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Association between Maternal LDL Level during Pregnancy and Offspring LDL Level at Age 8

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The pathological process of atherosclerosis begins in childhood and increases the risk of myocardial infarction, other cardiac diseases, and subsequent stroke. To investigate the relationship between maternal low-density lipoprotein cholesterol (LDL-C) level during pregnancy and LDL-C level in offspring at 8 years old. The Japan Environment and Children's Study (JECS) is an ongoing birth cohort study to elucidate the effects of environmental factors on health from the fetal period to early childhood. A total of 1,226 mother–child pairs were enrolled in the present study, which was conducted as an adjunct study to the JECS at the Kochi Unit Center (Kochi, Japan). Peripheral blood samples and anthropometric measurements of the children were collected at age 8. In addition, 540 of the enrolled children's fathers whose peripheral blood samples were collected at the time of JECS enrollment were also analyzed. The exposures of interest were maternal serum LDL-C level during pregnancy and paternal LDL-C level. The outcome of interest was serum LDL-C level of offspring at 8 years old. Mean (SD) serum LDL-C levels were 107.0 (25.6) mg/dL for mothers, 116.5 (27.4) mg/dL for fathers, and 89.9 (21.4) mg/dL for offspring. LDL-C level in mothers whose offspring had above-normal LDL-C levels (≥ 110 mg/dL) was significantly higher than that in mothers whose offspring had normal LDL-C levels (< 110 mg/dL). If a mother has a high LDL-C level during pregnancy, her offspring might also have a high LDL-C at age 8.

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Introduction

Dyslipidemia is a causative risk factor for atherosclerotic cardiovascular disease. The pathological process of atherosclerosis begins in childhood and increases the risk of myocardial infarction, other cardiac diseases, and subsequent stroke. Atherosclerotic cardiovascular disease is ultimately a cause of death; therefore, prevention starting from childhood is important.

Maternal lipid levels are determined mainly by genetics and lifestyle factors such as diet and obesity. Recently, maternal lipid levels in early pregnancy have been reported to be associated with pre-eclampsia and gestational diabetes (Enquobahrie et al. 2004; Ryckman et al. 2015; Adank et al. 2019, 2020). Gestational lipid levels have also been found to be associated with metabolic syndrome many years after pregnancy, suggesting that the maternal lipid profile during pregnancy may be used as an early marker of the woman's cardiovascular disease in later life (Ryckman et al. 2015). Maternal low-density lipoprotein cholesterol (LDL-C) level during pregnancy is reported to be associated with offspring LDL-C level in adulthood (Mendelson et al. 2016). Adank et al. reported that maternal lipid levels in early pregnancy (median, 13.2 weeks) might provide an insight into the lipid profile of offspring at the age of 6 and 10 years, and they suggested that gestational lipid levels might be used as an

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early predictor of children's long-term health (Adank et al. 2022). However, the influence of maternal lipid levels during pregnancy on the lipid levels of their offspring is less studied in Japan.

Here, we assessed the association between the LDL-C levels of mothers in pregnancy and fathers and the LDL-C levels of their offspring at age 8 years.

Methods

Study design

The Japan Environment and Children's Study (JECS) is an ongoing national birth cohort study being undertaken by the Ministry of the Environment of Japan to elucidate the influence of environmental factors during the fetal period and early childhood on children's health, with follow-up until age 13. The study recruited pregnant women living close to one of 15 Regional Centers located throughout Japan. If possible, the women's partners (fathers) were also approached and encouraged to participate. The protocol and baseline data of the JECS are described elsewhere (Kawamoto et al. 2014; Michikawa et al. 2018). The JECS protocol was reviewed and approved by the Institutional Review Board on Epidemiological Studies of the Ministry of the Environment, and by the Ethics Committees of all participating institutions. The JECS is being conducted in accordance with the Declaration of Helsinki and other internationally valid regulations and guidelines, and with written informed consent from all participants.

The present study was conducted as an adjunct study to the JECS at the Kochi Regional Center, which is one of the 15 Regional Centers. While the JECS mainly consisted of a questionnaire survey administered twice a year after the child's birth, a face-to-face survey was conducted for all participants for the first time when the child turned eight years old. During this face-to-face survey, Kochi Unit Center (KUC) conducted medical examination, including peripheral blood sampling, on children for whom informed consent was obtained. The study was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (approval no. A16723028) and by the Ethics Committee of Kochi Medical University (approval no. 30-167).

