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Article

Calcium intake during pregnancy is associated with decreased risk of emotional and hyperactivity problems in five-year-old Japanese children

Keiji Takahashi[1,2], Keiko Tanaka[1,3,*], Yoshitaka Nakamura[2], Hitomi Okubo[4], Satoshi Sasaki[5], Masashi Arakawa[6] and Yoshihiro Miyake[3,7]

[1] Department of Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, Ehime, Japan (These authors made an equal contribution to this work and share first authorship.); keiji.takahashi@meiji.com (K.Tak.); tanaka.keiko.jn@ehime-u.ac.jp (K.Tan.)
[2] Food Science & Technology Research Laboratories, R&D Division, Meiji Co., Ltd., Tokyo, Japan; yoshitaka.nakamura@meiji.com (Y.N.)
[3] Epidemiology and Medical Statistics Unit, Translational Research Center, Ehime University Hospital, Ehime, Japan; miyake.yoshihiro.ls@ehime-u.ac.jp (Y.M.)
[4] Department of Health Promotion, National Institute of Public Health, Saitama, Japan; okubo.h.aa@niph.go.jp (H.O.)
[5] Department of Social and Preventive Epidemiology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan; stssasak@m.u-tokyo.ac.jp (S.S.)
[6] Wellness Research Fields, Faculty of Global and Regional Studies, University of the Ryukyus, Okinawa, Japan; h069475@tm.u-ryukyu.ac.jp (M.A.)
[7] Department of Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime, Japan
* Correspondence: tanaka.keiko.jn@ehime-u.ac.jp; Tel.: +81-89-960-5283

Abstract: In recent years, more attention has been paid to behavioral problems in children. However, for the most part, risk factors for these problems have yet to be determined. The current prebirth cohort study investigated the relationship between maternal calcium consumption during pregnancy and behavioral problems in five-year-old Japanese children. Subjects were 1199 mother-child pairs. Dietary intake was assessed using a diet history questionnaire. Emotional problems, conduct problems, hyperactivity problems, and peer problems were assessed using the Strengths and Difficulties Questionnaire. Logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for four behavioral problems under study according to the quartile of calcium intake, with the lowest quartile as the reference. Adjustment was made 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 age, child's birth weight, postnatal secondhand smoke exposure at home during the first year of life, and breastfeeding duration. Higher maternal calcium intake during pregnancy was independently associated with a decreased risk of childhood emotional and hyperactivity problems; the adjusted ORs between extreme quartiles (95% CIs, P for trend) were 0.46 (0.27–0.79, 0.01) and 0.60 (0.37–0.97, 0.046). No such inverse associations were observed for childhood conduct problems or peer problems. Maternal calcium intake during pregnancy may decrease the risk of childhood emotional and hyperactivity problems.

Keywords: behavioral problems; calcium; child; maternal intake; prebirth cohort

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1. Introduction

The prevalence of mental health disorders in children, including developmental disabilities, is increasing [1]. In recent years, more attention has been paid to behavioral problems in children. However, for the most part, risk factors for these problems have yet to be determined.

Environmental factors during the perinatal period play a crucial role in the maturation of the brain and its function, which might link to childhood behavior or adulthood mental health [2, 3]. For example, some epidemiological studies suggest that pre- and postnatal smoking exposure is associated with increased risk for childhood behavioral problems [4-6]. Maternal intake of nutrients during pregnancy is one of the most important prenatal environmental factors because nutrients are transferred from the mother to the fetus through the placenta. However, epidemiological evidence on the association between maternal intake during pregnancy and developmental and behavioral outcomes has been poorly investigated. In a UK cohort study, lower maternal folate intake in early pregnancy was associated with higher childhood hyperactivity and peer problems scores [7]. Our previous study showed that maternal caffeine intake during pregnancy was associated with a reduced risk of childhood peer problems [8], whereas positive associations were observed between maternal intake of monounsaturated fatty acids, α-linolenic acid, ω-6 polyunsaturated fatty acids, and linoleic acid during pregnancy and the risk of childhood emotional problems [9].

As one of the important nutrients, calcium has been shown to be associated with many disorders, for example, cardiovascular diseases [10], colon cancer [11], and fractures [12]. Calcium is also associated with various neuronal processes, including brain development and function [13]. Thus, maternal calcium intake during pregnancy might play an important role in the behavioral development of a child in a variety of ways.

In the present study in Japan, we prospectively examined the association between maternal calcium intake during pregnancy and childhood behavioral problems at the age of 5 years, using data from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS).

