myoma of the uterus (34%) and polycystic ovary (19%).

DNA extraction and genotyping

Genomic DNA was extracted from peripheral white blood cells using a conventional protease K method. CYP1A1 Ile462Val (dbSNP rs1048943) and CYP1B1 Leu432Val (dbSNP rs1056836) polymorphisms were genotyped using PCR-RFLP analysis as described previously (Huang *et al.*, 1999; Tang *et al.*, 2000). Genotyping was conducted by laboratory personnel blinded to case-control status. To validate the genotyping, duplicate samples from some patients were provided in a manner blinded to the laboratory personnel; concordance for the blinded samples was 100%. Thus, experimenter bias was demonstrably minimized.

Measurement of organochlorines

Serum organochlorines were measured as described in our previous study (Tsukino *et al.*, 2005). Briefly, analyses were performed at the U.S. CDC using gas chromatography/high-resolution isotope dilution mass spectrometry for 58 compounds: 8 polychlorinated dibenzo-p-dioxin (PCDDs), 10 polychlorinated dibenzo-p-furans (PCDFs), 4 coplanar PCBs (cPCBs) and 36 ortho-substituted PCBs. The serum levels for these compounds were adjusted for serum lipid levels.

The term dioxins refers collectively to a group of PCDDs, PCDFs and cPCBs. To calculate the toxic equivalency (TEQ) of these compounds, a toxic equivalency factor (TEF) was assigned to each of the PCDDs, PCDFs and cPCBs (Van den Berg *et al.*, 1998). Summation of the TEQs of PCDDs, PCDFs and cPCBs gives the TEQ of dioxins (pg

TEQ/g lipid). In contrast, most of the PCBs are assigned a TEF of zero. Summation of the TEQs of mono-ortho-substituted PCBs (mPCBs) gives the TEQ of PCBs (pg TEQ/g lipid).

Statistical analysis

CYP1A1 Ile462Val and CYP1B1 Leu432Val polymorphisms were classified into two subgroups: genotypes homozygous for the major allele (CYP1A1: Ile/Ile; CYP1B1: Leu/Leu) and pooled heterozygous and minor allele homozygous genotypes (CYP1A1: Ile/Val and Val/Val; CYP1B1: Leu/Val and Val/Val). Concentrations of lipid-adjusted serum dioxins and PCB TEQ levels were defined as *low* or *high* based on the median value of control subjects.

To assess the main genetic and environmental effects on endometriosis, odds ratios (ORs) and their 95% confidence intervals (95% CIs) were calculated independently for CYP gene polymorphisms and serum levels of organochlorines using multivariate logistic regression analyses. To control for possible confounding factors, age was adjusted for in the multivariable logistic regression models. Secondly, risks of endometriosis were compared by a stratified model of genetic polymorphisms and organochlorine exposure. Multiplicative interactions were assessed by introducing a cross-product term between two-category genotypes and levels of serum organochlorines into the logistic regression models.

A two-sided $p < 0.05$ was considered significant in the analysis of main effects, while $p < 0.1$ was used when testing for the presence of interactions. SPSS for Windows software (version 11.0, SPSS JAPAN, Tokyo, Japan) was used for statistical analysis.

Results

Table I shows baseline characteristics of cases and controls. No significant difference was seen in mean age or body mass index between groups, or in the distribution of menstrual bleeding, hypermenorrhea, and smoking. The advanced endometriosis group displayed a significantly shorter menstrual cycle than controls (controls, 30.7 ±6.1 days; advanced endometriosis, 28.3 ±3.0 days; P=0.01) and was more likely to have menstrual cramp and dyspareunia.

The distributions of CYP gene polymorphisms and serum organochlorine levels are shown in Table II. The genotypic distributions of CYP1A1 Ile462Val and CYP1B1 Leu432Val polymorphisms were concordant with Hardy-Weinberg equilibrium (chi-square test: CYP1A1 Ile462Val, P = 0.42; CYP1B1 Leu432Val, P = 0.52). In the statistical analyses of dioxins and PCBs, we excluded one sample from each because the serum concentrations could not be reliably measured due to sample shortage. The range of concentrations among all subjects was 3.39 to 38.33 pg TEQ/g lipids for serum dioxins and 0.00 to 7.55 pg TEQ/g lipids for PCBs. Median values of serum dioxin and PCB concentrations were 18.18 and 1.21 pg TEQ/g lipids for controls, 17.69 and 1.05 pg TEQ/g lipids for early endometriosis, and 16.03 and 1.11 pg TEQ/g lipids for advanced endometriosis, respectively.

