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Maternal vitamin B12 during pregnancy and schizophrenia in offspring

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ABSTRACT

Background: Maternal nutritional deficiency is linked with several adverse outcomes in offspring but the link between maternal vitamin B12 levels and offspring schizophrenia remains unexplored.
Methods: In this nationwide population-based nested case-control design, 1145 schizophrenia cases were born between 1987-1997 and diagnosed by 2017 and each case were matched with a control. Maternal vitamin B12 levels during the first and early second trimesters of pregnancy were measured using chemiluminescence microparticle immunoassay from maternal sera. Conditional logistic regression was used to examine the association between maternal vitamin B12 levels and offspring schizophrenia.
Results: Low maternal vitamin B12 levels were not associated with offspring schizophrenia in unadjusted (OR 1.04, 95% CI 0.88-1.24) or adjusted analyses (aOR 1.14, 95% CI 0.95-1.37). When analyzed by quintiles, no significant association was observed between the lowest versus highest quintile of maternal vitamin B12 levels and schizophrenia in unadjusted (OR 1.01, 95% CI 0.78-1.30) or adjusted analyses (OR 0.89, 95% CI 0.68-1.17).
Conclusion: Maternal vitamin B12 levels in early pregnancy were not associated with offspring schizophrenia. Future studies measuring both genetic and environmental factors are required to elucidate the role of maternal vitamin B12 deficiency in schizophrenia and its potential pathways to influence schizophrenia in offspring.

1. Introduction

Schizophrenia is a chronic mental disorder characterized by positive and negative symptoms and cognitive impairment, with a worldwide prevalence of about 24 million (Solmi et al., 2023). Ranking among the top 20 causes of global disability, schizophrenia typically emerges during late adolescence to the early to mid-twenties (Combs & Mueser, 2017). The etiology of the disorder is complex and likely to include a combination of genetic, non-genetic/environmental and stochastic factors (Hilker et al., 2018; Misiak et al., 2018). Converging evidence supports the hypothesis that neurodevelopmental disruptions play a role in the vulnerability to schizophrenia (Eyles, 2021). Since the fetus depends on maternal nutrients, fetal prenatal nutrient deficiency could potentially lead to disruptions in fetal neurodevelopment (Cortés-Albornoz et al., 2021).

Vitamin B12, also known as Cobalamin, is a vital micronutrient crucial for neurodevelopment and functions during the antenatal and early postnatal periods. Functioning as an enzyme and co-factor, it mediates mitochondrial succinyl CoA formation and cytosol methionine synthesis and is essential for fat and protein metabolism, along with haemoglobin generation (Kräutler, 2012). Additionally, vitamin B12 supports DNA methylation and synthesis of epinephrine

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(Calderón-Ospina & Nava-Mesa, 2019). In human studies, folate and vitamin B12 deficiencies were related to adverse neurodevelopmental outcomes (del Río Garcia et al., 2009), cognitive functions (Bhate et al., 2008), insulin resistance (Yajnik et al., 2008) and increased risk for preterm birth (Rogne et al., 2017). As vitamin B12 is mainly found in animal products, vegan and vegetarian diets enhance the risk of B12 deficiency in pregnant women. Notably, women with vegan diets during pregnancy and B12-related deficiency have reported offspring with small for gestational age (Yisahak et al., 2020), increased irritability, and reduced brain growth (Pepper & Black, 2011). Maternal B12 deficiency with values below 200 pg/mL is linked with a higher risk of neural tube defects (Berti et al., 2011), which may share underlying risk factors with schizophrenia (Zammit et al., 2007).

The strongest evidence of prenatal nutritional deficiency and offspring schizophrenia derives from studies based on exposure to severe famine. The birth cohort exposed to the 1944-1945 Dutch Hunger Winter during World War II showed a two-fold increased risk for schizophrenia during adulthood (Hoek et al., 1998; Susser et al., 1996). Similar findings were reported in studies based on the Chinese famine of 1959-1961, with elevated risk of schizophrenia among those conceived or in early gestation at the height of the famine (Clair et al., 2005; Xu et al., 2009). The risk was higher in the areas where the severity of famine was greater (Xu et al., 2009). One study showed that elevated homocysteine, which is inversely related to vitamin B12 as well as folate, in the third trimester was associated with increased risk of schizophrenia in offspring (Brown et al., 2007). Of note, there is no study specifically examining the link between maternal vitamin B12 deficiency in early pregnancy and diagnosed offspring schizophrenia.

