Relations of Plasma Polyunsaturated Fatty Acids With Blood Pressures During the 26th and 28th Week of Gestation in Women of Chinese, Malay, and Indian Ethnicity

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Abstract: Observational and intervention studies have reported inconsistent results of the relationship between polyunsaturated fatty acids (PUFAs) and hypertension during pregnancy. Here, we examined maternal plasma concentrations of n-3 and n-6 PUFAs between the 26th and the 28th week of gestation in relation to blood pressures and pregnancy-associated hypertension.

We used data from a birth cohort study of 751 Chinese, Malay, and Indian women. Maternal peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) were taken from the brachial arm, and central SBP and pulse pressures (PPs) were derived from radial artery pressure waveforms between the 26th and the 28th week of gestation.

Pregnancy-associated hypertension (including gestational hypertension and preeclampsia) was ascertained from medical records. Plasma phosphatidylcholine n-3 and n-6 PUFAs were measured by gas chromatography and expressed as percentage of total fatty acids.

Peripheral SBP was inversely associated with total n-3 PUFAs [−0.51 (95% confidence interval, CI, −0.89 to −0.13) mm Hg] and long-chain n-3 PUFAs [−0.52 (CI −0.92 to −0.13) mmHg]. Similar but weaker associations were observed for central SBP and PP. Dihomo-γ-linolenic acid was marginally positively associated with peripheral SBP, central SBP, and PP, whereas linoleic acid and total n-6 PUFAs showed no significant associations with blood pressures. We identified 28 pregnancy-associated hypertension cases, and 1% increase in total n-3 PUFAs was associated with a 24% lower odds of pregnancy-associated hypertension (odds ratio 0.76; 95% CI 0.60 to 0.97). Maternal ethnicity modified the PUFAs–blood pressure relations, with stronger inverse associations with n-3 PUFAs in Chinese women, and stronger positive associations with n-6 PUFAs in Indian women (P values for interaction ranged from 0.02 to 0.07).

Higher n-3 PUFAs at midgestation are related to lower maternal blood pressures and pregnancy-associated hypertension in Asian women, and the ethnicity-related variation between PUFAs and blood pressures deserves further investigation.

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Abbreviations: BMI = body mass index, DBP = diastolic blood pressure, MUFAs = monounsaturated fatty acids, PC = phosphatidylcholine, PP = pulse pressure, PUFAs = polyunsaturated fatty acids, SBP = systolic blood pressure.

INTRODUCTION

Hypertensive disorders are major health concerns in pregnancy as they are associated with increased risks of maternal and fetal mortality and morbidity.[1] Therefore, strategies to prevent or limit pregnancy-associated hypertension could be very important in reducing maternal and fetal complications. Recent reports on n-3 polyunsaturated fatty acids (PUFAs) supplementation during pregnancy have been shown to prolong pregnancy gestation and increase offspring birth weight,[2,3] and lower the risk of pregnancy complications,[4,5] although the precise mechanisms are unclear.

Two meta-analyses of randomized trials have suggested that increasing dietary intake of long-chain n-3 PUFAs lowers blood pressures, with stronger effects in hypertensive patients.[6,7] This hypotensive effect of n-3 PUFAs is likely due to several mechanisms including reduced inflammation, improved vascular endothelial function, and increased nitric oxide production, effects that are well demonstrated in non-pregnant adults.[8,9] However, it is unclear whether the effects

persist on maternal blood pressures and pregnancy-associated hypertension,[2] and only 2 trials have examined the effect of n-3 supplementation on maternal blood pressures.[10,11] A number of observational studies have evaluated the relations of n-3 PUFAs and pregnancy-associated hypertension, with some reporting inverse association,[4,12,13] whereas others reporting null[14,15] or positive relation.[16,17] The results for n-6 PUFAs were also inconsistent.[4,12,15,18] Moreover, no observational study has examined the relations of n-3 and n-6 PUFAs with the continuous measures of maternal blood pressures during pregnancy, particularly in Asian women. Therefore, in this study, we aimed to evaluate the relations of maternal plasma concentrations of n-3 and n-6 PUFAs between the 26th and the 28th week of gestation with maternal blood pressures and pregnancy-associated hypertension in a birth cohort of Chinese, Malay, and Indian women.

METHODS

Study Participants

A birth cohort study on Asian women, known as the Growing Up in Singapore Towards healthy Outcomes (GUSTO) study, was initiated to recruit women in their early pregnancy from 2 public tertiary hospitals with maternity care in Singapore.[19] From 2009 to 2012, the GUSTO study enrolled 1162 Singapore citizens or residents with homogenous parental ethnic Chinese, Malay, or Indian background. Women were excluded if they received chemotherapy, psychotropic drugs, or had type 1 diabetes. The study was approved by the SingHealth Centralised Institutional Review Board and National Healthcare Group Domain Specific Review Board. Written informed consent was obtained from each study participant.

In the present analysis, we utilized information on maternal plasma phosphatidylcholine (PC) PUFAs and blood pressures measured during the GUSTO antenatal study visit between the 26th and the 28th week of gestation. Women with incomplete information on plasma PC PUFAs (n = 166) or blood pressures (n = 245) were excluded, leaving a final sample of 751 (64.6% of the cohort) women for analysis. Women who were included and excluded from the study had similar ages, education levels, and body mass index (BMI), but the excluded women were more likely to be smokers and alcohol drinkers before or during pregnancy than women who were included (17.2% vs 12.7%; 40.2% vs 33.5%, respectively; Supplemental Table 1, http://links.lww.com/MD/A216).

