

Research paper

Association between low MCV in early pregnancy and perinatal mental health in the Japan Environment and Children's Study and the possible effect of iron deficiency

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ABSTRACT

Background: Postpartum anemia and iron deficiency are associated with postpartum depression. This study investigated the association between a low mean corpuscular volume (MCV) without anemia (which implies early-stage iron deficiency) in early pregnancy and perinatal mental health outcomes.

Methods: The fixed data from the Japan Environment and Children's Study (JECS), a Japanese nationwide birth cohort, were used. Perinatal mental health was assessed using the Kessler 6-item psychological distress scale (K6) in mid-pregnancy and the Edinburgh Postnatal Depression Scale (EPDS) at 1- and 6-months postpartum.

Results: Among the 3635 women with MCVs <85 fL in early pregnancy, the proportions of women with K6 scores ≥13 in mid-pregnancy and EPDS scores ≥9 at 1- and 6-months postpartum were 2.7 %, 12.8 %, and 9.9 %, respectively, compared with the 33,242 women with MCVs ≥85 fL at 1.9 %, 11.9 %, and 9.0 %, respectively. Multivariate logistic regression models showed that an MCV <85 in early pregnancy was associated with a K6 score ≥ 13 in mid-pregnancy and an EPDS score ≥ 9 at 1- and 6-months postpartum (adjusted odds ratio (95 % confidence interval): 1.48 (1.16–1.87), 1.14 (1.01–1.28), and 1.09 (0.95–1.24), respectively).

Limitations: Low MCV values do not necessarily represent iron deficiency. Ferritin, currently the best indicator of iron deficiency, was not measured in the JECS.

Conclusions: This study results suggest that a low MCV without anemia in early pregnancy is associated with a slightly increased risk of perinatal mental health deterioration.

1. Introduction

Anemia, one of the most common diseases that affects women and men, is clinically diagnosed via low hemoglobin (Hb) levels. Among its various causes, iron-deficiency anemia (IDA) is highly prevalent. Women of reproductive age have high iron requirements because of menstruation, pregnancy, and childbirth. If the daily dietary intake and

absorption of iron do not match the demand for it, the negative balance of iron increases and iron deficiency progresses. In the early stage of iron deficiency, iron stores are first depleted. While the Hb level remains normal, the patient is in a latent state of iron deficiency (non-anemic iron deficiency, NAID) (Clénin, 2017). As iron deficiency progresses further, IDA occurs. IDA, a microcytic and hypochromic type of anemia, is preceded by a decrease in the erythrocyte indices such as mean

Abbreviations: BMI, body mass index; CI, confidence interval; EPDS, Edinburgh Postpartum Depression Scale; Hb, hemoglobin; IDA, iron-deficiency anemia; JECS, Japan Environment and Children's Study; K6, Kessler 6-item psychological; MCV, mean corpuscular volume; MD, mean difference; NAID, non-anemic iron deficiency; OR, odds ratio; SD, standard deviation.

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corpuscular volume (MCV) before a decrease in Hb levels (Clénin, 2017). Therefore, a decrease in the MCV without anemia may indicate the early stages of iron deficiency.

Perinatal mental health of mothers is an important global public health issue (Howard and Khalifeh, 2020). According to statistics obtained from 36 states in the United States between 2017 and 2019 published by the Centers for Disease Control and Prevention, mental health illnesses comprise the highest proportion (22.7 %) of causes of maternal deaths (Trost et al., 2022). Depression is the most important perinatal mental health condition, in terms of both severity and frequency. A systematic review and meta-analysis conducted in 2017 revealed that the overall pooled prevalence of perinatal depression was 11.9 % (95 % confidence interval (CI): 11.4–12.5) (Woody et al., 2017). In recent years, there have been reports that postpartum anemia and iron deficiency contribute to an increased risk of postpartum depression, as shown in a systematic review and meta-analysis of observational studies and RCTs (Moya et al., 2022). However, studies regarding the association between iron deficiency before childbirth and perinatal mental health are scarce. We previously conducted a pilot study involving pregnant patients in our hospital focusing on perinatal mental health and maternal iron status with and without anemia before childbirth. We investigated pregnant women without anemia (Hb ≥ 11 g/dL) during early pregnancy and found that the group of patients with iron deficiency (ferritin < 30 μ g/L) exhibited a significant increase in postpartum depression scores from mid-pregnancy to 1-month postpartum, while the non-iron deficiency group (ferritin ≥ 30 μ g/L) exhibited no increase (Ohsuga et al., 2022). Accordingly, we hypothesized that maternal mental health resilience may be affected by iron deficiency, even if it does not reach apparent anemic level, during the perinatal period. In other words, maternal mental health is likely to deteriorate during pregnancy and postpartum if there are insufficient iron stores in early pregnancy.

