RESEARCH ARTICLE

Plasma phospholipids *n*-3 polyunsaturated fatty acid is associated with metabolic syndrome

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The relationship between *n*-3 PUFA and metabolic syndrome (MS) is not clear. The aim of this study was to examine relationships between plasma phospholipids (PL) *n*-3 PUFA and MS in Chinese subjects. Nine hundred and twenty-nine subjects were recruited in Hangzhou, China. Two hundred and ten (183 males, 27 females) with MS and 719 (545 males, 174 females) healthy subjects were identified in this cross-sectional study. The prevalence of MS in females (24.56%) was significantly higher than that in males (10.04%) in this population. Total PUFA ($p < 0.001$), *n*-3 PUFA ($p < 0.001$), and *n*-3:*n*-6 ($p < 0.001$) were significantly lower in MS subjects compared to healthy subjects. Plasma phospholipid (PL), *n*-3 PUFA was significantly inversely associated with MS ($p = 0.013$). In addition, subjects with high levels of PL total fatty acids (FA) had a more than threefold higher likelihood of MS (OR = 3.44, 95% CI = 1.60–7.39) than the subjects with low levels of PL total FA. Our results suggest that plasma PL *n*-3 PUFA was significantly inversely associated with MS, while high total FA were positively associated with MS in Chinese.

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1 Introduction

The metabolic syndrome (MS) is a common metabolic disorder that is related to the increasing prevalence of obesity [1]. The MS classically refers to the combination of three or more different components, including abdominal obesity, hypertension, dyslipidaemia and impaired glucose tolerance [2, 3]. Over the past two decades, a striking increase in the number of people with MS has taken place on a worldwide basis, but its prevalence differs among ethnic groups [4]. According to a cross-sectional survey in China, the prevalence of MS was 9.8% in men and 17.8% in women. This large proportion of MS has become an important public health problem in China [5]. Therefore, there is an urgent need for strategies to prevent the emerging global epidemic [6, 7].

The increase of MS is associated with the global epidemic of obesity and diabetes [6], increased serum uric acid concentration [8]. While the mechanisms responsible for the onset of the MS have not been totally clarified, they certainly involve a combination of genetic and lifestyle factors. Although diet can affect the individual components of MS, few studies have evaluated the role of fatty acids (FA) on the risk of developing MS [3, 9–11]. Several studies have shown that plasma FA composition predicts the long-term development of MS [12, 13] and is related to components of MS [3, 14, 15]. Studies also suggested a role of dietary fat quality in the development of MS [12].

Several features of MS may be improved by nutritional manipulations, including increased dietary intake of *n*-3 PUFA [3, 15, 16], for example, *n*-3 PUFA has beneficial effects on improving lipid profiles [17] and improving insulin resistance [15, 17, 18]. Animal studies have also suggested that *n*-3

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Abbreviation: FA, fatty acids; **MS,** metabolic syndrome; **PL,** phospholipids; **SFA,** saturated fatty acids

PUFA reduce or prevent insulin resistance [19]. However, data from human studies are conflicting, with some studies suggesting benefit [3, 15, 20, 21], and others reporting no effect [22, 23]. An intervention study reported that increasing the *n*-3 PUFA content of a high saturated fatty acid (SFA) oral fat tolerance test did not acutely change postprandial TG or inflammatory responses in men with MS [11]. Therefore, understanding of the relationship between *n*-3 PUFA and MS remains limited.

To better understand the relationship between plasma phospholipids (PL) *n*-3 PUFA levels and MS in Chinese subjects, we conducted a cross-sectional study to compare the plasma PL FA (as biomarker of dietary intake of FA) in those with and without MS, and to investigate the relationship between plasma PL FA composition and MS in Chinese.

2 Research design and method

2.1 Study population

The study protocol was approved by the Ethics Committee, College of Biosystem Engineering and Food Science, Zhejiang University, China. Nine hundred and twenty-nine subjects were recruited through a health check program in the Zhejiang Hospital during the period of March 2006 through October 2006. All the subjects gave their written consent prior to participation in this study.

2.2 Definition of metabolic syndrome

MS was defined according to the updated National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) criteria [24], that is, the presence of at least three of the following abnormalities: (i) BMI $\geq 25\,kg/m^2$; (ii) triglycerides ≥ 1.7 mmol/L; (iii) HDL-*C* < 1.03 mmol/L in men or < 1.30 mmol/L in women; (iv) blood pressure $\geq 130/85$ mm Hg; (v) fasting plasma glucose ≥ 5.6 mmol/L.

2.3 Blood collection

Subjects attended the Zhejiang Hospital in the morning following an overnight fast. Subjects were allowed to sit relaxed for 10 min, and then venous blood was taken in plain and EDTA vacuum tubes with 21-gauge needles. Plasma samples were prepared quickly after the blood was drawn and the blood was stored at $-20^{\circ}C$ until analysis.