Blood Pressure Measurements

Maternal blood pressures and heart rates were taken by trained research coordinators based on a standardized protocol. Peripheral systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured thrice from the brachial arm at 30 to 60-second intervals with an oscillometric device MC3100 (HealthSTATS International Pte Ltd, Singapore). An average of the 3 readings was calculated if the difference between readings was <10 mm Hg; otherwise, measurements were repeated. An A-pulse tonometer (BPro; HealthSTATS International Pte Ltd) was applied on the radial artery of the same arm for continuous sampling of radial artery pressure waveforms over 1 minute, and these waveforms were calibrated using the average of brachial SBP and DBP, respectively. Maternal heart rate and central SBP was then estimated from the calibrated radial artery pressure waveforms using the N-point moving average.[20] Central pulse

pressure (PP) was calculated as the difference between central SBP and peripheral DBP.

Pregnancy-Associated Hypertension

Information on pregnancy-associated hypertension, including gestational hypertension and preeclampsia, was ascertained from medical records. The abstracted information was cross-checked by another obstetrician who was involved in the study. In practice, the diagnosis of gestational hypertension included de novo hypertension (defined as peripheral SBP ≥140 mm Hg or DBP ≥90 mm Hg) without proteinuria after the 20th week of gestation, measured at 2 separate occasions with at least 4 hours apart.[21] The definition for preeclampsia was hypertension with proteinuria after the 20th week of gestation. Preeclampsia is a multiorgan disorder that may also include impairments in kidney, liver functions, and low platelets.[21] As there were only 16 incident cases of gestational hypertension and 12 incident cases of preeclampsia, they were collectively analyzed as pregnancy-associated hypertension.

Plasma Phosphatidylcholine Fatty Acid Composition

Fasting blood samples were taken between the 26th and the 28th week of gestation. Plasma was prepared by centrifugation and was stored at −80°C until analysis. Total lipid extraction was carried out with chloroform/methanol (2:1 v/v) and PC, which contributes about 75% of plasma phospholipids, was isolated by solid-phase extraction on aminopropylsilica cartridges and eluted with chloroform/methanol (3:2 v/v). Fatty acid methyl esters were generated by reaction of purified PC with 2% sulfuric acid (v/v) at 50°C for 2 hours, extracted into hexane and separated by gas chromatography. A BPX-70 column (30 m × 220 μm; film thickness 0.25 μm) fitted to a Hewlett-Packard HP6890 gas chromatograph was used for separation with helium as the running gas and detection of fatty acid methyl esters by flame ionization before quantification using the ChemStation software in absolute concentration (μg/mL plasma). Plasma PC fatty acids were expressed as percentages of total plasma PC fatty acids, and the ratio of total n-3 to n-6 PUFAs were calculated accordingly.

Covariates

Information on maternal age, ethnicity and education level, smoking status, alcohol intake before and during pregnancy, hypertension before pregnancy, physical exercise, and dietary supplements during pregnancy were obtained via standardized questionnaires. Maternal anthropometry (height and weight) was measured by trained investigators between the 26th and the 28th week of gestation, and BMI was calculated as weight (kg) divided by the square of height (m^2). Women with BMI <25.0 kg/m^2 were categorized as normal weight, 25.0–29.9 kg/m^2 as overweight, and ≥30.0 kg/m^2 as obese. Oral glucose tolerance test was performed and gestational diabetes was defined as fasting glucose ≥7.0 mmol/L or 2-hour glucose ≥11.1 mmol/L.

Statistical Analysis

Crude trends of maternal baseline characteristics and pregnancy outcomes across tertiles of n-3 and n-6 PUFAs were done using Mantel–Haenszel test. The associations between plasma PC fatty acids and continuous measures of maternal peripheral and central blood pressures were examined using

multiple linear regression analysis. The relation of fatty acids with pregnancy-associated hypertension was examined using multiple logistic regression with exclusion of women with hypertension before pregnancy. All analyses were adjusted for maternal age, ethnicity, education level, exercise, smoking status, and alcohol intake before or during pregnancy, BMI, and height between the 26th and the 28th week of gestation, gestational diabetes, heart rate, and the use of fish oil supplements. As there were only 14 women with hypertension before pregnancy, we did not adjust for this covariate in our main analysis. However, to test the robustness of our results, we adjusted for maternal hypertension before pregnancy or excluded them in our sensitivity analysis, and the results remained unchanged. We further adjusted for plasma mono-unsaturated fatty acids (MUFAs) in the sensitivity analysis. We also repeated our analysis for the continuous measures of blood pressure outcomes in a subgroup of 383 women who did not use fish oil supplements.

Effect modification by maternal ethnicity was performed for the continuous measures of maternal blood pressures, but not for the binary outcomes of pregnancy-associated hypertension due to the limited number of cases (n = 28). To assess for ethnic modification, a multiplicative interaction term between ethnicity (Chinese, Malay, and Indian) and plasma PC fatty acids (continuous variable) was added in the models. Ethnicity stratified analysis was performed and the likelihood ratio test was used to examine the interaction effects. Stata version 11.2 (Statacorp, College Station, TX) was used for analysis, and 2-tailed *P* value <0.05 was considered statistically significant.

RESULTS

The women included in our analysis were predominantly Chinese (53.8%), followed by Malay (28.8%) and Indians (17.3%). Those with higher plasma PC n-3 PUFAs tended to have lower BMIs and were more physically active compared to those with higher plasma PC n-6 PUFAs (Table 1). The crude incidence of pregnancy-associated hypertension was 3.9% (n = 28) among women who were free from hypertension before pregnancy. Plasma PC n-3 PUFAs were inversely correlated with gestational hypertension or preeclampsia (*P* for trend = 0.02), but for plasma PC n-6 PUFAs, a marginal trend of positive correlation was observed instead (*P* for trend = 0.05).

