Nutrition 69 (2020) 110572

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Maternal consumption of vegetables, fruit, and antioxidants during pregnancy and risk for childhood behavioral problems

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ARTICLE INFO

Article History:
Received 20 February 2019
Received in revised form 23 April 2019
Accepted 15 May 2019

Keywords:
Behavioral problems
Fruit
Maternal intake
Pregnancy
Vegetables
Vitamin C

ABSTRACT

Objective: The aim of this pre-birth cohort study was to examine the associations between maternal intake of vegetables, fruit, and antioxidants during pregnancy and behavioral problems in Japanese children 5 y of age.
Methods: Participants were 1199 mother-child pairs. Dietary intake was assessed using a diet history questionnaire. Emotional, conduct, hyperactivity, and peer problems, as well as low prosocial behavior were assessed using the parent version of the Strengths and Difficulties Questionnaire. Adjustment was made for maternal age, gestation at baseline, region of residence, number of children, maternal and paternal education, household income, maternal depressive symptoms during pregnancy, maternal alcohol intake during pregnancy, maternal smoking during pregnancy, child's birth weight, child's sex, breastfeeding duration, and smoking in the household during the child's first year of life.
Results: Maternal intake of total vegetables and green and yellow vegetables during pregnancy was independently inversely associated with childhood low prosocial behavior. Maternal intake of other vegetables during pregnancy was independently inversely related to childhood hyperactivity problems and low prosocial behavior. Maternal intake of fruit and apples during pregnancy was independently inversely related to childhood hyperactivity problems. Maternal intake of citrus fruits during pregnancy was independently inversely related to childhood emotional, conduct, and hyperactivity problems. Maternal vitamin C intake during pregnancy was independently inversely associated with childhood conduct and hyperactivity problems and low prosocial behavior.
Conclusions: Maternal intake of vegetables, fruit, and vitamin C during pregnancy may be preventive against any of the behavioral problems assessed here except for peer problems in Japanese children 5 y of age.
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Introduction

Because of its high level of polyunsaturated fatty acids as well as its high rate of cellular metabolism, the brain is vulnerable to oxidative stress [1]. Moreover, the production of reactive oxygen species is increased during pregnancy in connection with the functioning of the placenta; therefore, maternal dietary intake of antioxidants could help to protect mothers and their fetuses against excessive oxidative stress and its debilitating complications [2]. Vitamins C and E and carotenoids not only function as pivotal antioxidants in the brain but also exert non-antioxidant neuroprotective effects [1–4]. To our knowledge, no epidemiologic study to date has examined the relationship between maternal intake of

This study was supported by JSPS KAKENHI (grant no. 19590606 JP, 20791654 JP, 21590673 JP, 22592355 JP, 22119507 JP, 24390158 JP, 25463275 JP, 25670305 JP, 17 K12011 JP, and 17 H04135 JP), by Health and Labour Sciences Research Grants for Research on Allergic Disease and Immunology and Health Research on Children, Youth and Families from the Ministry of Health, Labour and Welfare, Japan, by Meiji Co. Ltd., and by the Food Science Institute Foundation. YM conceptualized and designed the study, conducted the research, preformed the analyses, interpreted results, drafted the initial manuscript, and revised the manuscript. KT and MA conceptualized and designed the study, conducted the research, assisted in the interpretation of the data, and reviewed and revised the manuscript. HO and SS were responsible for the estimation of dietary factors. All authors approved the final manuscript as submitted.
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https://doi.org/10.1016/j.nut.2019.110572
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antioxidants, vegetables, and fruit during pregnancy and the risk for childhood behavioral problems. We aimed to investigate the association between maternal intake of vegetables, fruit, α-and β-carotene, and vitamins C and E during pregnancy and the risk for behavioral problems in Japanese children at 5 y of age using data from the KOMCHS (Kyushu Okinawa Maternal and Child Health Study).

Methods

Study population

The present study population was nested within the KOMCHS, a pre-birth cohort study designed to examine risk and preventive factors for maternal and child health problems [5–8]. Detailed participant recruitment at baseline was described previously [5]. In brief, in the baseline survey between April 2007 and March 2008, a set of leaflets explaining the KOMCHS, an application form to take part in the study, and a self-addressed and stamped return envelope were hand delivered to as many pregnant women as possible at 423 obstetric hospitals in seven prefectures on Kyushu Island in southern Japan, with a total population of ~13.26 million, and in Okinawa Prefecture, an island chain in the southwest of Japan, with a total population of nearly 1.37 million. Pregnant women who intended to participate in the KOMCHS mailed the application form including a written description of their personal information to the data management center. On receipt of this application form, research technicians gave each eligible pregnant woman a detailed explanation of the KOMCHS by telephone, obtained her agreement, and sent her a self-administered questionnaire. Consequently, 1757 pregnant women between pregnancy weeks 5 and 39 gave their written informed consent to take part in the KOMCHS and answered this self-administered questionnaire at baseline. Of the 1757 pregnant women, 1590, 1527, 1430, 1362, 1305, 1264, and 1201 mother–child pairs participated in all surveys from the baseline survey to the second (after delivery), third (around 4 mo postpartum), fourth (around 12 mo postpartum), fifth (around 24 mo postpartum), sixth (around 36 mo postpartum), seventh (around 48 mo postpartum), and eighth (around 60 mo postpartum) surveys, respectively. Two pairs with missing household income data were excluded. Thus, the current data analysis included 1199 pairs. The ethics committees of Fukuoka University School of Medicine and Ehime University Graduate School of Medicine approved the KOMCHS.

