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Preliminary communication

Dietary folate and vitamins B_{12}, B_6, and B_2 intake and the risk of postpartum depression in Japan: The Osaka Maternal and Child Health Study

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Abstract

Background: Previous studies showed an inverse association between folate intake and depression. However, epidemiological evidence for folate intake and postpartum depression is unavailable. This prospective study examined the relationship of dietary consumption of folate and B vitamins during pregnancy with the risk of postpartum depression.
Methods: Study subjects were 865 Japanese women. Dietary data were obtained during pregnancy from a validated self-administered diet history questionnaire. Postpartum depression was defined as present when subjects had an Edinburgh Postnatal Depression Scale score of 9 or higher between 2 and 9 months postpartum. Adjustment was made for age, gestation, parity, cigarette smoking, alcohol intake, family structure, family income, education, changes in diet in the previous 1 month, season when data at baseline were collected, body mass index, time of delivery before the second survey, medical problems in pregnancy, baby's sex, and baby's birth weight.
Results: Postpartum depression developed in 121 subjects (14.0%) 2 to 9 months postpartum. There was no measurable association between intake of folate, cobalamin, or pyridoxine and the risk of postpartum depression. Compared with riboflavin intake in the first quartile, only riboflavin consumption in the third quartile was independently related to a decreased risk of postpartum depression (multivariate odds ratio: 0.53, 95% CI: 0.29–0.95, P for trend=0.55).
Limitations: Personal and family psychiatric history, sociocultural factors, and personal and family relations were not controlled for. The possibility of misclassification of dietary information during pregnancy should be considered.

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Conclusions: Our results suggest that moderate consumption of riboflavin may be protective against postpartum depression.

Keywords: Dietary intake; Folate; Japan; Postpartum depression; Vitamin B_2

1. Introduction

Investigations on a possible role of nutritional factors in depressive symptoms are becoming more numerous. Components of 1-carbon metabolism such as folate and vitamin B_{12} are involved in important processes related to central nervous system functions (Bjelland et al., 2003a). A prospective cohort study among Finnish middle-aged men demonstrated that a lower dietary intake of folate was significantly associated with an increased risk of a discharge diagnosis of a depressive disorder (Tolmunen et al., 2004). In a cross-sectional study using baseline data from a previously cited cohort study, a significant positive relationship was observed between lower intake of folate and depressive symptoms (Tolmunen et al., 2003). However, no associations were shown between intake of cobalamin (vitamin B_{12}), pyridoxine (vitamin B_6), or riboflavin (vitamin B_2) and depression (Tolmunen et al., 2003, 2004). Bjelland et al. (2003b) reported that hyperhomocysteinemia and the T/T methylenetetrahydrofolate reductase genotype, but not low plasma folate or vitamin B_{12} levels, were significantly associated with the prevalence of depression in approximately 6000 middle-aged and elderly Norwegians; only in the subgroup of middle-aged women were plasma folate levels inversely related to depression. Some studies found low serum or red blood cell folate concentrations in patients with major depression (Abou-Saleh and Coppen, 1989; Bottiglieri et al., 2000; Carney et al., 1990; Ghadirian et al., 1980; Morris et al., 2003). On the other hand, a null (Hvas et al., 2004) or positive (Lee et al., 1998) relationship of erythrocyte folate levels with depression was found. Results regarding an association between serum vitamin B_{12} levels and depression are equivocal (Bottiglieri et al., 2000; Lindeman et al., 2000; Penninx et al., 2000; Ramos et al., 2004; Tiemeier et al., 2002). One report suggested an inverse association between plasma vitamin B_6 levels and depressive symptoms (Hvas et al., 2004).

The mother is the only nutrient source for the fetus. Depletion of crucial nutrients during pregnancy can adversely affect both mother and infant. In view of the lack of epidemiological evidence of a relationship of dietary intake of folate and vitamins B_{12}, B_6, and B_2 with the risk of postpartum depression, we investigated this issue using data from the Osaka Maternal and Child Health Study (OMCHS).

2. Methods

2.1. Study population

The OMCHS is an ongoing prospective cohort study that investigates preventive and risk factors for maternal and child health problems. The principal objective of the OMCHS is to clarify risk factors for childhood allergic disorders. We conducted a baseline survey to obtain information on prenatal environmental factors from pregnant women between November 2001 and March 2003. Details of the baseline survey of the OMCHS have been described elsewhere (Miyake et al., 2005). In brief, eligible females were those who became pregnant in Neyagawa City, which is 1 of the 44 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. Of the 3639 eligible females in Neyagawa City, 627 (17.2%) participated in this study between November 2001 and March 2003. Eight pregnant females who did not live in Neyagawa City but who had become aware of the present study at an obstetric clinic before August 2002 decided by themselves to participate in this study. Also, there were 77 participants who received explanations regarding the OMCHS from public health nurses in 6 other municipalities between August 2002 and March 2003. From October 2002 to March 2003, 290 participants were recruited from a university hospital and three obstetric hospitals in three other municipalities; these women were recommended for participation in the OMCHS by an obstetrician. A total of 1002 pregnant women gave their fully informed consent in writing and completed the baseline survey. Of the 1002 females, 867 mothers participated in the second survey at 2–9 months postpartum. Two mothers were excluded because of missing data on the baby's birth weight. The final analysis comprised 865 subjects. The ethics committee of the Osaka City University School of Medicine approved the OMCHS.

2.2. Measurements

At baseline, each participant filled out a set of 2 self-administered questionnaires. Also, a self-administered questionnaire was used in the second survey. Participants mailed these completed questionnaires to the data management center at the time of each survey. Research technicians completed missing or illogical data by telephone interview.

In the baseline survey, we collected information on dietary habits during the previous 1 month by using a validated self-administered diet history questionnaire. The structure and validity of the questionnaire were described in detail elsewhere (Sasaki et al., 1998, 2000). In this instrument, intake of 147 food items was calculated using an ad-hoc computer algorithm developed to analyze the questionnaire. Energy-adjusted intake by the residual approach was used for the analyses (Willett and Stampfer, 1986). Because only a small number of participants used calcium (5.3%), vitamin C (5.4%), vitamin B complex (4.3%), and multivitamin (3.9%) supplements at least once a week, use of these dietary supplements was not incorporated into the analysis in this study.

Another self-administered questionnaire at baseline inquired about age, gestation, parity, smoking habits, family structure, occupation, family income, education, weight, height, and changes in diet in the previous 1 month. Body mass index was calculated by dividing self-reported body weight (kg) by the square of self-reported height (m).

A self-administered questionnaire in the second survey included the Japanese version of the Edinburgh Postnatal Depression Scale (EPDS). The EPDS is a 10-item self-reported scale especially designed to screen for postpartum depression in community samples (Cox et al., 1987). Each item is scored on a 4-point scale (from 0 to 3) and the total score ranged from a minimum of 0 to a maximum of 30. The scale rates the intensity of depressive symptoms present within the previous 7 days. Although Cox and colleagues (Cox et al., 1987) proposed a cutoff level of 10 if the test is to be used for screening purposes in the postpartum period, a threshold score of 8/9 was found to detect depression among Japanese women with a specificity of 93% and sensitivity of 75% (Okano et al., 1996). Therefore, in the present study postpartum depression was defined as present when subjects had an EPDS score of 9 or higher. The questionnaire also elicited information on medical problems in pregnancy and sex, birth weight, and date of birth of the infant born after the baseline survey.

2.3. Statistical analysis

Intake of selected nutrients was categorized at quartile points based on the distribution among 865 pregnant women. Age was classified into 3 categories (<29, 29–31, and 32+ years); gestation into 3 (<15, 15–20, and 21+ weeks); parity into 2 (0 and 1+); cigarette smoking into 3 (never, former, and current); family structure into 2 (nuclear and expanded); occupation into 2 (outside work and housewife); family income into 3 (<4,000,000, 4,000,000–5,999,999, and 6,000,000+ yen/year); education into 3 (<13, 13–14, and 15+ years); changes in diet in the previous 1 month into 3 (none or seldom, slight, and substantial); season when data at baseline were collected into 4 (spring, summer, fall, and winter); time of delivery before the second survey into 2 (<4 and 4+ months); medical problems in pregnancy into 2 (yes and no); baby's sex into 2 (male and female); and baby's birth weight into 2 (<2500 and 2500+ g). Body mass index and energy-adjusted alcohol intake were used as continuous variables.

