

~50% of epilepsies have some genetic basis^{1,2,3} Find the underlying cause of the seizure



Real patient with CLN2 disease

- **Some rapidly progressive neurodegenerative disorders present with subtle and non-specific symptoms**, mimicking more common paediatric epilepsies.³
- **CLN2 disease (TPP1 deficiency) is one devastating genetic condition** that often presents with new-onset unprovoked seizures between 2-4 years of age and/or language delay and/or motor disturbance/ataxia.^{4,5}
- **Genetic testing can help identify the aetiology** of 100+ paediatric epilepsies with one test*²
- **Many genes are actionable:** A prompt diagnosis can be essential to adopt precise disease management strategies.^{3,2}
- If you have patients with seizures of unknown cause, **no-cost genetic testing may be available** in your country.³

Visit paediatricseizures.com to find a no-cost test sponsored by BioMarin near you.

The list of laboratories provided does not include all laboratories that perform CLN2 genetic and enzymatic diagnostic testing. Laboratories providing the no-cost tests are supported by BioMarin and participate in commercially-sponsored diagnostic testing programs. There may or may not be a sponsored program or test in your area. The sponsors receive de-identified patient data, but no patient identifiable information. Participants of this program have no obligation to recommend, purchase, order, prescribe, administer, use or support any product or service of the sponsors.

* Number of genes tested will vary in each country, ranging from a single gene to over 400+ genes

~ The genetic basis of epilepsy has a range according to country and publication from 14% -24.4%,² to 50%¹, to 70-80%³

References:

1) Pal DK et al. Genetic evaluation and counseling for epilepsy. *Nature Rev Neurology*. 2010;6:445-453. 2) Truty et al. Possible precision medicine implications from genetic testing using combined detection of sequence and intragenic copy number variants in a large cohort with childhood epilepsy. *Epilepsia Open*. 2019;4:397-408. 3) Amadori et al. 'Targeted re-sequencing for early diagnosis of genetic causes of childhood epilepsy' *Italian Journal of Pediatrics* (2020) 46:92 <https://doi.org/10.1186/s13052-020-00860-1> 4) Mei D, Parrini E, Marini C, Guerrini R. The Impact of Next-Generation Sequencing on the Diagnosis and Treatment of Epilepsy in Paediatric Patients. *Mol Diagn Ther*. 2017;21(4):357-373. doi:10.1007/s40291-017-0257-0 5) Berg AT, Coryell J, Saneto RP, et al. Early-Life Epilepsies and the Emerging Role of Genetic Testing. *JAMA Pediatr*. 2017;171(9):863-871. doi:10.1001/jamapediatrics.2017.1743



Visit paediatricseizures.com

2020 BioMarin International Ltd. All rights reserved.
GL/CLN2/0033 EU/CLN2/0922 August 2020

B:OMARIN

Sponsored by BioMarin Pharmaceutical Inc.

ORIGINAL ARTICLE

Maternal caffeine intake during pregnancy and risk of food allergy in young Japanese children

Keiko Tanaka ^{1,2} Hitomi Okubo,¹ Satoshi Sasaki,³ Masashi Arakawa⁴ and Yoshihiro Miyake^{1,2}

¹Department of Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, ²Epidemiology and Medical Statistics Unit, Translational Research Center, Ehime University Hospital, Toon, ³Department of Social and Preventive Epidemiology, School of Public Health, The University of Tokyo, Tokyo and ⁴Wellness Research Fields, Faculty of Global and Regional Studies, University of the Ryukyus, Okinawa, Japan

Aim: To examine the association between maternal caffeine intake during pregnancy and the development of food allergy in young Japanese children up to 3 years of age.

Methods: The study involved 1522 mother–child pairs. Data on maternal caffeine intake during pregnancy were assessed with a validated diet history questionnaire. Food allergy was defined by a self-reported claim of having a physicians' diagnosis of food allergy or of having an acute reaction to a food.