Measurements

In each survey, a self-administered questionnaire was sent to the participants, who were asked to fill out the questionnaire and mail it to the study's data management center. Research technicians completed missing or illogical data by telephone interview.

In the baseline survey, the first part of the questionnaire gathered information on maternal age, gestation, region of residence, number of children, maternal and paternal education, household income, and depressive symptoms. Depressive symptoms were measured using a Japanese version [9] of the Center for Epidemiologic Studies Depression Scale (CES-D), a 20-item questionnaire asking about frequency of being bothered by depressive symptoms during the previous week on a scale ranging from 0 (*rarely or none*) to 3 (*most or all of the time*) [10]. CES-D summary scores can range from 0 to 60, and depressive symptoms were considered present if the sum of the CES-D scores was ≥16 [9,10].

The second part of the questionnaire at baseline consisted of a semiquantitative, comprehensive diet history questionnaire (DHQ), which was designed to assess the dietary intake of Japanese adults over the previous month [11–17]. Pregnant women were asked to report their average consumption frequency of eight categories of foods and beverages, ranging from *never* to *≥2 times/d* for foods and from *<1 time/wk* to *≥6 times/d* for beverages, and their relative portion size in comparison with a standard portion size according to five categories: 50% smaller or less, 20% to 30% smaller, same, 20% to 30% larger, and "50% larger or more [11]. Estimates of daily intake for 150 food and beverage items, as well as for energy, nutrients, and alcohol, were calculated using an ad hoc computer algorithm for the DHQ, which was based on the Standard Tables of Food Composition in Japan [18]. In a validation study of 92 Japanese women 31 to 69 y of age, Pearson's correlation coefficient between the DHQ and 16-d semi-weighed dietary records was 0.59 for α-carotene, 0.64 for β-carotene, 0.52 for vitamin C, and 0.47 for vitamin E [13]. All dietary factors were adjusted for total energy intake using the residual method [19]. The DHQ included questions on consumption of six types of alcoholic beverages: beer, Japanese sake (rice wine), shochu (a distilled alcoholic beverage made in Japan), chuhai (made with shochu and carbonated water), whisky, and wine. Information on dietary supplements was not used in the calculation of dietary intake because of the lack of a reliable composition table in Japan. This should not make much difference, however, as only a small number of participants used vitamin C (4.6%) and multivitamin (5.5%) supplements at least once a week at baseline.

The questionnaire in the second survey asked about the baby's sex, birth weight, date of birth, and maternal smoking during pregnancy. The questionnaires in the third and fourth surveys included questions on household smoking and breastfeeding duration. In the eighth survey, behavioral development at 5 y of age was assessed using the Japanese parent-report version of the Strengths and Difficulties Questionnaire (SDQ) for 3- to 16-y-old children [20]. The SDQ comprises five separate scales, each including five questions (N = 25 questions) covering different behavioral aspects: an emotional problems scale, a conduct problems scale, a hyperactivity scale, a peer problems scale, and a prosocial scale. Each question was rated on a 3-point Likert scale, with 0 being *not true*, 1 being *somewhat true*, and 2 being *certainly true*. Therefore, each scale was scored between 0 and 10. A high score on the prosocial scale was considered a behavioral strength, whereas high scores on the other four scales indicated behavioral problems. These scale scores were categorized into three levels indicating a *normal, borderline*, or *abnormal* degree of difficulties according to cutoff points that previously had been established in a sample of Japanese children [21].

Statistical analysis

A dichotomous variable was created for each SDQ scale, in which children with borderline and abnormal scores were compared with those with normal scores; emotional, conduct, hyperactivity, and peer problems, or low prosocial behavior were defined as present when a child had a borderline or abnormal score in the respective scale. Intake of each of the dietary factors under study was categorized at quartile points according to its distribution among the 1199 mothers. Maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, household income, maternal depressive symptoms during pregnancy, maternal alcohol intake during pregnancy, maternal smoking during pregnancy, child's birth weight, child's sex, breastfeeding duration, and smoking in the household during the child's first year of life were selected a priori as potential confounding factors. Maternal age, gestation, and birth weight were used as continuous variables.