Participants

Of the 6,408 JECS participants enrolled at the Kochi Regional Center, we excluded individuals who did not attend the JECS face-to-face survey at age 8, or declined to participate in the present study (n = 4,488), individuals whose peripheral blood samples could not be collected (n = 545), individuals who transferred from other Regional Centers (n = 2), and individuals with missing maternal peripheral blood samples at enrolment in the JECS (n = 147). In total, 1,226 mother–child pairs were enrolled in the present study. For the enrolled children, 540 of their fathers participated in JECS and their peripheral blood samples were also obtained at JECS registration (Fig. 1).

In addition to the data collected specifically for this adjunct study, we also used JECS dataset "jecs-ta-20190930," which was released in October 2019. This dataset includes biomarker data from maternal and paternal blood samples as well as lifestyle and other background information collected from self-administered questionnaires distributed to the participating women at recruitment and later in pregnancy; clinical information on past and present pregnancies; and the physical status of the participants and their offspring collected from medical records transcribed by physicians, midwives/nurses, and/or research coordinators.

Exposures

The exposures of interest were maternal serum LDL-C level during pregnancy and paternal LDL-C level. Non-fasting blood samples were collected by medical staff when the pregnant women (mothers) and their partners (fathers)

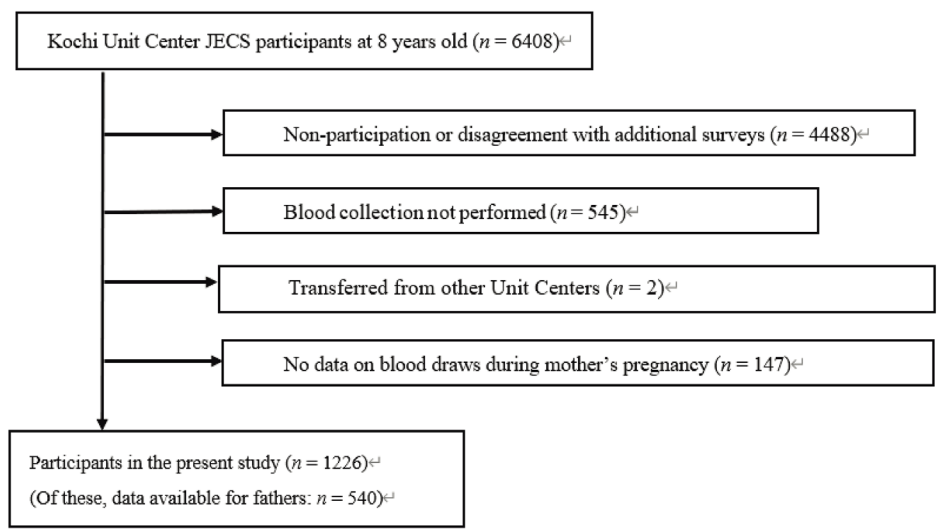

Fig. 1. Flow chart of participant selection. JECS, Japan Environment and Children's Study.

visited cooperating healthcare providers in early to mid-pregnancy. Serum LDL-C levels were assayed by a commercial clinical laboratory (SRL, Inc., Tokyo, Japan), along with other biomarkers, on a Hitachi 7700 Series instrument (Taniguchi et al. 2022) using an accelerator selective detergent method. Since maternal lipid levels during pregnancy are strongly correlated with gestational age at blood sampling, we used gestational age–adjusted lipid levels, which were calculated as the residuals from a regression model with each lipid level as the dependent variable plus predicted lipid levels for the mean gestational age at blood sampling of the study population (Willett and Stampfer 1986).

Outcome

The outcome of interest was serum LDL-C level of offspring at 8 years old. Non-fasting blood samples of offspring were collected by the medical staff of the Kochi Regional Center and used to assay LDL-C levels on a JCA-BM6070 instrument (JEOL Ltd., Tokyo, Japan) with an LDL-cholesterol assay kit (Sekisui Medical Co., Ltd., Tokyo, Japan) at Kochi Medical School Hospital (Kochi, Japan). Serum LDL-C level of offspring was dichotomized into normal (< 110 mg/dL) and above normal (≥ 110 mg/dL) in line with the criteria for normal serum lipid levels in Japanese children (Okada et al. 2002).