Logistic regression analysis was used to estimate crude odds ratios (ORs) and 95% confidence intervals (CIs) of postpartum depression in relation to consumption of selected dietary factors under study. Multiple logistic regression analysis was used to control for the potential confounding factors. Trend of association was assessed by a logistic regression model assigning consecutive integers (1 to 4) to the levels of the independent variable. Two-sided P-values less than 0.05 were regarded as statistically significant. All computations were performed using the SAS software, version 9.1 (SAS Institute, Inc., Cary, NC).

3. Results

About 30% of subjects were from 29 to 31 years of age at baseline. Approximately 70% of the women took part in the baseline survey by the 20th week of gestation and around half had a parity of 1 or more at baseline. Infants of 6% of mothers had a birth weight less than 2500 g. There were 24 premature deliveries (24 to 36 weeks of gestation) and 816 babies were born at 37 to 41 weeks of gestation. Mean daily total energy and energy-adjusted consumption of folate, cobalamin, pyridoxine, and riboflavin were 7752 kJ, 286.1 μg, 5.7 μg, 1.0 mg, and 1.4 mg, respectively.

Of the 865 mothers, 121 subjects (14.0%) developed postpartum depression at 2–9 months postpartum. No measurable association was observed between intake of folate, cobalamin, or pyridoxine and the risk of postpartum depression (Table 1). Adjustment for age, gestation, parity, cigarette smoking, alcohol intake, family structure, family income, education, changes in diet in the previous 1 month, season when data at baseline were collected, body mass index, time of delivery before the second survey, medical problems in pregnancy, baby's sex, and baby's birth weight did not appreciably change these findings. Compared with riboflavin intake in the first quartile, riboflavin consumption in the second and third quartiles, but not the fourth quartile, was significantly related to a decreased risk of

Table 1
Odds ratios and 95% CIs for postpartum depression according to quartile of intake of selected vitamins in 865 women, the Osaka Maternal Child Health Study, Japan[a]

Variable[b]	Quartile				P for trend
	1	2	3	4	
Folate					
Intake (μg/day)	204.8	255.4	294.5	377.3	
No. of cases	31	25	29	36	
Crude odds ratio (95% CI)	1.00	0.78 (0.44–1.37)	0.93 (0.53–1.60)	1.19 (0.71–2.01)	0.42
Multivariate odds ratio (95% CI)	1.00	0.81 (0.45–1.45)	0.99 (0.56–1.77)	1.20 (0.68–2.13)	0.40
Cobalamin (vitamin B_{12})					
Intake (μg/day)	3.3	4.6	5.9	8.3	
No. of cases	37	29	27	28	
Crude odds ratio (95% CI)	1.00	0.75 (0.44–1.27)	0.69 (0.40–1.18)	0.72 (0.42–1.22)	0.20
Multivariate odds ratio (95% CI)	1.00	0.75 (0.43–1.28)	0.73 (0.41–1.28)	0.73 (0.42–1.29)	0.29
Pyridoxine (vitamin B_6)					
Intake (mg/day)	0.7	0.9	1.0	1.2	
No. of cases	32	23	28	38	
Crude odds ratio (95% CI)	1.00	0.69 (0.38–1.21)	0.86 (0.49–1.48)	1.22 (0.73–2.05)	0.32
Multivariate odds ratio (95% CI)	1.00	0.75 (0.41–1.35)	0.95 (0.53–1.69)	1.30 (0.75–2.28)	0.25
Riboflavin (vitamin B_2)					
Intake (mg/day)	1.0	1.2	1.4	1.7	
No. of cases	40	25	22	34	
Crude odds ratio (95% CI)	1.00	0.58 (0.33–0.98)	0.50 (0.28–0.87)	0.82 (0.49–1.35)	0.35
Multivariate odds ratio (95% CI)	1.00	0.61 (0.34–1.06)	0.53 (0.29–0.95)	0.88 (0.51–1.50)	0.55

[a] Values for intake are medians for adjusted energy intake by using the residual method for each quartile.
[b] The multivariate models included the following: age (<29, 29–31, and 32+ years), gestation (<15, 15–20, and 21+ weeks), parity (0 and 1+), cigarette smoking (never, former, and current), energy-adjusted alcohol intake (continuous), family structure (nuclear and expanded), family income (<4,000,000, 4,000,000–5,999,999, and 6,000,000+ yen/year), education (<13, 13–14, and 15+ years), changes in diet in the previous 1 month (none or seldom, slight, and substantial), season when data at baseline were collected (spring, summer, fall, and winter), body mass index (continuous), time of delivery before the second survey (<4 and 4+ months), medical problems in pregnancy (yes and no), baby's sex (male and female), and baby's birth weight (<2500 and 2500+ g).

postpartum depression. The inverse relationship was slightly attenuated after multivariate adjustment: only riboflavin consumption in the third quartile was independently inversely associated with the risk of postpartum depression (multivariate OR: 0.53, 95% CI: 0.29–0.95, P for trend = 0.55).

4. Discussion

Folate and cobalamin are involved in the 1-carbon cycle (methylation) that furnishes *S*-adenosyl-methionine, the sole methyl donor for a broad range of reactions necessary for the synthesis of neuroactive substances, the formation of membrane phospholipids, and the metabolism of nucleic acids (Alpert et al., 2000; Bjelland et al., 2003a). Folate also appears to influence the biosynthesis of biopterin-dependent neurotransmitters (Alpert et al., 2000; Bjelland et al., 2003a). Methyltetrahydrofolate may have a neuromodulatory role at presynaptic sites by binding to glutamate receptors (Alpert et al., 2000; Bjelland et al., 2003a). Elevated levels of homocysteine, resulting from folate deficiency, may play a role in mediating some of the neuropsychiatric complications due to folate deficiency (Alpert et al., 2000; Bjelland et al., 2003a). The synthesis of serotonin and the catecholamines is dependent on the metabolite of pyridoxine (Hvas et al., 2004). Riboflavin coenzymes are needed for both the remethylation and transsulfuration of homocysteine (Ganji and Kafai, 2004).

In the present study, an inverse relationship between the intake of folate, cobalamin, or pyridoxine and the risk of postpartum depression was not observed. The findings are at variance with previous studies that showed an inverse association between folate intake and depressive symptoms (Tolmunen et al., 2003, 2004). We also found an inverted J-shaped association between riboflavin intake and postpartum depression. Dietary intake of riboflavin and folate, but not cobalamin and pyridoxine, was independently related to decreased concentrations of serum homocysteine in the third National Health and

Examination Survey (Ganji and Kafai, 2004). Hyperhomocysteinemia may play a critical role in mediating the relationship between a lower intake of riboflavin and the risk of postpartum depression. In this context, our findings may be in partial agreement with this observation regarding riboflavin.

The present study had several methodological strengths. The prospective design and relatively high rate of follow-up (86.3%) in this study minimized the possibility of recall bias or bias caused by loss of follow-up. Study subjects were homogeneous in terms of having the same residential background. Extensive information on potential confounding factors was adjusted for. However, we were not able to control for personal and family psychiatric history, sociocultural factors, and personal and family relations.

