OUKA
Osaka University Knowledge Archive

| | |
|---|---|
| Title | Influence of maternal pre-pregnancy and children's body mass index on cognitive functions. |
| Author(s) | Ichinose, Daisuke |
| Citation | 大阪大学, 2022, 博士論文 |
| Version Type | VoR |
| URL | https://doi.org/10.18910/89508 |
| rights | |
| Note | |

*Osaka University Knowledge Archive : OUKA*

https://ir.library.osaka-u.ac.jp/

Osaka University

# Influence of maternal pre-pregnancy and children's body mass index on cognitive functions.

（妊娠前の母の BMI と子どもの BMI が子どもの認知機能に与える影響について）

大阪大学大学院
大阪大学・金沢大学・浜松医科大学・千葉大学・福井大学
連合小児発達学研究科
小児発達学専攻

一之瀬　大資

2022年6月　博士学位論文

**Influence of maternal pre-pregnancy and children's body mass index on cognitive functions**

Daisuke Ichinose[1], Tomoko Nishimura[1,2*], Atsushi Senju[1,2], Akemi Okumura[1,2], Toshiki Iwabuchi[1,2], Taeko Harada[1,2], Md Shafiur Rahman[1,2], Nagahide Takahashi[2,3], Kenji J. Tsuchiya[1,2], Nori Takei[2]

[1] United Graduate School of Child Development, Hamamatsu University School of Medicine. 1-20-1 Handayama, Higashi-ku, Hamamatsu 4313192, Japan.

[2] Research Center for Child Mental Development, Hamamatsu University School of Medicine. 1-20-1 Handayama, Higashi-ku, Hamamatsu 4313192, Japan.

[3] Department of Child and Adolescent Psychiatry, Nagoya University Graduate School of Medicine, Nagoya, Japan

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Funding:** This work was supported by the Japan Society for the Promotion of Science, Grants-in-Aid for Scientific Research (grant numbers 19H03582 to KT and 20K07941 to TN), and by AMED (grant number JP21gk0110039h0003 to KT).

**Abstract**

Both pre-pregnancy maternal body mass index (BMI) and higher BMI of children themselves are reported to be associated with children's lower cognitive functions. The current study aimed to explore whether pre-pregnancy maternal BMI is directly related to children's cognitive functions or whether this relationship is mediated by children's BMI. Of the 1258 participants in the Hamamatsu Birth Cohort Study for Mothers and Children (HBC Study), 857 children who completed measurements at age 6 years were included. Cognitive functions were measured at age 9 using the Wechsler Intelligence Scale for Children – Fourth Edition (WISC–IV); full-scale IQ (FSIQ), and scores of the four subscales (verbal comprehension, perceptual reasoning, working memory, and processing speed) were obtained. The results of counterfactual-based mediation analysis showed a significant natural direct effect between maternal BMI and children's FSIQ and a natural indirect effect via children's BMI. The proportion of mediation was estimated to explain 49.8%. Similar direct and indirect effects were observed in the perceptual reasoning and working memory subscales. The association between higher maternal BMI and lower cognitive functions in children was partially mediated by higher BMI in children. On the other hand, higher maternal BMI had a direct negative effect on children's cognitive functions.

**Key words**: body mass index, cognitive functions, mediation analysis, natural indirect effect, cohort study

## INTRODUCTION

Maternal obesity is among the most common obstetric problems that influences the health of both the mother and child. The prevalence of obesity is projected to continue to increase in both developing and developed countries.[1-5] Therefore, the issue of obesity during pregnancy has attracted major attention. In Japan, on the other hand, lower BMI of pregnant women that may adversely affect the unborn child and cause long-term health problems has been a major concern.[6] However, obesity is also an important factor impacting the health of the mother and child in Japan because 8.9% of the women in their 20s and 15.0% women in their 30s are obese with a BMI of 25 or higher in Japan.[7]

More than a dozen observational studies have been conducted to examine the association between maternal BMI and cognitive functions of the child during infancy and adolescence. These studies largely support a negative correlation between maternal pre-pregnancy obesity and cognitive function in children.[8-17] Disturbances in the development of cognitive functioning can ultimately lead to problems with mental health, social development, peer relationships, and physical health, all of which can affect the quality of life in adulthood.[18]

Obesity in children has also been reported to negatively impact cognitive function. Animal models have shown that diet-induced obesity has a detrimental effect on cognitive

functions, such as working memory, learning, and executive function.[19-21] Boitard et al. [22] showed that early exposure to a high-fat diet negatively affected relational memory flexibility and decreased neurogenesis. Thus, early exposure to a high-fat diet may be particularly deleterious to cognition.[23] A recent longitudinal study showed that standardized BMI at age 10 is associated with school absence at ages 14–16 and educational attainment at age 16.[24] This study also found that in the examination of genetic liability, BMI polygenic scores were associated with both school absence and attainment. Furthermore, Mendelian randomization analysis performed to assess the causal influence of BMI showed that higher BMI in childhood and adolescence may causally impair educational outcomes.[24] Based on these results, it is likely that children's weight status has an impact on their cognitive functions as much as, or in addition to, the obesity of the mother before pregnancy.

However, many of the previous studies that investigated the relationship between maternal obesity and cognitive functions of the child did not take into account the child's BMI.[16,25] Similarly, studies that examined the relationship between child obesity and cognitive functions did not consider the maternal BMI.[26] Therefore, it is necessary to investigate how maternal BMI during pre-pregnancy and the child's BMI are associated with the child's cognitive functions. In addition, genetic disposition should be considered

when examining the association between maternal BMI and the child's BMI. The present study aimed to determine whether pre-pregnancy BMI directly affects the cognitive functions of the child or is indirectly related to it through the child's BMI. In the analysis, the polygenic risk score (PRS) of BMI was included as a genetic factor.