PUFAs accounted for about 40% of plasma PC fatty acids, with 6.4% as total n-3 PUFAs and 34.2% as total n-6 PUFAs (Table 2). The n-3 PUFAs identified were α-linolenic acid (18:3n-3; 0.2%) and long-chain n-3—eicosapentaenoic acid (20:5n-3), docosapentaenoic acid (22:5n-3), and docosahexanoic acid (22:6n-3); 5.9%—whereas the n-6 PUFAs included linoleic acid (18:2n-6; 21.7%), dihomo-γ-linolenic acid (20:3n-6; 3.9%), and arachidonic acid (20:4n-6; 7.9%). Chinese women had the highest total n-3 PUFAs (6.7%), whereas Indian women had the highest total n-6 PUFAs (35.2%). Furthermore, women who took fish oil supplements tended to have higher total n-3 PUFAs (6.8% vs 6.0%), higher long-chain n-3 PUFAs (6.4% vs 5.7%), and lower n-6 PUFAs (33.9% vs 34.4%) compared with women who did not take fish oil supplements (Supplemental Table 2, http://links.lww.com/MD/A216).

Relation of Plasma n-3 PUFAs With Maternal Blood Pressures

After multivariate adjustment, higher total and long-chain n-3 PUFAs and n-3/n-6 ratio was associated with lower peripheral SBP (Table 3 and Figure 1): the mean (95% confidence interval [CI]) was −0.51 (−0.89 to −0.13) mm Hg for a 1% increase in total n-3 PUFAs, −0.52 (−0.92 to −0.13) mm Hg for a 1% increase in long-chain n-3 PUFAs, and −1.51 (−2.63 to −0.38) mm Hg for a 0.1-unit increase in the n-3/n-6 ratio. Total and long-chain n-3 PUFAs and n-3/n-6 ratio were marginally associated with central SBP and PP, but not with DBP. The results were not materially changed in the sensitivity analyses: further adjustment or exclusion of women with hypertension before pregnancy, or further adjustment for plasma MUFAs (Supplemental Table 3, http://links.lww.com/MD/A216); and in women without fish oil supplementation (Supplemental Table 4, http://links.lww.com/MD/A216).

Relation of Plasma n-6 PUFAs With Blood Pressures

The relations of total n-6 PUFAs, linoleic acid, and arachidonic acid to blood pressure outcomes were not statistically significant, but dihomo-γ-linolenic acid was marginally positively associated with peripheral SBP, 0.58 (−0.02 to 1.18; *P* = 0.06), and central SBP, 0.52 (−0.04 to 1.07; *P* = 0.07; Table 4 and Figure 2). The results were not materially different with further adjustment for maternal hypertension before pregnancy or plasma MUFAs (Supplemental Table 5, http://links.lww.com/MD/A216) and in subgroup analysis of women who were not supplemented with fish oil (Supplemental Table 6, http://links.lww.com/MD/A216).

Relations Between Plasma PUFAs and Pregnancy-Associated Hypertension

The relations of total and long-chain n-3 PUFAs to pregnancy-associated hypertension were statistically significant (Table 5). The adjusted odds ratio (95% CI) for pregnancy-associated hypertension from 1% increase in total n-3 PUFAs and long-chain n-3 PUFAs was 0.76 (0.60 to 0.97) and 0.77 (0.60 to 0.98), respectively. No significant associations were found between n-6 PUFAs and pregnancy-associated hypertension.

Relations Between Plasma PUFAs and Blood Pressures in Different Ethnic Groups

The relations of total and long-chain n-3 PUFAs and n-3/n-6 ratio to peripheral SBP, DBP, and central SBP varied across maternal ethnic groups (*P* values for interaction ranged from 0.02 to 0.07). The inverse associations tended to be stronger in Chinese women and weaker in Indian women, but nonsignificantly positive in Malay women (Supplemental Table 7, http://links.lww.com/MD/A216).

The positive relations of linoleic acid with SBP and total n-6 PUFAs with DBP were stronger in Indian women compared with Chinese or Malay women (*P* for interaction = 0.02 and 0.05, respectively; Supplemental Table 8, http://links.lww.com/MD/A216). In Indian women, higher tertiles of total n-6 PUFAs and linoleic acid were associated with higher peripheral SBP, DBP, and central SBP (*P* for trend ranged from 0.002 to 0.09), and higher tertiles of dihomo-γ-linoleic acid with higher peripheral DBP and central SBP (*P* for trend = 0.07).

DISCUSSION

Plasma PC PUFAs reflect both intake[22] and levels of those fatty acids[23] in various cells and tissues. Thus, they are good

TABLE 1. Characteristics of Women by Tertiles of Plasma PC n-3 and n-6 PUFAs at the 26th to the 28th Week of Gestation

