



Change in cholesterol level during pregnancy and risk of postpartum depressive symptoms: the Japan Environment and Children's Study (JECS)

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Abstract

Objective: Women with postpartum depressive symptoms (PDS) are at higher risk of postpartum depression (PPD) and require further assessment. Emerging evidence indicates a relationship between the total cholesterol (TC) level of blood and PPD but the results are inconsistent. In this study, we investigated the possible association of change in serum TC levels during pregnancy with the risk of PDS in a Japanese population.

Methods: We analyzed complete data on questionnaire responses and serum lipid profiles of pregnant women from 12 datasets obtained from the Japan Environment and Children's Study ($n = 61,585$ to $n = 72,406$; 103,063 pregnancies in total). TC was measured at 3 time points—during early pregnancy, during mid-late pregnancy, and after delivery—and we calculated changes in TC in 3 ways: by subtracting early pregnancy from mid-late pregnancy, subtracting mid-late pregnancy from delivery, and subtracting early pregnancy from delivery. These

Study Group members are listed in the Appendix 1.

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6 factors were used as predictors to estimate the risk of PDS at 1 and 6 months after delivery.

Results: In multivariable logistic regression analysis, point serum cholesterol level did not predict PDS at any time point except for during mid-late pregnancy in the second quintile, indicating an increased risk at 6 months. As for change in TC levels, subtracting mid-late pregnancy from delivery and early pregnancy from delivery showed significant risk reduction for PDS at 1 month. A significant risk reduction was also found for subtracting early pregnancy from mid-late pregnancy and early pregnancy from delivery at 6 months.

Conclusions: Increased cholesterol level during pregnancy is associated with reduced risk of PDS.

KEYWORDS

cholesterol, cohort, epidemiology, postpartum depressive symptoms, pregnancy

1 | INTRODUCTION

Women with postpartum depressive symptoms (PDS) are at higher risk of postpartum depression (PPD) and require further assessment. PPD is defined by The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) as a depressive episode with moderate to severe severity that begins during pregnancy or within 4 weeks after delivery. The characteristics of PPD include anhedonia, anxiety symptoms, panic attacks, depressed mood, and sometimes suicidal thoughts.¹ A meta-analysis of the prevalence of depression (major depressive disorder and minor depressive disorder) during the first 3 and 6 months after delivery found that prevalence was as high as 12.8% during the first 3 months and remained high at roughly 10% during the first 6 months.² In recent studies of maternal populations representative of pregnant Japanese women, we found that the prevalence of PDS at 1 and 6 months was 13.8% and 11.6%, respectively.^{3,4}

Predictors of PPD have been examined in multiple studies. Beck et al. cited a number of factors associated with the development of PPD: history of previous depression, prenatal anxiety, self-esteem, life stress, social support, marital status, marital relationship, infant temperament, socioeconomic status, and unplanned/unwanted pregnancy.⁵ In addition to these social factors, multiple biological factors are also attracting attention as predictors of PPD, including postpartum blues,⁵ hormones, inflammatory markers, minerals, vitamins, and lipids.⁶

Many studies have examined the association between cholesterol and depression. The mechanism of this association is thought to involve effects on the serotonin system

Significant Outcomes

- This nationwide prospective cohort study found reduced risk of postpartum depressive symptoms in mothers whose total cholesterol level increased during pregnancy compared with the reference group.
- Postpartum depressive symptoms were predicted by point total cholesterol level during mid-late pregnancy but not at any other time point.
- Although a decrease in total cholesterol during the peripartum period has previously been linked to postpartum depression, to our knowledge this study is the first to examine the association between the risk of postpartum depressive symptoms and an increase in total cholesterol level during pregnancy.

Limitations

- The Edinburgh Postpartum Depression Scale screening test was used instead of a diagnostic test. In general, this scale indicates suspicion of postpartum depression that warrants confirmation, whereas diagnostic tests provide a definite diagnosis. Second, we cannot rule out the possibility that the exclusion of more than 30,000 women based on the eligibility criteria, while necessary, may have introduced some selection bias. Third, the findings may not necessarily apply to all nationalities and ethnicities.

or an altered inflammatory profile.⁷ A meta-analysis investigating the association of lipids (total cholesterol [TC], low-density lipoprotein cholesterol [LDL-C], high-density lipoprotein cholesterol [HDL-C]) with depression found an especially strong negative correlation with TC in untreated patients.⁸ Also, HDL-C was positively correlated with depression, particularly in women, while a non-significant negative correlation was observed between LDL-C and depression.⁸

The association between PPD and cholesterol has been examined in several studies. To our knowledge, 8 studies⁹⁻¹⁶: 4 reported TC associated with PPD,^{9,11,12,16} 3 reported no association,^{10,14,15} and 1 reported HDL-C associated with PPD.¹³ Serum lipid levels are known to increase as pregnancy progresses. Levels of triglycerides (TG), TC, and LDL-C peak in the third trimester, increasing by 170% (2.7-fold), 43%, and 36%, respectively, while levels of HDL-C peak in the second trimester (25% increase), before all return to pre-pregnancy levels after delivery.¹⁷ Three longitudinal studies have examined the association between decreased TC and PPD from late pregnancy to the early postpartum period.^{9,10,12} One of the studies conducted in Austria ($n = 20$) observed an association between decreased TC and PPD,⁹ whereas the other two studies were conducted in the Netherlands ($n = 266$)¹⁰ and Italy ($n = 47$)¹² did not.