## METHODS

### *Participants*

This study was conducted as part of an ongoing cohort study, the Hamamatsu Birth Cohort for Mothers and Children (HBC Study), which has been described in detail elsewhere.[27,28] In brief, all women who visited either of the two research sites, the Hamamatsu University Hospital and Kato Maternity Clinic, during the first or second trimester of pregnancy were invited to participate in the study. We registered all the mothers who agreed to participate in the study, which comprised a consecutive series of mothers ($n$ = 1138) and their infants born between December 24, 2007, and March 9, 2012 ($n$ = 1258). By referring to reports from the Japanese Ministry of Health, Labour and Welfare,[29] we found that the mothers enrolled in the cohort study were representative of Japanese mothers with respect to age and socioeconomic status, and that their offspring were representative of Japanese infants with respect to birth weight and gestational age at birth. Therefore, participants from this cohort were considered to be a representative

sample of the general population.

For the present study, children were excluded if they met the following criteria: early life death before one year ($n$ = 4), twins ($n$ = 38), and a diagnosis of Down's syndrome ($n$ = 2) (Figure 1). Twins were excluded because their maternal BMI were identical, and BMIs and cognitive functions were often similar between them. Further, we excluded 357 children for whom information on BMI (mediator, see below) was not available at 6 years of age. Thus, 787 mothers and 857 children were included in the analyses. The unbalanced sizes for mothers and infants were ascribed to the fact that some mothers ($n$ = 70) had multiple deliveries during the study period. Table 1 presents the demographic characteristics of the final sample.

***Ethical considerations***

The study protocol was approved by the Hamamatsu University School of Medicine and University Hospital Ethics Committee (Reference No. 18-166, 19-9, 20-82, 22-29, 24-67, 24-237, 25-143, 25-283, E14-062, E14-062-1, E14-062-3, 17-037, 17-037-3, 20-233). Written informed consent was obtained from each mother for her own and her infant's participation.

**Measures**

***Outcome: Cognitive functions***

To ascertain children's cognitive functions, we used the Weschler Intelligence Scale for Children – Fourth Edition (WISC–IV).[30] First, the full-scale intelligence quotient (FSIQ) consisting of 10 core subtests was used for the analysis, and scores of following four subscales were used; verbal comprehension index (VCI), perceptual reasoning index (PRI), working memory index (WMI), and processing speed index (PSI). Measurements were taken when the children were around 9 years old.

***Exposure: Maternal pre-pregnancy body mass index***

Maternal pre-pregnancy BMI (mpBMI; calculated as weight in kilograms divided by squared height in meters) immediately before pregnancy was obtained from self-reported data. The mpBMI was then categorized as underweight (mpBMI < 18.5 $kg/m^2$), normal (18.5-25 $kg/m^2$), overweight (25-30 $kg/m^2$), or obese ($\geq$ 30 $kg/m^2$).[31]

***Mediator: Children's body mass index***

The children's weight and height at 6 years of age that were most recently measured during periodic health checkups at medical facilities or body measurements at nurseries or kindergartens were reported by mothers. Children's BMI was calculated weight in kilograms divided by squared height in meters, and then transformed into standard deviation scores (SDS) according to the data from the WHO.[32] For children,

overweight was defined as SDS > 1.04 and obesity as SDS > 1.64.[33]

***Covariates***

The following factors known to be related to children's cognitive functions[34] were included as covariates: children's sex, low birth weight (< 2500g), preterm delivery (before 37 weeks), parity, parental age and educational years, annual household income, maternal smoking during pregnancy, and maternal alcohol consumption during pregnancy.

***Statistical analysis***

We performed linear regression analyses to investigate the relationship among mpBMI, children's BMI, and cognitive functions. To examine whether the association between mpBMI and children's cognitive functions was mediated by children's BMI, we employed a counterfactual-based mediation analysis (Figure 3).[35] Mediation analysis aims at estimating to what extent the effect of an exposure on an outcome is explained by a mediator on the causal pathway between the exposure and the outcome. This goal is achieved by decomposing the total effect of the exposure on the outcome into a natural indirect effect (NIE; the effect explained through the given mediator) and a natural direct effect (NDE; the effect unexplained by the mediator).[36] Of particular interest was the NIE that was interpreted as representing the proportion of pre-

pregnancy BMI in relation to cognitive functions, which could be explained by its association with changes in children's BMI. The NDE represented the effect of pre-pregnancy BMI on cognitive functions, which was independent of children's BMI. To quantify the magnitude of mediation, the proportion of the association mediated by children's BMI was estimated (NIE/Total effect).

In a "crude model," mpBMI was set as a predictor, cognitive functions as outcomes, and children' BMI as a mediator without any covariates. Next, the covariates described above were incorporated into the model (Model 1). We hypothesized that if the mpBMI and the children's BMI are determined by genetic traits, then the indirect effect would disappear. To verify this, we included the PRS in the analysis, which was calculated using specific information on the genes identified for defining the BMI by a genome-wide association study (GWAS). The PRS was generated by PRSice-2[37] using a recent BMI-GWAS in the Japanese adult population as a discovery cohort.[38] More details on the PRS can be found in the previous work.[39]

The missing data were handled by a process of full information maximum likelihood (FIML). The FIML adjusts the likelihood function so that each case contributes information for the variables that are observed and takes into consideration the conditions under which missing data occur while providing better estimates for

parameters.[40]

Planned additional sensitivity analyses were performed to examine the robustness of the results. First, to test whether the indirect effects differed between boys and girls, we conducted a multi-group analysis. Second, to account for the effects of missing data, we reran the final model of mediation analysis using listwise deletion and multiple imputation methods.