This study aimed to test our hypothesis by examining the association between low MCV values in early pregnancy and perinatal mental health using a large birth cohort dataset.

2. Methods

2.1. Participants

This study was conducted as part of the Japan Environment and Children's Study (JECS). The JECS is a nationwide prospective birth cohort study in Japan designed to investigate the association between environmental factors and child health and development. The design of the JECS has been described in detail (Kawamoto et al., 2014). Pregnant women were recruited at 15 Regional Centers in Japan from January 2011 to March 2014. The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies and by the Ethics Committees of all participating institutions. All participants gave their written informed consent. Datasets known as the “jecs-ta-20190930” and “jecs-qa-20210401” were used in this study, including data from the first trimester, second/third trimester, 1-month follow-up, and six-month follow-up. In the JECS, blood samples were collected from pregnant women during the MT1 (12–16 weeks' gestation) and MT2 (22–28 weeks' gestation) periods, respectively (Taniguchi et al., 2022). In addition, self-administered questionnaires were completed by the pregnant women during MT1 (early pregnancy) and MT2 (mid-late pregnancy). These questionnaires included questions on demographic factors, socioeconomic status, lifestyle characteristics, medical and obstetric history, and physical and mental health. The study protocol was approved by the Ethics Committee of Kyoto University (R3645).

2.2. Eligibility criteria

All pregnant women who participated in the JECS were included.

The full dataset comprised 104,059 fetal records, and the exclusion criteria were as follows: second and subsequent registrations, miscarriage, multiple pregnancy, hematologic malignancy, or missing blood sample data in early pregnancy. Participants with anemia or with high-level psychological stress were also excluded because, in this study, we investigated the relationship between the MCV and perinatal mental health in individuals who were not anemic and mentally healthy in early pregnancy.

2.3. Measurement

2.3.1. Hemoglobin and erythrocyte indices

The Hb level, MCV, mean corpuscular hemoglobin, and mean corpuscular hemoglobin concentration were measured only at MT1. Anemia in early pregnancy was defined as Hb < 11.0 g/dL (World Health Organization, 2016). In this study, the exposure factor was defined as the MCV with a cutoff value of 85 fL as a dichotomous variable (The Japanese Bioiron Society Treatment Guidelines Development Committee, 2015).

2.3.2. Psychological distress during pregnancy

Psychological distress during pregnancy was assessed using the Kessler 6-item psychological distress scale (K6) (Kessler et al., 2003). MT1 and MT2 questionnaires included the K6, respectively. The K6 is widely used as a screening measure of psychological distress in general populations. A Japanese version of the K6 was previously developed and has been shown to be valid and reliable (Furukawa et al., 2008). Response options and scores are as follows: none of the time (0 points), a little of the time (1 point), some of the time (2 points), most of the time (3 points), and all of the time (4 points). The total score ranges from 0 to 24 points. In the original versions, a K6 score of ≥ 13 is considered indicative of psychological distress (Kessler et al., 2003). The Japanese version demonstrated screening performances that are essentially equivalent to those of the original version (Furukawa et al., 2008). In this study, the cutoff value was set at a K6 score of 12/13 when psychological stress in pregnancy was treated as a binary variable. In this study, the MT1-K6 score was used as the baseline, and the MT2-K6 score as the outcome.

