	Quartile of plasma DHPPA concentrations (nmol/L)				*P* value for interaction
	Q1(referent), < 7.74	Q2, 7.75–12.30	Q3, 12.31–20.97	Q4, ≥ 20.98	
Sex					0.497
Male (822)	1	0.84 (0.54–1.30)	0.71 (0.45–1.11)	0.71 (0.45–1.13)	
Female (512)	1	0.70 (0.41–1.19)	0.67 (0.39–1.14)	0.51 (0.29–0.89)	
Age, years					0.121
< 50 (371)	1	0.46 (0.24–0.89)	0.44 (0.22–0.86)	0.39 (0.19–0.80)	
≥ 50 (963)	1	0.97 (0.65–1.45)	0.85 (0.57–1.26)	0.75 (0.50–1.14)	
Body mass index, kg/m^2					0.538
< 24 (650)	1	1.02 (0.62–1.67)	0.78 (0.48–1.27)	0.67 (0.39–1.14)	
≥ 24 (684)	1	0.59 (0.37–0.95)	0.58 (0.35–0.94)	0.58 (0.35–0.94)	
Current smoking					0.442
Yes (413)	1	0.75 (0.40–1.38)	0.62 (0.33–1.19)	0.52 (0.27–1.01)	
No (921)	1	0.79 (0.53–1.17)	0.72 (0.48–1.07)	0.68 (0.45–1.03)	
Current drinking					0.929
Yes (406)	1	0.59 (0.31–1.10)	0.59 (0.31–1.10)	0.61 (0.30–1.23)	
No (928)	1	0.87 (0.59–1.31)	0.74 (0.49–1.11)	0.63 (0.42–0.96)	
Physical activity					0.468

[a] Data are odds ratios (95% confidence intervals). The multivariate model was adjusted for sex, age (years), body mass index (kg/m^2), smoking (yes or no), drinking (yes or no), physical activity (yes or no) and educational level (none or elementary school, middle school, and high school or college). Abbreviations: DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; MetS, metabolic syndrome; Q, quartile.

Groups	Quartile of plasma DHPPA concentrations (nmol/L)				*P* value for interaction
	Q1(referent), < 7.74	Q2, 7.75–12.30	Q3, 12.31–20.97	Q4, ≥ 20.98	
Yes (543)	1	0.64 (0.38–1.08)	0.77 (0.45–1.34)	0.47 (0.28–0.82)	
No (791)	1	0.92 (0.59–1.44)	0.65 (0.42–1.01)	0.78 (0.49–1.25)	

[a] Data are odds ratios (95% confidence intervals). The multivariate model was adjusted for sex, age (years), body mass index (kg/m^2), smoking (yes or no), drinking (yes or no), physical activity (yes or no) and educational level (none or elementary school, middle school, and high school or college). Abbreviations: DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; MetS, metabolic syndrome; Q, quartile.

In spline regression models, the OR of MetS decreased significantly with increasing plasma DHPPA at less than 18.99 nmol/L, followed by an approximate plateau (Fig. 1). The nonlinear spline terms were statistically significant ($P = 0.024$), suggesting a potential nonlinear relationship between plasma DHPPA concentrations and MetS. The cubic spline analyses also revealed a nonlinear inverse relationship between plasma DHPPA / (cholesterol + triglycerides) index and MetS, with a drastically decrease of MetS risk at less than 2.84 nmol/mmol but levelled off after that (see Additional file 3. Figure S2).

Discussion

In this matched case-control study, we observed a nonlinear inverse association between plasma DHPPA concentration and MetS risk. The association did not change materially after adjustment for several confounding factors. Additionally, the association remained generally consistent across different subgroups, suggesting a robust relationship between plasma DHPPA and MetS. As far as we are aware, this is the first study to examine the association between plasma DHPPA, a biomarker of whole-grain wheat and rye intake, and risk of MetS.

Our study revealed that higher plasma DHPPA concentration was associated with lower OR of MetS, which also confirmed previous epidemiological studies used dietary recording methods to estimate whole-grain intake (26–29). In the Framingham Offspring Cohort, whole-grain intake assessed via 126-item Food frequency questionnaires (FFQs) was inversely related with the prevalence of MetS (26). Sahyoun et al also found that whole-grain intake, which was estimated by using 3-d food records, was favorably associated with the risk of MetS (29). However, Lutsey et al reported no association between whole-grain intake, which assessed through FFQs, and the risk of MetS among an America population (30). Perhaps because the FFQs used in this study containing only 66 items, which might not effectively differentiate whole-grain from refine-grain foods in the food list. Thus, whole grains might be misclassified and then the measurement errors might occur. Moreover, most dietary recording methods estimated overall whole-grain intake instead of each type of whole-grain intake, and different types of whole grains have different nutrient composition (8), which may be differentially related to human health.

The main source of whole grains is yeast breads, popcorn, and ready-to-eat breakfast cereals in America (31), brown rice and whole-wheat flour in China (32), and whole-grain bread in Scandinavian countries (33). Findings from a previous study indicated that intake of whole-grain wheat was associated with a reduced risk of colorectal cancer, while other types of whole-grain intake were not (34). Therefore, it is important to distinguish between whole grains when investigating their health-promoting effects. Compared with dietary recording methods which usually assess overall whole-grain intake, our study measuring plasma DHPPA as a biomarker of whole-grain wheat and rye intake seems to be more objective and specific.