In the present study, there were no independent associations between the CYP gene polymorphisms and risk of either early or advanced endometriosis (Table II). Although serum dioxin levels showed a non-significant inverse association with advanced endometriosis (Table II, adjusted OR: 0.46, 95% CI: 0.20-1.06), no other associations were seen between serum organochlorines and either early or advanced endometriosis. Further

adjustment for menstrual cycle and duration of menstrual bleeding did not substantially affect the results (data not shown).

To assess possible effect modifications by CYP gene polymorphisms, we evaluated the association between serum organochlorine TEQ levels and risk of endometriosis stratified by CYP genotypes. No interaction between serum organochlorine level and CYP genotype was observed in early endometriosis (Tables III and IV). On the other hand, the CYP1A1 Ile462Val pooled Ile/Val and Val/Val genotypes showed a statistically significant reduced risk of advanced endometriosis in combination with a high serum dioxin TEQ level (Table III, adjusted OR: 0.13, 95% CI: 0.02-0.76). There was a statistically significant interaction between the CYP1A1 Ile462Val polymorphism and serum dioxin TEQ level (Table III, P for interaction = 0.08). Although no association was found between serum PCB TEQ level and advanced endometriosis in any stratum of CYP1B1 Leu432Val polymorphism, a statistically significant interaction was noted (Table IV, P for interaction = 0.05). For advanced endometriosis, no interaction was found in other combinations of CYP gene polymorphism and serum organochlorine level (Tables III and IV).

Discussion

In the present study, we demonstrated statistically significant interactions between the CYP1A1 Ile462Val and CYP1B1 Leu432Val polymorphisms and serum organochlorine TEQ levels in the risk of advanced endometriosis. This interaction would suggest the presence of an underlying biologic effect modification, possibly resulting in an altered disease phenotype. The results of this study provide epidemiologic clues to the etiology and pathogenesis of endometriosis, and identify populations at altered risk because of CYP gene

polymorphisms and serum organochlorine TEQ levels.

Genetic factors were implicated in endometriosis by a large study in twins, which found that 51% of the variance of susceptibility may be attributable to genetic influences (Treloar *et al.*, 1999). The effect of single genetic or environmental factors is usually weak; rather, multiple genetic and environment factors collaboratively contribute to the phenotypic variation of endometriosis. Indeed, the analysis of gene-environment interactions in our present study identified synergistic effects between CYP gene polymorphisms and serum organochlorines, although genetic or environmental factors alone did not cause statistically significant differences in the risk of endometriosis.

In this study, we found that the presence of a CYP1A1 462Val allele was associated with a statistically significant decreased risk of advanced endometriosis among women with high serum dioxins. The CYP1A1 462Val allele has been reported to be positively associated with TCDD-induced CYP1A1 mRNA expression (Landi et al., 2005). The most plausible hypothesis to explain our results is that sustained activation of CYP1A1 by dioxins alters estrogen metabolism, resulting in a lower susceptibility to endometriosis.

Significant interactions indicate that the effect of organochlorines differ between two strata of CYP gene polymorphism. In contrast to the relationship between CYP1A1 Ile462Val and serum dioxin TEQ, we observed a statistically significant interaction between CYP1B1 Leu432Val polymorphism and serum PCB TEQ, and the CYP1B1 432Val allele seemed to be associated with an increased risk of endometriosis in combination with a high serum PCB TEQ. Considering the relatively small number of subjects, the statistically significant interactions observed may have occurred merely by chance. Intrinsically, some PCBs have estrogenic properties while dioxins and dioxin-like

PCBs have antagonistic effects (Toppari *et al.*, 1996). The effect of organochlorines in individuals might be defined by the variety of different activations by CYP gene polymorphisms.

The frequency of CYP1A1 Ile462Val and CYP1B1 Leu432Val polymorphisms is known to vary widely in different populations (Solus *et al.*, 2004). The discrepancy in previous studies of organochlorine exposure and endometriosis may arise in part from inter-individual variability in susceptibility to organochlorines and to a dose-related bimodal effect (Yang *et al.*, 2000). The CYP1A1 Ile462Val and CYP1B1 Leu432Val polymorphisms may be a useful genetic marker predicting susceptibility to dioxins. It is preferable to include both genetic and environmental assessment in the study of complex traits.