Confounders and covariates

Considering the causal relationships between the exposure and outcome variables, the following factors were considered as confounders and covariates: parental age at blood sampling; pre-pregnancy body mass index (BMI) of mothers; paternal BMI at blood sampling; maternal weight gain during pregnancy; parental smoking habit during pregnancy (1, never; 2, previously did, but quit before realizing current pregnancy; 3, previously did, but quit after realizing current pregnancy; 4, currently smoking); family income (1, < 4.0; 2, 4.0-7.9; 3, ≥ 8.0 million JPY); maternal physical activity before pregnancy; sex of offspring; and BMI of offspring at blood sampling. Physical activity was assessed by using the Japanese short version of the International Physical Activity Questionnaire, calculated as metabolic equivalent of a task (MET-min/week) and categorized into quartiles (Murase 2002; Craig et al. 2003). Children's height and weight were measured by the medical staff of the Kochi Regional Center on the same day as the blood sampling or within one month prior to the blood sampling. Information on these covariates was transcribed from medical records or from the responses to the questionnaires that were distributed to the parents during pregnancy.

Statistical analyses

We generated summary statistics with frequencies and means (SDs) for the demographic and clinical characteristics of the participants according to offspring LDL-C level at 8 years old. Categorical variables were compared with a chi-squared test, and continuous variables were compared with a Student's *t*-test. Pearson correlation coefficients were determined and used to evaluate the correlation between parental and offspring LDL-C levels. To illustrate the dose–response relationship between parental and offspring LDL-C levels, multivariate linear regression analyses and multivariate logistic regression analyses with restricted cubic splines were used. Relative change in offspring LDL-C level and the odds ratio for elevated offspring LDL-C level (above normal level), as well as their accompanying 95% confidence intervals, were calculated with five knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the distribution of parental LDL-C levels (Orsini and Greenland 2011); these were the recommended knot locations for the percentiles used (Harrell 2015). A significance level of 0.05 was used in these analyses. All analyses were performed using Stata 13.1 (Stata Corp., College Station, Texas, USA).

Results

Table 1 shows the baseline characteristics of the participants. The mean (SD) gestational week at maternal blood sampling was 16.0 (2.4) weeks and the mean age of offspring at blood sampling was 8.0 (0.3) years. The mean serum LDL-C levels were 107.0 (25.6) mg/dL for mothers, 116.5 (27.4) mg/dL for fathers, and 89.9 (21.4) mg/dL for offspring. The mean adjusted LDL-C for the mothers whose children's LDL-C level was above normal was significantly higher than that of the mothers whose children had a normal LDL-C level; there was no significant difference in paternal LDL-C level between these two groups. Children whose LDL-C levels were above normal had a significantly higher BMI than children whose LDL-C levels were in the normal range. Moreover, there was a weak correlation between pre-pregnancy BMI and offspring BMI (r = 0.25). However, there were no significant differences between these two groups in maternal pre-pregnancy BMI, gestational weight gain, or father's BMI at blood sampling.

Scatterplots of parental LDL-C versus offspring LDL-C revealed a mild positive correlation between maternal LDL-C level during pregnancy and offspring LDL-C level ($r = 0.26$) but not between paternal LDL-C level and offspring LDL-C ($r = 0.14$) (Fig. 2).

The obtained restricted cubic spline models and accompanying histograms showing the distribution of parental lipid levels are shown in Figs. 3 and 4. The models showed a dose–response relationship between maternal LDL-C and offspring LDL-C, indicating that a higher maternal LDL-C during pregnancy was associated with increased offspring LDL-C level at 8 years old, as well as increased risk that their offspring's LDL-C will exceed the normal level. Although a lower paternal LDL-C was associated with a lower offspring LDL-C, a higher paternal LDL-C was not associated with a significantly higher offspring LDL-C level.

Table 1. Baseline characteristics according to LDL cholesterol of offspring.