Multiple logistic regression analysis was performed to estimate adjusted odds ratios (ORs) and 95% CIs for each behavioral problem by quartiles of dietary factors under investigation, and the first quartile was used as the reference. We tested for linear trend using a logistic regression model assigning consecutive integers (1–4) to the quartiles of dietary factors under study. We conducted analyses using the SAS version 9.4 (SAS Institute, Inc., Cary, NC, USA).

Results

Among the 1199 children 59 to 71 mo of age, the prevalence values of emotional, conduct, hyperactivity, and peer problems, and low prosocial behavior were 12.9%, 19.4%, 13.1%, 8.6%, and 29.2%, respectively. Among the 1199 mothers in the baseline survey, the proportions of those aged <25, 25 to 29, 30 to 34, and ≥35 y were 4.3%, 25.6%, 47%, and 23%, respectively, and median age and gestation at baseline were 32 (interquartile range [IQR], 29–34 y) and 17 wk (IQR, 14–21 wk; Table 1). Median maternal daily intakes of total energy, total vegetables, total fruit, citrus fruit, α-carotene, β-carotene, and vitamins C and E during pregnancy were 7127 kJ (IQR, 6117–8465 kJ), 187.2 g (IQR, 139–264.4 g), 125.3 g (IQR, 80.8–185.8 g), 19.7 g (IQR, 7–46.2 g), 307.8 μg (IQR, 179.1–509.4 μg), 2439 μg (IQR, 1632–3515 μg), 96.8 mg (IQR, 76.5–123.9 mg), and 7.5 mg (IQR, 6.5–8.4 mg), respectively. Maternal total vegetable intake was positively associated with maternal education, household income, and breastfeeding duration and inversely related to maternal smoking during pregnancy and smoking in the household during the child's first year of life. Maternal citrus fruit intake was inversely associated with living in Fukuoka at baseline and total energy intake during pregnancy. There were increasing trends in breastfeeding duration and decreasing trends in gestational age at baseline and maternal smoking during pregnancy across increasing quartiles of maternal vitamin C intake.

Compared with maternal total vegetable intake during pregnancy in the first quartile, intake in the third and fourth quartiles was independently associated with a reduced risk for low prosocial behavior in the children, and the inverse linear trend was statistically significant: The adjusted OR between extreme quartiles was 0.55 (95% CI, 0.38–0.79, $P = 0.001$ for trend; Table 2). There were no material relationships between maternal total vegetable intake during pregnancy and the risk for emotional, conduct, hyperactivity, or

Table 1
Characteristics of 1199 parent–child pairs, in relation to quartile (Q) of maternal intake of total vegetables, citrus fruit, and vitamin C during pregnancy[*]

Variable	Total (N = 1199)[†]	Total vegetables			Citrus fruit			Vitamin C		
		Q1	Q4	*P*-value for trend[‡]	Q1	Q4	*P*-value for trend[‡]	Q1	Q4	*P*-value for trend[‡]
Baseline characteristics										
Maternal age, y	32 (29–34)	32	32	0.31	32	32	0.69	32	32	0.68
Gestation, wk	17 (14–21)	17	16	0.15	17	17	0.82	17	16	0.03
Region of residence, %				0.55			<0.0001			0.84
Fukuoka Prefecture	57.8	59.5	59.3		68.9	48.3		56.5	60.7	
Other than Fukuoka Prefecture in Kyushu	32.8	28.8	33		23.8	41		29.4	31	
Okinawa Prefecture	9.4	11.7	7.7		7.4	10.7		14.1	8.3	
Number of living children already born to same mother, %				0.55			0.47			0.31
0	40.4	41.1	42		41.5	40		38.5	40.3	
1	40	38.1	41.3		39.1	38		39.1	42	
≥2	19.6	20.7	16.7		19.4	22		22.4	17.7	
Maternal education, y, %				0.02			0.49			0.24
<13	20.9	25.1	18		24.1	23.3		23.4	20	
13–14	33.3	32.1	31		32.1	30.3		34.1	32.3	
≥15	45.9	42.8	51		43.8	46.3		42.5	47.7	
Paternal education, y, %				0.21			0.57			0.26
<13	28.6	30.8	25.3		27.8	30		30.8	27.3	
13–14	14.4	14.1	12.3		16.1	14.7		17.1	16.7	
≥15	57	55.2	62.3		56.2	55.3		52.2	56	
Household income, yen/y, %				0.003			0.82			0.36
<4 million	32.2	35.8	27		33.1	33		34.1	30.7	
4 million to 5,999,999	37.5	40.1	39.7		39.8	38.7		38.1	38	
≥6 million	30.4	24.1	33.3		27.1	28.3		27.8	31.3	
Maternal depressive symptoms during pregnancy, %	18.2	22.7	17.3	0.08	19.7	18.7	0.99	18.4	22	0.21
Maternal alcohol intake during pregnancy, %	13.2	16.1	12.7	0.09	14.4	13	0.69	15.4	11.7	0.22
Maternal daily intake										
Total energy, kJ	7127 (6117–8465)	7292	7400	0.61	8310	7382	<0.0001	7411	7434	0.64
Total vegetables, g[§]	187.2 (139–264.4)									
Green and yellow vegetables, g[§]	68.6 (45–102.3)									
Other vegetables, g[§]	111.2 (79.3–158.9)									
Total fruit, g[§]	125.3 (80.8–185.8)									
Apples, g[§]	10.4 (4.4–23.9)									
Citrus fruit, g[§]	19.7 (7–46.2)									
α-carotene, μg[§]	307.8 (179.1–509.4)									
β-carotene, μg[§]	2439 (1632–3515)									
Vitamin C, mg[§]	96.8 (76.5–123.9)									
Vitamin E, mg[§]	7.5 (6.5–8.4)									
Characteristics at postnatal assessment										
Maternal smoking during pregnancy, %	7.3	10.7	5.3	0.008	9.7	5.7	0.06	10	5	0.01
Birth weight, g	3012 (2772–3246)	3026	3009	0.07	3020	3037	0.12	2996	3034	0.22
Male sex, %	47.4	45.5	47.7	0.86	47.5	50	0.49	45.2	48.7	0.16
Breastfeeding duration, mo, %				0.0006			0.35			0.02
<6	10.8	17.4	9		13	10		15.7	9	
≥6	89.2	82.6	91		87	90		84.3	91	
Smoking in household during child's first year of life, %	27.4	31.8	22.3	0.01	29.1	26.7	0.42	30.8	26.7	0.27