2.3.3. Postpartum depressive symptoms

PPD was measured using the Japanese version of the Edinburgh Postnatal Depression Scale (EPDS) at 1- and 6-months postpartum (Okano et al., 1996). The EPDS is a self-administered questionnaire that is widely used to screen for PPD. The EPDS consists of 10 items rated on a 4-point scale (0–3), with a total score ranging from 0 to 30 (Cox et al., 1987). Herein, the cutoff value was set at an EPDS score of 8/9, where PPD was treated as a binary variable. This cutoff value has been shown to have validity and reliability in studies with Japanese participants (Okano et al., 1996).

2.4. Statistical analysis

The participants were divided into two groups according to the MCV level, and their characteristics were described. Continuous variables are presented as mean values and standard deviations (SDs), and categorical variables are presented as frequencies and percentages. K6 scores in mid-pregnancy and EPDS scores at 1- and 6-months postpartum for the two groups were also described. For the EPDS, the mean values and SDs and the frequencies and percentages of each category when divided by ≥ 9 and ≤ 8 points were described. For the K6, the mean and SD and the frequency and percentage of each category when divided by 0–4, 5–8, 9–12, and 13–24 points were described.

Logistic regression analyses were performed on K6 scores of ≥ 13 at mid-pregnancy and EPDS scores of ≥ 9 at 1- and 6-months postpartum in relation to the MCV (a binary variable). Next, linear regression analyses were conducted on the association between changes in K6 scores and

early-to-mid-pregnancy and the MCV (a binary variable). The following variables were used as adjustment factors: age (continuous variables), prepregnancy body mass index (<18.5, 18.5 to 25, or ≥ 25), parity (nulliparous or multiparous), maternal educational level (junior high school/high school or other), family income (<4 million yen, 4–6 million yen, ≥ 6 million yen), marital status (married or otherwise), and the K6 score in early pregnancy (continuous variable). We did not adjust for whether iron prescriptions were provided during pregnancy because this was considered an intermediate variable. These analyzes were carried out using R-4.2.2.

For sensitivity analyses, multiple imputations to account for missing values, including age, prepregnancy body mass index, parity, marital status, family income, maternal educational level, K6 score in early pregnancy, K6 score in mid-pregnancy, EPDS score at 1-month postpartum, and EPDS score at six months postpartum were conducted and adjusted odds ratios (ORs) for associations between the MCV in early pregnancy and perinatal mental health were calculated by logistic regression. These analyzes were carried out using R (the “mice 3.15.0” package).

We additionally conducted restricted cubic splines regression analyzes to explore the non-linearity of the relationship between the MCV and depression. Four prespecified knots were used according to the percentiles of the MCV distribution; i.e., the 5th, 25th, 75th, and 95th percentiles. These analyzes were performed using R (the “rms 1.0–11” package).

3. Results

A flowchart of the participant recruitment process is shown in Fig. 1. Of the 104,059 fetal records, 5689, 1902, 1102, and 37 were excluded due to the second and subsequent registrations, multiple pregnancy, miscarriage, and hematologic malignancy. In addition, cases with missing MT1 blood sample collection, MT1-blood sample collection after 16 weeks of pregnancy, unknown collection dates, anemia (Hb < 11 g/dL) in MT1 blood samples, missing Kessler 6-item psychological distress scale scores at MT1 (MT1-K6), and high psychological stress at baseline (MT1-K6 score ≥ 13), were excluded. A total of 36,877 women without anemia and psychological distress in early pregnancy were included in the analysis.

The group with MCV <85 fL had 3635 women and the group with MCV ≥ 85 fL had 33,242 women. The characteristics of each group are presented in Table 1 for important variables and Supplementary Table 1 for more detailed ones. The low MCV group had a slightly higher percentage of women with a history of excessive menstruation and a significantly higher percentage of iron prescriptions during pregnancy (Table 2). Morning sickness was more severe in the low MCV group. The K6 scores at mid-pregnancy and EPDS scores at 1- and 6-months postpartum for each group are presented in Table 1.