The aim of this study was to examine the association between maternal vitamin B12 levels during pregnancy and the risk of schizophrenia diagnosis in offspring. The Finnish Prenatal Study of Schizophrenia (FIPS-S) is a nationwide study, based on a nested case-control design which has several strengths, including a large sample of cases, prospectively collected maternal sera during pregnancies and comprehensive information from several nationwide registers facilitating adjustment for many potential confounding factors.

2. Methods

The FIPS-S is a nested case-control study including all singleton live births between 1987 and 1997 in Finland. Each child was followed for the diagnosis of schizophrenia in the Care Register for Health Care until the end of 2017. Ethical approval was obtained from the Ethics Committee of the Hospital District of Southwest Finland, the data protection authorities at the National Institute for Health and Welfare and the Institutional Review Board of the New York State Psychiatric Institute. The study design and the request for biobank serum samples were approved by the responsible Biobank Scientific Committee (Biobank Borealis of Northern Finland, University of Oulu, Oulu, Finland).

2.1. Finnish maternity cohort

The Finnish Maternity Cohort (FMC) is a nationwide serum biobank comprising around 2 million serum samples collected for prenatal screening during the first and early second trimesters of pregnancy (5th to 95th percentile: months 2–4 of pregnancy) from over 950,000 women. The remaining serum samples (one sample of 1–3 mL for each pregnancy) following informed consent were stored at -25°C in a protected biorepository at the Biobank Borealis in Oulu, Finland and are available for scientific research. Each sample in the FMC was linked with offspring and other Finnish nationwide registers using a unique personal identification code assigned to all Finnish residents since 1971.

2.2. Nationwide registers

The study utilized data from three national registers: the CRHC (Care Register of Health Care), the Finnish Medical Birth Register (FMBR), and the Finnish Population Register Centre (FCPR). The CRHC includes all inpatient diagnoses since 1967 and outpatient diagnoses from specialized services since 1998, based on the International Classification of Diseases (ICD) with ICD-8 from 1969 to 1986, ICD-9 from 1987 to 1995, and ICD-10 from 1996 onwards. The FMBR provides comprehensive national data on live births during the neonatal period up to seven days of age since 1987. The FCPR, established in 1969, serves as a computerized national archive containing essential demographic information for Finnish citizens and permanent residents in Finland.

2.3. Information on cases and controls

The schizophrenia cases were born in Finland between January 1987 and December 1997 and were registered in the CRHC with ICD-10 (F20) and ICD-9 (295) diagnoses before 2017. Controls consisted of singleton offspring born in Finland without a schizophrenia diagnosis. Each case was matched with one control on sex, date of birth (±30 days), and place of birth. The matched controls were alive and residing in Finland at the time of the matched case's diagnosis for the first time. Serum specimens with sufficient quantities of sera were available for 1145 cases and 1145 matched controls.

2.4. Maternal vitamin B12 measurement

Maternal prenatal vitamin B12 levels were assessed by measuring active B12 (HoloTC or Holotranscobalamin) using a chemiluminescence microparticle immunoassay on the Abbott Diagnostics Architect i2000SR automatic immunoassay analyzer. The coefficient of variation based on repeated quality control samples included in each set of daily assays, was 4.7% for control samples with high B12 levels (range: 43.7–49.6 pmol/L) and 6.4% for those with low B12 levels (range: 13.6–17.3 pmol/L).

2.5. Covariates

Potential confounders and mediators suggested to be associated with both maternal vitamin B12 levels and offspring schizophrenia were selected (Coury et al., 2023; Dean et al., 2010; McGrath et al., 2014; Niemelä et al., 2016; Robinson & Bergen, 2021). The FMBR was used to obtain information on the number of previous births, maternal socioeconomic status (SES), parental age, maternal smoking during pregnancy, gestational age, Apgar score at 1 min and weight for gestational age. The information on maternal and paternal psychiatric diagnoses and maternal substance abuse diagnoses was obtained from the CRHC, while maternal immigrant status was obtained from the FCPR. Information on the gestational week and season of blood draw was obtained from the FMC. A detailed description of potential confounders and mediators is available in Table 1.

2.6. Statistical analysis

Maternal vitamin B12 levels were initially assessed as a continuous variable. The variable was log-transformed before analyses due to the skewed distribution. The maternal vitamin B12 levels were categorized into quintiles and the cut-offs were based on the distribution of vitamin B12 level in the control group, with the fifth quintile defined as the reference group. Tests for possible associations of potential confounders with log-transformed maternal vitamin B12 levels among controls were carried out, for categorically defined confounders and mediators using Student's *t* and *F*-tests, and for continuous confounders using linear regression. Conditional logistic regression models for the matched sets were used to test for association between potential confounders and mediators with schizophrenia. The covariates were selected in the adjusted models based on their association with both the exposure and the outcome at p-value <0.1. Unadjusted odds ratios (OR) and adjusted

Table 1
Relationship between covariates and maternal serum vitamin B12 among controls, and covariates and schizophrenia in case and control subjects.