1.1 | Aims of the study

Although several studies have investigated the association between postpartum depression and cholesterol levels, none has examined the association between increased total cholesterol level during pregnancy and postpartum depression. In this study, we used data from the Japan Environment and Children's Study (JECS), a large-scale nationwide prospective cohort study, to examine the association between change in total cholesterol level and postpartum depressive symptoms. As exploratory research, we also examined other lipids such as low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides and the association between change in cholesterol levels and postpartum depressive symptoms risk in only those participants with a history of mental illness.

2 | METHOD

2.1 | Study population

The protocol of the JECS, a nationwide government-funded birth cohort study, has been described elsewhere.^{18,19} Briefly, JECS investigates the impact of

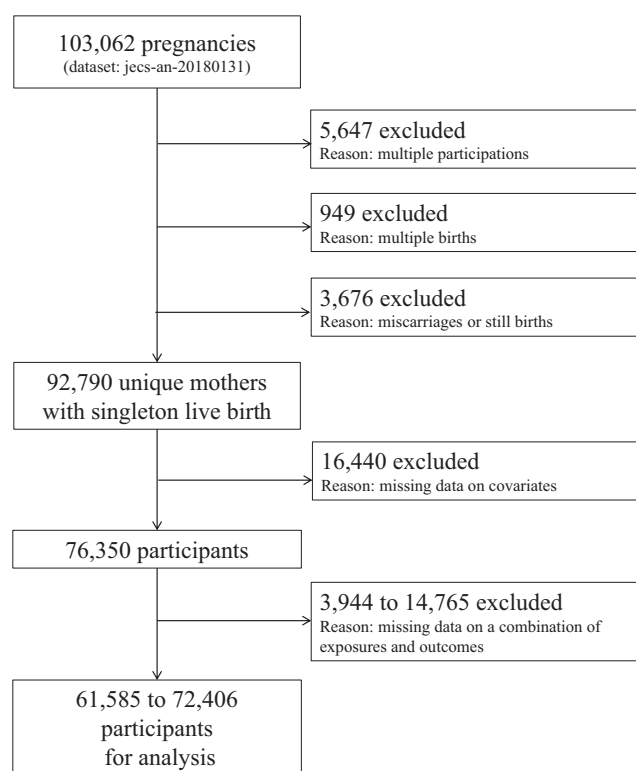


FIGURE 1 Participant flow diagram

certain environmental factors on child health and development. The pregnant participants in the JECS were enrolled from 15 Japanese regions from January 2011 to March 2014.^{18,19} The eligibility criteria for participants (expectant mothers) were as follows¹⁸: (1) residing in one of the 15 regions at the time of recruitment and expecting to reside continuously in Japan for the foreseeable future; (2) having an expected delivery date between August 1, 2011, and mid-2014; and (3) participating in the study without difficulty, that is, able to understand the Japanese language and complete a self-administered questionnaire. Those residing outside the 15 regions were excluded from the study even if they visited cooperating healthcare providers working within the study areas. The sample size was determined in advance to ensure sufficient statistical power for rare diseases with $\leq 1\%$ prevalence.

The present study uses data from the jecs-an-20180131 dataset, which was released in March 2018. The full dataset comprises 103,062 pregnancies, but we excluded 5647 multiple registrations, 949 multiple births, and 3676 miscarriages/stillbirths (Figure 1). From the remaining 92,790 pregnancies, we excluded 16,440 because of missing data on covariates and 3944 to 14,765 were excluded because of missing data on various combinations of exposure and outcomes. In total, depending on the combinations, 61,585 to 72,406 participants were analyzed. As exploratory research, we also examined the

association between change in cholesterol levels and PDS risk among only those participants with a history of depression and/or anxiety ($n = 3001$ for analysis of PDS at 1 month; $n = 3239$ for PDS at 6 months) and the association between other lipids such as LDL-C, HDL-C, and TG and PDS risk.

The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. All procedures involving human patients were approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (100910001), the ethics committees of all participating institutions, and the Ethics Committee, University of Toyama (R2019035). Written informed consent was obtained from all participants in the JECS.

2.2 | Measurement of serum lipids

Non-fasting blood samples were obtained from pregnant women during early pregnancy in weeks 12–16 (if informed consent was obtained during weeks 17–21, then the blood sample was taken right after informed consent was obtained), during mid-late pregnancy in weeks 22–28, and after delivery (during hospitalization). The blood collection tubes used, the method of storage until analysis, and so on all followed the same protocol. The serum biomarkers TC, LDL-C, HDL-C, and TG were assayed by a single contract clinical laboratory (SRL, Inc.), and enzymatically analyzed according to the standardized protocol, using a 7700 clinical chemistry/immunoassay hybrid analyzer (Hitachi High-Technologies Co., Ltd). TC, TG, HDL-C, and LDL-C were measured during early pregnancy and TC and TG during mid-late pregnancy and after delivery (Figure 2).