The crude ORs for the K6 score in mid-pregnancy ≥ 13 and the EPDS score of ≥ 9 at 1- and 6-months postpartum are shown in Table 3. The adjusted ORs were 1.48 (1.16–1.87), 1.14 (1.01–1.28), and 1.09 (0.95–1.24), respectively. The mean differences in K6 score changes from early-to-mid-pregnancy are shown in Table 4. The adjusted mean

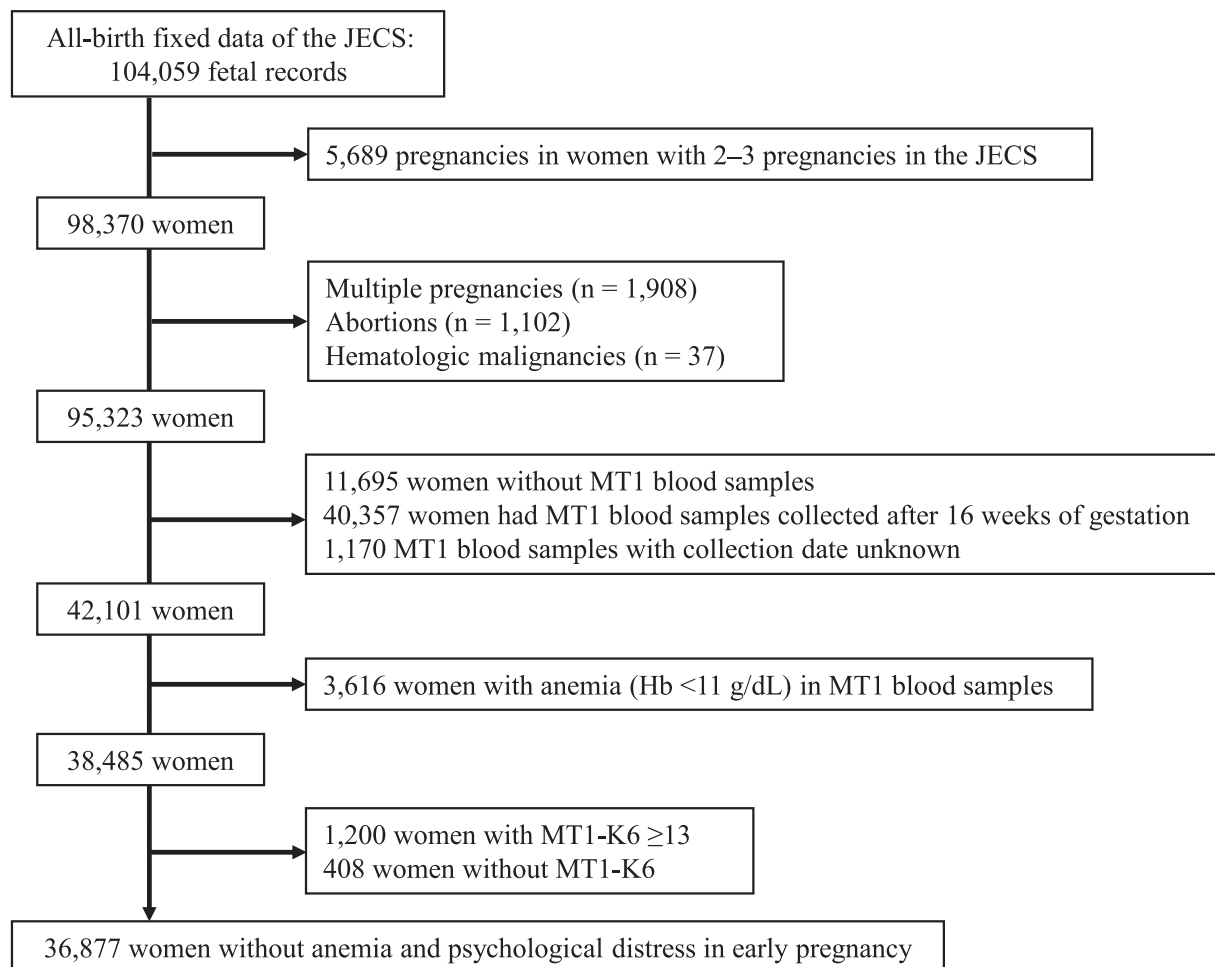


Fig. 1. Flow chart.