There are several weaknesses. The diagnosis of postpartum depression was established with the EPDS. Moreover, although the second survey was conducted at 2–9 months postpartum, a large majority of subjects, 89.2%, participated in the second survey at 3–4 months postpartum. Thus, it is difficult to estimate the incidence of postpartum depression accurately. The consequence would introduce a bias toward the null because of nondifferential outcome misclassification. Dietary data were obtained using a self-administered semiquantitative dietary assessment questionnaire. Since we did not assess the actual dietary habits of the subjects over a long period of time, the possibility of misclassification should be considered. Our diet history questionnaire was designed to assess recent dietary intake, i.e. for 1 month prior to completing the questionnaire. This disadvantage is likely to be alleviated after adjustment for the season when baseline data were collected, however. Changes in diet in the past 1 month were controlled for because pregnant females are likely to change their diet for reasons such as nausea gravidarum. We found no significant interaction between changes in diet in the past 1 month or timing of the baseline assessment and exposures under investigation in relation to postpartum depression (data not shown). Potential misclassification associated with variability across subjects in terms of the stability of diet during pregnancy and the timing of the dietary assessment is likely to be negligible. Thus, negative findings of our study could not simply mean that diet was assessed at the wrong time. The study subjects were an unrepresentative sample of Japanese females in the general population, and the present findings may not be generalized. In fact, educational levels were higher in the present study population than in the general population. According to the 2000 population census of Japan, the proportions of females aged 30 to 34 years in Osaka Prefecture with years of education of <13, 13–14, 15+, and unknown were 49.2, 32.3, 13.6, and 4.9%, respectively (Statistic Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications, Japan, 2002). The corresponding figures for the current study were 29.7, 42.4, 27.9, and 0.0%, respectively.

This is the first prospective study on intake of folate and B vitamins and the risk of postpartum depression. Our results suggest that moderate riboflavin consumption may be protective against postpartum depression. However, these results are preliminary. Further studies with more precise exposure and outcome measurements are warranted to determine whether moderate consumption of riboflavin is protective against postpartum depression, taking into consideration additional factors such as psychiatric history and sociocultural status.

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Appendix A

Other members of the Osaka Maternal and Child Health Study Group were as follows: Mr. Shoichi Miyamoto, Mr. Ichiro Matsunaga, Dr. Hajime Oda, Dr. Hideharu Kanzaki, Dr. Mitsuyoshi Kitada, Dr. Yorihiko Horikoshi, Dr. Osamu Ishiko, Dr. Yuichiro Nakai, Dr. Junko Nishio, Dr. Seiichi Yamamasu, Dr. Jinsuke Yasuda, Dr. Seigo Kawai, Dr. Kazumi Yanagihara, Dr. Koji Wakuda, Dr. Tokio Kawashima, Dr. Katsuhiko Narimoto, Dr. Yoshihiko Iwasa, Dr. Katsuhiko Orino, Dr. Itsuo Tsunetoh, Dr. Junichi Yoshida, Dr. Junichi Iito, Dr. Takuzi Kaneko, Dr. Takao Kamiya, Dr. Hiroyuki Kuribayashi, Dr. Takeshi Taniguchi, Dr. Hideo Takemura, and Dr. Yasuhiko Morimoto.

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Magnesium intake is inversely associated with the prevalence of tooth loss in Japanese pregnant women: the Osaka Maternal and Child Health Study

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Abstract. There have only been a few studies on the role of mineral intake in tooth loss. We investigated the association between mineral intake and the prevalence of tooth loss in Japan. We used the baseline data on 1002 pregnant women who were enrolled in the Osaka Maternal and Child Health Study between November 2001 and March 2003. Tooth loss was defined as the previous extraction of one or more teeth. Nutrient intake was assessed by a validated diet history questionnaire. Prevalence *odds ratios* and confidence intervals were estimated by applying a multiple logistic regression model. The adjusted *odds ratio* upon comparison of the highest quartile with the lowest quartile of magnesium intake was 0.64 (95% confidence interval, 0.42-0.99), showing a tendency for an inverse dose-response relationship (p for linear trend = 0.05). There were no associations between the level of consumption of calcium, phosphate, iron, zinc, or copper and tooth loss. The present findings suggest that intake of magnesium is related to reduced prevalence of tooth loss among young Japanese women.

Key words: cross-sectional study, Japanese women, magnesium, tooth loss

There is a two-way relationship between diet and oral health: a balanced diet with adequate energy and nutrients is essential for oral health, and the condition of the oral cavity may impact an individual's diet and nutritional status [1]. Many previous studies on the association between tooth loss and nutrient intake have focused on nutritional deficiency such as decreased consumption of vegetables, fruits, dietary fiber and antioxidant nutrients among the middle-aged and elderly who retain a few teeth or are edentulous [2-11]. There have been a few studies on the relationship between tooth loss and low mineral intake among elderly individuals [4, 6, 11]. A U.S. cross-sectional study of elderly people demonstrated that edentulism was associated with lower consumption of calcium and magnesium compared with the respective levels in the dentate [6].

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A paucity of information exists on the possible role that mineral intake plays in oral diseases. In a longitudinal study of black South African children, low magnesium intake was significantly associated with caries in deciduous teeth, although no associations were found for consumption of calcium, iron, phosphorus, zinc, or copper [12]. A cross-sectional study among Swedish adolescents found that iron intake was inversely associated with the prevalence of dental caries [13]. The Third National Health and Nutrition Examination Survey in the U.S. showed that low dietary intake of calcium was significantly associated with severe periodontitis [14]. Freeland and colleagues [15] reported that dietary calcium intake was significantly and inversely associated with the severity of periodontitis, although no association with serum concentrations of magnesium was observed among 80 dental patients. One interventional study indicated that taking calcium and vitamin D supplements was significantly associated with a lower risk of tooth loss among the elderly [16]. There has been no epidemiologic study on the association between mineral intake and tooth loss in Japan. Therefore, we examined the relationship between the level of mineral intake and tooth loss among pregnant Japanese women using the baseline data from the Osaka Maternal and Child Health Study (OMCHS).

Methods

Study population

The subjects of the present study were pregnant Japanese women who were enrolled in the OMCHS between November 2001 and March 2003. Details of the OMCHS were described previously [17, 18]. Briefly, the OMCHS is an ongoing prospective cohort study that examines preventive factors and risk factors for maternal and child health problems, such as allergic disorders. In Japan, when women become pregnant, they notify the municipality of the domicile of the conception, and the municipality provides them with a maternal and child health handbook. Women who were eligible for the OMCHS were those who lived in Neyagawa City, a municipality in Osaka Prefecture, Japan. The Neyagawa City Government provided all pregnant women with a set of leaflets explaining our study, an application form, and a self-addressed and stamped return envelope together with the maternal and child health handbook. Among the 3639 women, 627 pregnant women (17.2%) consented to participate in the OMCHS. Eight pregnant women who did not live in Neyagawa City but who became aware of the OMCHS at an obstetric clinic before August 2002, decided by themselves to participate in the OMCHS. Seventy-seven women received explanations of the OMCHS from public health nurses in 6 other municipalities from August 2002 to March 2003, and were enrolled in the OMCHS. From October 2002 to March 2003, 290 women were recruited from a university hospital and three obstetric hospitals in 3 other municipalities; it had been recommended that these women participate in the OMCHS by an obstetrician. Therefore, a total of 1002 pregnant women gave written informed consent to participate in the OMCHS between November 2001 and March 2003, and completed the two baseline questionnaires. The ethics committees of the Osaka City University School of Medicine and the Osaka Prefectural Institute of Public Health approved the OMCHS.

Questionnaire

At the time of enrollment in the OMCHS, each participant filled out two self-administered questionnaires. The participants mailed the questionnaires to the data management center. Research technicians completed missing and illogical data in the questionnaires by telephone interview.

The first questionnaire was a validated self-administered diet history questionnaire that was used to assess dietary habits over the previous one month. The structure and validity of this questionnaire were described previously [19, 20]. In this instrument, the intake of 147 food items is calculated using an *ad-hoc* computer algorithm that had been developed to analyze the questionnaire. Energy-adjusted intake was calculated by the residual method [21] and used in the analyses.

The second self-administered questionnaire elicited information on age, gestation, parity, smoking habit, passive smoking at home and at work, family income, education, height, weight, changes in diet in the previous one month, experience of extraction of one or more permanent teeth excluding third molars, and the number of remaining teeth. Tooth loss was defined as the extraction of one or more teeth. Body mass index was calculated by dividing body weight (kg) by the square of the height of the individual (m).