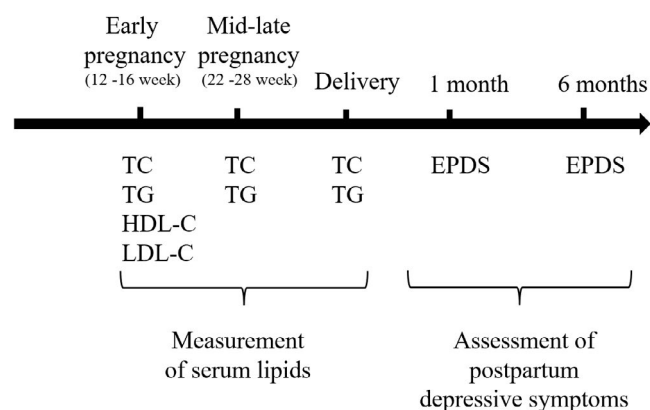


FIGURE 2 Study design

2.3 | Assessment of postpartum depression

The Edinburgh Postpartum Depression Scale (EPDS) was used to assess depression at 1 and 6 months after delivery (Figure 2). The EPDS consists of 10 items rated on a 4-point scale (0–3).²⁰ We defined an EPDS score ≥ 9 as indicating PDS; this has been suggested as the optimal cut-off for the Japanese population, and its validity and reliability have been reported elsewhere.^{21,22}

2.4 | Statistical analysis

Data are expressed as the mean \pm standard deviation or median unless stated otherwise. To estimate the risks of PDS for each level of TC change (subtractions of early pregnancy from delivery, mid-late pregnancy from delivery, and early pregnancy from mid-late pregnancy), we categorized the participants according to quintile of TC change. We then performed logistic regression analysis to calculate odds ratios (ORs) and 95% confidence intervals (CIs). In tests for trends, the number of participants in each category was assigned to quintile distributions for TC change and evaluated as continuous variables.

We included potential confounding factors and covariates in the statistical analysis if previous studies found them to be associated (or if they were theoretically inferred to be associated) with the outcome. The following confounding factors and covariates were considered: age at delivery; pre-pregnancy body mass index (<18.5 , 18.5 – 25 , or ≥ 25 kg/m^2); previous deliveries (primiparous or multiparous); annual household income (<4 million, 4 – 6 million, or >6 million JPY); highest maternal educational level (1, junior high or high school; 2, technical junior college, technical/vocational college, or associate degree; or 3, bachelor's or postgraduate degree); marital status during early pregnancy (1, married [including common-law status]; 2, single; or 3, divorced or widowed); smoking status during mid-late pregnancy (1, never smoked; 2, previously smoked; 3, currently smoking); alcohol intake during mid-late pregnancy (1, never; 2, previously drank alcohol but quit; 3, currently drinking); physical activity during mid-late pregnancy (MET min/day [metabolic equivalent of a task measured as the number of minutes per day]); employment status during mid-late pregnancy; history of depression (yes or no); history of anxiety disorder (yes or no); and presence of any congenital anomaly in the child (yes or no).

Two-sided p values <0.05 were considered to indicate statistical significance. Data were analyzed using SAS version 9.4 software (SAS Institute Inc.).

3 | RESULTS

During follow-up, 13.7% of women (8822/64,342) had PDS (EPDS ≥ 9) at 1 month after delivery and 11.1% (6829/61,585) at 6 months after delivery. Means \pm standard deviation (median, *n*) for TC during early pregnancy, during mid-late pregnancy, and after delivery were 200 ± 35 (median = 197, *n* = 66,798), 254 ± 41 (median = 252, *n* = 72,406), and 250 ± 45 (median = 247, *n* = 71,516), respectively. Levels of TG during those same periods were 131 ± 57 (median = 120, *n* = 66,798), 198 ± 83 (median = 183, *n* = 72,406), and 227 ± 90 (median = 212, *n* = 71,516), respectively. Levels of LDL-C and HDL-C during early pregnancy were 108 ± 28 (median = 105, *n* = 66,798) and 77 ± 14 (median = 76, *n* = 66,798), respectively.

Table 1 shows the characteristics of the participants who comprised the dataset used for determining associations between changes in TC from early pregnancy to delivery and depression at 1 month after delivery. Characteristics are listed for participants overall (*n* = 64,342) and by quintiles of TC change. Across all participants, median TC change was 49 mg/dl. In each quintile (Q1, Q2, Q3, Q4, and Q5), the median TC change was -1, 29, 49, 69, and 101 mg/dl, respectively. The percentage of participants with PDS in each quartile was 15.4% (1994/12,916), 13.8% (1805/13,034), 13.5% (1694/12,517), 12.9% (1670/12,940), and 12.8% (1659/12,935), respectively. Intriguingly, increases in TC were generally larger among younger participants. As for pre-pregnancy body mass index (BMI), increased TC was associated with underweight (BMI < 18.5), while obesity (BMI ≥ 25) was associated with decreased TC. In addition, greatly increased TC was common among primiparas. History of depression, history of anxiety disorder, and presence of congenital anomalies in the child were also associated with decreased TC.