Abbreviations: Hb, hemoglobin; JECS, the Japan Environment and Children's Study; K6, Kessler 6-item psychological distress scale.

Table 1

Distribution of participants according to MCV <85 fL or ≥85 fL in early pregnancy.

		MCV < 85 fL (n = 3635)		MCV ≥ 85 fL (n = 33,242)	
Hb in early pregnancy [g/dL]	Mean (SD)	12.2 (0.8)		12.4 (0.8)	
MCV in early pregnancy [fL]	Mean (SD)	82.3 (2.6)		90.6 (3.1)	
Age [years]	Mean (SD)	30.5 (5.0)		30.9 (4.9)	
	Missing	3	0.1 %	4	0.0 %
Prepregnancy BMI [kg/m ²]	Mean (SD)	21.8 (3.7)		21.2 (3.2)	
	<18.5	472	13.0 %	5224	15.7 %
	18.5–<25	2628	72.3 %	24,622	74.1 %
	≥25	532	14.6 %	3382	10.2 %
	Missing	3	0.1 %	14	0.0 %
Parity	Primiparous	1281	35.2 %	13,981	42.1 %
	Multiparous	2269	62.4 %	18,383	55.3 %
	Missing	85	2.3 %	878	2.6 %
Maternal educational level	Junior high school	139	3.8 %	1305	3.9 %
	High school	1083	29.8 %	9502	28.6 %
	Vocational high school	66	1.8 %	548	1.6 %
	Technical	839	23.1 %	7675	23.1 %
	Junior college	686	18.9 %	6174	18.6 %
	University	729	20.1 %	7027	21.1 %
	Graduate	40	1.1 %	569	1.7 %
	Missing	53	1.5 %	442	1.3 %
Income (million yen)	<2	178	4.9 %	1528	4.6 %
	2–<4	1246	34.3 %	10,441	31.4 %
	4–<6	1139	31.3 %	10,437	31.4 %
	6–<8	506	13.9 %	5114	15.4 %
	8–<10	189	5.2 %	2116	6.4 %
	≥10	112	3.1 %	1394	4.2 %
	Missing	265	7.3 %	2212	6.7 %
Marital status	Married	3472	95.5 %	31,737	95.5 %
	Not married	125	3.4 %	1148	3.5 %
	Divorced	21	0.6 %	226	0.7 %
	Widowed	1	0.0 %	5	0.0 %
	Missing	16	0.4 %	126	0.4 %
Iron prescription during pregnancy	Yes	2007	55.2 %	12,440	37.4 %
	Missing	0	0.0 %	0	0.0 %
The K6 score in early pregnancy	Mean (SD)	3.21 (3.10)		3.18 (3.10)	
	0–4	2591	71.3 %	23,607	71.0 %
	5–8	752	20.7 %	7003	21.1 %
	9–12	292	8.0 %	2632	7.9 %
	Missing	0	0.0 %	0	0.0 %

Abbreviations: BMI, body mass index; Hb, hemoglobin; K6, Kessler 6-item psychological; MCV, mean corpuscular volume; SD, standard deviation.

difference was 0.13 (0.03–0.24), with K6 elevated in the low MCV group.

When missing values were complemented by multiple imputations, adjusted ORs of ≥13 for the K6 score in mid-pregnancy and those for the EPDS score of ≥9 at 1- and 6-months postpartum were 1.45 (1.16–1.82), 1.13 (1.01–1.26), and 1.07 (0.94–1.21), respectively (Table 3).

Restricted cubic spline curves are shown in Fig. 2. All adjusted ORs showed U-shaped curves.

Table 2

K6 score in mid-pregnancy and EPDS score at 1 and 6 months postpartum according to MCV <85 fL or ≥85 fL in early pregnancy.