The present study showed statistically significant interactions between CYP gene polymorphisms and serum organochlorine TEQ levels in the risk of advanced endometriosis, but not in that of early endometriosis. This apparent inconsistency might be attributable to diagnostic bias in early endometriosis, as mentioned in Methods above. If early endometriosis reflects normal physiology rather than 'real endometriosis', it would lead to a null result. In this regard, we clarified the effect of case and control definitions on the results by repeating the analyses in Tables 2-4 using the previous definition by Tsukino et al. (2005), namely control (no endometriosis and stage I) and cases (stage II-IV). However, these additional analyses did not change the results, and the definition of cases and controls had no effect on our conclusions.

Although this is probably the first study of CYP gene polymorphisms and organochlorines in endometriosis, the CYP1A1 462Val allele has been reported to be

mainly associated with increased risk of post-menopausal breast cancer in women with high serum PCBs (Moysich *et al.*, 1999; Laden *et al.*, 2002; Zhang *et al.*, 2004; Li *et al.*, 2005). This discrepancy between breast cancer and endometriosis may be attributable to different effects of organochlorines on carcinogenesis (Whysner and Williams, 1996), different responsiveness of mammary gland and endometrium (Gottardis *et al.*, 1988) and the interaction of serum organochlorines with estradiol levels (Ohtake *et al.*, 2003). Further more detailed molecular studies are needed to clarify the relationships between CYP gene polymorphism and organochlorines in the risk of endometriosis.

Participants in the present study were infertile. Given previous reports that factors associated with endometriosis differed between parous women, who experienced neither primary nor secondary infertility, and nulliparous infertile women (Missmer *et al.*, 2004 a, Missmer *et al.*, 2004 b), our present findings may be limited to infertile women. In addition, the use of infertile women as the control group should also be considered. When the study population comprises infertile women only, comparing infertile cases with a control group comprising infertile women without endometriosis may yield results very different from those that would be observed when comparisons are made with fertile women without endometriosis (Signorello *et al*, 1997). This is particularly true when the exposure of interest, such as menstrual cycle characteristics or reproductive history, is correlated with endometriosis and infertility. As a result of this use of infertile women as the control group, an association between serum organocholorines and the risk of endometriosis might be weakened or masked. Further, we cannot rule out the possibility that serum organocholorines are associated with both endometriosis and infertility.

The major limitation of this study was the small sample size, which limits its statistical

power. A larger sample size would allow a more precise estimate of main effects and interactions. Therefore, our results should be interpreted with caution. After reanalysis using a case-only design, which is an efficient and valid method for screening gene-environment interactions (Yang *et al.*, 1997), however, the interaction term between CYP 1A1 Ile462Val polymorphism and serum dioxin level was calculated as 0.045. Measurement of serum estradiol and its CYP1A1/1B1 metabolites would allow further refinement of the association between CYP1A1 and CYP1B1 gene polymorphisms and serum organochlorines, as well as any drug-drug interaction between serum estradiol and organochlorines, in the risk of endometriosis.

In conclusion, this study suggests that the CYP1A1 Ile462Val polymorphism is an effect modifier of the relationship between serum dioxins and the risk of advanced endometriosis. The CYP1B1 Leu432Val polymorphism modulates the effect of PCBs in the risk of advanced endometriosis. Better understanding of the relationships between genetic and environmental factors in complex traits may enable the prediction of widely differing risks of individuals or populations. Genetic susceptibility to the effects of organochlorines may affect a woman's likelihood of developing endometriosis.

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References

American Fertility Society (1985) Revised American Fertility Society classification of endometriosis. Fertil Steril 43,351-2.

Brennan P (2002) Gene-environment interaction and aetiology of cancer: what does it mean and how can we measure it? Carcinogenesis 23,381-7.

Eskenazi B, Mocarelli P, Warner M, Samuels S, Vercellini P, Olive D, Needham LL, Patterson DG Jr, Brambilla P, Gavoni N, et al. (2002) Serum dioxin concentrations and endometriosis: a cohort study in Seveso, Italy. Environ Health Perspect 110,629-34.