Given that plasma alkylresorcinols are transported in plasma lipoproteins, the variations in carrier lipoprotein concentrations among individuals might affect their variations in plasma DHPPA concentrations (16). To adjust for the effect of lipoproteins concentrations on the DHPPA-MetS relationship, plasma DHPPA are expressed relative to plasma total cholesterol and triglycerides. Similar with the DHPPA-MetS association, an inverse association between plasma DHPPA / (total cholesterol and triglycerides) index and MetS was observed in our study. The result further confirmed the inverse association between plasma DHPPA and MetS risk.

Several potential mechanisms might explain the inverse association between plasma DHPPA and MetS. As whole grain intake is often companied with many other health behaviors, whole grain intake may be just a lifestyle marker. However, the beneficial effect of whole grain on MetS was not essentially altered by adjustment for known risk factors. Additionally, the inverse association was consistent among individuals with a greater BMI ($\geq$ 24 kg/m^2), and among nondrinkers and individuals with higher physical activity levels. It is more likely that the food compounds and biologically active nutrients in whole grains, such as dietary fiber, minerals, vitamins, and phytochemicals, act directly or indirectly to enhance the beneficial effects on MetS risk. A recent meta-analysis found that dietary fiber intervention lead to a higher abundance of fecal *Bifidobacterium* and *Lactobacillus* spp. (35), which has been associated with attenuation of metabolic syndrome (36). Moreover, findings from observational studies and clinical trials indicated that increased consumption of vitamin E, magnesium, and potassium was associated with lower risk of MetS and its components (37–41). The protective effects of whole grains on MetS might be partially explain by these nutrients present in whole grains. Other biologically plausible mechanisms to explain the beneficial effects of whole grain intake on MetS include its effects inflammatory factors, and oxidative stress (42, 43).

We observed a nonlinear inverse association between plasma DHPPA and MetS in the present study; in the spline regression model, a reduced curve was observed at the lower range of plasma DHPPA concentration, then followed by an approximate plateau. A possible explanation for this effect is that the increased benefits of whole-grain intake may occur among population with insufficient whole-grain intake, and increasing whole-grain intake might not bring further benefits to population with adequate intake. Further studies are needed to illuminate the potential mechanism and to confirm our findings. Persons with MetS are at increased risk of cardiovascular disease and diabetes, thus our findings were consistent with those from two previous meta-analyses that also revealed nonlinear inverse associations

between whole-grain intake and stroke and diabetes, with most risk reduced at lower range of whole-grain intake (11, 44).

Our study has several strengths. Firstly, we objectively determined concentration of plasma DHPPA, which appears to be a biomarker of whole-grain wheat and rye intake and has been used in several studies to assess whole-grain wheat and rye intake (19, 22). Compared with dietary recording methods, the measurement of plasma DHPPA concentration seems to be more objective and independent. Secondly, the matched case-control study design minimized the influence of key confounding factors. Thirdly, the use of a cubic spline regression model enabled us to explore the nonlinear relation between plasma DHPPA and MetS.

Despite these strengths, several limitations should also be acknowledged. The case-control study design did not allow us to establish a causal relationship. Also, because of the case-control design, we cannot exclude the likelihood of recall and selection biases. Moreover, considering that there is limited data on dose-response association between plasma DHPPA and estimated whole-grain wheat and rye intake and the lack of dietary information in our study, it was difficult to compare our results with findings from previous studies assessed whole-grain intake using dietary recording methods. Finally, plasma DHPPA is only a biomarker of whole-grain wheat and rye intake, meaning that intakes of other whole grains such as brown rice and corn, which are also consumed in this population, could not be assessed using this biomarker.

Conclusions

Our findings implied that higher concentrations of plasma DHPPA, reflecting high whole-grain wheat and rye intake, were associated with lower risk of MetS. Given that the MetS is an identifiable and potentially modifiable risk state for both type 2 diabetes and cardiovascular disease, increasing whole-grain intake may reduce the potential untoward effects of carbohydrate on risk of these diseases. Further prospective cohorts are required to confirmed our findings.

List Of Abbreviations

BMI, body mass index; CI, confidence interval; DHBA, 3,5-dihydroxybenozoic acid; DHPPA, 3-(3,5-dihydroxyphenyl)-1-propanoic acid; FFQ, food frequency questionnaire; HDL-C, high-density lipoprotein cholesterol; LC-MS/MS, high-performance liquid chromatography-tandem mass spectroscopy; LDL-C, low-density lipoprotein cholesterol; MetS, metabolic syndrome; OR, odds ratio; TJEZ, Tongji-Ezhou.