*Values are medians for continuous variables and percentages of subjects for categorical variables.
†Values are medians (interquartile ranges) for continuous variables and percentages of subjects for categorical variables.
‡For continuous variables, a linear trend test was used; for categorical variables, a Mantel-Haenszel χ^2 test was used.
§Food and nutrient intake levels were adjusted for total energy intake using the residual method.

peer problems. Similarly, higher green and yellow vegetable intake was independently related to a decreased risk for low prosocial behavior, but not the other problems, in the children: The adjusted OR between extreme quartiles was 0.55 (95% CI, 0.38–0.79, $P = 0.002$ for trend). Significant inverse exposure–response associations were observed between maternal other vegetable intake during pregnancy and the risk for childhood hyperactivity problems and low prosocial behavior: The adjusted ORs between extreme quartiles were 0.55 (95% CI, 0.33–0.90, $P = 0.009$ for trend) and 0.62 (95% CI, 0.43–0.88, $P = 0.02$ for trend), respectively. No relationships were found between maternal other vegetable intake during pregnancy and childhood emotional, conduct, or peer problems. There were significant inverse exposure–response relationships between maternal intake of total fruit and apples during pregnancy and the risk for childhood hyperactivity problems only ($P = 0.03$ and 0.04 for trend, respectively), although the adjusted ORs between extreme quartiles were not significant. Higher maternal citrus fruit intake during pregnancy was independently associated with a reduced risk for childhood emotional, conduct, and hyperactivity problems, but not peer problems or low prosocial behavior: The adjusted ORs between extreme quartiles were 0.61 (95% CI, 0.37–0.995, $P = 0.03$ for trend), 0.43 (95% CI, 0.28–0.66, $P = 0.0005$ for trend), and 0.55 (95% CI, 0.33–0.91, $P = 0.03$ for trend), respectively.

No significant exposure–response association was observed between maternal α-carotene intake during pregnancy and any of the outcomes under study; however, significant positive relationships were found between intake in the second and fourth quartiles and childhood conduct problems: The adjusted OR between extreme quartiles was 1.59 (95% CI, 1.03–2.45, $P = 0.21$ for trend; Table 3). Regarding the relationships between maternal intake of

Table 2
ORs and 95% CIs for behavioral problems assessed by the Strength and Difficulties Questionnaire in 1199 children 5 y of age in relation to quartile (Q) of maternal intake of vegetables and fruit during pregnancy