2. Materials and Methods

2.1. Study Population

The KOMCHS is an ongoing prospective multipurpose prebirth cohort study. Details of the baseline survey of the KOMCHS have been described elsewhere [14]. Eligible subjects were women who became pregnant in one of seven prefectures on Kyushu Island in southern Japan, with a total population of approximately 13.26 million, or Okinawa Prefecture, with a population of nearly 1.37 million, between April 2007 and March 2008. We asked 423 obstetric hospitals in the eight prefectures to provide a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed stamped return envelope to as many pregnant women as possible. Pregnant women who intended to participate in the KOMCHS mailed the application form to the data management center. Ultimately, a total of 1757 pregnant women between five and 39 weeks of gestation gave their written informed consent to take part in the KOMCHS and answered a self-administered questionnaire in the baseline survey. Of the 1757 pregnant women, 1590, 1527, 1430, 1362, 1305, 1264, and 1201 mother-child pairs participated in the second (after delivery), third (approximately 4 months postpartum), fourth (approximately 12 months postpartum), fifth (approximately 24 months postpartum), sixth (approximately 36 months postpartum), seventh (approximately 48 months postpartum), and eighth (approximately 60 months postpartum) surveys, respectively. Two pairs were excluded due to missing data on household income. The final analysis comprised 1199 parent-child pairs. The study protocol for the KOMCHS was approved by the ethics committees of the Faculty of Medicine, Fukuoka University and the Ehime University Graduate School of Medicine.

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2.2. Measurements

At the time of each survey, study subjects filled out self-administered questionnaires and mailed them to the data management center. Research technicians rectified missing or illogical data by telephone interview.

The first part of the questionnaire at baseline elicited information on maternal age, gestation, region of residence, number of children, maternal and paternal educational levels, household income, and maternal depressive symptoms during pregnancy. The second part of the questionnaire at baseline was a semi-quantitative, comprehensive diet history questionnaire (DHQ) to assess dietary habits during the preceding month [15-21]. Estimates of daily intake of foods (from a total of 150 foods), energy, and selected nutrients were calculated using an ad hoc computer algorithm for the DHQ based on the Standard Tables of Food Composition in Japan [22]. As only a small number of the study population (n = 73, 6.1%) used supplemental calcium on a weekly or more frequent basis, information on the supplement was not used in the calculation of dietary intake. In a validation study of 92 Japanese women aged 31–69 years, the Pearson's correlation coefficient between the DHQ and 16-day semi-weighed dietary records was 0.56 for calcium [17]. Energy-adjusted intake calculated by the residual method was used for the analyses [23].

The questionnaire in the second survey gathered data regarding the infant's sex, birth weight, date of birth, and maternal smoking during pregnancy. Information on household smoking and breastfeeding duration was obtained from the questionnaire until the fourth survey. In the eighth survey, children's behavioral problems at 5 years of age was assessed using a Japanese parent-report version of the Strength and Difficulties Questionnaire (SDQ), which was designed to assess the behavior and emotions of 3- to 16-year-old children [24]. The SDQ consists of five scales: an emotional problems scale, a conduct problems scale, a hyperactivity scale, a peer problems scale, and a prosocial scale, which are scored according to five items each, resulting in 25 items in total. Each item is rated on a three-point scale: "not true" (0), "somewhat true" (1), and "certainly true" (2). Positively worded items are reverse-scored. The items on each scale were summed to generate a score from 0 to 10. These scale scores were then categorized as normal, borderline, or abnormal according to cut-off points that had previously been reported in a sample of Japanese children [25].

2.3. Statistical Analysis

We dichotomized the first four scale scores, comparing children with borderline and abnormal scores to children with normal scores; we defined emotional problems, conduct problems, hyperactivity problems, or peer problems as present when a child had a borderline or abnormal score in the respective scale. 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, secondhand smoke exposure at home during the first of year of life, and breastfeeding duration were selected a prior as potential confounding factors.

Logistic regression analysis was conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for four behavioral problems under study according to the quartile of calcium intake, with the lowest quartile as the reference. The multivariate ORs were adjusted for potential confounding factors. The test of trend was assessed by a logistic regression model assigning consecutive integers (1–4) to the quartile of calcium intake. Two-sided P values less than 0.05 were considered statistically significant. All models were estimated using the SAS software package (version 9.4; SAS Institute, Inc., Cary, NC, USA).