Table 2 shows ORs and 95% CIs using multivariable logistic regression for PDS according to quintile of point serum TC level and delta change value. The point serum TC levels were not associated at any time point with PDS risk except for during mid-late pregnancy in the second quintile, which showed an increased risk at 6 months. As for change in TC levels, mid-late pregnancy to delivery and early pregnancy to delivery showed significant risk reduction for PDS at 1 month. Early to mid-late pregnancy and early pregnancy to delivery showed significant risk reduction at 6 months. Several previous studies²³⁻²⁵ have found that TC is higher in women with hypertensive disorders of pregnancy, but excluding these patients from our dataset did not notably change the results in Table 2.

Table S1 shows ORs and 95% CIs for PDS according to quintile of the other point serum lipid levels (LDL-C,

HDL-C, and TG) and delta change (TG). Associations were seen only in the fifth quintile of LDL-C (increased risk) for PDS at 1 month and in the fourth quintile of TG during mid-late pregnancy (decreased risk) at 6 months. No association was found in the delta change (TG) and PDS risk.

Table S2 shows the results for the association between TC change and PDS risk among only those participants with a history of depression and/or anxiety. Some significant reduced risk of PDS at both 1 month and 6 months was found in the quintiles of TC change between early and mid-late pregnancy. A significant reduced risk of PDS at 1 month was found in the highest quintile of TC change between early and delivery, as revealed by the trend test, but no reduced risk was found at 6 months.

4 | DISCUSSION

In this nationwide prospective cohort study, we found risk reductions for participants whose TC level increased during pregnancy compared with the reference group (whose median TC increase was -1 mg/dl). The point serum TC level did not predict PDS at any time point except during mid-late pregnancy. Some studies have examined the association between decrease in TC during the peripartum period and PPD,^{9,10,12} but to our knowledge, ours is the first study to examine the association between increased TC level during pregnancy and PDS risk.

Interestingly, the finding that point serum TC level did not predict PDS risk at any time except during mid-late pregnancy indicates that TC change is the important factor rather than the point level for predicting PDS risk. Also, the significant ORs for TC change from early pregnancy to delivery were all at or near 0.90. This finding shows that a larger TC change does not necessarily result in a further reduced OR and that the PDS risk was high in the reference group only (whose median TC increase was -1 mg/dl).

Changes in lipids during pregnancy are considered to occur because of changes in sex steroid hormones, hepatic metabolism, and lipid metabolism.²⁶ The increase in LDL-C is due primarily to progesterone, and this increased LDL-C is the chief substrate in subsequent placental progesterone synthesis.²⁶ In addition, increased estrogen concentrations in pregnant women trigger increases in TC, LDL-C, and TG.²⁶ The purpose of these changes in lipid metabolism during pregnancy is to accumulate maternal fat stores during early and mid-pregnancy and to mobilize fat during late pregnancy.²⁷ In future study, plasma estradiol levels should be incorporated into the analysis.

The mechanism underlying the association between cholesterol and depression remains unclear, but effects

TABLE 1 Characteristics of all participants analyzed as a whole and according to quintile of total cholesterol change (from early pregnancy to delivery) Quintile