		MCV <85 fL (n = 3635)		MCV ≥85 fL (n = 33,242)		P value
K6 score in mid-pregnancy	Mean (SD)	3.29 (3.50)		3.10 (3.34)		.002
	0–4	2611 (71.8 %)		24,506 (73.7 %)		.001
	5–8	683 (18.8 %)		5833 (17.5 %)		
	9–12	210 (5.8 %)		1925 (5.8 %)		
	13–24	97 (2.7 %)		617 (1.9 %)		
	Missing	34 (0.9 %)		361 (1.1 %)		
EPDS score at 1 month postpartum	Mean (SD)	4.96 (3.44)		4.89 (3.27)		.27
	<8	3048 (83.9 %)		28,258 (85.0 %)		.11
	≥9	464 (12.8 %)		3947 (11.9 %)		
	Missing	123 (3.4 %)		1037 (3.1 %)		
EPDS score at 6 months postpartum	Mean (SD)	4.54 (3.27)		4.39 (3.15)		.008
	<8	3005 (82.7 %)		27,945 (84.1 %)		.058
	≥9	360 (9.9 %)		2988 (9.0 %)		
	Missing	270 (7.4 %)		2309 (6.9 %)		

Abbreviations: EPDS, Edinburgh Postpartum Depression Scale; K6, Kessler 6-item psychological distress scale; MCV, mean corpuscular volume; SD, standard deviation.

4. Discussion

This study shows that a low MCV without anemia in early pregnancy is associated with a slightly increased risk of psychological distress during pregnancy and depressive symptoms at 1-month postpartum. In this study, we used high-quality data from a large birth cohort. With this dataset, we were able to adjust for potential confounders, including socioeconomic factors.

Women with low MCV without anemia in early pregnancy are considered to be a high-risk group for the later development of IDA. This is probably why iron was prescribed more frequently during pregnancy in the low MCV group in this study. Iron requirements increase during pregnancy, especially after the second trimester (Bothwell, 2000). This is due to increased blood volume, rapid fetal growth, and high placental metabolic activity (Georgieff, 2020). If iron stores are already low in early pregnancy, iron deficiency will likely progress through the course of pregnancy and deplete iron stores. Iron deficiency states, with or without anemia, can adversely affect the biosynthesis of neurotransmitters (such as serotonin and noradrenaline) involved in the pathogenesis of depression (Wassef et al., 2019). In recent years, an association between postpartum anemia, iron deficiency, and PPD has been reported. Moya et al. wrote a systematic review and meta-analysis of postpartum anemia/iron deficiency and PPD (Moya et al., 2022). Pooled results of observational studies showed that iron-deficient or anemic women were more likely to experience symptoms of depression than non-anemic or iron-sufficient women (risk ratio = 1.66, 95 % CI: 1.28–2.16). In the pooled results of four RCTs [n = 739 (treatment group = 372, control group = 367)], women who received intravenous iron had significantly lower depression scores than those who received oral iron or placebo (mean difference = 1.48, 95 % CI: –2.53 to –0.42). However, there are no previous studies on the association between iron deficiency in early pregnancy and perinatal mental health, except for our pilot study (Ohsuga et al., 2022). To the best of our knowledge, this study is the first to demonstrate a relationship between low MCV, which is suggestive of iron deficiency in early pregnancy, and mental health during pregnancy and early postpartum. Herein, although we did not adjust for iron prescriptions during pregnancy, which is considered an intermediary factor that weakens the association between exposure and the outcome, a small association remained. The results of this study indicate that iron supplementation administered after anemia becomes apparent may not be sufficient to contribute to improving mental health in pregnant and early postpartum patients.

Table 3
Association between MCV in early pregnancy and perinatal mental health.

	K6 score in mid-pregnancy ≥ 13		EPDS score at 1 month postpartum ≥ 9		EPDS score at 6 months postpartum ≥ 9	
	OR (95 % CI)	P-value	OR (95 % CI)	P-value	OR (95 % CI)	P-value
MCV <85 fL vs. ≥ 85 fL						
Crude OR	1.45 (1.16–1.79)	$<.001$	1.09 (0.98–1.21)	.10	1.12 (1.00–1.26)	.05
Adjusted OR ^a	1.48 (1.16–1.87)	.001	1.14 (1.01–1.28)	.03	1.09 (0.95–1.24)	.20
Sensitivity analysis: multiple imputation						
Adjusted OR ^a	1.45 (1.16–1.82)	.001	1.13 (1.01–1.26)	.03	1.07 (0.94–1.21)	.30

Abbreviations: CI, confidence interval; EPDS, Edinburgh Postpartum Depression Scale; K6, Kessler 6-item psychological distress scale; MCV, mean corpuscular volume; OR, odds ratio.