All analyses were estimated using bootstrapping (10000 replications) to recover the correct standard errors for direct and indirect effects. All *P*-values were 2-tailed, and statistical significance was set at a *P*-value of less than 0.05. Clustering of siblings with the same mother was performed throughout the analyses. Statistical analysis was performed using Mplus version 8.4.[41]

## RESULTS

The demographic characteristics of the sample included in the analyses are shown in Table 1. The main characteristics were as follows: out of the 857 children, 429 were male (50.1%), the average birthweight was 2954.3 g (SD = 429.8), the proportion of low birth weight was 11.9%, the average gestational age was 39.0 weeks (SD = 1.5), and the proportion of preterm infants was 5.6%. The average age of the mothers at the

time of birth was 31.9 years (SD = 5.0) and 33.6 years (SD = 5.7) for fathers. These values did not differ from the concurrent norms for infants in Japan, according to official national statistics.[29] The average mpBMI was 21.0 kg/m$^2$ (SD = 3.3), which was similar to the Japanese norm.[7] The average score on the FSIQ was 101.6 (SD = 14.0). The average BMI SDS of the children was -0.11 (SD = 0.95).

In the linear regression analyses, the association between mpBMI and children's FSIQ (coefficient = -0.37; 95% confidence interval [CI]: -0.71, -0.05), mpBMI and children's BMI (coefficient = -0.43; 95% CI: -0.74, -0.11), and the interaction of mpBMI with children's BMI and the FSIQ (coefficient = 0.25; 95% CI: 0.18, 0.32) were all significant, except for the association between children's BMI and FSIQ (coefficient = -0.14; 95% CI: -2.20, 0.05). Maternal underweight, overweight, and obesity had no significant effect on FSIQ (coefficient = 0.60; 95% CI: -1.97, 3.19; coefficient = -3.32; 95% CI: -7.36, 0.89; coefficient = -3.20; 95% CI: -11.34, 4.74, respectively). Overweight in children had no significant effect on FSIQ (coefficient = 0.24; 95% CI: -4.00, 4.34), while obesity had a significant effect (coefficient = -6.72; 95% CI: -12.31, -1.22). However, the number of children with obesity was small (n = 35, 4.1%) and convergence was not achieved in the model including children's obesity as a categorical variable. We also examined the association among mpBMI, children's BMI, and cognitive functions,

using locally weighted scatter plot smoothing (LOESS) methods.[42] As a result, we determined that a linear association could be hypothesized (Figure 2); therefore, mpBMI and children's BMI were treated as continuous variables in the subsequent mediation analyses.

Table 2 displays the results of the mediation analysis of the association between mpBMI and FSIQ through children's BMI at 6 years. In the crude model, both NIE and NDE were significant. These effects were negative for FSIQ. Figure 4 is a plot of the NIE and indicates that the higher the mpBMI, the stronger was the negative effect of NIE.

These effects remained significant after adjusting for covariates (Model 1). Moreover, when adjusted by PRS, which reflects the genetic component of BMI, these effects remained significant (Model 2). In this model, the proportion of mediation by children's BMI was 49.8%.

In two of the four subscales of the WISC-IV (PRI and WMI), both unadjusted and adjusted models revealed similar findings; significantly negative NIE and NDE were observed (Table 3). However, in VCI and PSI subscales, the total effects were not significant, indicating that there was no relationship between mpBMI and cognitive functions in these subscales.

### *Sensitivity analysis*

The Wald tests of the multigroup analyses were not significant in either FSIQ or the subscales, indicating that the indirect effects did not differ between males and females. The missing data were handled by FIML in this study, and the results were similar when missing data were handled by listwise deletion and multiple imputation.

## DISCUSSION

In this longitudinal study of a representative birth cohort, we found that maternal pre-pregnancy BMI was associated with children's cognitive functions at 9 years of age, and this association was partly mediated by children's BMI at 6 years of age. Furthermore, the indirect effect became stronger as the mother's BMI increased. These results did not change when adjusted for the genetic component (PRS) of BMI, suggesting that instead of genetic factors, other factors related to children's BMI affect cognitive functions.

Maternal obesity was reported to be associated with cognitive impairments in offspring.[34,43,44] According to a recent meta-analysis,[34] children born to overweight mothers were 17% more likely to have adverse neurodevelopmental outcomes (OR, 1.17; 95% CI, 1.11-1.24) and mothers who were obese before pregnancy were 51% more likely to have a child with adverse neurodevelopmental outcomes (OR, 1.51; 95% CI, 1.35-1.69.

In the present study, however, maternal overweight and obesity did not have significant effects on children's cognitive function. This inconsistency with previous studies may be related to the low prevalence of overweight and obesity in Japan. Therefore, we recategorized maternal BMI using the WHO recommendation for Asian populations (underweight: < 18.5 kg/m$^2$; overweight: ≥ 23.0 kg/m$^2$; obese: ≥ 27.5 kg/m$^2$);[45] however, even after doing so, the results were similar. Consistent with previous studies, we found that the higher the BMI of the mother, the stronger the effect on the children's cognitive functions. However, we could not confirm that a BMI above a certain cut-off value had any special risk.

Previous studies also found negative relationships between children's obesity and cognitive function, but the results have been mixed. Hughes et al.[24] reported that a higher BMI in childhood and adolescence may causally impair educational outcomes. In contrast, Afzal and Gortmaker [46] found no significant association between obesity and cognitive function after adjusting for the children's home environments. Liang et al.[47] conducted a systematic review to examine the relationship between obesity and various aspects of neurocognitive function and found stronger and more consistent evidence supporting a relationship between obesity and deficits in the areas of executive functioning, attention,

visuospatial skills, and motor skills. However, findings were mixed in the areas of general cognitive functioning, learning and memory, language, and academic achievement.[47] In the present study, we found an association between maternal BMI and children's cognitive functions only in the subscales of perceptual reasoning and working memory. This might support a robust association between executive functioning, visuospatial skills, and childhood obesity.