Covariates	Covariates and maternal serum vitamin B12 among controls			Covariates and schizophrenia in case and control subjects				
	Mean	SD	P-value	Cases n=1145		Controls n=1145		P-value
				n	(%)	n	(%)	
Maternal smoking[1]			0.49					**0.05**
No	4.56	0.46		903	80.63	946	83.79	
Yes	4.54	0.51		217	19.38	183	16.21	
Previous births[2]			0.13					0.14
0	4.54	0.44		435	38.22	472	41.22	
≥ 1	4.58	0.48		703	61.78	673	58.78	
History of maternal psychopathology[a]			0.25					**<0.001**
No	4.55	0.47		852	74.41	1000	87.34	
Yes	4.60	0.46		293	25.59	145	12.66	
History of paternal psychopathology[b]			0.30					**<0.001**
No	4.55	0.46		862	75.28	967	84.45	
Yes	4.59	0.50		283	24.72	178	15.55	
Maternal history of schizophrenia or schizoaffective disorder			0.24					**<0.001**
No	4.56	0.46		1105	96.51	1140	99.56	
Yes	4.80	0.37		40	3.49	5	0.44	
Paternal history of schizophrenia or schizoaffective disorder			0.34					**0.001**
No	4.56	0.46		1115	97.38	1143	99.83	
Yes	4.24	0.45		30	2.62	2	0.17	
Maternal SES			0.71					**0.002**
Upper white collar	4.54	0.41		98	8.56	113	9.87	
Lower white collar	4.56	0.46		305	26.64	362	31.62	
Blue collar	4.56	0.47		146	12.75	123	10.74	
Others	4.61	0.51		120	10.48	91	7.95	
Missing	4.57	0.46		476	41.57	456	39.83	
History of maternal substance abuse[c]			0.84					**0.001**
No	4.56	0.46		1069	93.36	1102	96.24	
Yes	4.55	0.56		76	6.64	43	3.76	
Gestational age (weeks)[3]			0.85					0.32
<37	4.56	0.46		60	5.56	54	4.91	
≥37	4.58	0.44		1020	94.44	1046	95.09	
Weight for gestational age[4]			0.67					**0.06**
<-2 SD	4.40	0.61		52	4.59	31	2.71	
-2 SD to +2 SD	4.58	0.45		1038	91.53	1065	93.01	
>+2 SD	4.53	0.49		44	3.88	49	4.28	
Maternal immigration status			0.57					**0.01**
No	4.56	0.46		1127	98.43	1140	99.56	
Yes	4.44	0.31		18	1.57	5	0.44	
Paternal immigration status[5]			**0.01**					**0.04**
No	4.57	4.59		1104	97.96	1125	99.12	
Yes	4.18	0.38		23	2.04	10	0.88	
Season of blood collection			0.15					0.31
Spring	4.55	0.45		263	22.97	266	23.23	
Summer	4.56	0.45		289	25.24	309	26.99	
Autumn	4.54	0.45		301	26.29	277	24.19	
Winter	4.58	0.49		292	25.50	293	25.59	
Season of birth			0.31					**0.04**
April-November	4.57	0.48		744	64.98	764	66.72	
December-March	4.53	0.44		401	35.02	381	33.28	
Region of birth [6]			0.89					**<0.001**
Urban	4.55	0.45		772	67.60	670	58.62	
Semi-urban	4.58	0.48		165	14.45	217	18.99	
Rural	4.58	0.49		205	17.95	256	22.40	
Apgar Score[7]			0.31					**0.06**
0-6	4.53	0.47		43	3.80	33	2.88	
7-8	4.54	0.44		235	20.76	202	17.64	
9-10	4.57	0.47		854	75.44	910	79.48	
	Beta	**SE**		Mean	SD	Mean	SD	
Maternal age (years)	4.70	0.08	**<0.001**	28.82	5.59	28.78	5.07	0.85
Paternal age (years)	4.63	0.07	**<0.001**	31.36	6.09	30.94	5.85	0.11
Gestational week of blood draw	4.76	0.04	**<0.001**	10.87	4.00	10.15	3.29	**<0.001**