Results: Compared with the lowest tertile of maternal caffeine intake during pregnancy, the second tertile, but not the highest tertile, was significantly associated with an increased risk of food allergy. Further adjustment on suspicion or diagnosis of atopic eczema at around 4 months postpartum in a follow-up survey did not substantially change the association between maternal caffeine intake during pregnancy and the risk of food allergy in children: further adjusted hazard ratios (95% confidence intervals) for the second (T2), the highest tertiles (T3) and the second and the highest tertiles combined (T2 + T3) were 1.46 (1.10–1.96), 1.16 (0.85–1.56) and 1.31 (1.01–1.70), respectively.

Conclusions: Our findings suggest that maternal caffeine intake during pregnancy may be positively associated with the risk of food allergy in children.

Key words: allergy; nutrition; prospective studies.

What is already known on this topic

- 1 There is limited evidence on the associations between maternal dietary intake during pregnancy and food allergy in children.
- 2 The effects that coffee or caffeine intake has on human health is widely studied.
- 3 To date, there is no evidence on the association between maternal caffeine intake and food allergy in children.

What this paper adds

- 1 Maternal caffeine intake during pregnancy was associated with an increased risk of food allergy in children.
- 2 A higher maternal caffeine intake during pregnancy might increase the risk of food allergy in children.
- 3 Further epidemiological studies are needed to determine conclusively whether maternal caffeine intake during pregnancy has an adverse effect on the development of food allergy.

Recently, food allergies have come to affect approximately 5% of young children and have become ever more prevalent worldwide as a new epidemic.¹ Not only the children with the food allergy but also their families have a lower quality of life due to social limitations, such as allergen avoidance, which significantly restricts school and social activities in children.²

The developing immune system during the fetal stage is very sensitive to environmental factors. Intra-uterine exposure influences immune maturation and might increase the risk of allergy

in the child.³ Because essential nutrients are transferred from the mother to the fetus through the placenta, maternal dietary intake during pregnancy has been proposed as a possible associated factor in the development of food allergy in children.¹ There is, however, limited evidence on the associations between maternal dietary intake during pregnancy and food allergy in children.⁴ A prospective cohort study in Australia reported that higher maternal intake of copper, but not β -carotene, vitamin C, vitamin E or zinc, during pregnancy was associated with reduced risk of food allergy at 12 months of age.⁵ In a Finnish birth cohort study, maternal dietary intake of vitamin D, but not folate, during the first 8 months of pregnancy was inversely associated with the risk of cows' milk allergy at 3 years of age.⁶ In order to clarify the effect of maternal intake during pregnancy on food allergy in children, further evidence is needed.

Coffee is the most widely consumed beverages in the world and contains bioactive components with antioxidant and

Correspondence: Dr. Keiko Tanaka, Department of Epidemiology and Preventive Medicine, Ehime University Graduate School of Medicine, Shitsukawa, Toon, Ehime 791-0295, Japan. Fax: +81 89 960 5284; email: tanaka.keiko.jn@ehime-u.ac.jp

Conflict of interest: None declared.

Accepted for publication 4 January 2021.

anti-inflammatory properties. The effects that coffee or caffeine intake has on human health is widely studied.⁷ Maternal intake of antioxidants during pregnancy might influence the

development of the fetal immune programming, resulting in the development of allergic diseases.⁸

Given the lack of studies on caffeine intake and food allergy, we examined the association between maternal caffeine intake during pregnancy and the development of food allergy in young Japanese children, using data from the fetal stage to 3 years of age from the Kyushu Okinawa Maternal and Child Health Study (KOMCHS).

Methods

Study population

The KOMCHS is an ongoing multipurpose prospective prebirth cohort study that investigates risk and preventive factors for maternal and child health problems.⁹ From April 2007 through March 2008, the baseline survey was carried out in all of the prefectures on Kyushu Island and Okinawa Prefecture in southern Japan. Eligible subjects were women who became pregnant in those prefectures. At 423 obstetric hospitals, a set of leaflets explaining the KOMCHS, an application form to participate in the study, and a self-addressed and stamped return envelope were distributed to pregnant women, insofar as this was possible. After giving fully written informed consent, 1757 pregnant women between the 5th and 39th week of pregnancy participated in the KOMCHS and completed the baseline survey. Follow-up surveys were conducted after delivery (second), around 4 months postpartum (third), around 12 months postpartum (fourth), around 24 months postpartum (fifth) and around 36 months postpartum (sixth) in order to collect updated information and environmental and life-style factors, and to identify newly diagnosed diseases. The follow-up rate was 74.3% at the sixth survey. In the current analysis, we included 1522 mother–child pairs after exclusion of 235 mother–child pairs who did not participate in the third follow-up survey and the subsequent follow-up surveys. The ethics committees of the Faculty of Medicine, Fukuoka University and Ehime University Graduate School of Medicine approved the KOMCHS.