In the present study, both a significant natural direct effect between maternal BMI and children's FSIQ and a natural indirect effect via children's BMI were observed. The proportion of mediation was estimated at 49.8%. The natural indirect effect and mediation proportion are important indices for exploring potential pathways and mechanisms underlying exposure-outcome relationships.[48] Although the present study is observational and a biological mechanism has not been investigated, there are many previous reports on the mechanism by which maternal BMI and children's BMI negatively affect children's cognitive function.[49-52] Further studies would be informative to explore the mechanisms underlying the relationship between maternal BMI and children's cognitive function, considering the pathways through children's BMI.

Maternal underweight had no significant effect on cognitive function in the present study. However, maternal BMI has been reported to display an inverted U-shaped

association with cognitive function in children.[16] In addition, staying slim during pregnancy has become a problem, especially in Japan.[6] Since it was reported that having low maternal weight pre-pregnancy was also associated with an increased risk of undernutrition among children,[53] the risks of maternal underweight need to be further investigated.

***Limitations***

The present study examined the role of children's BMI in the association between maternal BMI and children's cognitive functions in a representative Japanese population. In spite of the insights provided by the study, it has some limitations that should be considered. First, BMI at age 6 years was set as a mediator, but BMI may not necessarily be an ideal indicator of childhood obesity. In future studies, more obesity-related factors, such as body fat percentage, need to be investigated. Second, BMI was treated as a continuous variable, and the linear association between maternal BMI, children's BMI, and cognitive function was examined. However, in this study, maternal BMI had no significant effect on children's cognitive function. Further studies are needed to determine whether the effect of maternal BMI on children's cognitive function is linear or non-linear.

## Conclusion

The present study revealed that maternal pre-pregnancy BMI affects children's cognitive functions both directly and indirectly. Directly, the high BMI of the mother may affect the central nervous system of the child during pregnancy. Indirectly, biological and environmental factors may also influence children's cognitive functions through higher BMI in children. Further research is needed to understand the domains of cognitive function that are affected by maternal, and children's obesity and the mechanisms involved.

## Acknowledgments

The HBC Study team includes Ms. C. Nakayasu, H. Suzuki, Y. Amma, E. Higashimoto, N. Kodera, Mr. R. Nakahara, Dr. Y. Nomura, K. Wakusawa, Y. Kameno, D. Kurita, K. Takebayashi, M. Yokokura, T. Wakuda, S.S. Aoyagi, R. Asano, T. Ismail, K. Iwata, Y. Iwata, E. Kawai, M. Kawai, Y.K. Kuroda, K. Matsumoto, T. Mori, K. Nakaizumi, K. Nakamura, A.A. Pillai, Y. Seno, C. Shimmura, S. Suda, G. Sugihara, K. Suzuki, I. Thanseem, K. Yamada, S. Yamamoto, Y. Yoshihara, Y. Endoh, K. Hirano, T. Suzuki, H. Matsuzaki, N. Mori, T. Sugiyama, M. Tsujii, S. Takagai, H. Kuwabara and H. Yamasue. The authors thank Dr. Tetsuo Kato of the Kato Maternity Clinic, and Drs. K. Sugihara, M.

Sugimura, K. Takeuchi, K. Suzuki, Y. Murakami, Y. Kohmura, Y. Miyabe, K. Hirai, Y. Nakamura, R. Koizumi, H. Murakami, Y. Kobayashi-Kohmura, K. Muramatsu-Kato, H. Itoh, N. Kanayama, and all attending obstetricians of Hamamatsu University School of Medicine, for their full support with participant enrolment in the study. The authors also thank the chief midwife, Ms. Kiyomi Hinoki, and all midwives and staff at the maternity clinic of Hamamatsu University School of Medicine, for their support with participant enrolment. We thank all children and families who participated in the HBC Study.

**REFERENCES**

1. Poston L, Caleyachetty R, Cnattingius S, et al. Preconceptional and maternal obesity: epidemiology and health consequences. Lancet Diabetes Endocrinol.2016;4(12):1025-1036.

2. Chen C, Xu X, Yan Y. Estimated global overweight and obesity burden in pregnant women based on panel data model. PLoS One. 2018;13(8):e0202183.

3. Mariona FG. Perspectives in obesity and pregnancy. Womens Health (Lond). 2016;12(6):523-532.

4. van der Burg JW, Sen S, Chomitz VR, et al. The role of systemic inflammation linking maternal BMI to neurodevelopment in children. Pediatr Res. 2016;79(1-1):3-12.

5. Killion MM. Obesity in Pregnancy and Childbirth. MCN Am J Matern Child Nurs. 2021;46(6):360.

6. Normile D. Staying slim during prepregnancy carries a price. Science. 2018;361(6401):440.

7. Ministry of Health, Labour and Welfare, Japan. The National Health and Nutrition Survey in Japan, 2019. https://www.mhlw.go.jp/content/000710991.pdf Accessed 31 January 2022.

8. Lee PMY, Tse LA, László KD, et al. Association of maternal body mass index with intellectual disability risk. Arch Dis Child Fetal Neonatal Ed. 2021;106(6):584-590.

9. Basatemur E, Gardiner J, Williams C, et al. Maternal prepregnancy BMI and child cognition: a longitudinal cohort study. Pediatrics.2013;131(1):56-63.

10. Bliddal M, Olsen J, Støvring H, et al. Maternal pre-pregnancy BMI and intelligence quotient (IQ) in 5-year-old children- a cohort based study. PLoS One. 2014; 9(4):e94498.

11. Brion MJ, Zeegers M, Jaddoe V, et al. Intrauterine effects of maternal prepregnancy overweight on child cognition and behavior in 2 cohorts. Pediatrics. 2011; 127(1):e202-211.

12. Casas M, Chatzi L, Carsin A, et al. Maternal pre-pregnancy overweight and obesity, and child neuropsychological development- two Southern European birth cohort studies. Int J Epidemiol. 2013;42(2):506-517.

13. Craig WY, Palomaki GE, Neveux LM, et al. Maternal Body Mass Index during Pregnancy and Offspring Neurocognitive Development. Obstet Med. 2013;6(1):20-25.