Statistical methods

The study population was divided into quartiles with regard to the intake of each selected nutrient. The logistic regression model was used to estimate crude *odds ratios* (ORs) and their 95% confidence intervals

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(CIs) for tooth loss relative to intake of selected minerals. Multiple logistic regression analysis was used to control for potential confounders. Adjustment was made for age, gestation, parity, cigarette smoking, passive smoking at home and at work, family income, education, changes in diet in the previous one month, season when data were collected, and body mass index. Active and passive smoking exposure was controlled for because our previous study showed a significant positive association between active and passive smoking status and the prevalence of tooth loss [18]. Trend of association was assessed by a logistic model assigning scores to the levels of the independent variable. Analyses were conducted using SAS software (version 9.1, SAS Institute Inc., Cary, NC, USA). All p-values are 2-tailed. $p < 0.05$ was considered to be statistically significant.

Results

The 1002 pregnant women in this study ranged in age from 15 to 44 years (mean age, 29.8 years; median age, 30 years) at the time of enrollment in the OMCHS. Approximately 30% of the subjects were between 29 and 31 years old *(table 1)*. Approximately 70% were enrolled by the 20th week of gestation, and about 50% had a parity of one or more. Seven hundred two pregnant women (70.1%) had experienced slight or substantial changes in diet in the previous one month due to nausea gravidarum (585 women), maternal and fetal health (107 women), or other reason (10 women). The mean daily intake of total energy was 6815 kJ. Among the 1002 pregnant women, 256 women (25.5%) had previously had one or more teeth extracted *(table 2)*.

Table 3 shows the ORs and their 95% CIs for tooth loss according to the level of consumption of various minerals. Compared with magnesium intake in the lowest quartile, its consumption in the highest quartile was significantly associated with a decreased prevalence of tooth loss, showing a clear inverse dose-response relationship. After adjustment for the confounders under investigation, the inverse association remained significant although the linear trend fell just short of significance (adjusted OR in the highest quartile: 0.64, 95% CI: 0.42-0.99, p for linear trend = 0.05). There were no appreciable relationships between the level of intake of calcium, phosphate, iron, zinc, or copper and tooth loss.

Discussion

The current cross-sectional study found that intake of magnesium, but not calcium, phosphate, iron, zinc or copper, was significantly associated with a reduced prevalence of tooth loss. The present results are in partial agreement with a previous study that found an association between low magnesium intake and dental caries in children [12], but are not consistent with studies that found that calcium intake was inversely associated with periodontitis [14, 15]. The potential underlying mechanism for the observed inverse relationship between magnesium intake and the prevalence of tooth loss is not known. Magnesium *per se* may prevent tooth loss. A cross-sectional study among middle-aged and older U.S. women showed that magnesium intake was inversely associated with systemic inflammation [22]. Our previous study showed a tendency for an inverse relationship between magnesium intake and the prevalence of allergic rhinitis in the present subjects [23]. Magnesium intake might influence oral health thorough improving immunocompetence and reducing systemic inflammation. Magnesium deficiency caused loss of structure of periodontal tissues in adult rats [24]. On the other hand, the observed inverse association between magnesium intake and tooth loss may be ascribed to unknown nutritional factors related to bone metabolism. Magnesium is involved in bone and mineral homeostasis and is important in bone crystal growth and stabilization [25]. In a cross-sectional study of 62 healthy women aged 45-55 years in the U.S., intake of magnesium, potassium, and alcohol was significantly associated with increased bone mineral density [26]. There were significant linear relationships between the bone mineral density at the spine or radius and the total number of teeth among 329 healthy postmenopausal women aged 41-71 years [27]. Another possible explanation is that unknown factors related to magnesium intake produce a spurious inverse association between magnesium intake and tooth loss. Mineral intake in Japanese people may be associated with part of a larger pattern of traditional Japanese dietary customs or behaviors. Legumes and seaweed, which are the richest dietary sources of magnesium, are part of the traditional Japanese diet.

In this investigation, we used self-reported tooth loss as a measure of dental health status. We did not assess the validity of self-reported tooth loss in our subjects. However, in several validation studies of self-reported oral health, there was substantial agreement between the self-reported and observed number of remaining teeth regardless of age or sex

Table 1. Distribution of the baseline characteristics of the 1002 pregnant women, OMCHS[a], Japan[b].

Factor	Number (%) or mean (SD[c])
Age (years)	
< 29	380 (37.9)
29–31	299 (29.8)
32+	323 (32.4)
Gestation (weeks)	
< 15	357 (35.6)
15–20	329 (32.8)
21+	316 (31.5)
Parity of one or more	513 (51.2)
Cigarette smoking	
Never	697 (69.6)
Former	121 (12.1)
Current	184 (18.4)
Passive smoking at home	
Never	284 (28.3)
Former	224 (22.4)
Current	494 (49.3)
Passive smoking at work	
Never	344 (34.3)
Former	538 (53.7)
Current	120 (12.0)
Family income (JPY[d]/*year*)	
< 4,000,000	301 (30.0)
4,000,000–5,999,999	403 (40.2)
6,000,000+	298 (29.7)
Education (years)	
< 13	323 (32.2)
13–14	413 (41.2)
15+	266 (26.6)
Change in diet in the previous one month	
None or seldom	300 (29.9)
Slight	435 (43.4)
Substantial	267 (26.7)
Season when data were collected	
Spring	318 (31.7)
Summer	162 (16.2)
Fall	223 (22.3)
Winter	299 (29.8)
Body mass index (kg/m^2)	21.4 (2.8)
Daily nutrient intake[e]	
Total energy (kJ)	6815.3 (1793.8)
Calcium (mg)	556.0 (182.9)
Phosphate (mg)	890.0 (183.8)
Magnesium (mg)	194.4 (49.9)
Iron (mg)	7.5 (1.7)
Zinc (μg)	7222.8 (1320.7)
Copper (μg)	1094.9 (316.9)

[a] OMCHS, Osaka Maternal and Child Health Study.
[b] Characteristics of the women at the time of entry into the OMCHS are shown.
[c] SD, Standard deviation.
[d] JPY, Japanese Yen, US $1 = ¥118.
[e] Nutrient intake was adjusted for total energy intake by the residual method.

Table 2. Distribution of tooth loss among the 1002 pregnant women, OMCHS[a], Japan.

Number of teeth lost	Number of subjects (%)
0	746 (74.5)
1	85 (8.5)
2	57 (5.7)
3	29 (2.9)
4	43 (4.3)
5+	42 (4.2)

[a] OMCHS, Osaka Maternal and Child Health Study.

[28-30]. These results indicated that self-reported oral status can provide reasonably valid data on the remaining teeth. Hence, the use of self-reported tooth loss as a key indicator in epidemiological studies on dental health can be considered satisfactory.

The strengths of the current study include the homogeneity of the study subjects in that they consisted of pregnant Japanese women, and the comprehensive assessment of potential confounders. All dietary data were self-reported. However, since we did not actually observe the dietary habits of the subjects, there is a possibility of misclassification. According to the validation study of Sasaki and colleagues [19], the correlation coefficients of nutrient intake between those estimated from the diet history questionnaire and those observed in a 3-day dietary record in women were 0.49, 0.59, and 0.40 for calcium, phosphorus, and iron, respectively. The subjects with tooth loss in our study might not be aware of the possible ill effects of diet. The consequence would have been underestimation of values in our results due to nondifferential exposure misclassification. Japanese people, as well as European people, generally like seasonal ingredients in cooking. The diet history questionnaire used in the OMCHS was designed to assess recent dietary intake, i.e., the subject's diet during the one-month period prior to filling out this questionnaire. Allowance for the season when data were collected likely eased this weakness, however. We controlled for changes in the diet in the past one month because pregnant women are likely to change their diet for reasons such as nausea gravidarum. There are other limitations that may be of concern. Only 627 (17.2%) of the 3639 eligible pregnant women in Neyagawa City participated in the OMCHS. Regarding the remaining 375 subjects in the OMCHS who live in municipalities other than Neyagawa City, we can not calculate the participation rate because data on the exact number of eligible subjects were not available. Our sample cannot be considered representative of Japanese women. In fact, the educational level of our subjects was higher than that of the general population according to the 2000 population census of Japan [31]. However, the prevalence of tooth loss among our subjects (25.5%) was similar to that among Japanese women aged 25-30 years in a survey of dental diseases conducted in 1999 (27.3%) [32]. A study on the reasons for extraction of permanent teeth found that among Japanese individuals aged 9-35 years the proportion of extractions resulting from caries, periodontitis, eruption problems, orthodontic indications, trauma, and other causes were 51.5%, 6.2%, 21.9%, 5.1%, 0.1%, and 15.2%, respectively, and that more than 90% of extractions for eruption problems were third molars [33]. Among the 256 women with tooth loss, the tooth loss in more than 50% of the cases likely resulted from dental diseases although we do not have information on the reasons for tooth extraction because tooth loss was not a principal study outcome of the OMCHS. However, any outcome misclassification would likely to have been evenly distributed across the four categories of the exposures under study. Consequently, this would have given rise to an underestimation of our findings. Information regarding the point in time at which tooth loss occurred was not available. Therefore, the time sequence between mineral intake and tooth loss could not be determined. Although we adjusted our estimate for a wide range of potential confounders, we can not rule out the possibility that our findings were biased by unmeasured confounders such as the level of oral hygiene, caries, periodontitis, and oral health behavior including the frequency of toothbrushing and the pattern of dental visits. Because the outcome variable in our study was tooth loss, which is the ultimate endpoint of caries and periodontitis, early symptoms and subclinical symptoms of dental disease could not be taken into consideration in our estimate. The consequence would be underestimation of our results.