2.4 Laboratory measurements

Plasma lipids were determined on an autoanalyser (Olympus AU2700, Tokyo, Japan) *via* commercially available kits (Olympus). The total lipid content of the plasma was extracted with solvents, the PL fraction was separated by TLC and the fatty acid methyl esters were prepared and separated by gas-liquid chromatography as described previously [25].

2.5 Statistical analysis

Data analyses were performed using SAS for Windows, version 9.1 (SAS Institute). All continuous variables were examined for normal distribution. Men and women were analyzed together to ensure an adequate statistical power. We categorized plasma PL FA into quantiles (median, quintile (*Q*) and tertile (*T*)) using SAS program: PROC RANK. Differences between the two groups for each outcome were analyzed using ANOVA. The associations between plasma PL fatty acid composition and MS were determined by a logistical regression, controlling for potential confounding factors. The population medians for plasma PL FA such as total SFA, MUFA, and PUFA, and *n*-3:*n*-6 were used as cutoffs to dichotomize these variables. All data are expressed as mean $\pm$ SD. Differences between groups were considered to be statistically significant at $p < 0.05$.

3 Results

The characteristics of the participants are shown in Table 1. In the combined population (men and women), we identified 210 MS patients (Table 2). We observed a significantly different prevalence of MS in males and females ($p = 0.001$) with higher prevalence of MS in females (24.56%) compared to males (10.04%) in this population (Fig. 1).

Plasma total FA ($p = 0.025$) and MUFA ($p = 0.038$) were significantly higher in subjects with MS than in healthy people, while total PUFA ($p < 0.001$), *n*-3 PUFA ($p < 0.001$), *n*-6 PUFA ($p < 0.001$) and *n*-3:*n*-6 ($p < 0.001$) were significantly lower in MS compared to healthy people. A logistical regression showed that *n*-3 PUFA, total PUFA, *n*-3:*n*-6, 22:6*n*-3 and 22:5*n*-3 were inversely associated with MS. The risk of MS was lower with higher quintiles of plasma PL *n*-3 PUFA ($p = 0.013$) (Figs. 2 and 3).

Plasma PL total PUFA (OR = 0.34, 95% CI = 0.10–1.16), *n*-3 PUFA (OR = 0.11, 95% CI = 0.04–0.29) and *n*-3:*n*-6 (OR = 0.28, 95% CI = 0.08–0.95) were significantly associated with MS respectively.

In addition, we observed that PL total FA were significantly associated with MS ($p = 0.001$). Subjects with high levels of PL total FA had a more than threefold higher likelihood of MS (OR = 3.44, 95% CI = 1.60–7.39) than the subjects with low levels of total FA (Table 2). The risk of MS was higher increased with higher quintiles or tertiles of plasma PL total FA ($p = 0.034$) (Figs. 4 and 5).

Table 1. Characteristics of participants according to MS

Statistic variable	Normal F/M = 174/545	MS F/M = 27/183	*p*-Value
Age (year)	43.5±8.4	47.7±6.0	0.091
BMI (kg/m^2)	22.9±2.4	25.9±2.1	0.047
Plasma TG (mmol/L)	1.33±0.98	2.33±1.13	0.021
Plasma TC (mmol/L)	1.13±0.93	5.17±1.04	<0.001
Plasma HDL-C (mmol/L)	1.45±0.33	1.09±0.26	0.110
Plasma LDL-C (mmol/L)	2.77±0.84	3.21±1.00	0.087
Plasma glucose (mmol/L)	4.05±1.52	7.03±2.68	0.014
SBP (mm Hg)	124.2±9.3	137.7±10.8	0.038
DBP (mm Hg)	78.7±9.9	88.4±7.4	0.041

Data are mean±SD. We applied *t*-test to compare mean. F/M: number of female/male. TC: total cholesterol, TG: Total triglyceride, HDL-C: High-density cholesterol, LDL-C: Low-density cholesterol, SBP: Systolic blood pressure, DBP: Diastolic blood pressure.

Table 2. OR and 95% confidence interval (CI) for MS among plasma PL FA in logistic regression models

Plasma PL FA % of PL total FA	Normal F/M = 174/545	MS F/M = 27/183	*p*-Value	Controlled for age and sex	
				OR 95% CI	*p*-Value
18:3*n*-3	0.49±0.50	0.54±0.50	0.312	1.21 (0.55–2.65)	0.624
20:4*n*-6	0.53±0.50	0.33±0.47	<0.001	0.51 (0.19–1.36)	0.184
20:5*n*-3	0.52±0.50	0.37±0.48	<0.001	0.94 (0.39–2.24)	0.894
22:5*n*-3	0.52±0.50	0.34±0.48	<0.001	0.43 (0.20–0.93)	0.033
22:6*n*-3	0.57±0.50	0.14±0.35	<0.001	0.26 (0.07–0.93)	0.039
Total FA	180.98±65.99	183.31±39.28	0.025	3.44 (1.60–7.39)	0.001
Total SFA	50.31±22.71	49.59±10.21	0.155	1.26 (0.58–2.71)	0.559
Total MUFA	11.95±5.55	12.66±3.00	0.038	1.12 (0.54–2.33)	0.763
Total PUFA	54.76±30.10	42.73±15.17	<0.001	0.34 (0.10–1.16)	0.044
n-3 PUFA	9.50±6.63	5.64±4.09	<0.001	0.11 (0.04–0.29)	<0.001
n-6 PUFA	44.87±24.65	36.92±11.91	<0.001	1.18 (0.46–3.07)	0.731
n-3:*n*-6	0.23±0.30	0.15±0.08	<0.001	0.28 (0.08–0.95)	0.041