14. Eriksen HL, Kesmodel US, Underbjerg M, et al. Predictors of intelligence at the age of 5: family, pregnancy and birth characteristics, postnatal influences, and postnatal growth. PLoS One. 2013;8(11):e79200.

15. Hinkle SN, Schieve LA, Stein AD, et al. Associations between maternal prepregnancy body mass index and child neurodevelopment at 2 years of age. Int J Obes (Lond). 2012;36(10):1312-1319.

16. Huang L, Yu X, Keim S, et al. Maternal prepregnancy obesity and child neurodevelopment in the Collaborative Perinatal Project. Int J Epidemiol. 2014;43(3):783-792.

17. Pugh SJ, Richardson GA, Hutcheon JA, et al. Maternal Obesity and Excessive Gestational Weight Gain Are Associated with Components of Child Cognition. J Nutr. 2015;145(11):2562-2569.

18. Smith E, Hay P, Campbell L, Trollor JN. A review of the association between obesity and cognitive function across the lifespan: implications for novel approaches to prevention and treatment. Obes Rev. 2011;12(9):740-55.

19. Nguyen JC, Killcross AS, Jenkins TA. Obesity and cognitive decline: role of inflammation and vascular changes. Front Neurosci. 2014;8:375.

20. Jurdak N, Lichtenstein AH, Kanarek RB. Diet-induced obesity and spatial cognition in young male rats. Nutr Neurosci. 2008;11(2):48-54.

21. Molteni R, Barnard RJ, Ying Z, et al. A high-fat, refined sugar diet reduces hippocampal brain-derived neurotrophic factor, neuronal plasticity, and learning. Neuroscience. 2002;112(4):803-814.

22. Boitard C, Etchamendy N, Sauvant J, et al. Juvenile, but not adult exposure to high-fat diet impairs relational memory and hippocampal neurogenesis in mice. Hippocampus. 2012;22(11):2095-2100.

23. Wang C, Chan JS, Ren L, et al. Obesity Reduces Cognitive and Motor Functions across the Lifespan. Neural Plast. 2016; 2016:2473081.

24. Hughes A, Wade KH, Dickson M, et al. Common health conditions in childhood and adolescence, school absence, and educational attainment: Mendelian randomization study. NPJ Sci Learn. 2021;6(1):1–9.

25. Pugh SJ, Hutcheon JA, Richardson GA, et al. Child academic achievement in association with pre-pregnancy obesity and gestational weight gain. J Epidemiol Community Health. 2016;70(6):534-540.

26. Li Y, Dai Q, Jackson JC, et al. Overweight is associated with decreased cognitive functioning among school-age children and adolescents. Obesity. 2008;16(8):1809-1815.

27. Tsuchiya KJ, Matsumoto K, Suda S, et al. Searching for very early precursors of autism spectrum disorders: the Hamamatsu birth cohort for mothers and children (HBC). J Dev Orig Health Dis.2010;1(3):158–173.

28. Takagai S, Tsuchiya KJ, Itoh H, et al. Cohort profile: Hamamatsu birth cohort for mothers and children (HBC study). Int J Epidemiol.2016;45(2):333–342.

29. Ministry of Health Labour and Welfare. Vital Statistics in Japan. 2018. https://www.mhlw.go.jp/english/database/db-hw/dl/81-1a2en.pdf Accessed 31 January 2022.

30. Wechsler D. Wechsler Intelligence Scale for Children. 4th ed. San Antonio, TX: The Psychological Corporation, 2003.

31. World Health Organization. Obesity: Preventing and Managing the Global Epidemic: Report on a WHO Consultation (WHO Technical Report Series 894). Geneva, Switzerland: World Health Organization. 2000.

32. WHO Multicentre Growth Reference Study Group. WHO Child Growth Standards based on length/height, weight and age. Acta Paediatr Suppl.2006;450:76-85.

33. Vanderwall C, Eickhoff J, Randall Clark R, et al. BMI z-score in obese children is a poor predictor of adiposity changes over time. BMC Pediatr. 2018;18(1):187.

34. Sanchez CE, Barry C, Sabhlok A, et al. Maternal pre-pregnancy obesity and child neurodevelopmental outcomes: a meta-analysis. Obes Rev. 2018;19(4):464-484.

35. Valente MJ, Rijnhart JJM, Smyth HL, et al. Causal mediation programs in R, Mplus, SAS, SPSS, and Stata. Struct Equ Modeling. 2020;27(6):975-984.

36. Zugna D, Popovic M, Heude B, et al. Applied causal inference methods for sequential mediators. Research Square, 2021.

37. Shing Wan Choi, Paul F O'Reilly. PRSice-2: Polygenic Risk Score software for biobank-scale data. Gigascience. 2019;8(7):giz082.

38. Akiyama M, Okada Y, Kanai M, et al. Genome-wide association study identifies 112 new loci for body mass index in the Japanese population. Nat Genet. 2017;49(10):1458-1467.

39. Takahashi N, Nishimura T, Harada T, et al. Association Between Genetic Risks for Obesity and Working Memory in Children. Front Neurosci. 2021;15:749230.

40. Dong Y, Peng CY. Principled missing data methods for researchers. Springerplus. 2013;2(1):222.

41. Muthén LK, Muthén BO. Mplus User's Guide. Los Angeles. 8th ed. CA: Muthén & Muthén, 2017.

42. Wanishsakpong W, Notodiputro KA. Locally weighted scatter-plot smoothing for analysing temperature changes and patterns in Australia. Met. Apps, 2018;25:357-364.

43. Álvarez-Bueno C, Cavero-Redondo I, Lucas-de la Cruz L, et al. Association between pre-pregnancy overweight and obesity and children's neurocognitive development: a systematic review and meta-analysis of observational studies. Int J Epidemiol. 2017;46(5):1653-1666.