Declarations

Ethics approval and consent to participate

Approval of the Ethics and Human Subject Committee of Tongji Medical College was obtained before the start of the work.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Z.L., L.L., and T.S. designed the study. Z.L. analyzed the data and wrote the manuscript. X.M., Q.W., H.L., Y.L., Q.L., J.Y., X.P., Y.H. and X.L. conducted the experiments and performed the data collection. Z.S., G.L., C.X., J.C., and W.Y. commented on drafts and edited the manuscript. L.L. and T.S. had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final manuscript.

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Supplementary information

Additional file 1: Figure S1. Flowchart of the participant recruitment and case-control selection.

Additional file 2: Table S1. Associations of plasma DHPPA / (total cholesterol + triglycerides) index with MetS.

Additional file 3: Figure S2. Association of plasma DHPPA / (total cholesterol + triglycerides) with metabolic syndrome incidence.

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Figures

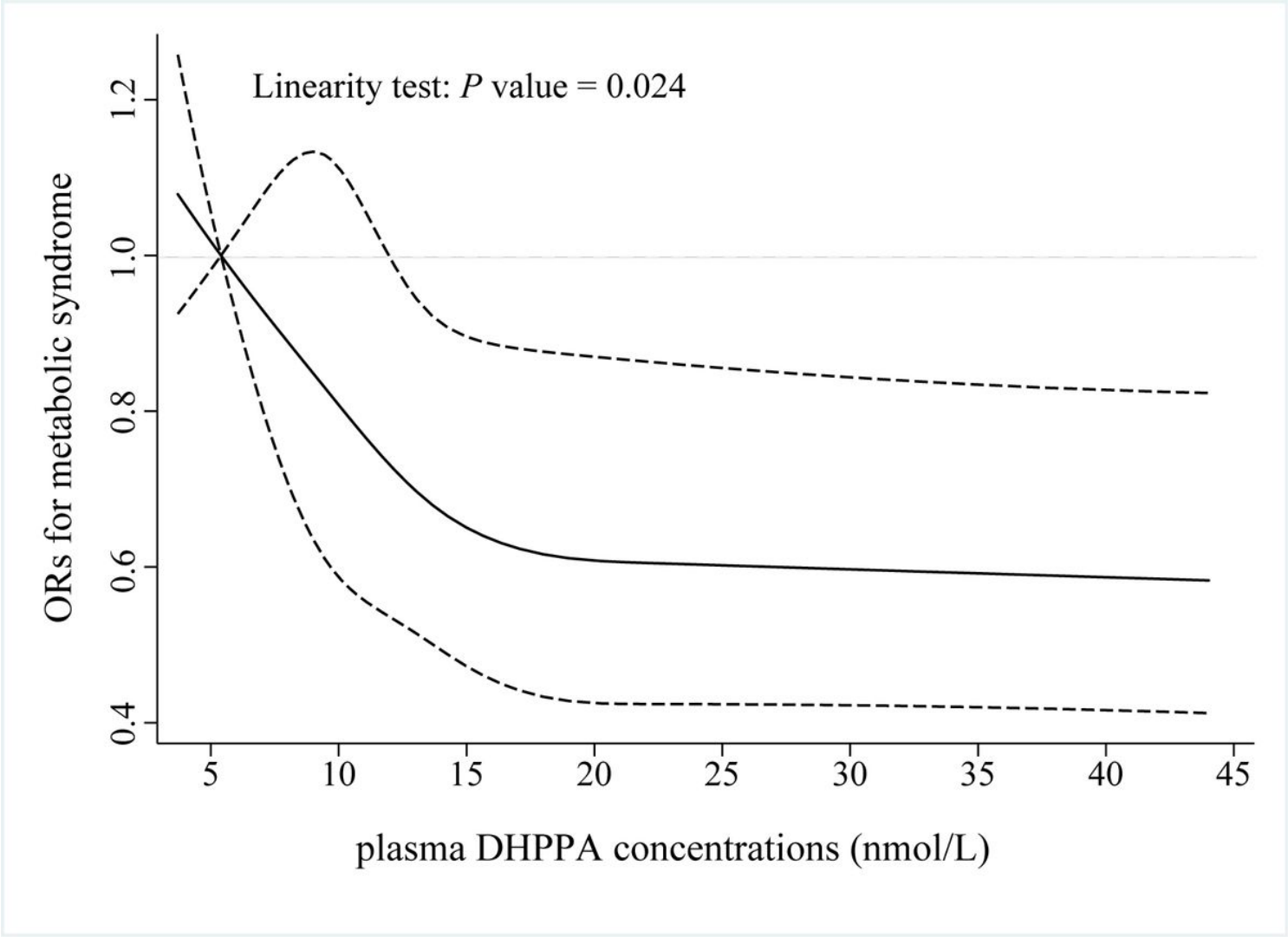

Figure 1

Association of plasma DHPPA concentrations with metabolic syndrome incidence. The restricted cubic spline regression was performed with the use of four knots (20th, 40th, 60th, and 80th percentiles of plasma DHPPA concentrations), and adjusted for sex, age, body mass index, smoking status, alcohol drinking status, physical activity, and education level. Solid lines represent odds ratios and dashed lines represent 95% confidence intervals. DHPPA, 3-(3, 5-dihydroxyphenyl)-1-propanoic acid; OR, odds ratio.

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