Table 3. Odds ratios for tooth loss by quartiles of intake of minerals, OMCHS[a], Japan.

Variable[b]	Prevalence	Crude *odds ratio* (95% CI[c])		Adjusted *odds ratio*[d] (*95% CI*[c])	
Calcium					
Q1 (368.0)	69/250 (27.6%)	1.00		1.00	
Q2 (491.7)	71/251 (28.3%)	1.04	0.70–1.53	1.12	0.74–1.69
Q3 (590.3)	59/250 (23.6%)	0.81	0.54–1.21	0.85	0.55–1.30
Q4 (739.4)	57/251 (22.7%)	0.77	0.51–1.16	0.81	0.53–1.25
p for linear trend		0.12		0.20	
Phosphate					
Q1 (713.1)	74/250 (29.6%)	1.00		1.00	
Q2 (828.7)	65/251 (25.9%)	0.83	0.56–1.23	0.83	0.55–1.26
Q3 (928.1)	55/250 (22.0%)	0.67	0.45–1.00	0.73	0.47–1.12
Q4 (1085.0)	62/251 (24.7%)	0.78	0.53–1.16	0.78	0.51–1.20
p for linear trend		0.13		0.21	
Magnesium					
Q1 (150.8)	76/250 (30.4%)	1.00		1.00	
Q2 (175.4)	64/251 (25.5%)	0.78	0.53–1.16	0.85	0.57–1.29
Q3 (199.4)	62/250 (24.8%)	0.76	0.51–1.12	0.83	0.55–1.26
Q4 (245.8)	54/251 (21.5%)	0.63	0.42–0.94	0.64	0.42–0.99
p for linear trend		0.03		0.05	
Iron					
Q1 (5.9)	73/250 (29.2%)	1.00		1.00	
Q2 (7.0)	63/251 (25.1%)	0.81	0.55–1.21	0.80	0.53–1.21
Q3 (7.9)	62/250 (24.8%)	0.80	0.54–1.19	0.83	0.55–1.26
Q4 (9.3)	58/251 (23.1%)	0.73	0.49–1.09	0.70	0.45–1.07
p for linear trend		0.13		0.14	
Zinc					
Q1 (5936.5)	77/250 (30.8%)	1.00		1.00	
Q2 (6816.2)	54/251 (21.5%)	0.62	0.41–0.92	0.68	0.44–1.03
Q3 (7493.8)	64/250 (25.6%)	0.77	0.52–1.14	0.84	0.56–1.28
Q4 (8608.4)	61/251 (24.3%)	0.72	0.49–1.07	0.78	0.51–1.19
p for linear trend		0.21		0.42	
Copper					
Q1 (819.2)	72/250 (28.8%)	1.00		1.00	
Q2 (977.7)	66/251 (26.3%)	0.88	0.60–1.31	0.88	0.59–1.33
Q3 (1104.0)	57/250 (22.8%)	0.73	0.49–1.09	0.72	0.47–1.10
Q4 (1415.8)	61/251 (24.3%)	0.79	0.53–1.18	0.78	0.50–1.20
p for linear trend		0.17		0.17	

[a] OMCHS, Osaka Maternal and Child Health Study.
[b] Median in each quartile in mg/d (except for zinc and cupper; μg/d) that had been adjusted for energy intake by the residual method, are given in parentheses.
[c] CI, Confidence interval.
[d] Odds ratios were calculated separately for each dietary variable and were adjusted for age (< 29, 29–31, and 32+ yr), gestation (< 15, 15–20, and 21+ weeks), parity (0 and 1+), cigarette smoking (never, former, and current), passive smoking at home (never, former and current), passive smoking at work (never, former, and current), family income (< 4,000,000, 4,000,000–5,999,999, and 6,000,000+ JPY/year), education (< 13, 13–14, and 15+ years), changes in diet in the previous one month (none or seldom, slight, and substantial), season when data were collected (spring, summer, fall, and winter), and body mass index as a continuous variable.

Appendix

Space limitations preclude the inclusion as authors of the following members of the Osaka Maternal and Child Health Study Group:

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Conclusion

This is the first epidemiological study that assessed the effects of intake of various minerals on tooth loss among young adults using a well-validated diet history questionnaire. We found that magnesium intake was inversely associated with the prevalence of tooth loss in pregnant Japanese women. Since this study was a cross-sectional study, only associations rather than causal relationships between magnesium intake and tooth loss can be inferred. Further studies with detailed and objective indicators of dental health status such as caries and periodontitis are needed to assess the beneficial effects of magnesium intake on dental diseases.

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Fat and fish intake and asthma in Japanese women: baseline data from the Osaka Maternal and Child Health Study

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SUMMARY

OBJECTIVE: It remains controversial whether the intake of n-3 polyunsaturated fatty acids and fish is preventive against asthma. This cross-sectional study investigated the relationship between fat and fish intake and the prevalence of asthma using baseline data from a prospective study.

DESIGN: The subjects were 1002 pregnant Japanese females. A diet history questionnaire was used to assess dietary habits. Current asthma and asthma after age 18 were defined as present if subjects had been treated with medications at some time in the previous 12 months and after reaching the age of 18, respectively.

RESULTS: Fish consumption was independently associated with a decreased prevalence of asthma after age 18 and current asthma. A significant inverse relationship was observed between the ratio of n-3 to n-6 polyunsaturated fatty acid intake and the prevalence of current asthma, but not asthma after age 18. Intake of total fat, saturated, monounsaturated, n-3 polyunsaturated and n-6 polyunsaturated fatty acids, cholesterol, meat, eggs or dairy products was not evidently related to either outcome for asthma.

CONCLUSION: Our results suggest that fish consumption and the high ratio of n-3 to n-6 polyunsaturated fatty acid intake may be associated with a reduced prevalence of asthma in young female Japanese adults.

KEY WORDS: asthma; cross-sectional study; fatty acids; fish; Japanese women

IN JAPAN, asthma is one of the major public health problems in both adults and children.[1,2] The International Study of Asthma and Allergies in Childhood has shown that the prevalence of asthma symptoms is very high in Japanese children, similar to that in Western countries,[2] but the reasons are unknown.

Many epidemiological studies have investigated the association of intake of fatty acids and/or foods high in fatty acids with asthma.[3–17] However, it remains controversial whether the intake of n-3 polyunsaturated fatty acids and fish is preventive against asthma and whether n-6 polyunsaturated fatty acid intake increases the risk of asthma. Oily fish intake was significantly inversely related to current asthma in a case-control study among Australian children,[3] whereas a positive association between fish intake and current asthma was observed in Japanese children.[4] A high ratio of n-6 to n-3 polyunsaturated fatty acid intake was significantly associated with an increased risk of asthma in Australian children.[5] Case-control studies of Spanish[6] and German[7] adults showed no difference in intake of n-3 polyunsaturated fatty acids between asthmatic and non-asthmatic subjects.