	Emotional problems		Conduct problems		Hyperactivity problems		Peer problems		Low prosocial behavior	
Variables*	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†b	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†
Total vegetables										
Q1 (107.2)	11.7	1.00	19.7	1.00	16.7	1.00	8.7	1.00	36.8	1.00
Q2 (162.2)	12.3	1.19 (0.72–2.00)	20.7	1.12 (0.74–1.69)	11.7	0.65 (0.40–1.06)	7.7	0.98 (0.53–1.78)	29.3	0.71 (0.50–1.01)
Q3 (220.5)	13.3	1.28 (0.77–2.13)	20	1.16 (0.76–1.77)	11.7	0.71 (0.44–1.16)	9	1.19 (0.66–2.13)	26.3	0.65 (0.45–0.94)
Q4 (321.7)	14.3	1.45 (0.88–2.40)	17.3	0.94 (0.61–1.44)	12.3	0.70 (0.43–1.12)	9	1.17 (0.65–2.09)	24.3	0.55 (0.38–0.79)
P-value for trend		0.15		0.84		0.18		0.49		0.001
Green and yellow vegetables										
Q1 (34.1)	16.4	1.00	21.4	1.00	14.4	1.00	9.7	1.00	35.8	1.00
Q2 (57.1)	12.0	0.71 (0.43–1.14)	22.0	1.15 (0.77–1.73)	14.0	1.04 (0.65–1.68)	9	1.02 (0.58–1.81)	29.7	0.77 (0.54–1.09)
Q3 (83.4)	9.3	0.60 (0.35–1.001)	16.3	0.86 (0.55–1.32)	11.7	0.88 (0.53–1.46)	7.7	0.91 (0.50–1.65)	28	0.70 (0.48–1.002)
Q4 (131.8)	14.0	0.93 (0.58–1.50)	18.0	0.95 (0.62–1.44)	12.3	0.93 (0.57–1.52)	8	0.93 (0.51–1.66)	23.3	0.55 (0.38–0.79)
P-value for trend		0.65		0.51		0.64		0.72		0.002
Other vegetables										
Q1 (62.3)	12.4	1.00	20.4	1.00	17.1	1.00	9	1.00	37.5	1.00
Q2 (95.9)	10.0	0.80 (0.47–1.36)	20	1.00 (0.66–1.51)	14	0.79 (0.50–1.25)	6.3	0.73 (0.39–1.35)	25.3	0.56 (0.39–0.81)
Q3 (129)	13.7	1.11 (0.68–1.83)	19.7	1.04 (0.69–1.58)	10.7	0.61 (0.37–0.995)	9.3	1.09 (0.62–1.94)	27	0.67 (0.46–0.95)
Q4 (204.1)	15.7	1.31 (0.81–2.14)	17.7	0.88 (0.57–1.34)	10.7	0.55 (0.33–0.90)	9.7	1.11 (0.63–1.97)	27	0.62 (0.43–0.88)
P-value for trend		0.15		0.61		0.009		0.45		0.02
Total fruit										
Q1 (53.2)	12.7	1.00	20.7	1.00	13.7	1.00	7.4	1.00	30.1	1.00
Q2 (101.8)	15.7	1.40 (0.87–2.29)	22	1.07 (0.71–1.60)	15	1.11 (0.69–1.79)	10.3	1.50 (0.83–2.73)	29	0.92 (0.64–1.33)
Q3 (150.8)	13.3	1.03 (0.62–1.72)	17.7	0.79 (0.51–1.21)	13.3	0.86 (0.52–1.40)	9.7	1.27 (0.70–2.33)	29.7	0.90 (0.62–1.29)
Q4 (256.1)	10	0.75 (0.44–1.28)	17.3	0.74 (0.48–1.14)	10.3	0.61 (0.36–1.02)	7.0	0.87 (0.45–1.66)	28.0	0.79 (0.54–1.15)
P-value for trend		0.17		0.08		0.03		0.53		0.22
Apples										
Q1 (1.2)	13.4	1.00	22.7	1.00	16.4	1.00	11.4	1.00	32.8	1.00
Q2 (7.2)	14.3	1.21 (0.75–1.97)	18.7	0.84 (0.56–1.27)	15	0.98 (0.62–1.56)	8.7	0.75 (0.43–1.31)	26.7	0.75 (0.52–1.07)
Q3 (13.6)	13.3	1.11 (0.68–1.82)	16.7	0.73 (0.48–1.11)	11	0.66 (0.40–1.07)	7.3	0.65 (0.36–1.16)	28.7	0.82 (0.57–1.18)
Q4 (39.3)	10.7	1.02 (0.61–1.72)	19.7	0.99 (0.66–1.50)	10	0.66 (0.40–1.10)	7	0.65 (0.36–1.17)	28.7	0.81 (0.56–1.17)
P-value for trend		0.98		0.78		0.04		0.12		0.37
Citrus fruit										
Q1 (0.4)	17.4	1.00	27.1	1.00	16.7	1.00	10.7	1.00	33.1	1.00
Q2 (13.4)	12.7	0.72 (0.44–1.15)	16	0.53 (0.35–0.79)	12.3	0.76 (0.47–1.23)	5.7	0.55 (0.29–1.02)	28	0.85 (0.59–1.22)
Q3 (30.1)	10.7	0.57 (0.34–0.93)	20.3	0.67 (0.45–0.99)	13.3	0.78 (0.49–1.25)	8.0	0.79 (0.44–1.40)	25.7	0.69 (0.48–0.998)
Q4 (78.5)	11.0	0.61 (0.37–0.995)	14.3	0.43 (0.28–0.66)	10.0	0.55 (0.33–0.91)	10.0	0.96 (0.56–1.66)	30	0.84 (0.59–1.20)
P-value for trend		0.03		0.0005		0.03		0.90		0.22

CI, confidence interval; OR, odds ratio.