44. Duffany KO, McVeigh KH, Kershaw TS, et al. Maternal Obesity: Risks for Developmental Delays in Early Childhood. Matern Child Health J. 2016;20(2):219-230.

45. WHO Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies [published correction appears in Lancet. 2004;363:902]. Lancet. 2004; 363: 157–163.

46. Afzal AS, Gortmaker S. The Relationship between Obesity and Cognitive Performance in Children: A Longitudinal Study. Child Obes. 2015;11(4):466-474.

47. Liang J, Matheson BE, Kaye WH, et al. Neurocognitive correlates of obesity and obesity-related behaviors in children and adolescents. Int J Obes. 2014;38(4):494-506.

48. Cheng C, Spiegelman D, Li F. Estimating the natural indirect effect and the mediation proportion via the product method. BMC Med Res Methodol. 2021;21(1):253.

49. Rivera HM, Christiansen KJ, Sullivan EL. The role of maternal obesity in the risk of neuropsychiatric disorders. Front Neurosci. 2015;9:194.

50. Gyllenhammer LE, Rasmussen JM, Bertele N, et al. Maternal Inflammation During Pregnancy and Offspring Brain Development: The Role of Mitochondria. Biol Psychiatry Cogn Neurosci Neuroimaging. 2021;17:S2451-9022(21)00316-5

51. Smith L, Toussaint L, Micoli A, et al. Obesity, putative biological mediators, and cognitive function in a national sample of children and adolescents. Prev Med. 2021;150:106659.

52. Mattey-Mora PP, Nelson EJ. Sleep Disturbances, Obesity, and Cognitive Function in Childhood: A Mediation Analysis. Curr Dev Nutr. 2021;5(10):nzab119.

53. Li C, Zhu N, Zeng L, et al. Effect of maternal pre-pregnancy underweight and average gestational weight gain on physical growth and intellectual development of early school-aged children. Sci Rep. 2018;8(1):12014.

Table 1. Characteristics of participating children and their parents

| | |
|---|---|
| **Children** | |
| Total, n | 857 |
| Gender (Male / Female), n (%) | 429 (50.1) / 428 (49.9) |
| Low birthweight, n (%) | 102 (11.9) |
| Preterm birth, n (%) | 48 (5.6) |
| Children's BMI SDS at 6 years, mean (SD) | -0.11 (0.95) |
| WISC-IV scores at 9 years, mean (SD) | |
| Full Scale Intelligence Quotient (FSIQ) | 101.6 (13.9) |
| Verbal Comprehension Index (VCI) | 104.7 (14.2) |
| Perceptual Reasoning Index (PRI) | 100.6 (15.3) |
| Working Memory Index (WMI) | 96.0 (14.) |
| Processing Speed Index (PSI) | 100.3 (13.5) |
| **Mothers** | |
| Maternal age, mean (SD), years | 31.9 (5.0) |
| Maternal education, years, n (%) | |
| ≦9 | 9 (1.1) |
| 10-16 | 805 (93.9) |
| ≧17 | 43 (5.0) |
| Parity, n (%) | |
| 0 (primipara) | 434 (50.6) |
| ≧1 (multipara) | 423 (49.4) |
| Smoking during pregnancy, n (%) | 67 (7.8) |
| Drinking alcohol during pregnancy, n (%) | 115 (13.4) |
| Pre-pregnancy BMI, mean (SD), $kg/m^2$ | 21.0 (3.3) |
| **Fathers** | |
| Paternal age, mean (SD), years | 33.6 (5.7) |
| Paternal education, years, n (%) | |
| ≦9 | 48 (5.6) |
| 10-16 | 7.9 (82.7) |
| ≧17 | 100 (11.7) |
| Household income, million JPY, n (%) | |
| ≦300 | 38 (4.4) |
| 300-1000 | 733 (85.5) |
| >1000 | 86 (10.0) |

Abbreviation: BMI, body mass index; SDS, standard deviation scores; WISC-IV, Wechsler Intelligence Scale for Children-Fourth Edition

Table 2. Mediation analysis of the association between maternal pre-pregnancy BMI and cognitive function (WISC-IV Full Scale IQ) through children's BMI (n=857)

| | Full Scale IQ (FSIQ) | | |
|---|---|---|---|
| | Unadjusted | Model 1 | Model 2 |
| Natural indirect effect | -2.30 (-4.52, -0.46)* | -2.47 (-4.56, -0.74)* | -2.48 (-4.59, -0.77)* |
| Natural direct effect | -2.66 (-4.73, -0.82)* | -2.45 (-4.56, -0.66)* | -2.50 (-4.63, -0.73)* |
| Total effect | -4.96 (-9.09, -1.51)* | -4.91 (-8.89, -1.1)* | -4.98 (-9.02, -1.70)* |
| Proportion mediated, % | 46.37 | 50.31 | 49.80 |

*P < 0.05

Model 1: Adjusted for parental age, parental education years, parity, parental income, children's sex, low birthweight, preterm birth, smoking during pregnancy, drinking during pregnancy

Model2: Further adjusted for polygenic risk score (PRS) of BMI.