Table 1 Distribution of selected characteristics in 1522 parent–child pairs, Kyushu Okinawa Maternal and Child Health Study, Japan

Variable	n (%) or mean $\pm$ SD
Baseline characteristics	
Region of residence	
Fukuoka Prefecture	862 (56.6)
Other than Fukuoka Prefecture in Kyushu	512 (33.6)
Okinawa Prefecture	148 (9.7)
Maternal smoking during pregnancy	128 (8.4)
Maternal education, years	
<13	343 (22.5)
13–14	513 (33.7)
≥ 15	666 (43.8)
Paternal education, years	
<13	481 (31.6)
13–14	218 (14.3)
≥ 15	823 (54.1)
Household income, yen/year	
<4 000 000	523 (34.4)
4 000 000–5 999 999	554 (36.4)
$\geq 6 000 000$	445 (29.2)
Maternal history of asthma	204 (13.4)
Maternal history of atopic eczema	276 (18.1)
Maternal history of allergic rhinitis	639 (42.0)
Paternal history of asthma	170 (11.2)
Paternal history of atopic eczema	153 (10.1)
Paternal history of allergic rhinitis	419 (27.5)
Characteristics at follow-up surveys	
Male sex	737 (48.4)
Post-natal secondhand smoke exposure at home until the third survey	655 (43.0)

SD, standard deviation.

Table 2 Crude and adjusted HRs and 95% CIs for food allergy in children according to maternal caffeine intake during pregnancy, Kyushu Okinawa Maternal and Child Health Study, Japan

Caffeine intake, mg/day (median) [†]	No. of events	Person-months of follow-up	Crude HR (95% CI)	Adjusted HR [‡] (95% CI)	Adjusted HR [§] (95% CI)
T1 (104.9)	80	14 806	1.00	1.00	1.00
T2 (232.3)	113	13 966	1.48 (1.11–1.97)	1.46 (1.09–1.94)	1.46 (1.10–1.96)
T3 (409.5)	93	14 198	1.21 (0.90–1.63)	1.19 (0.88–1.61)	1.16 (0.85–1.56)
P for trend			0.23	0.27	0.37
T2 + T3 (301.9)	206	28 164	1.34 (1.04–1.74)	1.32 (1.02–1.72)	1.31 (1.01–1.70)

CI, confidence interval; HR, hazard ratio.

[†]Adjusted for energy intake using the residual method.

[‡]Adjustment for region of residence at baseline, maternal smoking during pregnancy, maternal and paternal education levels, household income, maternal and paternal history of asthma, atopic eczema, and allergic rhinitis, infant's sex, and post-natal secondhand smoke exposure at home until the third survey.

[§]Further adjusted on suspicion or diagnosis atopic eczema at the third survey (around 4 months postpartum).

Measurements

In the baseline and follow-up surveys, participants received and filled out self-administered questionnaires and then mailed them to the data management centre at the time of each survey.