In view of the paucity of epidemiological studies of the relationship between intake of fatty acids and high-fat foods and asthma in Japan, where intake of fish is high, the present cross-sectional study examined the association of intake of specific types of fatty acids, cholesterol, and selected foods high in fatty acids with the prevalence of asthma in pregnant females using baseline information from the Osaka Maternal and Child Health Study (OMCHS).

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STUDY POPULATION AND METHODS

Subjects

The OMCHS, an ongoing prospective cohort study, investigates preventive and risk factors for maternal and child health problems such as allergic disorders. We investigated the relationships of diet, smoking and other environmental factors with the prevalence of allergic disorders among pregnant women using data from the baseline survey. Details of the OMCHS have been described elsewhere.[18] Eligible females were those who became pregnant in Neyagawa City, one of the 44 municipalities in Osaka Prefecture, a metropolis in Japan with a total population of approximately 8.8 million. Of the 3639 eligible females in Neyagawa City, 627 (17.2%) participated in the study between November 2001 and March 2003. An additional 375 pregnant women from other areas participated. A total of 1002 pregnant women gave fully informed consent in writing and completed the baseline survey. The ethics committee of the Osaka City University School of Medicine approved the OMCHS.

Questionnaires

At baseline, each participant filled out a set of two self-administered questionnaires and collected two dust samples. Participants then mailed these materials to the data management centre. Research technicians completed missing or illogical data by telephone interview.

A validated self-administered diet history questionnaire was used to assess dietary habits during the previous month. The structure and validity of the questionnaire are described in detail elsewhere.[19,20] Measures of dietary intake for 147 food items were calculated by using an ad hoc computer algorithm for the diet history questionnaire, which was based on the Standard Tables of Food Composition in Japan.[21] Energy-adjusted intake by the residual method was used for the analyses.[22]

A second self-administered questionnaire asked about age, gestation, parity, smoking habits, personal history of asthma, family history of asthma, atopic eczema, and allergic rhinitis, indoor domestic pets, family income, education, weight, height, and changes in diet in the previous month. Current asthma was defined as present when subjects had been treated with medications at some time in the previous 12 months. Asthma after age 18 was considered to be present if subjects had used an asthma medication at any time after reaching the age of 18. A family history of asthma, atopic eczema, and allergic rhinitis (including Japanese cedar pollinosis) was considered to be present if one or more parents or siblings of the study subject had manifested any of these allergic disorders. Body mass index (BMI) was calculated by dividing self-reported body weight (kg) by the square of self-reported height (m).

Two dust samples were collected from a 1 m^2 area of the bedclothes and flooring for 1 min using a vacuum cleaner fitted with a collection apparatus. Antigen levels from extracts of fine dust fractions were measured by a double-antibody sandwich enzyme-linked immunosorbent assay using a soluble antigen prepared from whole *Dermatophagoides farinae* mite bodies as a reference standard, and were expressed as antigen equivalent in $\mu g/m^2$ of surface area (Mitey checker®, Shinto Fine Co, Osaka, Japan).[23,24] Antigen levels were semi-quantitatively classified with scores of − (<2 $\mu g/m^2$), ± (5 $\mu g/m^2$), + (10–15 $\mu g/m^2$) and ++ (>35 $\mu g/m^2$). In this study, we used only antigen levels in the sample collected from the bedclothes because the correlation between antigen levels from the bedclothes and flooring was collinear (Spearman correlation coefficient = 0.54, $P < 0.0001$).

Statistical analysis

Intake of dietary factors under investigation was categorised at tertile points based on the distribution of all study subjects.

Logistic regression analysis was used to compare the prevalence of asthma associated with intake of specific types of fatty acids, cholesterol and selected foods high in fatty acids. Multiple logistic regression analysis was used to control for the potential confounding factors under study. Trend of association was assessed by a logistic regression model assigning scores to the levels of the independent variable. Two-sided P values <0.05 were considered statistically significant. All computations were performed using the SAS software package version 9.1 (SAS Institute, Inc, Cary, NC, USA).

RESULTS

The prevalence values for asthma after age 18 and current asthma were 4.7% and 2.1%, respectively, among 1002 women. About 50% of the women were aged ⩾30 years had enrolled by the 17th week of gestation and had a parity of one or more (Table 1). Slight or substantial changes in diet in the previous 1 month were experienced by 702 pregnant females due to nausea gravidarum (585 females), maternal and foetal health (107 females) and other reasons (10 females). Mean daily total energy, energy-adjusted total fat and n-3 and n-6 polyunsaturated fatty acid intake were 6815 kJ, 54.3 g, 2.3 g and 11.0 g, respectively (Table 2).

Odds ratios (ORs) and their 95% confidence intervals (CIs) for the prevalence of asthma in relation to dietary intake of specific types of fatty acids and cholesterol are presented in Table 3. A significant inverse dose-response relationship was found between docosahexaenoic acid intake and the prevalence of asthma after age 18, but not current asthma, although the OR for comparison of the third with the first tertile was of borderline significance. After adjustment for age, gestation, parity, cigarette smoking, indoor domestic pets, family history of asthma, atopic eczema and allergic

Table 1 Distribution of selected characteristics in 1002 pregnant females, OMCHS, Japan

Variable	*n* (%)
Age, years	
<30	473 (47.2)
⩾30	529 (52.8)
Gestation, weeks	
<18	508 (50.7)
⩾18	494 (49.3)
Parity of 1 or more	513 (51.2)
Cigarette smoking	
Never	697 (69.6)
Former	121 (12.1)
Current	184 (18.4)
Family history of asthma	101 (10.1)
Family history of atopic eczema	138 (13.8)
Family history of allergic rhinitis	429 (42.8)
Indoor domestic pets (cats, dogs, birds or hamsters)	114 (11.4)
Family income, yen/year	
<4 000 000	301 (30.0)
4 000 000–5 999 999	403 (40.2)
⩾6 000 000	298 (29.7)
Education, years	
<13	323 (32.2)
13–14	413 (41.2)
⩾15	266 (26.6)
Mite allergen level in house dust*	
–	436 (43.5)
±	297 (29.6)
+ and ++	269 (26.9)
Changes in diet in the previous month	
None or seldom	300 (29.9)
Slight	435 (43.4)
Substantial	267 (26.7)
Season when data were collected	
Spring	318 (31.7)
Summer	162 (16.2)
Fall	223 (22.3)
Winter	299 (29.8)

* Antigen levels were semi-quantitatively classified with scores of – (<2 μg/m²), ± (5 μg/m²), + (10–15 μg/m²), and ++ (>35 μg/m²).
OMCHS = Osaka Maternal and Child Health Study.

Table 2 Distribution of daily nutrients and food intake and BMI in 1002 pregnant females, OMCHS, Japan

Variable	Mean (SD)
Daily nutrient intake*	
Total energy (kJ)	6815.3 (1793.7)
Total fat (g)	54.3 (10.3)
Saturated fatty acids (g)	16.6 (3.5)
Monounsaturated fatty acids (g)	19.0 (4.2)
n-3 polyunsaturated fatty acids (g)	2.3 (0.8)
Eicosapentaenoic acid (g)	0.2 (0.2)
Docosahexaenoic acid (g)	0.3 (0.2)
n-6 polyunsaturated fatty acids (g)	11.0 (2.8)
Cholesterol (mg)	265.2 (105.3)
Daily intake*	
Meat (g)	59.8 (29.2)
Eggs (g)	28.3 (20.3)
Dairy products (g)	192.5 (123.1)
Fish (g)	48.3 (27.4)
BMI (kg/m²)	21.4 (2.8)

* Nutrients and food intake were adjusted for total energy intake using the residual method.
BMI = body mass index; OMCHS = Osaka Maternal and Child Health Study; SD = standard deviation.

rhinitis, family income, education, mite allergen level in house dust, changes in diet in the past month, the season when data were collected and BMI, the inverse relationship completely disappeared. Compared with the ratio of n-3 to n-6 polyunsaturated fatty acid intake in the lowest tertile, the ratio in the highest tertile was significantly associated with a decreased prevalence of asthma after age 18 and current asthma, showing clear inverse dose-response relationships. After multivariate adjustment, these inverse relationships were attenuated, although the inverse relationship with current asthma, but not asthma after age 18, remained significant. No statistically significant associations were observed between intake of total fat, saturated, monounsaturated, n-3 polyunsaturated and n-6 polyunsaturated fatty acids, eicosapentaenoic acid, or cholesterol and either outcome for asthma.