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3. Results

The prevalence values of emotional problems, conduct problems, hyperactivity problems, and peer problems were 12.9%, 19.4%, 13.1%, and 8.6%, respectively, among the 1199 children aged 59 to 71 months. Table 1 shows participants' characteristics. The mean maternal age and gestation at baseline were 31.6 years and 18.1 weeks, respectively, and approximately 18% of mothers had depressive symptoms during pregnancy. Mean daily total energy consumption and mean daily energy-adjusted intake of calcium during pregnancy were 7386.7 kJ and 504 mg, respectively. Maternal calcium intake during pregnancy was positively associated with maternal age at baseline and maternal and paternal educational levels, and inversely associated with number of children, maternal depressive symptoms during pregnancy, maternal smoking during pregnancy, children's birth weight, and exposure to smoking in household during the first year of life.

Table 1. Characteristics of 1199 parent-child pairs, according to quartile of maternal calcium intake during pregnancy[1]

Variable	Total (n = 1199) N (%) or mean ± SD	Quartile				
		1 (n = 299)	2 (n = 300)	3 (n = 300)	4 (n = 300)	*P* for trend[a]
Baseline characteristics						
Maternal age, years	31.6 ± 4.0	31.1 ± 4.0	31.4 ± 4.3	31.9 ± 3.6	32.1 ± 3.9	0.002
Gestation, weeks	18.1 ± 5.3	17.9 ± 5.1	18.0 ± 5.3	17.8 ± 5.2	18.9 ± 5.5	0.06
Region of residence, %						0.71
Fukuoka Prefecture	693 (57.8)	175 (58.5)	170 (56.7)	171 (57.0)	177 (59.0)	
Other than Fukuoka Prefecture in Kyushu	393 (32.8)	92 (30.8)	98 (32.7)	101 (33.7)	102 (34.0)	
Okinawa Prefecture	113 (9.4)	32 (10.7)	32 (10.7)	28 (9.3)	21 (7.0)	
Number of living children already born to same mother, %						0.006
0	484 (40.4)	101 (33.8)	125 (41.7)	124 (41.3)	134 (44.7)	
1	480 (40.0)	135 (45.2)	103 (34.3)	125 (41.7)	117 (39.0)	
≥ 2	235 (19.6)	63 (21.1)	72 (24.0)	51 (17.0)	49 (16.3)	
Maternal education, years, %						0.002
< 13	250 (20.9)	83 (27.8)	60 (20.0)	60 (20.0)	47 (15.7)	
13−14	399 (33.3)	98 (32.8)	95 (31.7)	98 (32.7)	108 (36.0)	
≥ 15	550 (45.9)	118 (39.5)	145 (48.3)	142 (47.3)	145 (48.3)	
Paternal education, years, %						0.001
< 13	343 (28.6)	102 (34.1)	92 (30.7)	84 (28.0)	65 (21.7)	
13−14	173 (14.4)	42 (14.1)	40 (13.3)	45 (15.0)	46 (15.3)	
≥ 15	683 (57.0)	155 (51.8)	168 (56.0)	171 (57.0)	189 (63.0)	
Household income, yen/year, %						0.11
< 4,000,000	386 (32.2)	116 (38.8)	90 (30.0)	92 (30.7)	88 (29.3)	
4,000,000−5,999,999	449 (37.5)	97 (32.4)	116 (38.7)	116 (38.7)	120 (40.0)	
≥ 6,000,000	364 (30.4)	86 (28.8)	94 (31.3)	92 (30.7)	92 (30.7)	
Maternal depressive symptoms	218 (18.2)	68 (22.7)	55 (18.3)	50 (16.7)	45 (15.0)	0.01

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during pregnancy, %						
Maternal alcohol intake during pregnancy, %	158 (13.2)	43 (14.4)	44 (14.7)	36 (12.0)	35 (11.7)	0.22
Maternal daily intake						
Total energy, kJ	7386.7 ± 1983.8	7785.1 ± 2350.1	6973.4 ± 1921.5	7128.9 ± 1694.8	7660.7 ± 1796.6	0.68
Calcium, mg/day[2]	503.8 ± 165.1	325.1 ± 67.0	440.6 ± 23.9	529.6 ± 31.4	719.3 ± 141.2	< 0.0001
Characteristics at the postnatal assessment						
Maternal smoking during pregnancy, %	87 (7.3)	36 (12.0)	22 (7.3)	15 (5.0)	14 (4.7)	0.0003
Birth weight, g	3005.5 ± 397.6	3033.6 ± 363.8	3046.8 ±409.9	2960.1 ± 416.3	2981.7 ± 393.9	0.02
Male gender, %	568 (47.4)	141 (47.2)	141 (47.0)	140 (46.7)	146 (48.7)	0.74
Breastfeeding duration, months, %						0.08
< 6	130 (10.8)	39 (13.0)	30 (10.0)	39 (13.0)	22 (7.3)	
≥ 6	1069 (89.2)	260 (87.0)	270 (90.0)	261 (87.0)	278 (92.7)	
Smoking in household during the first year of life, %	329 (27.4)	96 (24.9)	87 (29.0)	85 (28.3)	61 (20.3)	0.002

[1] For continuous variables, a linear trend test was used; for categorical variables, a Mantel-Haenszel $\chi 2$-test was used.
[2] Nutrient intake was adjusted for total energy intake using the residual method.