Measurement of caffeine intake

At the baseline survey during pregnancy, women were asked to fill out a semi-quantitative, comprehensive diet history questionnaire (DHQ) that assessed dietary habits during the preceding month.^{10,11} The DHQ assessed the average consumption frequency of foods and beverages based on eight categories (from 'never' to '≥2 times/day' for foods and from '<1 time/week' to '≥6 times/day' for beverages) and their relative portion size consumed in comparison with a standard portion size based on five categories ('50% smaller or less', '20–30% smaller', 'same', '20–30% larger' and '50% larger or more').¹¹ Using an *ad hoc* computer algorithm for the DHQ, which was based on the Standard Tables of Food Composition in Japan,¹² estimates of the daily intake of 150 food and beverage items, as well as for energy, nutrients and alcohol, were calculated. Maternal intake of caffeine during pregnancy was evaluated based on seven items: Japanese and Chinese tea (such as green tea and oolong tea), coffee, black tea, cola and sports drinks, hot chocolate, diet cola and non-energy containing soft drinks and confectionaries (mainly chocolate).^{13,14} Total caffeine intake was computed by multiplying the caffeine content of each beverage/food by the frequency of consumption and portion size and then summing up those values. Information on medicines was not used in the caffeine calculation because of the lack of a reliable composition table for such items in Japan. A validation study revealed that the Pearson's correlation coefficient was 0.37 between the DHQ and 16-day, semi-weighted dietary records for caffeine intake in 92 Japanese women aged 31–69 years (S. Sasaki, unpublished observation, 2014). Caffeine intake was energy-adjusted using the residual method.¹⁵

Measurement of food allergy

The fourth, fifth and sixth follow-up questionnaires included questions regarding food allergies. The fourth follow-up questionnaire included the following two questions: 'Has your child ever had an allergic reaction, including anaphylaxis, within 2 hours after eating food?' and 'Has your child ever had a medical diagnosis of any food allergy?' At the fifth and sixth follow-up surveys, the following questions were included: 'Since the previous survey, has your child had an allergic reaction, including anaphylaxis, within 2 hours after eating food?' and 'Since the previous survey, has your child had a medical diagnosis of any food allergy?' Participants who reported a positive response to these food allergy questions in the fourth, fifth and/or sixth follow-up surveys were asked to complete additional question about the age (in months) at the allergic reaction or diagnosis. A food allergy was defined as a positive response to any one of the questions related to having allergic reactions after eating food or a medical diagnosis of food allergy at the fourth, fifth and sixth follow-up surveys.

Measurement of covariate

The questionnaire at baseline elicited information on the region of residence, parental educational levels, household income and parental history of asthma, atopic eczema and allergic rhinitis. Parental history of asthma, atopic eczema and allergic rhinitis was defined as positive if a physician had diagnosed the respective parent with any of these allergic diseases.

The questionnaire in the second survey at birth included questions about the infant's sex, date of birth and maternal smoking during pregnancy. The questionnaires in the third survey asked about the smoking habits of adult household members and atopic eczema status. Secondhand smoke exposure at home was defined as positive if the child had lived with at least one smoker from birth to the date of the third survey.

Statistical analyses

Participants contributed person-months from at birth until the months of age of the positive response to the question of food allergy or the months of age when completing the follow-up survey at 36 months postpartum, whichever came first. Follow-up ranged from 0 to 42 months, with a median of 35 months. We used Cox proportional hazard models to assess the association between maternal caffeine intake during pregnancy and food allergy in children. The multivariable hazard ratios (HRs) were adjusted for the following potential confounding factors: region of residence at baseline, maternal smoking during pregnancy, parental educational levels, household income, parental history of asthma, atopic eczema, and allergic rhinitis, infant's sex, and Secondhand smoke exposure at home until the third survey. All statistical analyses were performed using the SAS software package version 9.4 (SAS Institute, Inc., Cary, NC, USA). Two-sided *P*-values <0.05 were considered statistically significant.

Results

Until the sixth follow-up survey, a total of 286 children reported having a physician's diagnosis of food allergy or reported having an allergic reaction after eating food. The characteristics of the study population are provided in Table 1.

Crude and adjusted HRs and 95% confidence intervals (CIs) for food allergy in children in relation to maternal caffeine intake during pregnancy are shown in Table 2. Compared with the lowest tertile of maternal caffeine intake during pregnancy, the second tertile was significantly associated with an increased risk of food allergy: adjusted HR = 1.19, 95% CI 1.09–1.94. The adjusted HR of food allergy comparing extreme tertiles of maternal caffeine intake during pregnancy was not statistically significant, however.