All the plasma PL FA were dichotomized based on the median. Logistical regression was used to determine the OR for MS (subjects with FA below median as reference, OR = 1). In this model, MS was the dependent variable, the plasma PL FA was the independent variables adjusted for age and sex.

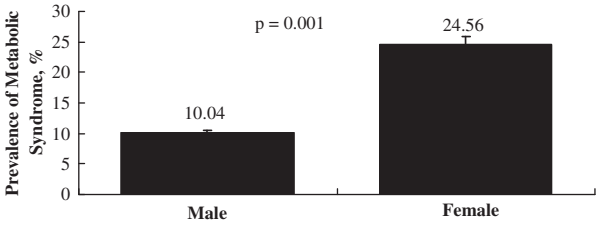

Figure 1. Prevalence of MS in male and female. Adjusted for age. The prevalence of MS was tested using chi-square test based on sex.

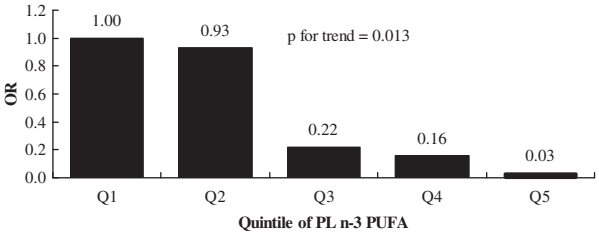

Figure 2. Plasma phospholipids *n*-3 PUFA and OR of MS by quintile (*Q*) of plasma phospholipids. PL: phospholipids; PUFA: polyunsaturated FA; OR: odds ratio. Adjusted age, sex, PL total FA. The OR of MS was tested using a logistical regression based on quintile of plasma PL *n*-3 PUFA.

We further analyzed the association between plasma PL FA and components of MS. The logistical regression showed that *n*-3 PUFA, total PUFA, and *n*-3:*n*-6 were significantly associated with the components of MS (Table 3). Plasma PL total FA were positively associated with BMI (OR = 10.58, 95% CI = 5.71–19.61), glucose (OR = 2.23, 95% CI = 1.14–4.35) and TG (OR = 3.04, 95% CI = 1.69–5.48) (Table 3). Plasma PL *n*-3 PUFA were significantly associated with BMI (OR = 0.03, 95% CI = 0.01–0.11), blood pressure (OR = 0.46, 95% CI = 0.12–0.76) and TG (OR = 0.81, 95%

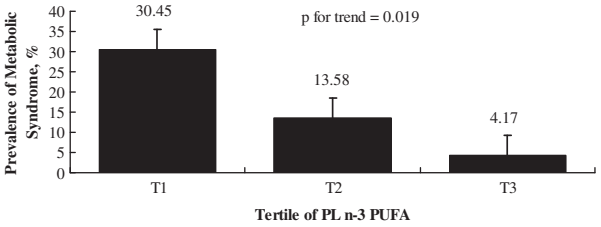

Figure 3. Prevalence of MS by tertile of plasma PL *n*-3 PUFA. Adjusted age, sex and PL total FA. The prevalence of MS was tested using chi-square test based on tertile of plasma PL *n*-3 PUFA.

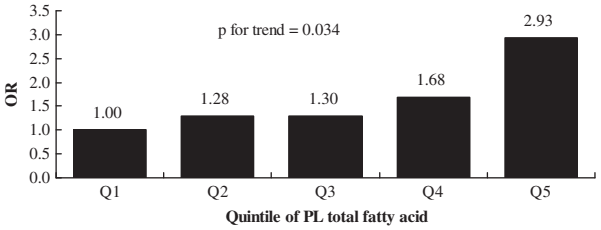

Figure 4. Phospholipids total fatty acid and OR of MS by quintile (Q) of plasma phospholipids. Adjusted age and sex. The OR of MS was tested using a logistical regression based on quintile of plasma PL total FA.