	n	n-3 PUFAs				n-6 PUFAs			
		1st Tertile	2nd Tertile	3rd Tertile	P (Trend)	1st Tertile	2nd Tertile	3rd Tertile	P (Trend)
Age, y	751	29.9 ± 5.2	30.0 ± 5.2	31.7 ± 4.8	<0.001	31.1 ± 5.1	30.4 ± 5.1	30.1 ± 5.2	0.04
Ethnicity (%)									
Chinese	404	114 (45.8%)	122 (48.4%)	168 (67.2%)	<0.001	152 (61.8%)	133 (50.2%)	119 (49.6%)	<0.001
Malay	217	82 (32.9%)	82 (32.5%)	53 (21.2%)		64 (26.0%)	88 (33.2%)	65 (27.1%)	
Indian	130	53 (21.3%)	48 (19.0%)	29 (11.6%)		30 (12.2%)	44 (16.6%)	56 (23.3%)	
Education (%)									
Primary to secondary	232	94 (38.4%)	82 (33.1%)	56 (22.5%)	<0.001	71 (29.1%)	86 (32.9%)	75 (31.6%)	0.49
GCE/Vocational/Polytechnic	265	81 (33.1%)	90 (36.3%)	94 (37.8%)		88 (36.1%)	92 (35.2%)	85 (35.9%)	
Tertiary	245	70 (28.6%)	76 (30.6%)	99 (39.8%)		85 (34.8%)	83 (31.8%)	77 (32.5%)	
Exercise (%)									
None to gentle exercise	547	188 (75.8%)	184 (73.0%)	175 (70.3%)	0.16	162 (66.1%)	202 (76.5%)	183 (76.2%)	0.01
Moderate to strenuous exercise	202	60 (24.2%)	68 (26.9%)	74 (29.7%)		83 (33.9%)	62 (23.5%)	57 (23.8%)	
Body mass index, kg/m²	737	26.7 ± 4.5	26.5 ± 4.6	25.5 ± 3.9	0.001	25.6 ± 4.1	26.3 ± 4.5	26.7 ± 4.2	0.02
Height, cm	744	157.8 ± 5.4	158.5 ± 5.7	158.7 ± 5.8	0.03	157.8 ± 5.6	158.5 ± 5.3	158.8 ± 6.0	0.14
Smoking status (%)									
Nonsmoker	653	212 (85.8%)	206 (82.1%)	235 (94.0%)	0.006	212 (86.2%)	228 (86.7%)	213 (89.1%)	0.33
Ever smoker	95	35 (14.2%)	45 (17.9%)	15 (6.0%)		34 (13.8%)	35 (13.3%)	26 (10.9%)	
Alcohol intake (%)									
No	486	163 (67.9%)	164 (65.9%)	159 (65.7%)	0.61	141 (58.8%)	179 (70.2%)	166 (70.3%)	0.007
Yes	245	77 (32.1%)	85 (34.1%)	83 (34.3%)		99 (41.2%)	76 (29.8%)	70 (29.7%)	
Gestational diabetes (%)									
No	577	194 (83.6%)	197 (82.8%)	186 (80.2%)	0.33	196 (82.4%)	207 (85.2%)	174 (78.7%)	0.33
Yes	125	38 (16.4%)	41 (17.2%)	46 (19.8%)		42 (17.6%)	36 (14.8%)	47 (21.3%)	
Hypertension before pregnancy (%)									
No	722	238 (97.5%)	243 (98.4%)	241 (98.4%)	0.50	239 (98.4%)	255 (98.5%)	228 (97.4%)	0.47
Yes	14	6 (2.5%)	4 (1.6%)	4 (1.6%)		4 (1.6%)	4 (1.5%)	6 (2.6%)	
Pregnancy-associated hypertension* (%)									
Normotensive pregnancy	694	224 (94.1%)	233 (95.9%)	237 (98.4%)	0.02	233 (97.5%)	247 (96.9%)	214 (93.9%)	0.05
Gestational hypertension	16	8 (3.4%)	5 (2.1%)	3 (1.2%)		4 (1.7%)	4 (1.6%)	8 (3.5%)	
Preeclampsia	12	6 (2.5%)	5 (2.1%)	1 (0.4%)		2 (0.8%)	4 (1.6%)	6 (2.6%)	
Fish oil supplementation									
No	383	146 (65.5%)	129 (58.4%)	108 (45.9%)	<0.001	111 (49.3%)	130 (55.8%)	142 (64.2%)	0.002
Yes	296	77 (34.5%)	92 (41.6%)	127 (54.0%)		114 (50.7%)	103 (44.2%)	79 (35.8%)	

GCE = General Certificate of Education, PC = phosphatidylcholine, PUFAs = polyunsaturated fatty acids, SD = standard deviation. Data are presented in n (%) or mean ± SD. P values were derived from Cochran–Mantel–Haenszel test. Variables with missing information were education (n = 9), exercise (n = 2), body mass index (n = 14), height (n = 7), smoking status (n = 3), alcohol intake (n = 20), gestational diabetes (n = 49), hypertension before pregnancy (n = 15), and fish oil supplementation (n = 72). They were coded as missing.
* Incident cases were reported having excluded 14 women with hypertension before pregnancy.

markers of maternal PUFA status. The main findings from this cohort of Asian women are as follows: total and long-chain n-3 PUFAs and n-3/n-6 ratio were all inversely associated with peripheral SBP and central SBP and PP between the 26th and the 28th week of gestation, whereas dihomo-γ-linolenic acid was marginally positively associated with peripheral and central SBP; higher n-3 PUFAs were associated with lower odds of pregnancy-associated hypertension; and maternal ethnicity modified the relationship between plasma PC PUFAs and blood pressures, with stronger inverse associations for n-3 PUFAs in Chinese women and stronger but positive associations for n-6 PUFAs in Indian women.

Our findings on the inverse relations between plasma PC n-3 PUFAs and maternal blood pressures and pregnancy-associated hypertension are consistent with evidence from clinical and epidemiological studies[8,24,25] on the direct and indirect mechanisms of action of n-3 PUFAs,[9,26] and they lend support to the potentially beneficial role of long-chain n-3 PUFAs in pregnancy. Although the earlier 2 trials in pregnant women reported no significant findings,[10,11] trials in the general population have found consistent hypotensive and cardioprotective effects from n-3 supplementation,[6,7,9] and this has led to the development of several national and international guidelines for their consumption.[9] Further trials on n-3 supplementation are still needed as hypertension in pregnancy is a major complication in pregnancy, and as demonstrated in the general population,[9,27] fish oil supplementation may be a useful adjunct to prevent or limit hypertension disorders and associated complications in pregnancy.