	Whole	Quintile of total cholesterol change					
		Q1	Q2	Q3	Q4	Q5	
	<i>n</i>	64,342	12,916	13,034	12,517	12,940	12,935
Total cholesterol change	Median, mg/dl	49	-1	29	49	69	101
	Range, mg/dl	-178-322	-178-16	17-39	40-58	59-82	83-322
Age at delivery, y	M ± SD	31.0 ± 4.9	31.6 ± 5.1	31.1 ± 4.9	30.9 ± 4.8	30.7 ± 4.8	30.6 ± 4.7
Pre-pregnancy body mass index	<18.5	10,130 (15.7)	1745 (13.5)	1888 (14.5)	1927 (15.4)	2196 (17.0)	2374 (18.4)
	18.5- <25	47,462 (73.8)	9251 (71.6)	9430 (72.4)	9268 (74.0)	9684 (74.8)	9829 (76.0)
	≥25	6750 (10.5)	1920 (14.9)	1716 (13.2)	1322 (10.6)	1060 (8.2)	732 (5.7)
Previous deliveries	Primipara	26,713 (41.5)	6050 (46.8)	5753 (44.1)	5142 (41.1)	5192 (40.1)	4576 (35.4)
	Multipara	37,629 (58.5)	6866 (53.2)	7281 (55.9)	7375 (58.9)	7748 (59.9)	8359 (64.6)
Annual household income, million yen	<4	25,238 (39.2)	5033 (39.0)	5131 (39.4)	5066 (40.5)	5010 (38.7)	4998 (38.6)
	4- <6	21,588 (33.6)	4316 (33.4)	4399 (33.8)	4163 (33.3)	4335 (33.5)	4375 (33.8)
	≥6	17,516 (27.2)	3567 (27.6)	3504 (26.9)	3288 (26.3)	3595 (27.8)	3562 (27.5)
Maternal education	≤12 years	22,334 (34.7)	4519 (35.0)	4637 (35.6)	4416 (35.3)	4441 (34.3)	4321 (33.4)
	>12- <16 years	27,699 (43.0)	5587 (43.3)	5559 (42.7)	5382 (43.0)	5531 (42.7)	5640 (43.6)
	≥16 years	14,309 (22.2)	2810 (21.8)	2838 (21.8)	2719 (21.7)	2968 (22.9)	2974 (23.0)
Marital status	Married	61,907 (96.2)	12,418 (96.1)	12,515 (96.0)	12,073 (96.5)	12,435 (96.1)	12,466 (96.4)
	Single	1942 (3.0)	392 (3.0)	413 (3.2)	346 (2.8)	408 (3.2)	383 (3.0)
	Divorced or widowed	493 (0.8)	106 (0.8)	106 (0.8)	98 (0.8)	97 (0.8)	86 (0.7)
Smoking status	Never	37,605 (58.4)	7553 (58.5)	7546 (57.9)	7307 (58.4)	7573 (58.5)	7626 (59.0)
	Former	24,038 (37.4)	4870 (37.7)	4960 (38.1)	4662 (37.3)	4774 (36.9)	4772 (36.9)
	Current	2699 (4.2)	493 (3.8)	528 (4.1)	548 (4.4)	593 (4.6)	537 (4.2)
Alcohol intake	Never	21,490 (33.4)	4425 (34.3)	4374 (33.6)	4246 (33.9)	4218 (32.6)	4227 (32.7)
	Former	41,116 (63.9)	8184 (63.4)	8304 (63.7)	7945 (63.5)	8350 (64.5)	8333 (64.4)
	Current	1736 (2.7)	307 (2.4)	356 (2.7)	326 (2.6)	372 (2.9)	375 (2.9)
Physical activity during mid-late pregnancy, METs h/day	M ± SD	4.0 ± 8.3	3.6 ± 7.5	3.9 ± 8.0	4.0 ± 8.4	4.1 ± 8.2	4.3 ± 9.3
Employment status during mid-late pregnancy	No	28,590 (44.4)	6367 (49.3)	5881 (45.1)	5448 (43.5)	5474 (42.3)	5420 (41.9)
	Yes	35,752 (55.6)	6549 (50.7)	7153 (54.9)	7069 (56.5)	7466 (57.7)	7515 (58.1)
History of depression	No	62,469 (97.1)	12,515 (96.9)	12,631 (96.9)	12,142 (97.0)	12,590 (97.3)	12,591 (97.3)
	Yes	1873 (2.9)	401 (3.1)	403 (3.1)	375 (3.0)	350 (2.7)	344 (2.7)
History of anxiety disorder	No	62,552 (97.2)	12,506 (96.8)	12,670 (97.2)	12,150 (97.1)	12,612 (97.5)	12,614 (97.5)
	Yes	1790 (2.8)	410 (3.2)	364 (2.8)	367 (2.9)	328 (2.5)	321 (2.5)
Presence of congenital anomaly of child	No	62,910 (97.8)	12,556 (97.2)	12,740 (97.7)	12,269 (98.0)	12,652 (97.8)	12,693 (98.1)
	Yes	1432 (2.2)	360 (2.8)	294 (2.3)	248 (2.0)	288 (2.2)	242 (1.9)

Note: Values in the parentheses indicate percentages.

on the serotonin system and an altered inflammatory profile might be key.⁷ Sun et al.²⁸ found in animal studies that decreased cholesterol level in the medial prefrontal cortex, which was caused by exposure to chronic mild stress, was associated with depressive-like behavior. This

behavior was reversed by cholesterol supplementation via food; however, pre-injection of 5-HT_{1A} receptor antagonist blocked the treatment effects, indicating that cholesterol may confer benefits through modulation of the brain 5-HT_{1A} receptor.²⁸ In applying the results of their

TABLE 2 Odds ratios and 95% confidence intervals for postpartum depressive symptoms according to quintile of point serum cholesterol level and delta change value