^a A multivariable logistic regression model adjusting for the K6 score in early pregnancy, age, prepregnancy body mass index, parity, marital status, family income, and maternal educational level.

Table 4
Association between MCV in early pregnancy and the K6 score change from early-to-mid-pregnancy (The T2-K6 score - the T1-K6 score).

MCV <85 fL vs. MCV ≥ 85 fL			
	The K6 score change from early-to-mid-pregnancy		
	MD	95 % CI	P-value
Model 1	0.18	(0.08–0.27)	$<.001$
Model 2	0.13	(0.03–0.24)	.01

Abbreviations: CI, confidence interval; K6, Kessler 6-item psychological distress scale; MCV, mean corpuscular volume; MD, mean difference.

Model 1: A multivariable linear regression model adjusting for the K6 score in early pregnancy.

Model 2: A multivariable linear regression model adjusting for the K6 score in early pregnancy, age, prepregnancy body mass index, parity, marital status, family income, maternal educational level.

This study focuses on NAID in early pregnancy, which is important from a preventive medicine perspective. In Japan, the Hb level is routinely measured during pregnancy; however, iron stores are rarely evaluated in actual clinical practice. Nevertheless, many pregnant women develop IDA during pregnancy or postpartum. Iron supplementation by pharmaceutical agents and nutritional guidance from the earlier stage of NAID not only reduces the progression to IDA but may

also benefit the quality of life (Moya et al., 2022), including mental health, and lead to health economic benefits. Future research should examine the effects of interventions for NAID on various outcomes, including mental health, and identify optimal management modalities for iron deficiency.

This study has several limitations. First, low MCV values do not necessarily fully represent iron deficiency. Although there is no perfect biomarker of iron deficiency, ferritin is currently recognized as the best one. The dataset available for this study did not include ferritin. Thus, in our analysis, we aimed to use the MCV value as an indicator of iron status, which has the advantage of requiring no additional costs worldwide as well as in the current study. Second, the MCV values are modified by several factors other than iron deficiency, including deficiencies in folate, vitamin B12, and vitamin B6; inflammation; and thalassemia. Therefore, we excluded from the analysis of women with apparent anemia (Hb <11 g/mL) in early pregnancy, which may possibly include various idiopathic conditions. The impact of these factors on the MCV in the absence of anemia is unknown and might contribute to the U-shape of the association with mental health as shown in Fig. 2. Third, the EPDS and the K6 are indicative scales of depressive and psychological status, respectively, but not diagnostic hard outcomes. However, many studies on postpartum depression use the EPDS as an outcome measure. Only a few previous studies have used the K6 scale to assess psychological distress as prenatal depression; however, no specialized scale currently exists to evaluate the mental state of pregnant