This study is one of the few that has comprehensively examined the relations between PUFA status and blood pressures in pregnant Asian women. Our findings are consistent with

TABLE 2. Composition of Maternal Plasma PC Fatty Acids (% of Total Fatty Acids) at the 26th to the 28th Week of Gestation by Ethnicity

Plasma Fatty Acids	Overall	Chinese	Malay	Indian	*P*
n	751	404	217	130	
SFAs	45.8 ± 3.2	46.0 ± 3.1	45.1 ± 3.1	46.5 ± 3.4	<0.001
MUFAs	13.6 ± 2.3	13.5 ± 2.1	14.6 ± 2.3	12.3 ± 2.0	<0.001
PUFAs	40.5 ± 3.3	40.5 ± 3.4	40.2 ± 3.1	41.1 ± 3.6	0.05
Total n-3 PUFAs	6.3 ± 1.9	6.7 ± 1.9	6.0 ± 1.7	5.9 ± 1.8	<0.001
α-Linolenic acid (18:3n-3)	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.12
Long chain n-3 PUFAs	5.9 ± 1.8	6.3 ± 1.9	5.6 ± 1.6	5.6 ± 1.8	<0.001
Total n-6 PUFAs	34.2 ± 3.2	33.8 ± 3.1	34.2 ± 3.0	35.2 ± 3.7	<0.001
Linoleic acid (18:2n-6)	21.7 ± 3.3	21.6 ± 3.2	22.1 ± 3.4	21.2 ± 3.2	0.02
Dihomo-γ-linolenic acid (20:3n-6)	3.9 ± 1.2	3.7 ± 1.2	4.1 ± 1.2	4.4 ± 1.3	<0.001
Arachidonic acid (20:4n-6)	7.9 ± 1.7	7.8 ± 1.5	7.3 ± 1.5	8.9 ± 1.9	<0.001
n-3/n-6 ratio	0.19 ± 0.06	0.20 ± 0.06	0.18 ± 0.06	0.17 ± 0.06	<0.001

MUFAs = monounsaturated fatty acids, PC = phosphatidylcholine, PUFAs = polyunsaturated fatty acids, SD = standard deviation, SFAs = saturated fatty acids. Data are presented in mean ± SD. *P* values were derived from 1-way analysis of variance test.

a recent meta-analysis of 70 randomized clinical trials in nonpregnant populations[6] that n-3 PUFA provision reduces blood pressures (SBP, −1.52 mm Hg; DBP, −0.99 mm Hg) compared with placebo. Other studies have found that higher n-3 PUFA concentrations in the blood stream were associated with lower cardiovascular risk.[28] Data from observational studies in nonpregnant populations support the hypotensive effects of n-3 PUFAs measured from dietary intake[29] or plasma phospholipid[30] or serum.[31] For example, plasma phospholipid n-3 PUFAs was inversely associated with hypertension in a

TABLE 3. Multivariate-Adjusted Association Between Maternal Plasma PC n-3 PUFAs and Blood Pressures at the 26th to the 28th Week of Gestation

Fatty Acids (%)	Blood Pressure Outcomes					
	Model 1		Model 2		Model 3	
	β (95% CI)	*P*	β (95% CI)	*P*	β (95% CI)	*P*
Peripheral SBP						
Total n-3 PUFAs	−0.65 (−1.08 to −0.23)	0.003	−0.48 (−0.86 to −0.11)	0.01	−0.51 (−0.89 to −0.13)	0.008
α-Linolenic acid	−2.95 (−8.81 to 2.91)	0.32	−0.02 (−5.18 to 5.14)	0.99	−0.11 (−5.28 to 5.06)	0.97
Long-chain n-3 PUFAs	−0.68 (−1.13 to −0.24)	0.003	−0.50 (−0.89 to −0.11)	0.01	−0.52 (−0.92 to −0.13)	0.01
n-3/n-6 ratio*	−2.17 (−3.43 to −0.91)	0.001	−1.44 (−2.55 to −0.33)	0.01	−1.51 (−2.63 to −0.38)	0.009
Peripheral DBP						
Total n-3 PUFAs	−0.23 (−0.56 to 0.09)	0.15	−0.09 (−0.39 to 0.20)	0.52	−0.08 (−0.38 to 0.21)	0.58
α-Linolenic acid	−3.43 (−7.83 to 0.97)	0.13	−0.81 (−4.79 to 3.17)	0.69	−1.03 (−5.01 to 2.95)	0.61
Long-chain n-3 PUFAs	−0.23 (−0.57 to 0.10)	0.17	−0.09 (−0.39 to 0.21)	0.55	−0.07 (−0.38 to 0.23)	0.63
n-3/n-6 ratio*	−0.83 (−1.78 to 0.12)	0.09	−0.23 (−1.08 to 0.63)	0.60	−0.19 (−1.05 to 0.68)	0.67
Central SBP						
Total n-3 PUFAs	−0.49 (−0.88 to −0.11)	0.01	−0.30 (−0.65 to 0.05)	0.09	−0.31 (−0.67 to 0.04)	0.09
α-Linolenic acid	−3.63 (−8.96 to 1.69)	0.18	−1.15 (−5.96 to 3.66)	0.64	−1.33 (−6.15 to 3.48)	0.59
Long-chain n-3 PUFAs	−0.50 (−0.90 to −0.09)	0.02	−0.29 (−0.65 to 0.08)	0.12	−0.30 (−0.67 to 0.07)	0.12
n-3/n-6 ratio*	−1.60 (−2.74 to −0.46)	0.01	−0.89 (−1.93 to 0.15)	0.09	−0.91 (−1.96 to 0.13)	0.09
Central PP						
Total n-3 PUFAs	−0.26 (−0.51 to 0.00)	0.05	−0.12 (−0.45 to 0.04)	0.10	−0.13 (−0.48 to 0.02)	0.07
α-Linolenic acid	−0.20 (−3.69 to 3.28)	0.91	−0.34 (−3.69 to 3.01)	0.84	−0.30 (−3.66 to 3.06)	0.86
Long-chain n-3 PUFAs	−0.26 (−0.52 to 0.00)	0.05	−0.20 (−0.45 to 0.06)	0.13	−0.22 (−0.48 to 0.04)	0.09
n-3/n-6 ratio*	−0.77 (−1.53 to −0.02)	0.04	−0.66 (−1.38 to 0.06)	0.07	−0.73 (−1.46 to 0.00)	0.05