	<i>n</i>	Model	Quintile of each exposure					<i>p</i> for trend
			Q1	Q2	Q3	Q4	Q5	
Postpartum depressive symptoms 1 month after delivery								
Point serum cholesterol level								
During early pregnancy	66,798	COR	1.00 (Ref.)	0.95 (0.89–1.02)	1.02 (0.95–1.09)	0.95 (0.88–1.02)	1.03 (0.97–1.11)	0.42
		AOR	1.00 (Ref.)	0.96 (0.89–1.03)	1.03 (0.96–1.11)	0.97 (0.90–1.04)	1.07 (1.00–1.15)	0.07
During mid-late pregnancy	72,406	COR	1.00 (Ref.)	1.03 (0.97–1.10)	0.95 (0.89–1.02)	0.96 (0.90–1.02)	0.98 (0.92–1.05)	0.16
		AOR	1.00 (Ref.)	1.05 (0.98–1.12)	0.99 (0.92–1.06)	1.00 (0.94–1.07)	1.03 (0.96–1.10)	0.90
After delivery	71,516	COR	1.00 (Ref.)	0.93 (0.87–0.99)	0.91 (0.86–0.98)	0.88 (0.82–0.94)	0.83 (0.78–0.89)	< 0.001
		AOR	1.00 (Ref.)	0.95 (0.89–1.02)	0.96 (0.90–1.03)	0.95 (0.88–1.01)	0.94 (0.87–1.00)	0.06
Delta changes of serum cholesterol								
Early to mid-late pregnancy	66,068	COR	1.00 (Ref.)	0.98 (0.92–1.05)	0.96 (0.90–1.03)	0.94 (0.88–1.01)	0.95 (0.89–1.02)	0.09
		AOR	1.00 (Ref.)	0.98 (0.92–1.06)	0.97 (0.91–1.05)	0.95 (0.88–1.02)	0.98 (0.91–1.05)	0.31
Mid-late pregnancy to delivery	70,016	COR	1.00 (Ref.)	0.93 (0.87–0.99)	0.87 (0.82–0.93)	0.85 (0.79–0.91)	0.86 (0.80–0.92)	< 0.001
		AOR	1.00 (Ref.)	0.95 (0.88–1.01)	0.90 (0.84–0.96)	0.90 (0.84–0.97)	0.93 (0.87–1.00)	0.013
Early pregnancy to delivery	64,342	COR	1.00 (Ref.)	0.88 (0.82–0.94)	0.86 (0.80–0.92)	0.81 (0.76–0.87)	0.81 (0.75–0.87)	< 0.001
		AOR	1.00 (Ref.)	0.89 (0.83–0.96)	0.88 (0.82–0.95)	0.86 (0.80–0.92)	0.88 (0.82–0.95)	< 0.001
Postpartum depressive symptoms 6 months after delivery								
Point serum cholesterol level								
During early pregnancy	64,027	COR	1.00 (Ref.)	1.01 (0.94–1.10)	1.05 (0.98–1.14)	0.99 (0.92–1.07)	1.07 (0.99–1.16)	0.19
		AOR	1.00 (Ref.)	1.02 (0.94–1.11)	1.06 (0.98–1.15)	1.00 (0.92–1.09)	1.08 (1.00–1.17)	0.15
During mid-late pregnancy	69,297	COR	1.00 (Ref.)	1.06 (0.99–1.14)	0.97 (0.90–1.05)	0.92 (0.85–0.99)	0.96 (0.89–1.03)	0.006
		AOR	1.00 (Ref.)	1.09 (1.01–1.17)	1.01 (0.93–1.08)	0.95 (0.88–1.03)	1.00 (0.92–1.08)	0.13
After delivery	68,379	COR	1.00 (Ref.)	1.02 (0.95–1.10)	1.02 (0.95–1.10)	0.96 (0.89–1.03)	0.93 (0.86–1.01)	0.016
		AOR	1.00 (Ref.)	1.03 (0.95–1.11)	1.02 (0.94–1.10)	0.96 (0.89–1.04)	0.96 (0.89–1.04)	0.11
Delta changes of serum cholesterol								
Early to mid-late pregnancy	63,302	COR	1.00 (Ref.)	0.97 (0.89–1.04)	0.91 (0.84–0.98)	0.85 (0.79–0.92)	0.84 (0.78–0.91)	< 0.001
		AOR	1.00 (Ref.)	0.99 (0.91–1.07)	0.93 (0.86–1.01)	0.88 (0.81–0.95)	0.89 (0.82–0.96)	< 0.001
Mid-late pregnancy to delivery	66,927	COR	1.00 (Ref.)	1.05 (0.98–1.13)	0.99 (0.91–1.06)	0.96 (0.89–1.04)	1.04 (0.96–1.12)	0.78
		AOR	1.00 (Ref.)	1.03 (0.95–1.11)	0.95 (0.88–1.03)	0.93 (0.86–1.01)	1.00 (0.93–1.09)	0.33
Early pregnancy to delivery	61,585	COR	1.00 (Ref.)	0.92 (0.85–0.99)	0.91 (0.84–0.98)	0.84 (0.78–0.91)	0.90 (0.83–0.97)	< 0.001
		AOR	1.00 (Ref.)	0.91 (0.84–0.98)	0.89 (0.82–0.97)	0.84 (0.78–0.92)	0.91 (0.84–0.98)	0.003

Note: Adjusted for age at delivery, pre-pregnancy body mass index, previous deliveries, annual household income, highest maternal educational level, marital status during early pregnancy, smoking status during mid-late pregnancy, alcohol intake during mid-late pregnancy, physical activity during mid-late pregnancy, employment status during mid-late pregnancy, history of depression, history of anxiety disorder, and presence of congenital anomaly in the child. Values in bold are significant.

Abbreviations: AOR, adjusted odds ratio; COR, crude odds ratio.

experiment to the present observational study, pregnancy itself causes women varying degrees of stress, triggering a decrease in TC levels in the prefrontal cortex, which is supplemented by the physiological response of an increase in TC levels during pregnancy. This mechanism may explain why PDS manifested in the group of participants with no TC supplementation whatsoever (ie, the group with no TC increase). In addition, if a stress-induced decrease in cholesterol in the frontal cortex also occurs in humans, it would be important to store cholesterol during pregnancy (ie, a higher-than-usual TC level), and this may be why the present results showed an association in terms of change but not in absolute values. However, we also have to keep in mind that because this study was not able to clarify the cause-and-effect relationship because of its observational nature, we cannot rule out the possibility of some other residual factor that may be associated with changes in both variables. In the future, determining the association of stress and serotonin with PDS may be a fascinating avenue of research.