Table 3. Mediation analysis of the association between maternal pre-pregnancy BMI and cognitive functions (WISC-IV subscales) through children's BMI (n=857)

| | Verbal Comprehension Index (VCI) | | |
|---|---|---|---|
| | Unadjusted | Model 1 | Model 2 |
| Natural indirect effect | -1.74 (-3.77, -0.01)** | -1.95 (-3.95, -0.17)* | -1.96 (-4.00, -0.18)* |
| Natural direct effect | -1.01 (-3.00, 0.74) | -0.89 (-2.93, 0.96) | -0.95 (-3.05, 0.91) |
| Total effect | -2.74 (-6.59, 0.54) | -2.83 (-6.69, 0.55) | -2.91 (-6.88, 0.50) |
| Proportion mediated, % | 63.5 | 68.9 | 67.35 |
| | Perceptual Reasoning Index (PRI) | | |
| | Unadjusted | Model 1 | Model 2 |
| Natural indirect effect | -1.98 (-4.23, -0.20)** | -2.17 (-4.29, -0.44)* | -2.19 (-4.34, -0.45)* |
| Natural direct effect | -2.37 (-4.36, -0.63)* | -2.32 (-4.32, -0.57)* | -2.38 (-4.41, -0.63)* |
| Total effect | -4.35 (-8.30, -1.12)* | -4.49 (-8.36, -1.26)* | -4.57 (-8.55, -1.33)* |
| Proportion mediated, % | 45.52 | 48.33 | 47.92 |
| | Working Memory Index (WMI) | | |
| | Unadjusted | Model 1 | Model 2 |
| Natural indirect effect | -2.22 (-4.31, -0.35)* | -2.22 (-4.24, -0.50)* | -2.23 (-4.25, -0.52)* |
| Natural direct effect | -3.23 (-5.21, -1.42)* | -3.07 (-5.05, -1.27)* | -3.09 (-5.10, -1.29)* |
| Total effect | -5.45 (-9.34, -2.02)* | -5.29 (-9.13, -1.98)* | -5.32 (-9.16, -2.04)* |
| Proportion mediated, % | 40.73 | 41.97 | 41.92 |
| | Processing Speed Index (PSI) | | |
| | Unadjusted | Model 1 | Model 2 |
| Natural indirect effect | -1.35 (-3.42, 0.52) | -1.41 (-3.47, 0.37) | -1.40 (-3.47, 0.38) |
| Natural direct effect | -2.12 (-4.12, -0.21)* | -1.77 (-3.87, 0.18) | -1.77 (-3.88, 0.18) |
| Total effect | -3.47 (-7.36, 0.15) | -3.18 (-7.13, 0.38) | -3.17 (-7.14, 0.37) |
| Proportion mediated, % | 38.9 | 44.34 | 44.16 |

*P < 0.05; **P < 0.01

Model 1: Adjusted for parental age, parental education years, parity, parental income, children's sex, low birthweight, preterm birth, smoking during pregnancy, drinking during pregnancy

Model2: Further adjusted for polygenic risk score (PRS) of BMI.

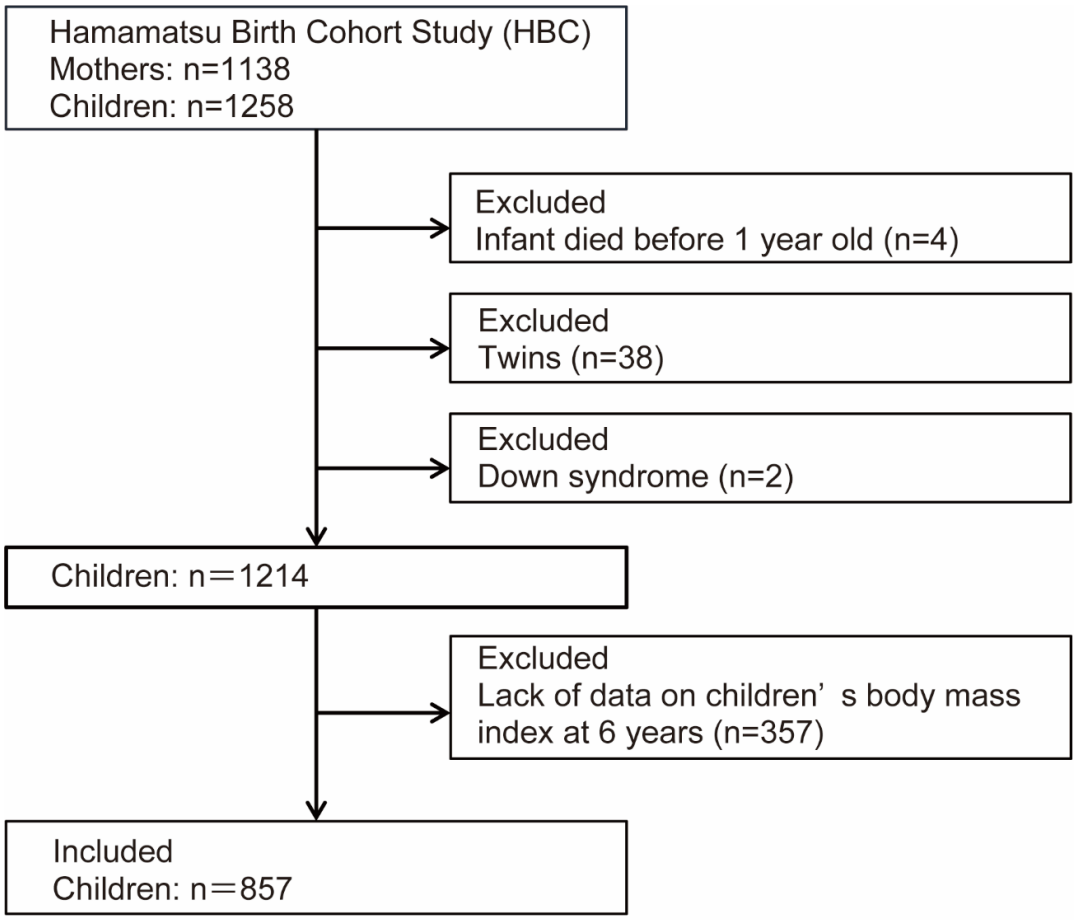


Figure 1. Flow chart of participants who met inclusion/exclusion criteria.