*Quartile medians in g/d adjusted for energy intake using the residual method are given in parentheses.

†Adjustment for maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, household income, maternal depressive symptoms during pregnancy, maternal alcohol intake during pregnancy, maternal smoking during pregnancy, child's birth weight, child's sex, breastfeeding duration, and smoking in the household during child's first year of life.

Table 3
ORs and 95% CIs for behavioral problems assessed by the Strength and Difficulties Questionnaire in 1199 children 5 y of age in relation to quartile (Q) of maternal intake of antioxidants during pregnancy

	Emotional problems		Conduct problems		Hyperactivity problems		Peer problems		Low prosocial behavior		
Variables*	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†	Risk (%)	Adjusted OR (95% CI)†	Mutual adjusted OR (95% CI)
α-carotene											
Q1 (119.2)	13.7	1.00	16.7	1.00	15.1	1.00	8.4	1.00	30.8	1.00	
Q2 (250.9)	11.7	0.82 (0.49–1.35)	24.0	1.69 (1.12–2.57)	12.7	0.83 (0.51–1.35)	9	1.10 (0.62–1.99)	29.7	0.96 (0.67–1.38)	
Q3 (382.5)	12.3	1.06 (0.64–1.75)	15.7	1.00 (0.63–1.56)	12.7	0.91 (0.56–1.47)	10	1.40 (0.79–2.51)	25.3	0.75 (0.52–1.09)	
Q4 (634.2)	14	1.32 (0.81–2.16)	21.3	1.59 (1.03–2.45)	12	0.90 (0.55–1.48)	7	0.92 (0.49–1.72)	31	1.09 (0.75–1.57)	
P-value for trend		0.19		0.21		0.75		0.97		0.98	
β-carotene											
Q1 (1269)	15.1	1.00	19.4	1.00	15.4	1.00	7.7	1.00	35.1	1.00	1.00‡
Q2 (2038)	11.3	0.80 (0.49–1.32)	21	1.11 (0.73–1.68)	12.7	0.77 (0.47–1.24)	11.3	1.69 (0.96–3.02)	28.7	0.69 (0.48–0.98)	0.74 (0.51–1.07)
Q3 (2890)	12.3	0.92 (0.56–1.51)	19.3	1.13 (0.74–1.73)	11.3	0.73 (0.45–1.20)	8	1.22 (0.66–2.28)	25.3	0.61 (0.42–0.87)	0.70 (0.47–1.04)
Q4 (4479)	13	1.11 (0.68–1.81)	18	1.07 (0.70–1.65)	13	0.96 (0.59–1.55)	7.3	1.07 (0.57–2.02)	27.7	0.70 (0.49–1.01)	0.89 (0.57–1.38)
P-value for trend		0.62		0.73		0.78		0.89		0.04	0.52
Vitamin C											
Q1 (62.1)	13.4	1.00	24.8	1.00	16.4	1.00	9.7	1.00	35.1	1.00	1.00§
Q2 (86.3)	15	1.19 (0.73–1.93)	19.3	0.74 (0.50–1.11)	13	0.77 (0.48–1.23)	8.7	0.91 (0.51–1.62)	28.7	0.77 (0.54–1.10)	0.79 (0.55–1.13)
Q3 (110.1)	14.3	1.09 (0.67–1.77)	16.3	0.59 (0.39–0.90)	12.7	0.68 (0.42–1.08)	8	0.79 (0.44–1.41)	27	0.63 (0.44–0.90)	0.66 (0.45–0.97)
Q4 (148.6)	9	0.64 (0.37–1.09)	17.3	0.61 (0.40–0.92)	10.3	0.53 (0.32–0.87)	8	0.76 (0.42–1.35)	26	0.61 (0.42–0.88)	0.66 (0.44–0.99)
P-value for trend		0.11		0.01		0.01		0.30		0.004	0.03
Vitamin E											
Q1 (5.9)	11.4	1.00	22.7	1.00	16.7	1.00	8.7	1.00	33.4	1.00	1.00‖
Q2 (7.0)	12.7	1.12 (0.67–1.88)	19.3	0.90 (0.60–1.36)	11.7	0.63 (0.39–1.02)	6.7	0.76 (0.40–1.41)	32.0	0.97 (0.68–1.38)	1.04 (0.68–1.60)
Q3 (7.9)	13.3	1.19 (0.72–1.99)	16.7	0.70 (0.46–1.07)	11	0.59 (0.36–0.96)	10.7	1.23 (0.71–2.17)	25.0	0.66 (0.46–0.96)	0.75 (0.44–1.28)
Q4 (9.4)	14.3	1.37 (0.83–2.28)	19	0.84 (0.56–1.27)	13	0.74 (0.46–1.18)	8.3	0.92 (0.51–1.67)	26.3	0.70 (0.48–1.01)	0.86 (0.41–1.84)
P-value for trend		0.22		0.24		0.18		0.81		0.01	0.11