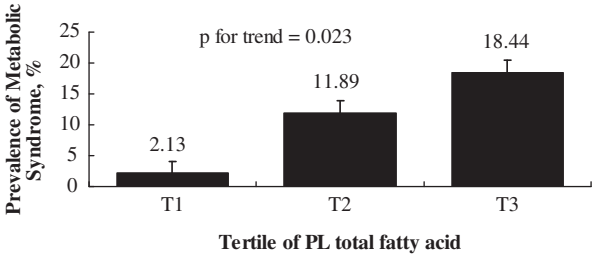

Figure 5. Prevalence of MS by tertile of plasma PL total FA. Adjusted age and sex. The prevalence of MS was tested using chi-square test based on tertile of plasma PL total FA.

CI = 0.17–1.58). We also found that *n*-3:*n*-6 was inversely associated with several MS components (Table 3).

We examined the associations between *n*-3 PUFA and MS measures by tertile of plasma PL *n*-3 PUFA. We observed that *n*-3 PUFA was significantly associated with BMI, plasma lipids and fasting glucose. BMI, low-density lipoprotein cholesterol (LDL-C), diastolic blood pressure (DBP) and glucose were lower with higher tertiles of plasma PL *n*-3 PUFA (Table 4).

4 Discussion

In this study, we found that PL total fatty acid and MUFA were significantly higher in people with MS than in healthy people, whereas total PUFA, *n*-3 PUFA, *n*-6 PUFA and

Table 3. OR and 95% confidence interval (CI) for MS components among plasma PL FA in logistic regression models

Plasma PL FA	High BMI		High glucose		High blood pressure		High TG	
(% of PL total FA)	OR 95% CI	*p*-Value	OR 95% CI	*p*-Value	OR 95% CI	*p*-Value	OR 95% CI	*p*-Value
18:3*n*-3	3.45 (1.04–11.46)	0.042	1.04 (0.52–2.07)	0.919	1.71 (0.72–4.07)	0.229	1.07 (0.63–1.83)	0.804
20:4*n*-6	0.23 (0.09–0.55)	0.001	1.07 (0.45–2.56)	0.878	0.23 (0.08–0.64)	0.005	0.95 (0.46–1.97)	0.892
20:5*n*-3	2.15 (0.52–8.85)	0.287	0.66 (0.31–1.40)	0.281	0.20 (0.04–0.97)	0.046	1.24 (0.72–2.14)	0.443
22:5*n*-3	0.26 (0.09–0.73)	0.010	1.22 (0.57–2.61)	0.616	0.84 (0.37–1.91)	0.679	0.63 (0.36–1.11)	0.109
22:6*n*-3	0. 32 (0.38–1.62)	0.098	0.55 (0.20–1.47)	0.230	0.33 (0.13–0.81)	0.032	2.55 (1.11–5.84)	0.027
Total FA	10.58 (5.71–19.61)	$<$0.001	2.23 (1.14–4.35)	0.018	1.48 (0.74–2.97)	0.264	3.04 (1.69–5.48)	$<$0.001
Total SFA	0.41 (0.17–0.97)	0.084	0.66 (0.34–1.28)	0.225	0.77 (0.38–1.53)	0.458	2.22 (1.23–4.04)	0.008
Total MUFA	1.51 (0.58–3.91	0.396	1.07 (0.56–2.06)	0.823	0.32 (0.15–0.72)	0.005	1.39 (0.82–2.34)	0.032
Total PUFA	0.42 (0.13–1.34)	0.146	0.38 (0.18–0.81)	0.012	0.15 (0.06–0.35)	$<$0.001	1.74 (1.00–3.04)	0.047
Total *n*-3 PUFA	0.03 (0.01–0.11)	$<$0.001	0.56 (0.26–1.19)	0.132	0.46 (0.12–0.76)	0.013	0.81 (0.17–1.58)	0.029
Total *n*-6 PUFA	0.25 (0.08–0.75)	0.013	0.44 (0.21–0.92)	0.029	0.18 (0.08–0.38)	$<$0.001	1.93 (1.09–3.42)	0.024
n-3:*n*-6	0.34 (0.15–0.77)	0.009	0.39 (0.19–0.81)	0.012	0.43 (0.14–0.89)	0.043	1.02 (0.56–1.88)	0.924

All the plasma PL FA were dichotomized based on the median. Logistical regression was used to determine the OR for MS (subjects with fatty acids below median as reference, OR = 1). In this model, MS was the dependent variable, the plasma PL fatty acids was the independent variables adjusted for age and sex.