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, PC = phosphatidylcholine, PP = pulse pressure, PUFAs = polyunsaturated fatty acids, SBP = systolic blood pressure. Model 1: adjusted for age and ethnicity using multiple linear regression. Model 2: adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI, and height at the 26th to 28th week of gestation, gestational diabetes, and heart rate. Model 3: adjusted for variables in Model 2 and fish oil supplementation.
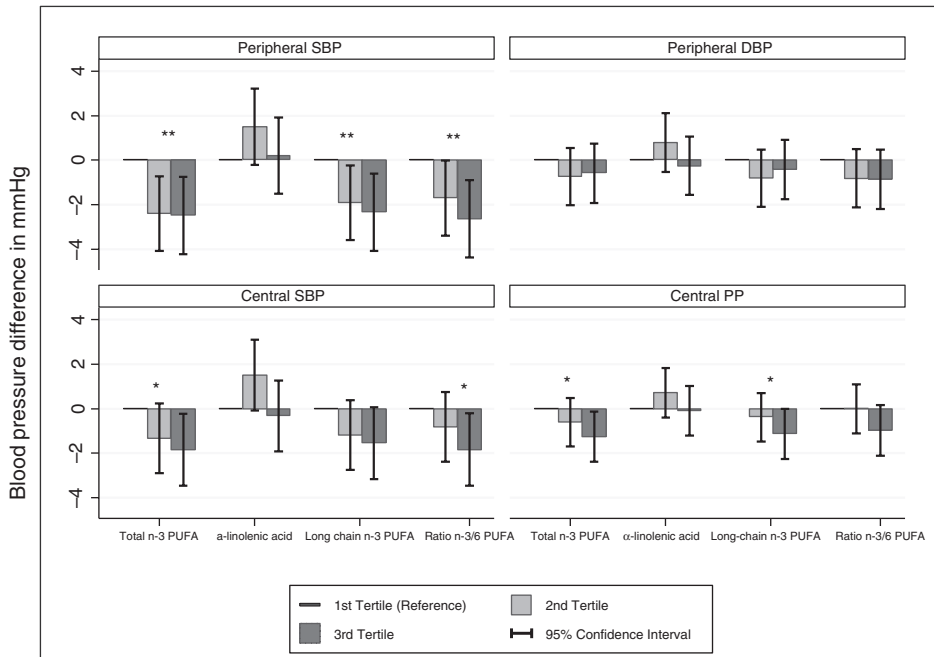* The values were β (95% CI) for blood pressures in 0.1-unit increase of the n-3/n-6 ratio.

FIGURE 1. Multivariate-adjusted association between maternal plasma PC n-3 PUFAs (tertiles) and blood pressures at the 26th to the 28th week of gestation. DBP = diastolic blood pressure, PC = phosphatidylcholine, PP = pulse pressure, PUFA = polyunsaturated fatty acid, SBP = systolic blood pressure. $^{*}P$ for trend ≤ 0.05; $^{**}P$ for trend < 0.001.

TABLE 4. Multivariate-Adjusted Association Between Maternal Plasma PC n-6 PUFAs and Blood Pressures at the 26th to the 28th Week of Gestation