Gonzalez FJ (1988) The molecular biology of cytochrome P450s. Pharmacol Rev 40,243-88.

Gottardis MM, Robinson SP, Satyaswaroop PG, Jordan VC (1988) Contrasting actions of tamoxifen on endometrial and breast tumor growth in the athymic mouse. Cancer Res 48,812-5.

Heilier JF, Nackers F, Verougstraete V, Tonglet R, Lison D, Donnez J (2005) Increased dioxin-like compounds in the serum of women with peritoneal endometriosis and deep endometriotic (adenomyotic) nodules. Fertil Steril 84,305-12.

Huang CS, Shen CY, Chang KJ, Hsu SM, Chern HD (1999) Cytochrome P4501A1 polymorphism as a susceptibility factor for breast cancer in postmenopausal Chinese women in Taiwan. Br J Cancer 80,1838-43.

Kennedy S (1998) The genetics of endometriosis. J Reprod Med 43,263-8.

Laden F, Ishibe N, Hankinson SE, Wolff MS, Gertig DM, Hunter DJ, Kelsey KT (2002) Polychlorinated biphenyls, cytochrome P450 1A1, and breast cancer risk in the Nurses' Health Study. Cancer Epidemiol Biomarkers Prev 11,1560-5.

Landi MT, Bergen AW, Baccarelli A, Patterson DG Jr, Grassman J, Ter-Minassian M, Mocarelli P, Caporaso N, Masten SA, Pesatori AC, et al. (2005) CYP1A1 and CYP1B1 genotypes, haplotypes, and TCDD-induced gene expression in subjects from Seveso, Italy. Toxicology 207,191-202

Lebel G, Dodin S, Ayotte P, Marcoux S, Ferron LA, Dewailly E (1998) Organochlorine exposure and the risk of endometriosis. Fertil Steril 69,221-8.

Li Y, Millikan RC, Bell DA, Cui L, Tse CK, Newman B, Conway K (2005) Polychlorinated biphenyls, cytochrome P450 1A1 (CYP1A1) polymorphisms, and breast cancer risk among African American women and white women in North Carolina: a population-based case-control study. Breast Cancer Res 7,R12-8.

Louis GM, Weiner JM, Whitcomb BW, Sperrazza R, Schisterman EF, Lobdell DT, Crickard K, Greizerstein H, Kostyniak PJ (2005) Environmental PCB exposure and risk of endometriosis. Hum Reprod 20,279-85.

Marchino GL, Gennarelli G, Enria R, Bongioanni F, Lipari G, Massobrio M (2005) Diagnosis of pelvic endometriosis with use of macroscopic versus histologic findings. Fertil Steril 84,12-5.

Martucci CP, Fishman J (1993) P450 enzymes of estrogen metabolism. Pharmacol Ther 57,237-57.

Mayani A, Barel S, Soback S, Almagor M (1997) Dioxin concentrations in women with endometriosis. Hum Reprod 12,373-5.

Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Marshall LM, Hunter DJ. (2004 a) Incidence of laparoscopically confirmed endometriosis by demographic, anthropometric, and lifestyle factors. Am J Epidemiol 160,784-96.

Missmer SA, Hankinson SE, Spiegelman D, Barbieri RL, Malspeis S, Willett WC, Hunter DJ. (2004 b) Reproductive history and endometriosis among premenopausal women. Obstet Gynecol 104,965-74.

Moysich KB, Shields PG, Freudenheim JL, Schisterman EF, Vena JE, Kostyniak P, Greizerstein H, Marshall JR, Graham S, Ambrosone CB (1999) Polychlorinated biphenyls, cytochrome P4501A1 polymorphism, and postmenopausal breast cancer risk. Cancer Epidemiol Biomarkers Prev 8,41-4.

Ohtake F, Takeyama K, Matsumoto T, Kitagawa H, Yamamoto Y, Nohara K, Tohyama C, Krust A, Mimura J, Chambon P, et al. (2003) Modulation of oestrogen receptor signalling by association with the activated dioxin receptor. Nature 423,545-50.

Pauwels A, Schepens PJ, D'Hooghe T, Delbeke L, Dhont M, Brouwer A, Weyler J (2001) The risk of endometriosis and exposure to dioxins and polychlorinated biphenyls: a case-control study of infertile women. Hum Reprod 16,2050-5.