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for behavioral problems assessed by the Strength and Difficulties Questionnaire in 1199 five-year-old children by quartiles of maternal calcium intake during pregnancy.

Calcium	Quartile				*P* for trend
	1 (Lowest) (n = 299)	2 (n = 300)	3 (n = 300)	4 (Highest) (n = 300)	
Intake, mg/day[1]	341.9	438.9	523.9	676.1	
Emotional problems, (score > 3)					
Risk (%)	16.1	13.0	14.3	8.3	
Crude OR (95% CI)	1.00	0.78 (0.49–1.23)	0.88 (0.56–1.37)	0.48 (0.28–-0.79)	0.01
Adjusted OR (95% CI)[2]	1.00	0.76 (0.47–1.23)	0.87 (0.54–1.39)	0.46 (0.27–0.79)	0.01
Conduct problems, (score > 3)					
Risk (%)	23.1	18.7	17.0	19.0	
Crude OR (95% CI)	1.00	0.77 (0.51–1.14)	0.68 (0.45–1.02)	0.78 (0.53–1.16)	0.17
Adjusted OR (95% CI)[2]	1.00	0.87 (0.57–1.30)	0.78 (0.51–1.19)	0.97 (0.64–1.47)	0.76
Hyperactivity problems, (score > 5)					
Risk (%)	18.4	10.3	11.7	12.0	
Crude OR (95% CI)	1.00	0.51 (0.32–0.82)	0.59 (0.37–0.92)	0.61 (0.38–0.95)	0.04
Adjusted OR (95% CI)[2]	1.00	0.52 (0.31–0.84)	0.58 (0.35-–0.93)	0.60 (0.37–0.97)	0.046
Peer problems, (score > 3)					

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Risk (%)	8.7	9.0	8.0	8.7	
Crude OR (95% CI)	1.00	1.04 (0.59–1.83)	0.91 (0.51–1.63)	1.00 (0.56–1.77)	0.88
Adjusted OR (95% CI)[2]	1.00	1.14 (0.64–2.05)	0.98 (0.53–1.73)	1.11 (0.61–2.01)	0.88

[1]Values for intake are medians for adjusted energy intake using the residual method for each quartile.

Table 2 presents crude and adjusted ORs and their 95% CIs for childhood behavioral problems by quartiles of maternal calcium intake during pregnancy. In the unadjusted model, compared with the lowest quartile of maternal calcium intake during pregnancy, the highest quartile was significantly associated with a reduced risk of childhood emotional problems, showing a clear inverse linear trend. Adjustment for confounders under study did not change the results: the adjusted ORs for emotional problems in the second, third, and fourth quartiles of maternal calcium intake during pregnancy were 0.76 (95% CI; 0.47–1.23), 0.87 (95% CI; 0.54–1.39), and 0.46 (95% CI; 0.27–0.79), respectively (P for trend = 0.01). We also observed an independent inverse association between maternal calcium intake during pregnancy and the risk of childhood hyperactivity problems: the adjusted OR for quartiles 2, 3, and 4 were 0.52 (95% CI; 0.31–0.84), 0.58 (95% CI; 0.35–0.93), and 0.60 (95% CI; 0.37–0.97), respectively (P for trend = 0.046). There were no measurable associations between maternal calcium intake during pregnancy and the risk of conduct problems or peer problems in children.

4. Discussion

To the best of our knowledge, this is the first study to show that a higher maternal calcium intake during pregnancy was independently associated with a reduced risk of childhood emotional and hyperactivity problems. No such preventive effect was observed for conduct problems or peer problems in children.

In a case-control study on the association between dietary nutrient patterns and the risk of attention deficit hyperactivity disorder (ADHD) in Chinese children aged 6–14 years, a mineral-protein nutrient pattern with high loadings for zinc, protein, phosphorus, selenium, calcium and riboflavin was associated with a reduced risk of ADHD [26]. A case-control study in Qatar found that 1331 ADHD children below 18 years of age had a statistically significant lower mean serum calcium level compared with that of 1331 control children [27]. In a cross-sectional study of 107 Korean schoolchildren, calcium intake in children who were categorized as high risk of ADHD was only 60% of the recommended dietary reference intake [28]. These findings appear to be in partial agreement with our results.