	Blood Pressure Outcomes					
	Model 1		Model 2		Model 3	
Fatty Acids (%)	β (95% CI)	P	β (95% CI)	P	β (95% CI)	P
Peripheral SBP						
Total n-6 PUFAs	0.35 (0.10 to 0.59)	0.006	0.18 (−0.04 to 0.40)	0.11	0.18 (−0.04 to 0.40)	0.11
Linoleic acid	0.03 (−0.21 to 0.27)	0.80	0.14 (−0.07 to 0.35)	0.19	0.14 (−0.07 to 0.35)	0.19
Dihomo-γ-linolenic acid	1.42 (0.76 to 2.08)	<0.01	0.58 (−0.02 to 1.17)	0.06	0.58 (−0.02 to 1.18)	0.06
Arachidonic acid	0.45 (−0.05 to 0.94)	0.08	−0.22 (−0.66 to 0.22)	0.33	−0.22 (−0.66 to 0.23)	0.34
Peripheral DBP						
Total n-6 PUFAs	0.23 (0.05 to 0.42)	0.01	0.09 (−0.08 to 0.25)	0.32	0.08 (−0.09 to 0.25)	0.35
Linoleic acid	−0.03 (−0.22 to 0.15)	0.71	0.02 (−0.15 to 0.18)	0.85	0.02 (−0.14 to 0.18)	0.83
Dihomo-γ-linolenic acid	0.92 (0.42 to 1.41)	<0.001	0.33 (−0.12 to 0.79)	0.15	0.29 (−0.17 to 0.75)	0.21
Arachidonic acid	0.47 (0.10 to 0.84)	0.01	0.00 (−0.34 to 0.34)	0.99	0.00 (−0.34 to 0.34)	0.99
Central SBP						
Total n-6 PUFAs	0.25 (0.02 to 0.47)	0.03	0.13 (−0.07 to 0.34)	0.20	0.13 (−0.07 to 0.33)	0.22
Linoleic acid	−0.08 (−0.30 to 0.14)	0.46	0.05 (−0.15 to 0.24)	0.64	0.05 (−0.15 to 0.24)	0.63
Dihomo-γ-linolenic acid	1.22 (0.62 to 1.81)	<0.001	0.54 (−0.02 to 1.09)	0.06	0.52 (−0.04 to 1.07)	0.07
Arachidonic acid	0.55 (0.10 to 1.00)	0.02	−0.03 (−0.44 to 0.38)	0.89	−0.03 (−0.44 to 0.38)	0.89
Central PP						
Total n-6 PUFAs	0.01 (−0.13 to 0.16)	0.85	0.05 (−0.10 to 0.19)	0.52	0.05 (−0.09 to 0.19)	0.50
Linoleic acid	−0.05 (−0.19 to 0.09)	0.51	0.03 (−0.10 to 0.17)	0.65	0.03 (−0.11 to 0.17)	0.66
Dihomo-γ-linolenic acid	0.30 (−0.10 to 0.69)	0.14	0.20 (−0.18 to 0.59)	0.30	0.22 (−0.16 to 0.61)	0.26
Arachidonic acid	0.08 (−0.22 to 0.37)	0.62	−0.03 (−0.32 to 0.26)	0.84	−0.03 (−0.31 to 0.26)	0.85

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, PC = phosphatidylcholine, PP = pulse pressure, PUFA = polyunsaturated fatty acids, SBP = systolic blood pressure. Model 1: adjusted for age and ethnicity using multiple linear regression. Model 2: adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI, and height at the 26th to 28th week of gestation, gestational diabetes, and heart rate. Model 3: adjusted for variables in Model 2 and fish oil supplementation.
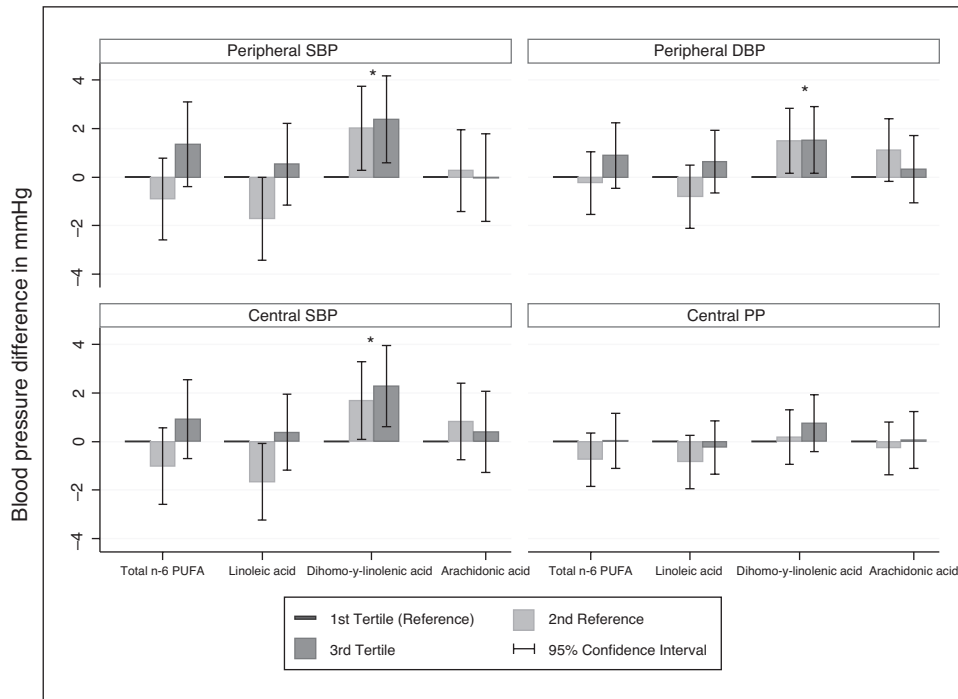
FIGURE 2. Multivariate-adjusted association between maternal plasma PC n-6 PUFAs (tertiles) and blood pressures at the 26th to the 28th week of gestation. DBP = diastolic blood pressure, PC = phosphatidylcholine, PP = pulse pressure, PUFA = polyunsaturated fatty acid, SBP = systolic blood pressure. *P for trend ≤ 0.05.

cross-sectional study among 1154 Chinese men and women,[30] and serum n-3 PUFAs was inversely associated with peripheral SBP and PP in 778 healthy Finnish men and women.[31]

In contrast to our findings, reports from randomized trials of n-3 PUFA supplementation during pregnancy did not find significant blood pressure reduction[10,11] or prevention of pregnancy hypertension.[2,32] This may possibly be due to baseline variation across study populations such as inclusion of women with high risk of pregnancy complications, or differences in the timing and duration of fish oil supplementation. Reports on

TABLE 5. Multivariate-Adjusted Relation of Maternal Plasma PC n-3 and 6 PUFAs at the 26th to the 28th Week of Gestation With Pregnancy-Associated Hypertension