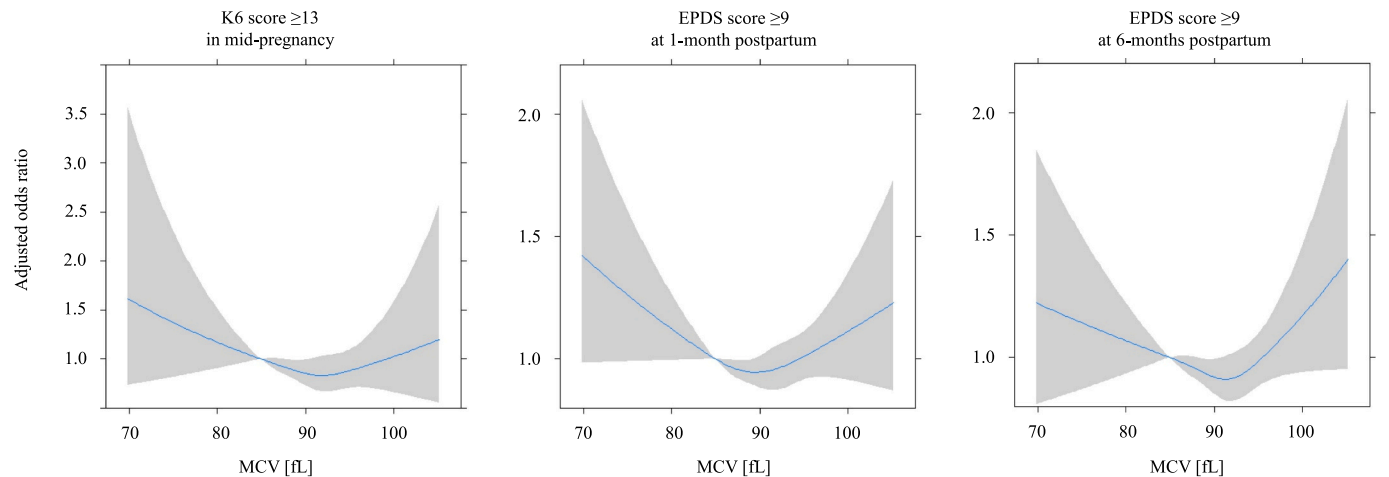


Fig. 2. Association between MCV in early pregnancy and prenatal mental health.

The association between the MCV in early pregnancy and the K6 cores of ≥ 13 in mid-pregnancy ≥ 13 , the EPDS score of ≥ 9 at 1one month postpartum ≥ 9 , and the EPDS score of ≥ 9 at 6-months postpartum ≥ 9 allowing for nonlinear effects, with 95 % CIs. Models fitted with 4four knots restricted cubic spline for MCV adjusting for the K6 score in early pregnancy, age, prepregnancy body mass index, parity, marital status, family income, and maternal educational level. Curves show ORs compared with to the chosen reference MCV of 85 fL.

Abbreviations: CI, confidence interval; EPDS, Edinburgh Postpartum Depression Scale; K6, Kessler 6-item psychological distress scale; MCV, mean corpuscular volume; OR, odds ratio.

women. The K6 was recently developed and is suitable as an indicator in large-population studies such as the present one. Fourth, as Hb levels and MCVs were only measured once in MT1 in this cohort, we did not investigate the relationship between temporal changes in MCV and mental health outcomes. Lastly, because the JECS is a long-term population-based cohort research project that encourages participants to maintain cooperation with the survey, there may be a selection bias in that the participating mothers are emotionally supported by the community of the research system.

This large-scale, high-quality cohort study shows that the low MCV values in early pregnancy without anemia, possibly indicating subclinical iron deficiency, are associated with a slight risk of deteriorating perinatal mental health. The occurrence of iron deficiency is quite frequent among reproductive-aged women and, moreover, amenable once it is recognized. This study is an analysis of the existing data from a birth cohort originally designed to elucidate environmental factors affecting child health and development. The study's findings should be interpreted with caution because of potential unadjusted confounding factors. A new and well-designed cohort study should be conducted to conclude a causal relationship between iron deficiency in early pregnancy and perinatal mental health. However, the results of this study can serve as a solid basis for further research on iron deficiency with or without anemia and perinatal mental health from the perspective of preconception care.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jad.2024.04.013>.

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Ethical standards

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.

CRediT authorship contribution statement

T. Ohsuga: Conceptualization, Formal analysis, Methodology, Writing – original draft, Writing – review & editing. **M. Egawa:** Conceptualization, Writing – review & editing. **Y. Takahashi:** Formal analysis, Methodology, Writing – review & editing. **Y. Ikeda:** Writing – review & editing. **K. Tsuyuki:** Writing – review & editing. **K. Kanatani:** Writing – review & editing. **F. Niwa:** Writing – review & editing. **K. Hirabayashi:** Writing – review & editing. **T. Nakayama:** Supervision. **M. Mandai:** Supervision.

Declaration of competing interest

None.

Availability of data and materials

Data are unsuitable for public deposition due to ethical restrictions and the legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of May 30, 2003, amendment on September 9, 2015) to publicly deposit the data containing personal information. Ethical Guidelines for Medical and Health Research Involving Human Subjects 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

epidemiologic data. All inquiries about access to data should be sent to jeecs-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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