We then evaluated the prevalence of asthma based on intake of selected high-fat foods (Table 4). Compared with fish intake in the first tertile, consumption of fish in the third tertile was independently related to a reduced prevalence of both outcomes for asthma in the multivariate model; the inverse trends were also statistically significant (*P* for trend = 0.02 and 0.04, respectively). After further adjustment for docosahexaenoic acid intake, the inverse associations of fish consumption with asthma after age 18 and current asthma remained significant: adjusted ORs for comparison of the third with the first tertile were 0.27 (95%CI 0.08–0.92) and 0.12 (95%CI 0.01–0.99), respectively. There were no significant associations of consumption of meat, eggs or dairy products with either outcome for asthma.

DISCUSSION

The present findings are partially in agreement with previous studies that showed no association between n-3 polyunsaturated fatty acid intake and asthma.[6,7] A cross-sectional study in Australian adults demonstrated that plasma levels of n-3 polyunsaturated fatty acids and the ratio of n-6 to n-3 polyunsaturated fatty acids were not measurably related to asthma, whereas n-6 polyunsaturated fatty acid dihomo γ-linolenic acid was positively associated with asthma.[8] Our findings regarding the ratio are at variance with those results.

The pro-inflammatory eicosanoids prostaglandin E_2 and leukotriene B_4 are derived from n-6 fatty acid, arachidonic acid, which is maintained at high cellular concentrations by the high n-6 polyunsaturated fatty acid content of the modern Western diet.[25] Prostaglandin E_2 is an important immune regulator known to suppress Th1 activation and enhance Th2 activation, thereby enhancing the formation of IgE in B cells.[26] On the other hand, eicosapentaenoic acid, the n-3 homo-

Table 3 ORs and 95%CIs of specific types of dietary fat, OMCHS, Japan

	Asthma after age 18			Current asthma		
Variable*	Prevalence (%)	Crude OR (95%CI)	Adjusted OR (95%CI)†	Prevalence (%)	Crude OR (95%CI)	Adjusted OR (95%CI)†
Total fat						
<50.49	14/334 (4.2)	1.00	1.00	6/334 (1.8)	1.00	1.00
50.49–57.64	18/334 (5.4)	1.30 (0.64–2.71)	1.46 (0.68–3.21)	11/334 (3.3)	1.86 (0.70–5.46)	2.66 (0.87–9.03)
>57.64	15/334 (4.5)	1.08 (0.51–2.29)	1.21 (0.55–2.68)	4/334 (1.2)	0.66 (0.17–2.34)	0.80 (0.19–3.08)
P for trend		0.86	0.63		0.59	0.83
Saturated fatty acids						
<15.108	18/334 (5.4)	1.00	1.00	7/334 (2.1)	1.00	1.00
15.108–17.77	13/334 (3.9)	0.71 (0.34–1.47)	0.80 (0.36–1.74)	8/334 (2.4)	1.15 (0.41–3.30)	1.42 (0.45–4.67)
>17.77	16/334 (4.8)	0.88 (0.44–1.77)	1.08 (0.51–2.30)	6/334 (1.8)	0.86 (0.27–2.60)	1.17 (0.33–4.10)
P for trend		0.72	0.87		0.79	0.78
Monounsaturated fatty acids						
<17.48	18/334 (5.4)	1.00	1.00	8/334 (2.4)	1.00	1.00
17.48–20.21	12/334 (3.6)	0.65 (0.30–1.37)	0.62 (0.27–1.36)	8/334 (2.4)	1.00 (0.36–2.75)	1.02 (0.33–3.22)
>20.21	17/334 (5.1)	0.94 (0.47–1.87)	0.93 (0.45–1.92)	5/334 (1.5)	0.62 (0.19–1.88)	0.59 (0.16–1.95)
P for trend		0.86	0.84		0.42	0.41
n-3 polyunsaturated fatty acids						
<2.0196	15/334 (4.5)	1.00	1.00	9/334 (2.7)	1.00	1.00
2.0196–2.4789	17/334 (5.1)	1.14 (0.56–2.35)	1.13 (0.53–2.44)	9/334 (2.7)	1.00 (0.39–2.59)	0.96 (0.32–2.79)
>2.4789	15/334 (4.5)	1.00 (0.48–2.10)	1.08 (0.50–2.36)	3/334 (1.0)	0.33 (0.07–1.11)	0.36 (0.07–1.31)
P for trend		1.00	0.84		0.11	0.16
Eicosapentaenoic acid						
<0.137	19/334 (5.7)	1.00	1.00	9/334 (2.7)	1.00	1.00
0.137–0.2232	16/334 (4.8)	0.83 (0.42–1.65)	0.76 (0.36–1.57)	7/334 (2.1)	0.77 (0.27–2.10)	0.48 (0.14–1.49)
>0.2232	12/334 (3.6)	0.62 (0.29–1.28)	0.78 (0.35–1.69)	5/334 (1.5)	0.55 (0.17–1.61)	0.72 (0.19–2.43)
P for trend		0.20	0.50		0.28	0.50
Docosahexaenoic acid						
<0.2475	23/334 (6.9)	1.00	1.00	11/334 (3.3)	1.00	1.00
0.2475–0.3616	12/334 (3.6)	0.50 (0.24–1.01)	0.51 (0.23–1.08)	5/334 (1.5)	0.45 (0.14–1.24)	0.38 (0.10–1.21)
>0.3616	12/334 (3.6)	0.50 (0.24–1.01)	0.62 (0.28–1.31)	5/334 (1.5)	0.45 (0.14–1.24)	0.57 (0.16–1.84)
P for trend		0.05	0.17		0.11	0.28
n-6 polyunsaturated fatty acids						
<9.89	17/334 (5.1)	1.00	1.00	9/334 (2.7)	1.00	1.00
9.89–11.72	11/334 (3.3)	0.64 (0.29–1.36)	0.50 (0.21–1.14)	7/334 (2.1)	0.77 (0.27–2.10)	0.59 (0.18–1.84)
>11.72	19/334 (5.7)	1.13 (0.57–2.22)	1.03 (0.50–2.13)	5/334 (1.5)	0.55 (0.17–1.61)	0.53 (0.15–1.69)
P for trend		0.72	0.88		0.28	0.28
n-3/n-6 polyunsaturated fatty acid ratio						
<0.1914	20/334 (6.0)	1.00	1.00	12/334 (3.6)	1.00	1.00
0.1914–0.2218	18/334 (5.4)	0.89 (0.46–1.73)	0.84 (0.42–1.70)	6/334 (1.8)	0.49 (0.17–1.28)	0.36 (0.11–1.07)
>0.2218	9/334 (2.7)	0.44 (0.19–0.94)	0.53 (0.22–1.19)	3/334 (0.9)	0.24 (0.06–0.77)	0.26 (0.05–0.93)
P for trend		0.05	0.14		0.02	0.03
Cholesterol						
<215.70	18/334 (5.4)	1.00	1.00	9/334 (2.7)	1.00	1.00
215.70–303.76	19/334 (5.7)	1.06 (0.54–2.07)	1.33 (0.65–2.74)	8/334 (2.4)	0.89 (0.33–2.35)	1.19 (0.39–3.58)
>303.76	10/334 (3.0)	0.54 (0.24–1.17)	0.62 (0.26–1.41)	4/334 (1.2)	0.44 (0.12–1.36)	0.45 (0.10–1.57)
P for trend		0.15	0.32		0.18	0.27