	Total	Normal (<110 mg/dL)	Above normal (≥110 mg/dL)	*P*-value
Characteristics of children	***n* = 1,226**	***n* = 1,013**	***n* = 213**	
LDL cholesterol level (mg/dL)	89.9 (21.4)	82.8 (15.1)	123.9 (12.8)	< 0.001
Age at blood sampling, years	8.0 (0.3)	8.0 (0.3)	8.0 (0.3)	0.442
BMI, kg/m^2	16.0 (2.1)	15.9 (1.9)	16.5 (2.6)	< 0.001
Sex (male)	624 (51%)	551 (54%)	73 (34%)	< 0.001
Characteristics of mothers	***n* = 1,226**	***n* = 1,013**	***n* = 213**	
LDL cholesterol level (mg/dL)*	107.0 (25.6)	105.6 (25.3)	113.7 (26.1)	< 0.001
Timing of blood sampling, weeks	16.0 (2.4)	16.0 (2.4)	15.8 (2.2)	0.171
Maternal age at delivery, years	32.2 (4.7)	32.1 (4.6)	32.3 (4.9)	0.551
Pre-pregnancy BMI, kg/m^2	21.2 (3.0)	21.2 (3.0)	21.2 (3.1)	0.720
Weight gain during pregnancy, kg	9.5 (4.1)	9.5 (4.0)	9.7 (4.1)	0.387
Family income, million JPY				
< 4	460 (39%)	383 (40%)	77 (37%)	0.053
4-7.9	605 (52%)	503 (52%)	102 (49%)	
≥ 8	107 (9.1%)	79 (8.2%)	28 (14%)	
Maternal smoking during pregnancy				
Never	822 (67%)	688 (68%)	134 (63%)	
Previously did, but quit before realizing current pregnancy	263 (22%)	221 (22%)	42 (20%)	0.002
Previously did, but quit after realizing current pregnancy	99 (8.1%)	68 (6.7%)	31 (15%)	
Currently smoking	39 (3.2%)	33 (3.3%)	6 (2.8%)	
Physical activity before pregnancy (MET-min/week)	350 (625)	339 (584)	400 (790)	0.196
Characteristics of fathers	***n* = 540**	***n* = 451**	***n* = 89**	
LDL cholesterol level, mg/dL	116.5 (27.4)	116.0 (27.5)	118.9 (26.9)	0.356
Father's age at blood sampling, years	33.6 (5.6)	33.7 (5.6)	33.1 (5.9)	0.341
BMI, kg/m^2	23.4 (3.3)	23.4 (3.3)	23.5 (3.6)	0.804
Smoking habit				
Never	176 (33%)	145 (32%)	31 (35%)	0.709
Previously did, but quit before realizing current pregnancy	137 (25%)	115 (26%)	22 (25%)	
Previously did, but quit after realizing current pregnancy	31 (5.8%)	24 (5.3%)	7 (7.9%)	
Currently smoking	195 (36%)	166 (37%)	29 (33%)	

Data are presented as mean (standard deviation), or n (%).
*Adjusted for gestational age at blood sampling.

Discussion

Here, we found a significant positive relationship between maternal LDL-C during pregnancy and offspring LDL-C level at 8 years old. The implication is that if a mother has high LDL-C during pregnancy, her unborn child will likely also have high LDL-C from childhood. We found that the higher the mother's LDL-C, the higher the child's LDL-C level at age 8, whereas that of the father had no association with that of the child. These findings agree with findings from the Framingham Heart Study that demonstrated that elevated maternal LDL-C before pregnancy correlates with offspring LDL-C in young adulthood (mean age, 26 years) but paternal LDL-C does not (Mendelson et al. 2016). Adank et al. showed that high blood lipid levels in women during early pregnancy are positively associated with high blood lipid levels in offspring at 6 and 10 years of age (Adank et al. 2022). Our study is based on data from Japanese people, and it is also important that the data was collected at the age of 8.

A study by Christensen et al. (2016) that included women in early pregnancy (gestational weeks 14-16) showed that 27 women with LDL-C levels in the 90th percentile or greater had offspring with significantly higher LDL-C levels (0.4 mmol/L) at the age of 6-13 years, as compared with 34 women with LDL-C level within the 10th percentile. However, the number of individuals enrolled was small and the ages of the offspring varied widely.