Fatty Acids (%)	Pregnancy Associated Hypertension*					
	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*	OR (95% CI)	*P*	OR (95% CI)	*P*
n-3 PUFAs						
Total n-3 PUFAs	0.69 (0.54 to 0.89)	0.004	0.69 (0.53 to 0.90)	0.007	0.76 (0.60 to 0.97)	0.03
Long-chain n-3 PUFAs	0.69 (0.54 to 0.90)	0.006	0.69 (0.53 to 0.92)	0.01	0.77 (0.60 to 0.98)	0.04
n-6 PUFAs						
Total n-6 PUFAs	1.14 (1.01 to 1.29)	0.04	1.10 (0.97 to 1.26)	0.15	1.09 (0.97 to 1.22)	0.16
Linoleic acid	1.05 (0.94 to 1.18)	0.40	1.09 (0.96 to 1.24)	0.17	0.82 (0.56 to 1.19)	0.29
Dihomo-γ-linolenic acid	1.09 (0.81 to 1.49)	0.55	0.85 (0.57 to 1.26)	0.42	1.05 (0.82 to 1.34)	0.70
Arachidonic acid	1.23 (1.02 to 1.48)	0.03	1.10 (0.87 to 1.40)	0.42	1.07 (0.95 to 1.22)	0.26

BMI = body mass index, CI = confidence interval, DBP = diastolic blood pressure, OR = odds ratio, PC = phosphatidylcholine, PP = pulse pressure, PUFA = polyunsaturated fatty acids, SBP = systolic blood pressure. Results for α-linolenic acid and ratio of n-3 to n-6 PUFAs were not reported as their plasma concentrations were very low, leading to unstable estimates and large CIs in the regression analysis. Model 1: adjusted for age and ethnicity using multiple logistic regression. Model 2: adjusted for age, ethnicity, education, exercise, alcohol intake, smoking status, BMI, and height at the 26th to the 28th week of gestation, gestational diabetes, and heart rate. Model 3: adjusted for variables in Model 2 and fish oil supplementation.
*Pregnancy-associated hypertension (n = 28) included gestational hypertension (n = 16) and preeclampsia (n = 12). A total of 14 women with hypertension before pregnancy were excluded from analysis.

dietary n-3 PUFAs measured from food frequency questionnaires were inconsistent, with some studies reporting increased risk to preeclampsia from higher dietary n-3 PUFAs intake at mid-trimester[16] or fish oil supplementation at first trimester.[17] However, other studies reported a lower risk of preeclampsia with higher mean n-3 PUFA intake during the first and second trimesters[4] or null findings with retrospective recall of pregnancy diet.[14] The discrepant findings may be due to the varying gestation period when diet was assessed as well as measurement errors from questionnaires, leading to misclassification of n-3 PUFA status. As for the biomarker assessment, higher levels of erythrocyte n-3 PUFAs were associated with lower risk to preeclampsia[12,13] and a lower risk but not statistically significant in another report.[15]

As to the overall positive but not statistically significant associations between plasma PC n-6 PUFAs and maternal blood pressures, the findings are broadly consistent with 2 observational studies that reported an increased risk of hypertension in pregnancy with higher erythrocyte[15] or plasma n-6 PUFAs.[18] Other reports, however, found null relations with higher dietary[4] or plasma n-6 PUFA levels.[12]

Ethnic differences were found in plasma PC fatty acid composition and in the relations of plasma PC fatty acids to blood pressures. Chinese women had higher plasma PC n-3 PUFAs, possibly because of their higher intake of foods rich in n-3 PUFAs such as eggs, meat (poultry and nonpoultry), and fish, whereas the higher plasma PC n-6 PUFAs among the Indian women may be because of their higher use of n-6 PUFA-rich oils for cooking.[33] We postulate that the greater consumption of dietary n-3 PUFAs among the Chinese women may be linked with lower blood pressures,[30] whereas in Indian women, the high intake of n-6 PUFAs may lead to higher blood pressures.[8,18] Further investigations into the influences of genetic, dietary, and lifestyle factors on n-3 PUFAs and blood pressures in Asian women are needed.

Our study has several strengths. First, as data was acquired from a prospective birth cohort study, we were able to account for important confounders. Second, the blood pressure measurements were performed by trained research personnel, following a standard protocol. Last, our study sample of Chinese, Malay, and Indian women enabled us to examine the ethnicity-related variations in the relations of plasma PC n-3 and 6 PUFAs with blood pressures. However, the results should be cautiously interpreted because of the small sample size in the stratified analysis.

Limitations include the cross-sectional nature of our study and therefore we are unable to establish causality of the association between PUFAs and blood pressures. We were also unable to examine maternal blood pressure changes during pregnancy as they were measured only between the 26th and the 28th week of gestation. Our findings on the relations of PUFAs with pregnancy-associated hypertension were constrained by the lack of study power as there were only 28 cases of pregnancy-associated hypertension. Although we have excluded a total of 409 (35.4%) women in the GUSTO study, it is unlikely that selection bias would affect our results as most baseline characteristics between women who were included and excluded in the study were not materially different. Our effect estimates may be affected by residual confounding from imperfectly self-reported measures such as physical activity and supplement use. Last, we did not measure dietary intake of PUFAs, and this may have limited the interpretation of our study findings. However, plasma PC n-3 PUFAs have been found to be good markers of n-3 PUFA dietary intake,[22,23] and a dose–response relationship has been recently demonstrated in a randomized trial on the dose and time-dependent response of eicosapentaenoic acid and docosahexaenoic acid incorporation into various biosamples.[22]

In conclusion, plasma PC n-3 PUFAs were inversely related to peripheral and central SBP and central PP in pregnancy with stronger inverse relations of plasma PC n-3 in Chinese women, but positive relations with plasma PC n-6 PUFAs in Indian women. Higher plasma n-3 PUFAs between the 26th and the 28th week of gestation were associated with lower odds of pregnancy-associated hypertension.

ACKNOWLEDGMENTS

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