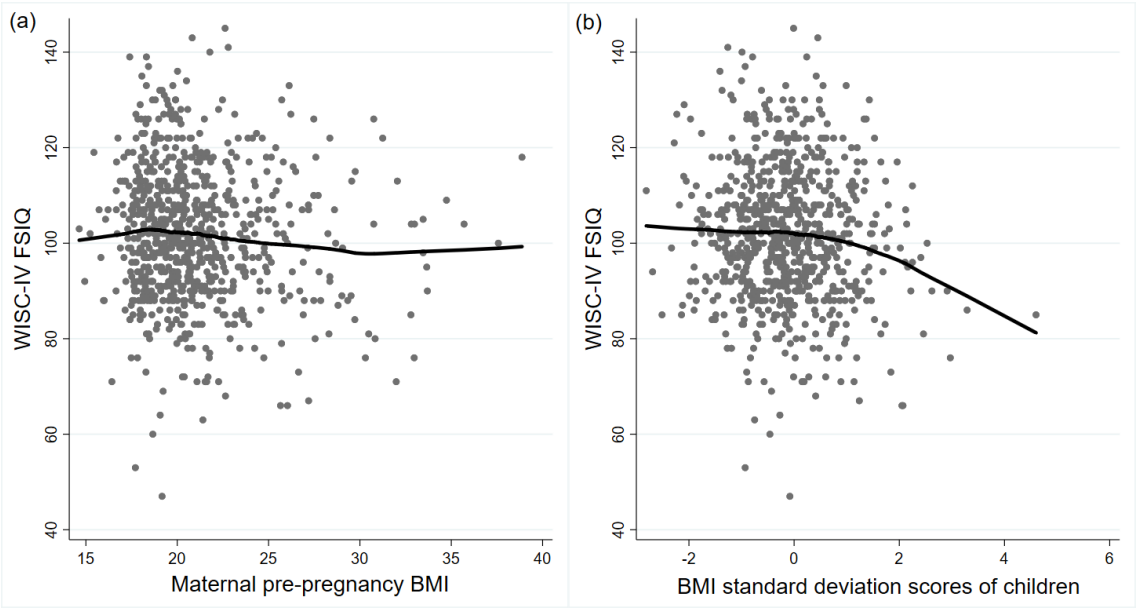


Figure 2. Association between (a) maternal pre-pregnancy BMI and children's cognitive functions and (b) children's BMI and cognitive functions by locally weighted scatter plot smoothing (LOESS).

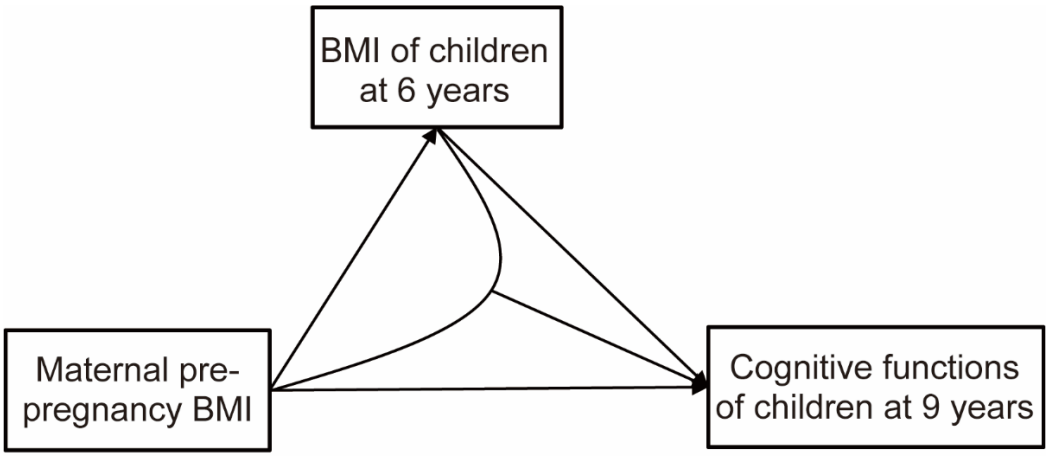


Figure 3. Counterfactual-based mediation model

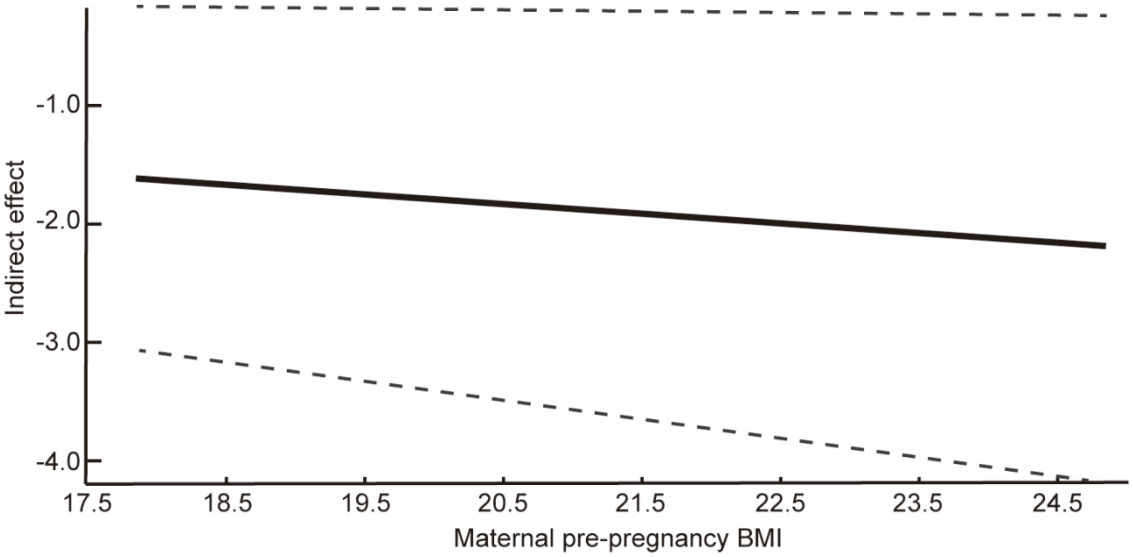


Figure 4. Association between the natural indirect effect and maternal pre-pregnancy BMI