Table 4. Characteristics of the study population by tertile (*T*) of plasma PL *n*-3 PUFA

Number of subjects	Tertile (*T*) of plasma PL *n*-3 PUFA			*p* for trend
	*T*1 264	*T*2 258	*T*3 253	
Age (year)	45.93 ± 11.53	46.93 ± 14.25	43.94 ± 13.05	0.030
BMI (kg/m^2)	23.96 ± 2.61	22.85 ± 2.76	22.20 ± 2.71	<0.001
TG (mmol/L)	1.53 ± 0.96	1.33 ± 0.85	1.65 ± 1.41	0.003
TC (mmol/L)	4.97 ± 0.96	4.83 ± 0.95	5.13 ± 0.96	0.001
HDL-C (mmol/L)	1.38 ± 0.29	1.43 ± 0.33	1.39 ± 0.42	0.238
LDL-C (mmol/L)	2.94 ± 0.91	2.57 ± 0.84	2.38 ± 0.57	<0.001
SBP (mm Hg)	123.60 ± 13.72	127.46 ± 20.83	127.21 ± 19.12	0.132
DBP (mm Hg)	80.63 ± 8.60	78.31 ± 11.06	77.40 ± 9.55	0.009
Glucose (mmol/L)	6.58 ± 2.70	5.42 ± 1.77	5.13 ± 1.08	<0.001

PL: phospholipids, SBP: systolic blood pressure, DBP: diastolic blood pressure, adjusted by sex, total FA.

n-3:*n*-6 were significantly lower in those with MS compared to healthy people. We identified a relationship between plasma FA and MS such that high levels of plasma PL *n*-3 PUFA were significantly associated with lower risk of MS in a Chinese population, while total FA were associated with greater risk of MS in this group.

Diet and lifestyle play an important role in the development of MS, and nutritional modulation may alter the development of MS [26]. As the fatty acid composition in patients with MS is typically characterized by high levels of SFA and low levels of PUFA [27], previous studies suggested a role for dietary fat quality in the development of MS [12]. High consumption of SFA and *trans*-fatty acids adversely affect individuals with MS [28]. Because fatty acid profiles of platelet and plasma/serum phospholipids reflect an individual's type of dietary fat intake [29], in addition, the database on the individual fatty acid content of all foods is not available for Chinese, no method had been developed to accurately estimate the dietary intake of individual fatty acid since it is rare for people to prepare all meals at home. The amount of fat intake is highly variable depending on the ingredients used to prepare dishes in restaurants or canteens. Thus, compositions of platelet PL FA were used as a surrogate marker of dietary intake of FA. In the present study, we confirmed that PL total FA were positively associated with MS. Potential mechanisms are not very clear, but SFA may be associated with MS related components even in the short-term. High-fat diets, particularly those rich in SFA, adversely affect insulin action and alter HOMA-IR [30]. Diets high in total fat and SFA have been shown to exacerbate the chronic inflammatory state of MS [31]. The present study may add support to previous studies, which showed that serum/plasma fatty acid composition predicts the long-term development of MS [12].

The beneficial properties of *n*-3 PUFA have been documented in populations consuming large amounts of fatty fish and marine mammal oils [32]. Consumption of *n*-3 PUFA from marine sources positively affected certain MS components [28]. Similarly, insulin resistance syndromes including MS are associated with plasma fatty acid profiles characterized by a relative predominance of saturated and *n*-6 PUFA [12, 33, 34]. In addition, elevated 18:3*n*-3 concentration in adipose tissue is associated with lower prevalence of the MS [35]. Consistent with previous studies, we observed that *n*-3 PUFA are significantly inversely associated with MS in this population. Thus, these results provide further evidence that *n*-3 PUFA may be a valuable nutritional tool for preventing MS or improving MS related components. An intervention study also suggested that *n*-3 PUFA supplements in rats fed a high-fat diet completely prevent insulin resistance in muscle by decreasing fat content and maintaining normal phosphatidylinositol-3′ kinase activity and expression and translocation of GLUT4 receptors and in liver by maintaining the inhibition of hepatic glucose production [36]. Supplementation of *n*-3 PUFA to premenopausal, non-diabetic female subjects was also reported to markedly decrease the insulin response to an oral glucose load in those with a high level of inflammatory indexes, whereas the effect was reduced and not significant in those with low inflammatory status [37].

The potential mechanisms for the relationships between *n*-3 PUFA and MS are not fully understood. However, previous studies have demonstrated that *n*-3 PUFA exert beneficial effects through reduction of plasma TG [17], blood pressure [38] and markers of systemic inflammation such as high sensitive-C reactive protein [36] and also in improving the lipoprotein profiles [17]. Moreover, at the molecular level, *n*-3 PUFA exert their beneficial effects by regulating the expression of genes encoding proteins involved in fatty acid or suppressing lipogenic gene expression by reducing the nuclear abundance and DNA-binding affinity of transcription factors responsible for imparting insulin [39].