A study from the Rhea pregnancy cohort also showed a positive association in 348 mother–child pairs between gestational total cholesterol and LDL-C with total cholesterol of children at age 4 years, independent of maternal pre-pregnancy BMI. Metabolic profile in early pregnancy is associated with offspring adiposity at age 4 years (Daraki et al. 2015). In our study, there was a weak correlation

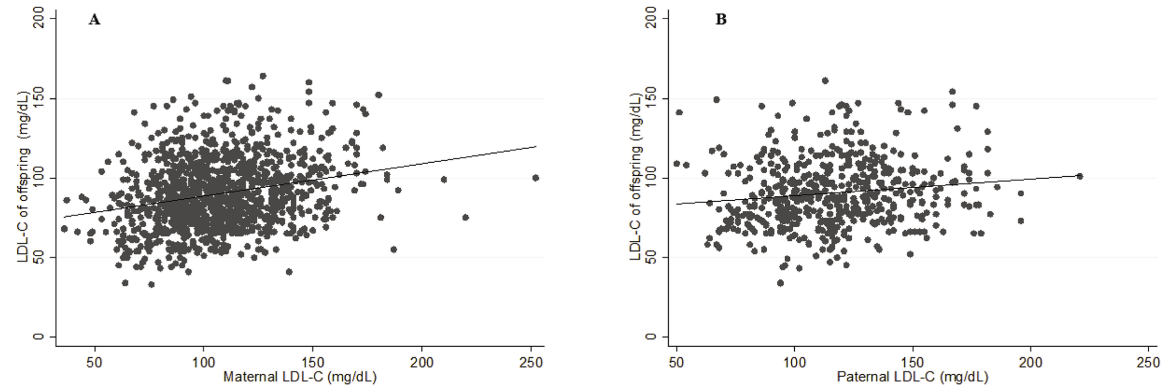

Fig. 2. The association between offspring low-density lipoprotein cholesterol (LDL-C) level and parents LDL-C level.
Scatter plot showing the association between offspring low-density lipoprotein cholesterol (LDL-C) level and maternal (A) or paternal (B) LDL-C level.

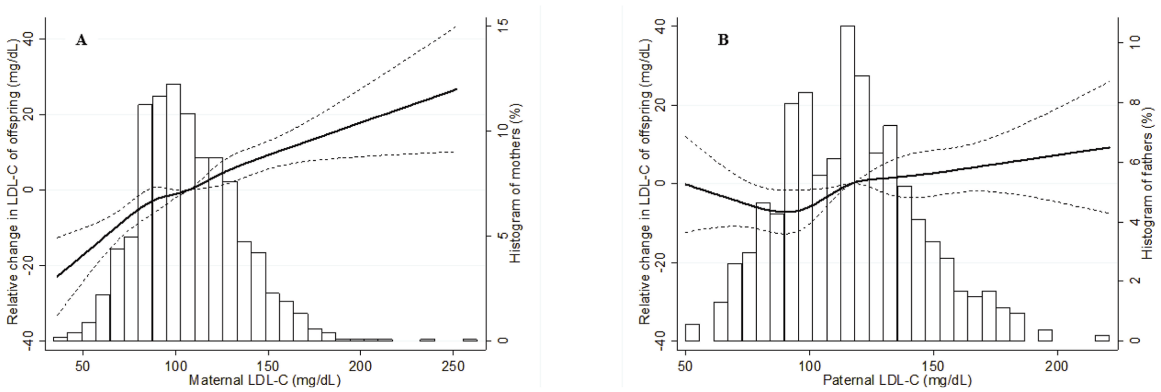

Fig. 3. The association between parental low-density lipoprotein cholesterol (LDL-C) level and relative change in LDL-C level of offspring.
Association between parental low-density lipoprotein cholesterol (LDL-C) level and offspring LDL-C level (Reference: LDL cholesterol of mothers = 107 mg/dL, LDL cholesterol of fathers = 117 mg/dL). Adjusted for maternal age, pre-pregnancy body mass index (BMI), gestational weight gain, smoking during pregnancy, physical activity before pregnancy, family income, obesity of offspring, and sex of offspring in (A), and for paternal age, BMI, smoking habit, obesity of offspring, and sex of offspring in (B). Dashed lines indicate 95% confidence intervals. Histograms show distribution of parents by LDL-C level.