Rawson JM (1991) Prevalence of endometriosis in asymptomatic women. J Reprod Med 36,513-5.

Signorello LB, Harlow BL, Cramer DW, Spiegelman D, Hill JA (1997) Epidemiologic determinants of endometriosis: a hospital-based case-control study. Ann Epidemiol 7,267-271.

Solus JF, Arietta BJ, Harris JR, Sexton DP, Steward JQ, McMunn C, Ihrie P, Mehall JM, Edwards TL, Dawson EP (2004) Genetic variation in eleven phase I drug metabolism genes in an ethnically diverse population. Pharmacogenomics 5,895-931.

Tang YM, Green BL, Chen GF, Thompson PA, Lang NP, Shinde A, Lin DX, Tan W, Lyn-Cook BD, Hammons GJ, et al. (2000) Human CYP1B1 Leu432Val gene

polymorphism: ethnic distribution in African-Americans, Caucasians and Chinese; oestradiol hydroxylase activity; and distribution in prostate cancer cases and controls. Pharmacogenetics 10,761-6.

Toppari J, Larsen JC, Christiansen P, Giwercman A, Grandjean P, Guillette LJ Jr, Jegou B, Jensen TK, Jouannet P, Keiding N, et al. (1996) Male reproductive health and environmental xenoestrogens. Environ Health Perspect 104,741-803.

Treloar SA, O'Connor DT, O'Connor VM, Martin NG (1999) Genetic influences on endometriosis in an Australian twin sample. Fertil Steril 71,701-10.

Tsukino H, Hanaoka T, Sasaki H, Motoyama H, Hiroshima M, Tanaka T, Kabuto M, Niskar AS, Rubin C, Patterson DG Jr, et al. (2005) Associations between serum levels of selected organochlorine compounds and endometriosis in infertile Japanese women. Environ Res 99,118-25.

Van den Berg M, Birnbaum L, Bosveld AT, Brunstrom B, Cook P, Feeley M, Giesy JP, Hanberg A, Hasegawa R, Kennedy SW, et al. (1998) Toxic equivalency factors (TEFs) for PCBs, PCDDs, PCDFs for humans and wildlife. Environ Health Perspect 106,775-92.

Whysner J, Williams GM (1996) 2,3,7,8-Tetrachlorodibenzo-p-dioxin mechanistic data and risk assessment: gene regulation, cytotoxicity, enhanced cell proliferation, and tumor promotion. Pharmacol Ther 71,193-223.

Yang JZ, Agarwal SK, Foster WG (2000) Subchronic exposure to 2,3,7,8-tetrachlorodibenzo-p-dioxin modulates the pathophysiology of endometriosis in the cynomolgus monkey. Toxicol Sci 56,374-81.

Yang Q, Khoury MJ, Flanders WD (1997) Sample size requirements in case-only designs to

detect gene-environment interaction. Am J Epidemiol 146,713-20.

Zhang Y, Wise JP, Holford TR, Xie H, Boyle P, Zahm SH, Rusiecki J, Zou K, Zhang B, Zhu Y, et al. (2004) Serum polychlorinated biphenyls, cytochrome P-450 1A1 polymorphisms, and risk of breast cancer in Connecticut women. Am J Epidemiol 160,1177-83

Zondervan KT, Cardon LR, Kennedy SH (2002) What makes a good case-control study? Design issues for complex traits such as endometriosis. Hum Reprod 17,1415-23.

Table I. Baseline characteristics of cases and controls

(Number of subjects)	Controls (n=59)	Endometriosis			
		Early (Stage I-II) (n=31)	P for difference	Advanced (Stage III-IV) (n=48)	P for difference
Age (years), mean±SD	33.1±4.1	32.3±3.2	0.35	32.6±3.7	0.52
Body mass index (kg/m2), mean±SD	21.0±3.4	20.6±2.1	0.47	20.2±2.1	0.12
Menstrual cycle (days), mean±SD	30.7±6.1	29.6±3.6	0.34	28.3±3.0	0.01
Menstrual bleeding, no. (%)			0.79		0.65
<7 days	42 (71)	21 (68)		35 (73)	
>=7 days	15 (25)	6 (19)		10 (21)	
Missing	2 (3)	4 (13)		3 (6)	
Hypermenorrhea, no. (%)			0.80		0.83
No	39 (66)	20 (65)		29 (60)	
Yes	18 (31)	7 (23)		15 (31)	
Missing	2 (3)	4 (13)		4 (8)	
Menstrual cramping, no. (%)			0.32		0.02
No	10 (17)	2 (6)		1 (2)	
Yes	47 (80)	25 (81)		44 (92)	
Missing	2 (3)	4 (13)		3 (6)	
Dyspareunia, no. (%)			0.48		<0.01
No	31 (53)	12 (39)		10 (21)	
Yes	25 (42)	14 (45)		34 (71)	
Missing	3 (5)	5 (16)		4 (8)	
Smoking status, no. (%)			0.81		>0.99