* Tertiles were based on intake in g/day (except for cholesterol mg/day) adjusted for energy intake using the residual method, except for tertiles of the ratio of n-3 to n-6 polyunsaturated fatty acids, which were based on crude intake in g/day.
† Adjustment for age, gestation, parity, cigarette smoking, indoor domestic pets, family history of asthma, atopic eczema and allergic rhinitis, family income, education, mite allergen level in house dust, changes in diet in the previous month, season when data were collected and BMI (continuous).
OR = odds ratio; CI = confidence interval; OMCHS = Osaka Maternal and Child Health Study; BMI = body mass index.

logue of arachidonic acid, can inhibit arachidonic acid metabolism competitively via enzymatic pathways, and can thus suppress production of n-6 eicosanoid inflammatory mediators.[25] A balance between n-3 and n-6 polyunsaturated fatty acid metabolism may be important. The lack of an association between intake of n-3 or n-6 polyunsaturated fatty acids and the prevalence of asthma in the current study may be because study subjects reported very high intake of n-3 polyunsaturated fatty acids. In the typical Western diet, 20- to 25-fold more n-6 fats than n-3 fats are consumed.[25] Thus, a potential beneficial and adverse effect of n-3 and n-6 polyunsaturated fatty acids, respectively, on asthma may be detected when the intake of n-3 polyunsaturated fatty acids is very low. In the current study a significant inverse association between fish intake and asthma persisted after additional adjustment for docosahexaenoic acid intake; therefore, other constituents in

Table 4 ORs and 95%CIs of intake of selected foods high in fat, OMCHS, Japan

	Asthma after age 18			Current asthma		
Variable*	Prevalence (%)	Crude OR (95%CI)	Adjusted OR (95%CI)†	Prevalence (%)	Crude OR (95%CI)	Adjusted OR (95%CI)†
Fish						
<36.14	24/334 (7.2)	1.00	1.00	11/334 (3.3)	1.00	1.00
36.14–54.44	15/334 (4.5)	0.61 (0.31–1.17)	0.59 (0.28–1.19)	8/334 (2.4)	0.72 (0.28–1.80)	0.57 (0.19–1.62)
>54.44	8/334 (2.4)	0.32 (0.13–0.69)	0.36 (0.15–0.83)	2/334 (0.6)	0.18 (0.03–0.67)	0.19 (0.03–0.83)
P for trend		0.004	0.02		0.02	0.04
Meat						
<46.16	14/334 (4.2)	1.00	1.00	7/334 (2.1)	1.00	1.00
46.16–67.13	17/334 (5.1)	1.23 (0.60–2.57)	1.20 (0.56–2.62)	8/334 (2.4)	1.15 (0.41–3.30)	1.03 (0.32–3.34)
>67.13	16/334 (4.8)	1.15 (0.55–2.43)	1.23 (0.56–2.72)	6/334 (1.8)	0.86 (0.27–2.60)	0.78 (0.22–2.63)
P for trend		0.72	0.61		0.79	0.69
Eggs						
<17.99	20/334 (6.0)	1.00	1.00	9/334 (2.7)	1.00	1.00
17.99–37.76	17/334 (5.1)	0.84 (0.43–1.64)	0.93 (0.46–1.88)	8/334 (2.4)	0.89 (0.33–2.35)	1.03 (0.35–3.02)
>37.76	10/334 (3.0)	0.49 (0.21–1.03)	0.55 (0.23–1.21)	4/334 (1.2)	0.44 (0.12–1.36)	0.44 (0.10–1.55)
P for trend		0.07	0.16		0.18	0.26
Dairy products						
<129.74	19/334 (5.7)	1.00	1.00	7/334 (2.1)	1.00	1.00
129.74–221.79	19/334 (5.7)	1.00 (0.52–1.93)	1.14 (0.56–2.30)	8/334 (2.4)	1.15 (0.41–3.30)	1.51 (0.48–4.93)
>221.79	9/334 (2.7)	0.46 (0.20–1.00)	0.61 (0.25–1.41)	6/334 (1.8)	0.86 (0.27–2.60)	1.66 (0.46–6.15)
P for trend		0.07	0.33		0.79	0.42

* Tertiles were based on intake in g/day adjusted for energy intake using the residual method.
† Adjustment for age, gestation, parity, cigarette smoking, indoor domestic pets, family history of asthma, atopic eczema and allergic rhinitis, family income, education, mite allergen level in house dust, changes in diet in the previous month, season when data were collected and BMI (continuous).
OR = odds ratio; CI = confidence interval; OMCHS = Osaka Maternal and Child Health Study; BMI = body mass index.

fish might to some extent explain the inverse association. Alternatively, unknown dietary or non-dietary factors may have confounded the inverse relationship between fish intake and asthma. Japanese persons who eat large amounts of fish are likely to follow the traditional Japanese diet or engage in behaviours that may be protective against asthma.

The present study had several methodological advantages, in that study subjects were homogeneous, they were all pregnant and this study incorporated extensive information on potential confounding factors.

We used a self-administered semiquantitative dietary assessment questionnaire.[19,20] As we did not actually observe the dietary habits of the subjects, the results should be interpreted cautiously. To minimise data inaccuracy, we used a questionnaire that was validated as follows: the correlation coefficients for nutrient intake between those estimated from the diet history questionnaire and those observed by a 3-day dietary record were 0.75, 0.50, 0.37 and 0.49 for saturated fatty acids, monounsaturated fatty acids, polyunsaturated fatty acids and cholesterol, respectively, in women.[19] A highly positive correlation was also observed between marine-origin n-3 polyunsaturated fatty acid intake estimated by the diet history questionnaire and the corresponding concentration in the serum phospholipid fraction (r = 0.51 and 0.69 in men and women, respectively).[20] Our diet history questionnaire was designed to assess recent dietary intake, i.e., for 1 month prior to completing the questionnaire. Adjustment for the season when data were collected is likely to mitigate this disadvantage, however. Changes in diet in the past month were controlled for because pregnant females are likely to change their diet for reasons such as nausea gravidarum. Potential exposure misclassification associated with the stability of diet during pregnancy was likely to be non-differential. The consequence would have given rise to an underestimation of our findings.

Other disadvantages should be clarified. Of a total of 3639 eligible pregnant females in Neyagawa City, only 627 (17.2%) participated in this study. With regard to the remaining 375 participants, we were not able to calculate the participation rate because the exact number of eligible subjects was not available. Our subjects were an unrepresentative sample of Japanese females in the general population (pregnant women), and the present findings may not be generalised. Moreover, educational levels were higher in the present study population than in the general population. According to the 2000 population census of Japan, the proportions of females aged 30–34 years in Osaka Prefecture with <13, 13–14, 15+ and unknown years of education were 49.2%, 32.3%, 13.6%, and 4.9%, respectively.[27] Because the definition of asthma was based on drug treatment, there was a loss of patients with milder asthma. Moreover, females who want to become pregnant or who are pregnant might tend to avoid taking drugs of any kind. The consequence could be a bias toward the null. In addition, this cross-sectional study was unable to establish cause and effect relationships on the subject under investigation.

The interface between allergy/immunology and pregnancy should be discussed, which may have an influence on the association of interest. It has been suggested that pregnancy involves a shift to the Th2 side of the immune response,[28] whereas the importance of the role of natural killers (NK) and interleukin (IL)-12, IL-15, and IL-18 tripods in successful or failed pregnancy in humans was suggested beyond the Th1/Th2 paradigm.[29]

Four of 47 women who suffered from asthma after age 18 (8.5%) and one of 21 current asthma sufferers (4.7%) had received medical treatment due to allergies such as food allergy, but not for asthma, atopic eczema or allergic rhinitis, at some time after reaching the age of 18. Data on the precise diagnosis of these allergies were not available. Some of those with asthma in this study might have made a conscious decision to avoid or reduce their intake of fish because of a fear of sensitivity to fish. If correct, such a hypothesis would have given rise to an overestimation of our findings. Our study did not have substantial statistical power because the prevalence values of both outcomes for asthma were low.

This is the first epidemiological study on the association of intake of fat and high-fat foods with asthma in Japan. Our results suggest that consumption of fish and the high ratio of n-3 to n-6 polyunsaturated fatty acid intake may be associated with a reduced prevalence of asthma in young female Japanese adults. Further evaluation in prospective studies of the effects of dietary fat on asthma is required.

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