When the second and highest tertiles of maternal caffeine intake during pregnancy were combined, compared with children in the lowest tertile (T1), those in the group combining the second and the highest tertiles (T2 + T3) had a 32% higher risk of food allergy: adjusted HR = 1.32, 95% CI 1.09–1.94.

We investigated whether the association between maternal caffeine intake during pregnancy and risk of food allergy varied by allergic history in at least one parent. An independent positive association was found between the group combining the second and the highest tertiles (T2 + T3) and the risk of food allergy only

in children without a parental allergic history ($n = 467$): the adjusted HR (95% CI) was 1.99 (1.11–3.57). The corresponding figure for children with a parental allergic history ($n = 1055$) was 1.18 (0.88–1.58). There was a statistically significant interaction between maternal caffeine intake during pregnancy and the risk of food allergy (P for multiplicative interaction = 0.002).

Further adjustment for suspicion or diagnosis of atopic eczema at the 4-month postpartum follow-up survey ($n = 133$) did not substantially change the association between maternal caffeine intake during pregnancy and the risk of food allergy in children: further adjusted HR (95% CI) for the second, the highest tertiles, and the second and the highest tertiles combined (T2 + T3) were 1.46 (1.10–1.96), 1.16 (0.85–1.56) and 1.31 (1.01–1.70), respectively.

Discussion

The anti-inflammatory effects of coffee intake are mainly attributed to caffeine, and its beneficial effects on chronic diseases, which are linked to inflammation.^{16,17} The apparent opposite effects, however, have also been observed.^{17,18} A preclinical study found that caffeine treatment caused significant downregulation of most inflammation mediators in several individuals, while the contradictory effects were observed among other healthy individuals.¹⁷ An *in vivo* study of a cohort of preterm infants indicated that the anti-inflammatory property of caffeine might be dependent on the serum caffeine levels; extreme caffeine levels out of the therapeutic range ($>20 \mu\text{g/mL}$) might be potentially associated with a proinflammatory cytokine profile.¹⁸ Thus caffeine may have both pro- and anti-inflammatory properties. The intake of nutrients related to proinflammatory properties is supposed to be associated with an increased risk of allergic disease.^{19,20} Although the biological mechanisms underlying the observed association between caffeine intake and food allergy are unclear, higher maternal caffeine intake during pregnancy might affect the development of food allergy in children through the potential immunomodulation effects of caffeine.¹⁸

Another possible explanation is that atopic eczema might impact the association between maternal caffeine intake and the risk of food allergy. The dual allergen exposure hypothesis, in which exposure to environmental food allergens through the skin barrier may induce early severe eczema and the subsequent development of food allergy, was proposed by Lack.²¹ In the present study, however, observed associations between maternal caffeine intake during pregnancy and the risk of food allergy in children remained effectively unchanged when we made an additional adjustment on suspicion or diagnosis of atopic eczema.

In the present study population, the sources of caffeine intake were Japanese and Chinese tea (74.5%), coffee (13.2%), black tea (4.5%), confectionaries (4.1%) and soft drinks (3.7%). The effects of maternal caffeine intake during pregnancy on food allergy in children might vary according to its sources and doses.

Alternatively, we cannot rule out the possibility that observed association arose by chance or was confounded by other life-style factors that were not taken into consideration in the current study. In fact, a significant positive association between maternal caffeine intake and the risk of food allergy in children was only observed in the second tertile comparing with the lowest tertile. We also found no dose–response relationship in the present study. This could be due to by chance or small sample size in the lowest tertile.

One of the major methodological advantages of the present study was its prospective study design. Additionally, several potential confounding factors were controlled in multivariable models.