Never smoker	38 (64)	19 (61)	29 (60)
Current or ever smoker	19 (32)	8 (26)	15 (31)
Missing	2 (3)	4 (13)	4 (8)

Table II. Effects of CYP gene polymorphisms and serum organochlorine levels considered separately in the risk of endometriosis

CYP gene polymorphism	Controls	Endometriosis			
		Early (Stage I-II)		Advanced (Stage III-IV)	
	n	n	Adjusted ORs (95% CI)[a]	n	Adjusted ORs (95% CI)[a]
CYP1A1 Ile462Val					
Ile/Ile	40	19	1	31	1
Ile/Val, Val/Val	19	12	1.35 (0.54-3.37)	17	1.20 (0.53-2.71)
CYP1B1 Leu432Val					
Leu/Leu	40	21	1	34	1
Leu/Val, Val/Val	19	10	1.01 (0.40-2.71)	14	0.90 (0.39-2.06)
Serum organochlorines[b]					
Dioxins					
Low (<18.18)	29	17	1	32	1
High (>=18.18)	30	14	0.93 (0.36-2.41)	15	0.46 (0.20-1.06)
PCBs					
Low (<1.21)	29	17	1	27	1
High (>=1.21)	30	13	0.84 (0.33-2.14)	21	0.80 (0.35-1.81)

Total dioxins/ PCBs					
Low (<20.32)	29	17	1	32	1
High (>=20.32)	30	13	0.84 (0.33-2.16)	15	0.47 (0.21-1.05)

[a]Adjusted for age.
[b]pg TEQ/g lipids

Table III. Effect modifications of the association between endometriosis and serum organochlorine levels by CYP 1A1 gene polymorphism

CYP gene polymorphism	Serum organochlorines[a]	Controls	Endometriosis			
			Early (Stage I-II)		Advanced (Stage III-IV)	
		n	n	Adjusted ORs (95% CI)[b]	n	Adjusted ORs (95% CI)[b]
CYP1A1 Ile462Val	Dioxins					
Ile/Ile	*Low (<18.18)*	20	9	1	18	1
Ile/Ile	*High (>=18.18)*	20	10	1.10 (0.32-3.75)	13	0.75 (0.28-2.06)
Ile/Val, Val/Val	*Low (<18.18)*	9	8	1	14	1
Ile/Val, Val/Val	*High (>=18.18)*	10	4	0.63 (0.13-3.15)	2	0.13 (0.02-0.76)*
P for interaction				0.30		0.08†
CYP1A1 Ile462Val	PCBs					
Ile/Ile	*Low (<1.21)*	19	10	1	19	1
Ile/Ile	*High (>=1.21)*	21	9	0.73 (0.21-2.56)	12	0.57 (0.20-1.62)
Ile/Val, Val/Val	*Low (<1.21)*	10	7	1	8	1
Ile/Val, Val/Val	*High (>=1.21)*	9	4	0.65 (0.13-3.28)	9	1.38 (0.36-5.34)
P for interaction				0.68		0.36

CYP1A1 Ile462Val	Total dioxins/ PCBs					
Ile/Ile	*Low (<20.32)*	19	10	1	19	1
Ile/Ile	*High (>=20.32)*	21	9	0.75 (0.23-2.51)	12	0.58 (0.21-1.58)
Ile/Val, Val/Val	*Low (<20.32)*	10	7	1	13	1
Ile/Val, Val/Val	*High (>=20.32)*	9	4	0.89 (0.17-4.55)	3	0.27 (0.06-1.27)
P for interaction				0.74		0.38

[a]pg TEQ/g lipids

[b]Adjusted for age.

*P < 0.05 for main effects.

†P < 0.1 for interaction terms.