However, results from studies evaluating the association of *n*-3 PUFA with MS components are not always consistent. A case–control study in Korea which investigated the

relationship between *n*-3 PUFA and *trans*-FA and MS suggested that red blood cell *trans*-FA, but not *n*-3 FA, might be a predictor of increased risk for the MS [3]. They did not find significant associations between fish consumption rich in *n*-3 PUFA and MS, or between plasma *n*-3 PUFA and MS [3]. Studies also showed that plasma 20:5*n*-3 and 22:6*n*-3 was not significantly different in patients with MS [27, 40]. These results are inconsistent with those of this study and previous studies. In addition, other previous studies did not detect associations between *n*-3 PUFA and the components of MS. For example, *n*-3 PUFA did not restore insulin sensitivity in the liver [41] and appear to be no longer efficacious once type-2 diabetes is established [42]. *In vitro* studies have also raised concerns about the possibility of *n*-3 PUFA inhibiting pancreatic insulin secretion [41]. Moreover, adverse effects have been reported for *n*-3 PUFA used in patients with type-2 diabetes in a previous study, which showed that *n*-3 PUFA transiently raised fasting glucose levels in diabetic patients with treated hypertension [43]. In this study, we found that the tertile 2 of PL *n*-3 PUFA has the lowest TG, while the tertile 3 has the highest plasma TG. This inconsistent result may be a result from the genotype–FA interactions. These disparities may reflect different research designs, different populations studied and variable sample sizes. We speculate that genetic polymorphisms involved in metabolic pathways affecting MS components may also contribute to these inconsistent results. Different populations may respond differently to the dietary FA based on differing genetic backgrounds. Recent emerging data documenting gene–FA interactions for MS-related traits support the hypothesis that inconsistent observations are based, in part, on genetic makeup [44–46]. Study reported that *IL1b* genetic variants were associated with MS risk, and that genetic influences were more evident among subjects with low *n*-3 PUFA intake [47]. Plasma PUFA also modulated the susceptibility to MS that is conferred by complement component (C3) polymorphisms [48]. All these results provide new insights into the causes of MS. These observations suggest that MS results from the combined effects of environments and genetics, and provide a possible explanation for discrepancies among earlier studies.

In conclusion, total FA and MUFA were significantly higher in people with MS than in healthy people, whereas total PUFA, *n*-3 PUFA, *n*-6 PUFA and the *n*-3:*n*-6 were significantly lower in MS compared to healthy subjects. Plasma PL *n*-3 PUFA were significantly inversely associated with MS, while PL total FA were positively associated with MS in Chinese. The combined effects of environmental and genetic factors need to be considered in future investigations of dietary FA and MS.

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The authors have declared no conflict of interest.

5 References

[1] Eckel, R. H., Grundy, S. M., Zimmet, P. Z., The metabolic syndrome. *Lancet* 2005, *365*, 1415–1428.

[2] Executive summary of the third report of the National Cholesterol Education Program (NCEP) expert panel on detection, evaluation, and treatment of high blood cholesterol in adults (adult treatment panel III). *JAMA* 2001, *285*, 2486–2497.

[3] Lee, E., Lee, S., Park, Y., *n*-3 Polyunsaturated fatty acids and trans fatty acids in patients with the metabolic syndrome: a case-control study in Korea. *Br. J. Nutr.* 2008, *100*, 609–614.

[4] Sibbitt, W. L., Jr., Brandt, J. R., Johnson, C. R., Maldonado, M. E. *et al.*, The incidence and prevalence of neuropsychiatric syndromes in pediatric onset systemic lupus erythematosus. *J. Rheumatol.* 2002, *29*, 1536–1542.

[5] Gu, D., Reynolds, K., Wu, X., Chen, J. *et al.*, Prevalence of the metabolic syndrome and overweight among adults in China. *Lancet* 2005, *365*, 1398–1405.

[6] Zimmet, P., Alberti, K. G., Shaw, J., Global and societal implications of the diabetes epidemic. *Nature* 2001, *414*, 782–787.

[7] Shi, Z., Hu, X., Yuan, B., Hu, G. *et al.*, Coexistence of anaemia and the metabolic syndrome in adults in Jiangsu, China. *Asia Pac. J. Clin. Nutr.* 2008, *17*, 505–513.

[8] Cai, Z., Xu, X., Wu, X., Zhou, C., Li, D., Hyperuricemia and the metabolic syndrome in Hangzhou. *Asia Pac. J. Clin. Nutr.* 2009, *18*, 81–87.

[9] Esposito, K., Ceriello, A., Giugliano, D., Diet and the metabolic syndrome. *Metab. Syndr. Relat. Disord.* 2007, *5*, 291–296.

[10] Feldeisen, S. E., Tucker, K. L., Nutritional strategies in the prevention and treatment of metabolic syndrome. *Appl. Physiol. Nutr. Metab.* 2007, *32*, 46–60.

[11] Tulk, H. M., Robinson, L. E., Modifying the *n*-6/*n*-3 polyunsaturated fatty acid ratio of a high-saturated fat challenge does not acutely attenuate postprandial changes in inflammatory markers in men with metabolic syndrome. *Metabolism* 2009, *58*, 1709–1716.

[12] Warensjo, E., Riserus, U., Vessby, B., Fatty acid composition of serum lipids predicts the development of the metabolic syndrome in men. *Diabetologia* 2005, *48*, 1999–2005.