Our study has some limitations. First, dropouts may have led to bias. Of 1522 mother–child pairs included in the present analysis, 217 dropped out prior to the 36-month postpartum survey or were excluded because of incomplete information. Children who participated in the 36-month postpartum survey live in families with higher incomes, have higher educated parents, and are less exposed to prenatal and post-natal smoking exposure than were those who were not included in the final analysis. Regarding maternal caffeine intake during pregnancy, however, there was no material difference between included and excluded subjects. Additionally, we cannot generalise our findings because selection bias might have occurred at the baseline survey. The participation rate at the baseline survey could not be calculated due to the lack of information on the exact number of eligible pregnant women who were provided with our study materials. In fact, the parents of the current study population had higher educational levels than the general population.²²

Second, the definition of food allergy in the present study was based on self-reported information. The absence of a physician's diagnosis or laboratory data is likely to introduce an outcome misclassification. In general, food allergy is often over-reported.²³ The prevalence of food allergies in our study population at 12, 24 and 36 months of age were 7.0, 8.6 and 6.9%, respectively. These are within the range of the estimated prevalence of food allergy in Japan (5–10% among infants).²⁴

Third, it is possible that misclassification of exposure occurred. Our DHQ was designed to assess dietary intake for 1 month before completing the questionnaire and could only approximate consumption. Random misclassification of exposure would introduce a bias towards the null. Because a collection of dietary information with the DHQ was performed during pregnancy, 444 pregnant women experienced substantial changes in diet in the previous month due to nausea gravidarum ($n = 419$), maternal and fetal health ($n = 23$) and other reasons ($n = 2$). When these 444 women were excluded, the positive association between maternal caffeine intake during pregnancy and a risk of food allergy in children was more pronounced: the adjusted HRs (95% CIs) from lowest to highest category of intake by tertile were 1.00, 1.59 (1.11–2.29) and 1.49 (1.03–2.16), respectively (P for trend = 0.04). In the present study, data on serum caffeine concentrations were not available.

Conclusion

Our prospective study is the first to show preliminary findings that a positive association between maternal caffeine intake during pregnancy and a risk of food allergy in children. The underlying mechanisms of maternal caffeine intake on food allergy are unclear. Further epidemiological studies are needed to determine conclusively whether maternal caffeine intake during pregnancy has an adverse effect on the development of food allergy as well as the underlying biological mechanisms involved.

Acknowledgements

The authors would like to acknowledge the Kyushu Branch of the Japan Allergy Foundation, the Fukuoka Association of Obstetricians and Gynecologists, the Okinawa Association of

Obstetricians and Gynecologists, the Miyazaki Association of Obstetricians and Gynecologists, the Oita Association of Obstetricians and Gynecologists, the Kumamoto Association of Obstetricians and Gynecologists, the Nagasaki Association of Obstetricians and Gynecologists, the Kagoshima Association of Obstetricians and Gynecologists, the Saga Association of Obstetricians and 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. The Kyushu Okinawa Maternal and Child Health Study is funded by JSPS KAKENHI grant numbers 19590606, 20791654, 21590673, 22592355, 22119507, 24390158, 25463275, 25670305, 17H04135 and 17K12011; Health and Labour Sciences Research Grants for Research on Allergic Disease and Immunology; Health Research on Children, Youth and Families from the Ministry of Health, Labour, and Welfare, Japan; Meiji Co. Ltd.; the Food Science Institute Foundation; and Nipponham Foundation for the Future of Food. These organisations did not have any influence on the study design; the collection, analysis or interpretation of data; the writing of the report; or the decision to submit the article for publication.