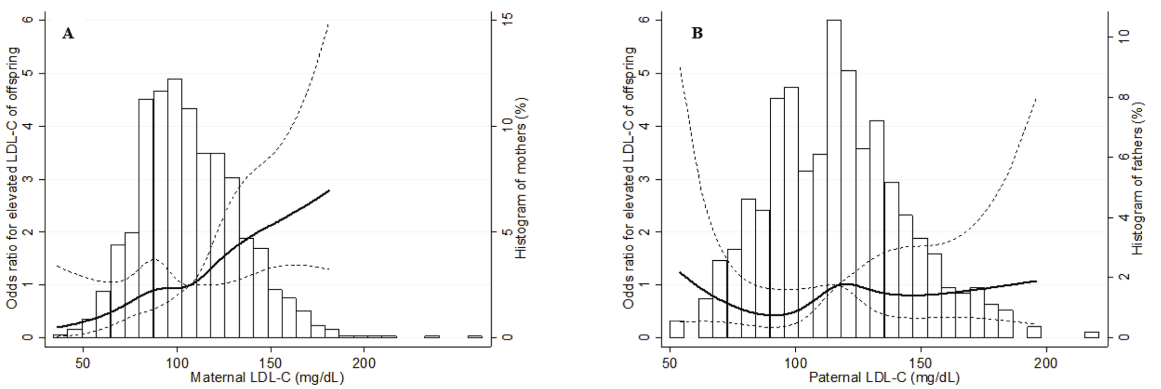

Fig. 4. The association between parental low-density lipoprotein cholesterol (LDL-C) level and odds ratio for elevated LDL-C of offspring.
Association between parental low-density lipoprotein cholesterol (LDL-C) level and offspring LDL-C level (Reference: LDL cholesterol of mothers = 107 mg/dL, LDL cholesterol of fathers = 117 mg/dL). Adjusted for maternal age, pre-pregnancy body mass index (BMI), gestational weight gain, smoking during pregnancy, physical activity before pregnancy, family income, obesity of offspring, and sex of offspring in (A), and for paternal age, BMI, smoking habit, obesity of offspring, and sex of offspring in (B). Dashed lines indicate 95% confidence intervals. Histograms show distribution of parents by LDL-C level.

between the mother's BMI before pregnancy and the child's BMI at age 8. However, a positive association was found between LDLC during pregnancy and child's LDL-C in a multivariate model adjusted for the mother'' pre-pregnancy BMI, indicating that pregnancy is independent of the mother's obesity.

Juhola et al. (2011) found a strong relationship between childhood lipid levels and lipid levels measured in middle age, which underlines the importance of early markers for cardiovascular disease risk in children not only during childhood but also in the subsequent decades.

A high LDL-C level is thought to induce arteriosclerosis, which is a risk factor for the development of ischemic heart disease and vascular diseases such as myocardial infarction and angina pectoris, as well as cerebral infarction, cerebral hemorrhage, and subarachnoid hemorrhage. Increased levels of total cholesterol, triglycerides, LDL-C, and non-LDL-C, and low HDL-C levels, are associated with cardiovascular disease and mortality later in life (Duncan et al. 2019). Evidence demonstrates that early and prolonged exposure to elevated LDL-C levels carries significant adverse cardiovascular disease consequences beyond those of developing dyslipidemia later in life (Ference et al. 2012; Stanesby et al. 2024).

Several reviews discuss how a mother's abnormal lipid metabolism and obesity during pregnancy can affect offspring health at birth, in childhood, and in adulthood (Cechinel et al. 2022; Rastogi and Rastogi 2022; Simoes-Alves et al. 2022). As to why gestational lipids in early pregnancy may be associated with childhood lipids, we hypothesize first that lifestyle factors would largely explain this association. However, we found no relationship between paternal LDL-C (determined at the same time as maternal LDL-C) and offspring LDL-C level at 8 years old. This suggests that there is little involvement of dietary habits at home, but we cannot fully reject lifestyle problems because fathers only might have attention about health, and we don't have paternal LDL-C data collected when their offspring were 8 years of age. Our second hypothesis is that genetic inheritance is an important contributor to the association between gestational lipid levels with lipid levels in childhood. In otherwise healthy women, LDL-C levels above the 99th percentile have been found to be caused by unfavorable genotypes or mutations causing familiar hypercholesterolemia (Balder et al. 2018). Unfortunately, in the present study we were unable to examine genetic inheritance. As already noted, although our results point toward genetic inheritance as an important contributor, the possible effects of maternal lifestyle during pregnancy cannot be entirely ruled out. We therefore hypothesize that our results may be explained by a combination of genetic inheritance and lifestyle or pregnancy-related factors.