[13] Wang, L., Folsom, A. R., Zheng, Z. J., Pankow, J. S., Eckfeldt, J. H., Plasma fatty acid composition and incidence of diabetes in middle-aged adults: the Atherosclerosis Risk in Communities (ARIC) Study. *Am. J. Clin. Nutr.* 2003, *78*, 91–98.

[14] Tremblay, A. J., Despres, J. P., Piche, M. E., Nadeau, A. *et al.*, Associations between the fatty acid content of triglyceride, visceral adipose tissue accumulation, and components of the insulin resistance syndrome. *Metabolism* 2004, *53*, 310–317.

[15] Nigam, A., Frasure-Smith, N., Lesperance, F., Julien, P., Relationship between *n*-3 and *n*-6 plasma fatty acid levels and insulin resistance in coronary patients with and without metabolic syndrome. *Nutr. Metab. Cardiovasc. Dis.* 2009, *19*, 264–270.

[16] Carpentier, Y. A., Portois, L., Malaisse, W. J., *n*-3 fatty acids and the metabolic syndrome. *Am. J. Clin. Nutr.* 2006, *83*, 1499S–1504S.

[17] Mori, T. A., Burke, V., Puddey, I. B., Watts, G. F. *et al.*, Purified eicosapentaenoic and docosahexaenoic acids have differential effects on serum lipids and lipoproteins, LDL particle size, glucose, and insulin in mildly hyperlipidemic men. *Am. J. Clin. Nutr.* 2000, *71*, 1085–1094.

[18] Huang, T., Wahlqvist, M. L., Xu, T., Xu, A. *et al.*, Increased plasma *n*-3 polyunsaturated fatty acid is associated with improved insulin sensitivity in type 2 diabetes in China. *Mol. Nutr. Food Res.* 2010, *54*, S112–S119.

[19] Lombardo, Y. B., Chicco, A. G., Effects of dietary polyunsaturated *n*-3 fatty acids on dyslipidemia and insulin resistance in rodents and humans. A review. *J. Nutr. Biochem.* 2006, *17*, 1–13.

[20] Ebbesson, S. O., Risica, P. M., Ebbesson, L. O., Kennish, J. M., Tejero, M. E., Omega-3 fatty acids improve glucose tolerance and components of the metabolic syndrome in Alaskan Eskimos: the Alaska Siberia project. *Int. J. Circumpolar Health* 2005, *64*, 396–408.

[21] Popp-Snijders, C., Schouten, J. A., Heine, R. J., van der Meer, J., van der Veen, E. A., Dietary supplementation of omega-3 polyunsaturated fatty acids improves insulin sensitivity in non-insulin-dependent diabetes. *Diabetes Res.* 1987, *4*, 141–147.

[22] Friedberg, C. E., Janssen, M. J., Heine, R. J., Grobbee, D. E., Fish oil and glycemic control in diabetes. A meta-analysis. *Diabetes Care* 1998, *21*, 494–500.

[23] Riccardi, G., Giacco, R., Rivellese, A. A., Dietary fat, insulin sensitivity and the metabolic syndrome. *Clin. Nutr.* 2004, *23*, 447–456.

[24] Grundy, S. M., Cleeman, J. I., Daniels, S. R., Donato, K. A. *et al.*, Diagnosis and management of the metabolic syndrome. An American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement. Executive summary. *Cardiol. Rev.* 2005, *13*, 322–327.

[25] Mann, N. J., Li, D., Sinclair, A. J., Dudman, N. P. *et al.*, The effect of diet on plasma homocysteine concentrations in healthy male subjects. *Eur. J. Clin. Nutr.* 1999, *53*, 895–899.

[26] Orchard, T. J., Temprosa, M., Goldberg, R., Haffner, S. *et al.*, The effect of metformin and intensive lifestyle intervention on the metabolic syndrome: the Diabetes Prevention Program randomized trial. *Ann. Intern. Med.* 2005, *142*, 611–619.

[27] Warensjo, E., Sundstrom, J., Lind, L., Vessby, B., Factor analysis of fatty acids in serum lipids as a measure of dietary fat quality in relation to the metabolic syndrome in men. *Am. J. Clin. Nutr.* 2006, *84*, 442–448.

[28] Ebbesson, S. O., Tejero, M. E., Nobmann, E. D., Lopez-Alvarenga, J. C. *et al.*, Fatty acid consumption and metabolic syndrome components: the GOCADAN study. *J. Cardiometab. Syndr.* 2007, *2*, 244–249.

[29] Li, D., Yu, X. M., Xie, H. B., Zhang, Y. H. *et al.*, Platelet phospholipid *n*-3 PUFA negatively associated with plasma homocysteine in middle-aged and geriatric hyperlipaemia patients. *Prostaglandins Leukot. Essent. Fatty Acids* 2007, *76*, 293–297.

[30] Stettler, R., Ith, M., Acheson, K. J., Decombaz, J. *et al.*, Interaction between dietary lipids and physical inactivity on insulin sensitivity and on intramyocellular lipids in healthy men. *Diabetes Care* 2005, *28*, 1404–1409.