CI, confidence interval; OR, odds ratio.
*Quartile medians in μg/d (except for vitamins C and E, mg/d) adjusted for energy intake using the residual method are given in parentheses.
†Adjustment for maternal age, gestation at baseline, region of residence at baseline, number of children at baseline, maternal and paternal education, household income, maternal depressive symptoms during pregnancy, maternal alcohol intake during pregnancy, maternal smoking during pregnancy, child's birth weight, child's sex, breastfeeding duration, and smoking in the household during child's first year of life.
‡Further adjustment for maternal intake of vitamins C and E during pregnancy as continuous variables.
§Further adjustment for maternal intake of β-carotene and vitamin E during pregnancy as continuous variables.
‖Further adjustment for maternal intake of β-carotene and vitamin C during pregnancy as continuous variables.

β-carotene and vitamin E during pregnancy and childhood low prosocial behavior, the adjusted ORs between extreme quartiles fell just short of the significance level, although the inverse linear trends were significant ($P = 0.04$ and 0.01 for trend, respectively). Maternal intake of β-carotene and vitamin E during pregnancy was not associated with the other outcomes. Maternal vitamin C intake during pregnancy was independently inversely related to childhood conduct and hyperactivity problems and low prosocial behavior, but not emotional or peer problems. The adjusted ORs between extreme quartiles were 0.61 (95% CI, 0.40−0.92, $P = 0.01$ for trend), 0.53 (95% CI, 0.32−0.87, $P = 0.01$ for trend), and 0.61 (95% CI, 0.42−0.88, $P = 0.004$ for trend), respectively. Additional adjustment for maternal intake of β-carotene and vitamin E during pregnancy did not materially alter the relationship between maternal vitamin C intake during pregnancy and the risk for childhood low prosocial behavior: The additional adjusted OR between extreme quartiles was 0.66 (95% CI, 0.44−0.99, $P = 0.03$ for trend). On the other hand, the inverse associations between maternal intake of β-carotene and vitamin E during pregnancy and the risk for childhood low prosocial behavior completely disappeared after mutual adjustment for maternal intake of β-carotene, vitamin C, and vitamin E during pregnancy.

The significant inverse relationships between maternal intake of other vegetables, total fruit, apples, and citrus fruit in the highest quartile and childhood hyperactivity and between maternal other vegetable intake during pregnancy and childhood low prosocial behavior were completely attenuated by further adjustment for maternal vitamin C intake during pregnancy. On the other hand, after further adjustment for maternal vitamin C intake during pregnancy, the inverse associations between maternal citrus fruit intake during pregnancy and childhood conduct problems and between maternal intake of total vegetables and green and yellow vegetables and childhood low prosocial behavior remained.

Discussion

To our knowledge, the current pre-birth cohort study was the first to demonstrate that higher maternal intake levels of total vegetables and green and yellow vegetables during pregnancy were independently associated with a reduced risk for childhood low prosocial behavior, that higher maternal intake of other vegetables during pregnancy was independently associated with a reduced risk for childhood hyperactivity problems and low prosocial behavior, that higher maternal intake levels of total fruit and apples during pregnancy were independently inversely related to the risk for childhood hyperactivity problems, that higher maternal intake of citrus fruit during pregnancy was independently inversely related to the risk for childhood emotional, conduct, and hyperactivity problems, and that higher maternal vitamin C intake during pregnancy was independently inversely associated with the risk for conduct and hyperactivity problems and low prosocial behavior in the children.

A cross-sectional study of 986 Korean children 8 to 11 y of age showed that higher vegetable, but not fruit, intake was significantly associated with fewer external behavioral problems based on the Child Behavior Checklist, whereas neither vegetable nor fruit intake was related to the risk for probable or definite attention-deficit/hyperactivity disorder (ADHD) based on the Diagnostic Interview Schedule for Children version IV ADHD module [22]. In a Spanish case-control study of 60 children and adolescents 6 to16 y of age newly diagnosed with ADHD based on the Diagnostic and Statistical Manual of Mental Disorders, fourth edition text revision, and 60 sex- and age-matched controls, consumption of vegetables and citrus fruit was significantly inversely associated with the risk for ADHD [23]. Higher maternal fruit intake during pregnancy was associated with increased cognitive development at 1 y of age as assessed by the Bayley scale of infant development in a pre-birth cohort study of 688 Canadian children [24]. These findings are in partial agreement with our results.