HDL is known to have anti-inflammatory properties,²⁹ whereas oxidized LDL is known to have inflammatory properties.³⁰ Furthermore, depression is known to be associated with neuroinflammation.³¹ In the present study, LDL-C during early pregnancy was linearly (positively) associated with PDS risk at 1 and 6 months after delivery. Also, the highest quintile of LDL-C (95 mg/dl) compared with the lowest quintile (60 mg/dl) showed significantly increased PDS risk at 1 month. This result is not in line with the previous studies related to pregnancy, which found no such association.^{13,15} We did not find any association between HDL-C and PDS risk at either 1 or 6 months. Among the 3 previous studies, the longitudinal study¹³ showed a negative association between HDL-C and PPD, but the 2 cross-sectional studies showed no association.^{12,15} These mixed and inconclusive findings may be attributable to differences in study design, sample size, timing of assessment, participant background factors, and/or the tools used to assess depression, suggesting that further research is warranted. Although HDL-C and LDL-C are components of T-Chol, they have different mechanisms of action on depression, and not all fractions seem to show similar results, as mentioned above. Because LDL-C and HDL-C were closely linked to TC metabolism, future study should also clarify the association with change in both LDL-C and HDL-C.

TG and PPD were examined in 2 previous studies, but neither observed an association between TG and PPD.^{9,15} In the present study, the fourth quartile during mid-late pregnancy was associated with reduced risk of depression at 6 months after delivery. However, in a previous meta-analysis, TG was significantly higher in patients with first-episode major depressive disorder than in

healthy controls.³² Thus, it cannot be ruled out that the results in the present study were coincidental. In addition, the present study used casual blood samples, meaning that the results might have been affected by diet.

Blood samples are typically not taken at delivery unless there are maternal complications or sudden changes, and therefore one of the clinical implications of the present study is that measurement of TC during both early and mid-late pregnancy may enable prediction of PDS at 6 months after delivery. In most pregnant women, TC is usually measured during both periods. Also, as shown in Table S2, for patients with a history of anxiety disorder or depression, PDS at 1 and 6 months after delivery can perhaps be predicted by measuring TC changes.

The strengths of this study are that it is the largest study to date to have investigated the association between serum TC (and other lipid) levels and PDS. Because the study was conducted in 15 regions nationwide, the participants can be considered representative of pregnant women in Japan. However, we acknowledge some limitations. First, unmeasured residual factors such as health consciousness might have confounded the results. Second, we cannot rule out the possibility that excluding more than 30,000 women based on the eligibility criteria, while necessary, may have introduced some selection bias. Third, the findings may not necessarily apply to all nationalities and ethnicities. Fourth, because the participants' blood samples were taken after delivery while still hospitalized (for 6 days in average in Japan) and cholesterol levels are known to return rapidly to the level of the first trimester by 72 h after delivery,²⁶ we might have missed the peak TC. Also, the association between change in cholesterol and PDS risk might be biased toward the null due to the variation in the date of blood sampling after delivery. Finally, the EPDS screening test was used instead of diagnostic tests. In general, the EPDS indicates suspicion of disease that warrants confirmation, whereas diagnostic tests provide a definite diagnosis. Future studies should incorporate the diagnosis of depression such as in the DSM.

In conclusion, the present findings suggest that the group of participants with the smallest increase in TC during pregnancy (ie, the group with almost no change in TC during pregnancy) were at high risk of PDS. Tracking changes in serum TC during pregnancy may help to identify high-risk groups.

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CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Data are unsuitable for public deposition due to ethical restrictions and Japan's legal framework. The Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amended on 9 September 2015) prohibits public deposition of data containing personal information. The Ethical Guidelines for Epidemiological Research enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restricts the open sharing of the epidemiological data. All inquiries about access to data should be sent to jecs-en@nies.go.jp. The person responsible for handling enquiries sent to this e-mail address is Dr Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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REFERENCES