References

- Prescott S, Allen KJ. Food allergy: Riding the second wave of the allergy epidemic. *Pediatr. Allergy Immunol.* 2011; **22**: 155–60.
- Springston EE, Smith B, Shulruff J, Pongracic J, Holl J, Gupta RS. Variations in quality of life among caregivers of food allergic children. *Ann. Allergy Asthma Immunol.* 2010; **105**: 287–94.
- Dietert RR, Zelikoff JT. Early-life environment, developmental immunotoxicology, and the risk of pediatric allergic disease including asthma. *Birth Defects Res. B Dev. Reprod. Toxicol.* 2008; **83**: 547–60.
- Miles EA, Calder PC. Maternal diet and its influence on the development of allergic disease. *Clin. Exp. Allergy* 2015; **45**: 63–74.
- West CE, Dunstan J, McCarthy S *et al.* Associations between maternal antioxidant intakes in pregnancy and infant allergic outcomes. *Nutrients* 2012; **4**: 1747–58.
- Tuokkola J, Luukkainen P, Kaila M *et al.* Maternal dietary folate, folic acid and vitamin D intakes during pregnancy and lactation and the risk of cows' milk allergy in the offspring. *Br. J. Nutr.* 2016; **116**: 710–8.
- Grosso G, Godos J, Galvano F, Giovannucci EL. Coffee, caffeine, and health outcomes: An umbrella review. *Annu. Rev. Nutr.* 2017; **37**: 131–56.
- Devereux G, Barker RN, Seaton A. Antenatal determinants of neonatal immune responses to allergens. *Clin. Exp. Allergy* 2002; **32**: 43–50.
- Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal consumption of dairy products, calcium, and vitamin D during pregnancy and infantile allergic disorders. *Ann. Allergy Asthma Immunol.* 2014; **113**: 82–7.
- Sasaki S, Yanagibori R, Amano K. Self-administered diet history questionnaire developed for health education: A relative validation of the test-version by comparison with 3-day diet record in women. *J. Epidemiol.* 1998; **8**: 203–15.
- Sasaki S, Ushio F, Amano K *et al.* Serum biomarker-based validation of a self-administered diet history questionnaire for Japanese subjects. *J. Nutr. Sci. Vitaminol.* 2000; **46**: 285–96.
- Science and Technology Agency. *Standard Tables of Food Composition in Japan, Fifth Revised and Enlarged Edition.* Tokyo: Printing Bureau of the Ministry of Finance; 2005 (in Japanese).
- Yamada M, Sasaki S, Murakami K *et al.* Estimation of caffeine intake in Japanese adults using 16 d weighed diet records based on a food composition database newly developed for Japanese populations. *Public Health Nutr.* 2010; **13**: 663–72.
- Okubo H, Miyake Y, Tanaka K, Sasaki S, Hirota Y. Maternal total caffeine intake, mainly from Japanese and Chinese tea, during pregnancy was associated with risk of preterm birth: The Osaka Maternal and Child Health Study. *Nutr. Res.* 2015; **35**: 309–16.
- Willett W, Stampfer MJ. Total energy intake: Implications for epidemiologic analyses. *Am. J. Epidemiol.* 1986; **124**: 17–27.
- Paiva C, Beserra B, Reis C, Dorea JG, Da Costa T, Amato AA. Consumption of coffee or caffeine and serum concentration of inflammatory markers: A systematic review. *Crit. Rev. Food Sci. Nutr.* 2019; **59**: 652–63.
- Muqaku B, Tahir A, Klepeisz P *et al.* Coffee consumption modulates inflammatory processes in an individual fashion. *Mol. Nutr. Food Res.* 2016; **60**: 2529–41.
- Chavez Valdez R, Ahlawat R, Wills-Karp M, Nathan A, Ezell T, Gauda EB. Correlation between serum caffeine levels and changes in cytokine profile in a cohort of preterm infants. *J. Pediatr.* 2011; **158**: 57–64.
- Devereux G, Seaton A. Diet as a risk factor for atopy and asthma. *J. Allergy Clin. Immunol.* 2005; **115**: 1109–17.
- Sausenthaler S, Koletzko S, Schaaf B *et al.* Maternal diet during pregnancy in relation to eczema and allergic sensitization in the offspring at 2 y of age. *Am. J. Clin. Nutr.* 2007; **85**: 530–7.
- Lack G. Epidemiologic risks for food allergy. *J. Allergy Clin. Immunol.* 2008; **121**: 1331–6.
- Statistic Bureau, Ministry of Public Management, Home Affairs, Posts and Telecommunications. *2000 Population Census of Japan, Labour Force Status of Population, Industry (Major Groups) of Employed Persons, and Education: Fukuoka-Ken.* **3-2-40.** Tokyo: Japan Statistical Association; 2002 (in Japanese).
- American College of Allergy, Asthma, & Immunology. Food allergy: A practice parameter. *Ann. Allergy Asthma Immunol.* 2006; **96**: S1–68.
- Ebisawa M, Nishima S, Ohnishi H, Kondo N. Pediatric allergy and immunology in Japan. *Pediatr. Allergy Immunol.* 2013; **24**: 704–14.