Vitamin C plays an important role in maintaining redox balance in the brain as a powerful antioxidant and scavenger of reactive oxygen species and is also a key factor in the recycling of other brain antioxidants such as vitamin E [1]. Vitamin C is involved in modulation of the cholinergic, catecholinergic, and glutamatergic systems of the brain, as well as the general development of neurons through maturation, differentiation, and myelin formation [1]. In the developing brain, neuronal density and maturation is compromised by vitamin C deficiency, giving rise to decreased brain volume [1]. Therefore, higher maternal vitamin C intake during pregnancy might be expected to decrease the risk for childhood conduct and hyperactivity problems and low prosocial behavior. Further control for maternal intake of vitamin C completely removed the inverse relationships between maternal intake of other vegetables, total fruit, apples, and citrus fruit in the highest quartile and childhood hyperactivity and between maternal intake of other vegetables during pregnancy and childhood low prosocial behavior; such preventive relationships may be attributable to some extent to vitamin C or unmeasured constituents in relation to vitamin C. Because the inverse associations between maternal citrus fruit intake during pregnancy and childhood conduct problems and between maternal intake of total vegetables and green and yellow vegetables and childhood low prosocial behavior persisted after further adjustment for maternal vitamin C intake, such protective associations are unlikely to be ascribed to vitamin C.

Methodological strengths of the present study included its pre-birth prospective cohort design with a relatively large sample size, its relatively long duration of follow up, and its extensive data on potential confounding factors.

The present study had some limitations. The results may have been influenced by residual confounding. Although the DHQ used in the present study, which is designed to assess dietary intake for 1 mo before completing the DHQ, had a relatively high validity for antioxidants as mentioned previously, misclassification of consumption is inevitable. Additionally, the study's participants answered the DHQ anywhere between weeks 5 and 39 of pregnancy. Any misclassification of dietary factors is likely to be non-differential with respect to exposure and consequently to result in a bias toward the null, making our estimate more conservative than the true effect size.

Data on the SDQ were reported by the mothers. Moreover, it is not certain that the cutoff points of dichotomization of the five outcomes based on the SDQ were reasonable; however, they were chosen according to a previous study performed in Japan [21]. The possibility of non-differential outcome misclassification might skew our observed associations toward the null.

Of the 1757 study participants who participated in the baseline survey, 556 mother−child pairs did not take part in the eighth survey. No measurable differences were shown between the 556 non-participants and the 1201 participants in the eighth survey with respect to distribution of number of children, depressive symptoms during pregnancy, or alcohol intake during pregnancy. Compared with non-participants in the eighth survey, participants were more likely to be older, to have participated in the baseline survey earlier in their gestation, to live in Fukuoka Prefecture, and to report high maternal and paternal educational levels and high household income. In the baseline survey, the participation rate could not be calculated because data on the number of pregnant women who were provided by the 423 collaborating obstetric hospitals with a set of leaflets explaining the KOMCHS, an application form, and a self-addressed and stamped return envelope were not available. Of the 1757 mothers at baseline, 978 lived in Fukuoka Prefecture. According to data collected by the government of Fukuoka Prefecture, the number of childbirths was 46 393 in 2007 and 46 695 in 2008; thus, the participation rate must have been low. The participants in the present study were probably not representative of Japanese women in the general population. According to a population census conducted in 2000 in Fukuoka Prefecture, the percentages of women 30 to 34 y of age with $<$13, 13 to 14, $\geq$15, and an unknown number of years of education were 52%, 31.5%, 11.8%, and 4.8%, respectively [25]. The corresponding figures for the present study were 20.9%, 33.3%, 45.9%, and 0%, respectively.

Conclusion

The findings from the present study indicated the following:

- Maternal intake of citrus fruit during pregnancy may be preventive against emotional problems.
- Maternal intake of citrus fruit and vitamin C during pregnancy may be protective against conduct problems.
- Maternal intake of other vegetables, total fruit, apples, citrus fruit, and vitamin C during pregnancy may be preventive against hyperactivity problems.
- Maternal intake of total vegetables, green and yellow vegetables, other vegetables, and vitamin C during pregnancy may be protective against low prosocial behavior in children at the age of 5 y.

Further work should be carried out to confirm the reported results. The mechanisms underlying our results deserve further exploration.

Acknowledgments

The authors acknowledge the Kyushu Branch of the Japan Allergy Foundation, the Fukuoka Association of Obstetricians & Gynecologists, the Okinawa Association of Obstetricians & Gynecologists, the Miyazaki Association of Obstetricians & Gynecologists, the Oita Association of Obstetricians & Gynecologists, the Kumamoto Association of Obstetricians & Gynecologists, the Nagasaki Association of Obstetricians & Gynecologists, the Kagoshima Association of Obstetricians & Gynecologists, the Saga Association of Obstetricians & Gynecologists, the Fukuoka Society of Obstetrics and Gynecology, the Okinawa Society of Obstetrics and Gynecology, the Fukuoka City Government, and the Fukuoka City Medical Association for their valuable support.

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