In humans, low maternal serum cholesterol levels are associated with preterm birth and lower birthweight (Edison et al. 2007). In contrast, fetal overnutrition with excess cholesterol due to increased LDL-C uptake likely has pathologic effects on the developing fetus. In humans, fetuses of hypercholesterolemic mothers have an increase of aortic fatty streak (Napoli et al. 1997). Current guidelines of the American Heart Association and of the European Heart Association do not recommend to measure lipid levels in early pregnancy (Bushnell et al. 2014; Authous/Task Force Members et al. 2016). However, based on this study, we suggest that in addition to routine glucose measurements it may be meaningful to measure lipid levels in order to initiate dietary changes if necessary. This may be beneficial for timely interventions, especially since women are willing to improve their lifestyle (van der Zee 2011; Lindqvist et al. 2017).

Our present data indicate that a child is more likely to be hyperlipidemic if their mother was hyperlipidemic when pregnant, regardless of environmental factors or diet. Cholesterol in pregnant women is known to be generally higher (Ying et al. 2015), and cholesterol transfer from mother to child is an important part of fetal development such that if the mother is hypocholesterolemic, her unborn child will weigh less (Jiang et al. 2017). It is also reported that maternal malnutrition during pregnancy leads to obesity after birth due to the fetus adapting to its environment by eating a high-calorie diet (Gantenbein and Kanaka-Gantenbein 2022). Therefore, the nutritional balance of the mother during pregnancy is very important.

The strengths of the present study are a long prospective data collection from early pregnancy onwards, a large sample of 1,226 mother–child pairs with lipid measurements out to 8 years after pregnancy, and Japanese data.

The present study has several limitations. The first is that genetic factors cannot be ruled out and hyperlipidemia can manifest as familial hyperlipidemia regardless of obesity and diet. Familial hyperlipidemia was not included in the questionnaire, so I will only mention it as a relationship. The second limitation is the lack of data on postnatal diet, which may be a major contributing factor to the lipid profile of the children. The third limitation is the lack of information on complications and medications for diseases that predispose to hyperlipidemia. However, the incidence of hyperlipidemia-prone endocrine disorders in children, for example, is low, and similarly, we assumed that very few of the children included in this study were taking medications that lead to hyperlipidemia. The fourth limitation is that many mother–child pairs could not participate in the study because of the COVID19 pandemic.

The fifth limitation is that maternal lipid levels were measured only once during pregnancy, we are unable to assess the effect of pre-pregnancy lipid levels or changes in lipid levels during pregnancy on offspring lipid levels.

The sixth limitation, maternal lipid levels increases during pregnancy and gestational age at blood sampling was variable in this population. However, the effect of this variation in gestational age was minimized by using gestational age-adjusted lipid levels.

Further studies are warranted to consider whether the

association obtained at the 8 years-old will persist even after the children grow up because children's lipid levels will change as they grow.

Conclusion

The gestational lipid profile in early pregnancy is associated with the lipid profile of children at age 8 years. Monitoring of these gestational lipid levels may give an opportunity to start early interventions to decrease offspring's lipid levels and possibly diminish their cardiovascular risk later in life. The early elevation of LDL-C level among offspring exposed to preconceptional elevated LDL-C levels may carry further consequences for the subsequent generation.

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Author Contributions

T.O. and N.M. made a significant contribution to the manuscript, have read and approved its final version, and affirm that no part of the present manuscript has been submitted elsewhere for publication. T.O. prepared the initial draft. NM and KW performed the analysis. The paper was critiqued by N.M., K.W., M.A., R.N., M.E., M.F., and N.S., and finalized by M.F. and N.S.

Conflict of Interest

The authors declare no conflict of interest.

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