[31] Mozaffarian, D., Pischon, T., Hankinson, S. E., Rifai, N. *et al.*, Dietary intake of trans fatty acids and systemic inflammation in women. *Am. J. Clin. Nutr.* 2004, *79*, 606–612.

[32] Bang, H. O., Dyerberg, J., Nielsen, A. B., Plasma lipid and lipoprotein pattern in Greenlandic West-coast Eskimos. *Lancet* 1971, *1*, 1143–1145.

[33] Salomaa, V., Ahola, I., Tuomilehto, J., Aro, A. *et al.*, Fatty acid composition of serum cholesterol esters in different degrees of glucose intolerance: a population-based study. *Metabolism* 1990, *39*, 1285–1291.

[34] Borkman, M., Storlien, L. H., Pan, D. A., Jenkins, A. B. *et al.*, The relation between insulin sensitivity and the fatty-acid composition of skeletal-muscle phospholipids. *N. Engl. J. Med.* 1993, *328*, 238–244.

[35] Truong, H., DiBello, J. R., Ruiz-Narvaez, E., Kraft, P. *et al.*, Does genetic variation in the Delta6-desaturase promoter modify the association between alpha-linolenic acid and the prevalence of metabolic syndrome? *Am. J. Clin. Nutr.* 2009, *89*, 920–925.

[36] Mensink, R. P., Zock, P. L., Kester, A. D., Katan, M. B., Effects of dietary fatty acids and carbohydrates on the ratio of serum total to HDL cholesterol and on serum lipids and apolipoproteins: a meta-analysis of 60 controlled trials. *Am. J. Clin. Nutr.* 2003, *77*, 1146–1155.

[37] Browning, L. M., *n*-3 Polyunsaturated fatty acids, inflammation and obesity-related disease. *Proc. Nutr. Soc.* 2003, *62*, 447–453.

[38] Troisi, R., Willett, W. C., Weiss, S. T., Trans-fatty acid intake in relation to serum lipid concentrations in adult men. *Am. J. Clin. Nutr.* 1992, *56*, 1019–1024.

[39] Clarke, S. D., Polyunsaturated fatty acid regulation of gene transcription: a molecular mechanism to improve the metabolic syndrome. *J. Nutr.* 2001, *131*, 1129–1132.

[40] Klein-Platat, C., Drai, J., Oujaa, M., Schlienger, J. L., Simon, C., Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. *Am. J. Clin. Nutr.* 2005, *82*, 1178–1184.

[41] Holness, M. J., Greenwood, G. K., Smith, N. D., Sugden, M. C., Diabetogenic impact of long-chain omega-3 fatty acids on pancreatic beta-cell function and the regulation of endogenous glucose production. *Endocrinology* 2003, *144*, 3958–3968.

[42] Delarue, J., LeFoll, C., Corporeau, C., Lucas, D., *N*-3 long chain polyunsaturated fatty acids: a nutritional tool to prevent insulin resistance associated to type 2 diabetes and obesity? *Reprod. Nutr. Dev.* 2004, *44*, 289–299.

[43] Woodman, R. J., Mori, T. A., Burke, V., Puddey, I. B. *et al.*, Effects of purified eicosapentaenoic and docosahexaenoic acids on glycemic control, blood pressure, and serum lipids in type 2 diabetic patients with treated hypertension. *Am. J. Clin. Nutr.* 2002, *76*, 1007–1015.

[44] Tai, E. S., Corella, D., Demissie, S., Cupples, L. A. *et al.*, Polyunsaturated fatty acids interact with the PPARA-L162V

polymorphism to affect plasma triglyceride and apolipoprotein C-III concentrations in the Framingham Heart Study. *J. Nutr.* 2005, *135*, 397–403.

[45] Garaulet, M., Lee, Y. C., Shen, J., Parnell, L. D. *et al.*, CLOCK genetic variation and metabolic syndrome risk: modulation by monounsaturated fatty acids. *Am. J. Clin. Nutr.* 2009, *90*, 1466–1475.

[46] Mattei, J., Demissie, S., Tucker, K. L., Ordovas, J. M., Apolipoprotein A5 polymorphisms interact with total dietary fat intake in association with markers of metabolic syndrome in Puerto Rican older adults. *J. Nutr.* 2009, *139*, 2301–2308.

[47] Shen, J., Arnett, D. K., Peacock, J. M., Parnell, L. D. *et al.*, Interleukin1beta genetic polymorphisms interact with polyunsaturated fatty acids to modulate risk of the metabolic syndrome. *J. Nutr.* 2007, *137*, 1846–1851.

[48] Phillips, C. M., Goumidi, L., Bertrais, S., Ferguson, J. F. *et al.*, Complement component 3 polymorphisms interact with polyunsaturated fatty acids to modulate risk of metabolic syndrome. *Am. J. Clin. Nutr.* 2009, *90*, 1655–1673.