Potential mechanisms underlying observed inverse associations are unknown. Brain development in humans begins early in embryogenesis, and this developmental period is sensitive to environmental exposure [29]. Calcium level in the fetus might be expected to be parallel to maternal calcium intake during pregnancy. The free calcium ion (Ca^{2+}) plays an important role in controlling the development and differentiation of cells and in mediating the activity of cells [30]. Higher maternal calcium intake during pregnancy might have beneficial effects on these Ca^{2+}-controlling cellular processes.

Alternatively, maternal mental health might contribute to childhood behavioral problems. Our previous cross-sectional study using the KOMCHS demonstrated that a higher calcium intake was independently related to a lower prevalence of depressive symptoms during pregnancy [31]. Maternal calcium intake during pregnancy might be a surrogate measurement of maternal mental health. In the present study, however, maternal depression symptoms during pregnancy were controlled for in the multivariate models.

A major methodological strength of the current study is that data were obtained prospectively from a prebirth cohort study with a relatively large sample size and a relatively long duration of follow-up. The prospective design implies that the possibility of recall bias is minimal. Furthermore, several potentially important confounders were controlled for. Residual or unmeasured confounding effects could not be completely ruled out, however.

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There are limitations in the present study that deserve recognition. The validity of the DHQ regarding dietary calcium under study seems reasonable, as described above. Nevertheless, the DHQ could only approximate consumption, and was designed to assess dietary intake for one month prior to completing the DHQ. The consequence of non-differential exposure misclassification would be likely to have attenuated the true associations. Moreover, our participants answered the DHQ at any time between the 5th and 39th week of pregnancy. Due to nausea gravidarum, maternal and fetal health, and other reasons, 357 mothers had largely changed their diet in the previous month. The results of a sensitivity analysis, in which these 357 mothers were excluded, were similar to those of the overall analysis: the adjusted ORs for emotional and hyperactivity problems between extreme quartiles were 0.46 (95% CI; 0.23–0.88) and 0.56 (95% CI; 0.31–1.003).

The parents of the children in this study answered the SDQ, which could lead to misclassification of outcomes. This possible misclassification might have led to an underestimation of values in our results. Moreover, based on a report conducted in Japan [25], it is uncertain whether the cut-off points of dichotomization of the outcomes under investigation were reasonable.

Of the 1757 participants at baseline, 556 mother-child pairs did not take part in the eighth survey. Regarding the distribution of the number of children, depressive symptoms during pregnancy, and alcohol intake during pregnancy, no material differences were observed between the 556 non-participants and the 1201 participants in the eighth survey. 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. Moreover, unfortunately, at baseline, we could not estimate the participation rate because we do not have exact figures for the number of pregnant women to whom the 423 collaborating obstetric hospitals provided a set of leaflets explaining the KOMCHS, an application form, and a self-addressed and stamped return envelope. Of the 1757 participants at baseline, 978 participants lived in Fukuoka Prefecture. According to 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 very low. Our subjects were probably not representative of Japanese women in the general population. For example, a population census conducted in 2000 in Fukuoka Prefecture found that the percentages of women aged 30 to 34 years with < 13, 13−14, ≥ 15, and an unknown number of years of education were 52.0%, 31.5%, 11.8%, and 4.8%, respectively [32]. The corresponding figures for this study were 20.9%, 33.3%, 45.9%, and 0.0%, respectively. Thus, our study subjects were more educated and probably more aware of health topics than were women in the general population. Maternal calcium intake in this study population was similar to that in the general Japanese population, however. According to the National Health and Nutrition Survey in Japan, the average daily per capita intake of calcium in adult women was 501 mg [33], whereas the mean daily intake of our study subjects was 504 mg.

Data on paternal history of depressive symptoms, parental behavioral problems, and parental substance use were not available in the present study.

5. Conclusions

In conclusion, the current prebirth cohort study in Japan suggests that maternal calcium intake during pregnancy may reduce the risk of emotional and hyperactivity problems in children at the age of 5 years. Further epidemiological investigation of the effects of maternal dietary calcium intake in pregnancy on childhood behavioral problems is required.**6. Patents**

Author Contributions: KTan, YM, and MA contributed to the study concept and design and the data acquisition. HO and SS were responsible for the estimation of dietary factors. KTak and KTan were responsible for the analysis and interpretation of data and the drafting of the manuscript. YN assisted in manuscript preparation. All authors read and approved the final manuscript.

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