- Association AP. Diagnostic and Statistical Manual of Mental Disorders Fifth Edition DSM-V, 5th ed. American Psychiatric Association; 2013.
- Gavin NI, Gaynes BN, Lohr KN, Meltzer-Brody S, Gartlehner G, Swinson T. Perinatal depression: a systematic review of prevalence and incidence. *Obstet Gynecol.* 2005;106:1071-1083.
- Hamazaki K, Matsumura K, Tsuchida A, et al. Dietary intake of fish and n-3 polyunsaturated fatty acids and risk of postpartum depression: a nationwide longitudinal study - the Japan Environment and Children's Study (JECS). *Psychol Med.* 2020;50:2416-2424.
- Hamazaki K, Takamori A, Tsuchida A, et al. Dietary intake of fish and n-3 polyunsaturated fatty acids and risks of perinatal depression: the Japan Environment and Children's Study (JECS). *J Psychiatr Res.* 2018;98:9-16.
- Beck CT. Predictors of postpartum depression: an update. *Nurs Res.* 2001;50(5):275-285.
- Serati M, Redaelli M, Buoli M, Altamura AC. Perinatal major depression biomarkers: a systematic review. *J Affect Disord.* 2016;15(193):391-404.
- Parekh A, Smeeth D, Milner Y, Thure S. The role of lipid biomarkers in major depression. *Healthcare (Basel).* 2017;3:5.
- Shin JY, Suls J, Martin R. Are cholesterol and depression inversely related? A meta-analysis of the association between two cardiac risk factors. *Ann Behav Med.* 2008;36:33-43.
- Ploekinger B, Dantendorfer K, Ulm M, et al. Rapid decrease of serum cholesterol concentration and postpartum depression. *BMJ.* 1996;14(313):664.
- van Dam RM, Schuit AJ, Schouten EG, Vader HL, Pop VJ. Serum cholesterol decline and depression in the postpartum period. *J Psychosom Res.* 1999;46:385-390.
- Nasta MT, Grussu P, Quatraro RM, Cerutti R, Grella PV. Cholesterol and mood states at 3 days after delivery. *J Psychosom Res.* 2002;52:61-63.
- Troisi A, Moles A, Panepuccia L, Lo Russo D, Palla G, Scucchi S. Serum cholesterol levels and mood symptoms in the postpartum period. *Psychiatry Res.* 2002;15(109):213-219.
- Teofilo MM, Farias DR, Pinto Tde J, et al. HDL-cholesterol concentrations are inversely associated with Edinburgh Postnatal Depression Scale scores during pregnancy: results from a Brazilian cohort study. *J Psychiatr Res.* 2014;58:181-188.
- Grussu P, Nasta MT, Quatraro RM. Serum cholesterol concentration and distress in the initial days after childbirth. *Psychiatry Res.* 2007;30(151):159-162.
- Ramachandran Pillai R, Wilson AB, Premkumar NR, Kattimani S, Sagili H, Rajendiran S. Low serum levels of High-Density Lipoprotein cholesterol (HDL-c) as an indicator for the development of severe postpartum depressive symptoms. *PLoS One.* 2018;13:e0192811.
- Troisi A, Croce NR. Normal cholesterol levels in the immediate postpartum period: a risk factor for depressive and anxiety symptoms? *Psychiatry Res.* 2018;269:394-398.
- Piechota W, Staszewski A. Reference ranges of lipids and apolipoproteins in pregnancy. *Eur J Obstet Gynecol Reprod Biol.* 1992;16(45):27-35.
- Kawamoto T, Nitta H, Murata K, et al. Rationale and study design of the Japan environment and children's study (JECS). *BMC Public Health.* 2014;14:25.
- Michikawa T, Nitta H, Nakayama SF, et al. Baseline profile of participants in the Japan Environment and Children's Study (JECS). *J Epidemiol.* 2018;5(28):99-104.
- Cox JL, Holden JM, Sagovsky R. Detection of postnatal depression. Development of the 10-item Edinburgh Postnatal Depression Scale. *Br J Psychiatry.* 1987;150:782-786.
- Okano T, Murata M, Masuji F, et al. Validation and reliability of Japanese version of EPDS (Edinburgh Postnatal Depression Scale). *Arch Psychiatr Diagn Clin Eval.* 1996;7:525-533.
- Yamashita H, Yoshida K, Nakano H, Tashiro N. Postnatal depression in Japanese women. Detecting the early onset of postnatal depression by closely monitoring the postpartum mood. *J Affect Disord.* 2000;58:145-154.
- Zhang Y, Lan X, Cai C, et al. Associations between maternal lipid profiles and pregnancy complications: a prospective population-based study. *Am J Perinatol.* 2021;38(8):834-840.
- Shen H, Liu X, Chen Y, He B, Cheng W. Associations of lipid levels during gestation with hypertensive disorders of pregnancy and gestational diabetes mellitus: a prospective longitudinal cohort study. *BMJ Open.* 2016;23(6):e013509.
- Wang Y, Shi D, Chen L. Lipid profile and cytokines in hypertension of pregnancy: a comparison of preeclampsia therapies. *J Clin Hypertens (Greenwich).* 2018;20:394-399.
- Bartels A, O'Donoghue K. Cholesterol in pregnancy: a review of knowns and unknowns. *Obstet Med.* 2011;4:147-151.
- Butte NF. Carbohydrate and lipid metabolism in pregnancy: normal compared with gestational diabetes mellitus. *Am J Clin Nutr.* 2000;71:1256S-1261S.
- Sun S, Yang S, Mao Y, Jia X, Zhang Z. Reduced cholesterol is associated with the depressive-like behavior in rats through modulation of the brain 5-HT1A receptor. *Lipids Health Dis.* 2015;24(14):22.

29. Barter P. The role of HDL-cholesterol in preventing atherosclerotic disease. *Eur Heart J Suppl.* 2005;7:F4-F8.
30. Rhoads JP, Major AS. How oxidized low-density lipoprotein activates inflammatory responses. *Crit Rev Immunol.* 2018;38:333-342.
31. Furtado M, Katzman MA. Examining the role of neuroinflammation in major depression. *Psychiatry Res.* 2015;229(1-2):27-36.
32. Wei YG, Cai DB, Liu J, et al. Cholesterol and triglyceride levels in first-episode patients with major depressive disorder: a meta-analysis of case-control studies. *J Affect Disord.* 2020;24(266):465-472.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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APPENDIX 1

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