SES, socioeconomic status, SD, standard deviation, SE, standard error

[a] ICD-8 (291-308), ICD-9 (291-316) or ICD-10 (F10-99, excluding maternal substance abuse diagnosis,

[b] ICD-8 (291-308), ICD-9 (291-316) or ICD-10 (F10-99);

[c] ICD-8 (291, 303, 304), ICD-9 (291, 292, 303,304,305) or ICD-10 (F10-19)

Data missing:

[1] 41

[2] 7

[3] 110

[4] 11

[5] 28
[6] 5
[7] 13.

odds ratios (aORs) and 95% confidence intervals (CI) were calculated. Additionally, a test of interaction between offspring sex and continuous vitamin B12 levels in association with schizophrenia was performed. Statistical significance was based on two-sided p-value <0.05. All statistical analyses were performed with SAS 9.4 software (SAS 9.4, SAS Institute, Cary, N.C.).

3. Results

The study included 1145 matched case-control pairs with mean age at first schizophrenia diagnosis for cases of 20.63 (standard deviation 3.33) years. The mean maternal vitamin B12 level among cases was 4.57 (0.46) pmol/L and 4.56 (0.46) pmol/L among controls. The mean gestational week of maternal blood draw for cases was 10.87 weeks (range: 4–36), and for controls was 10.15 (range: 4–36) weeks. The overall sample of cases and controls was 69.34% male and 30.66% female.

Table 1 shows the association between potential covariates and maternal vitamin B12 levels among controls and the association between potential covariates and offspring schizophrenia among cases and controls. Maternal age, paternal age, paternal immigration status and gestational week of blood draw were associated with vitamin B12 levels among controls. Maternal smoking, history of maternal psychopathology, history of paternal psychopathology, maternal history of schizophrenia or schizoaffective disorder, paternal history of schizophrenia or schizoaffective disorder, maternal socioeconomic status (SES), history of maternal substance abuse, weight for gestational age, maternal immigration status, paternal immigration status, season of birth, region of birth, Apgar score and gestational week of blood draw were associated with schizophrenia. Gestational week of blood draw and paternal immigration status were associated with both maternal vitamin B12 levels and offspring schizophrenia with p-value <0.1; thus, adjustments were made for these covariates.

Table 2 shows the association between log-transformed maternal serum vitamin B12 levels and offspring schizophrenia. The maternal serum vitamin B12 levels, measured as a continuous variable, were not associated with offspring schizophrenia in either unadjusted (OR 1.04, 95% CI 0.88–1.24, p-value = 0.65) or adjusted analyses (aOR 1.14, 95% CI 0.95–1.37, p-value = 0.16). There was no significant association between the lowest versus highest quintile of maternal vitamin B12 levels and schizophrenia in either unadjusted (OR 1.01, 95% CI 0.78–1.30, p-value = 0.95) or adjusted analyses (OR 0.89, 95% CI 0.68–1.17, p-value = 0.39). Further, no significant association was observed when maternal vitamin B12 levels were measured in deciles.

Testing for sex-by-maternal vitamin B12 levels did not show evidence of effect modification by sex on the relationship between continuous maternal vitamin B12 levels and offspring schizophrenia (p-value=0.13).

4. Discussion

This is the first nationwide population-based study examining maternal vitamin B12 levels in prenatal sera and schizophrenia. Maternal vitamin B12 levels in early pregnancy were not found to be associated with the risk of offspring schizophrenia diagnosis. There is a possibility that vitamin B12 could be related to offspring schizophrenia

Table 2
Odds ratios and 95% CI of the association between maternal serum vitamin B12 and offspring schizophrenia.

Maternal serum vitamin D (nmol/L)	Cases (n=1145) Mean (SD)	Controls (n=1145) Mean (SD)	Odds Ratio (unadjusted) 95% CI	P-value	Odds Ratio [a] (adjusted) 95% CI	P-value
Log transformed maternal vitamin B12	4.57 (0.46)	4.56 (0.46)	1.04 (0.88-1.24)	0.65	1.14 (0.95-1.37)	0.16
Quintiles	**Cases n (%)**	**Controls n (%)**				
< 20	226 (19.74)	228 (19.91)	1.01 (0.78-1.30)	0.95	0.89 (0.68-1.17)	0.39
20-39	189 (16.51)	230 (20.09)	0.83 (0.64-1.09)	0.19	0.77 (0.58-1.02)	0.06
40-59	265 (23.14)	229 (20.00)	1.18 (0.91-1.52)	0.22	1.16 (0.89-1.50)	0.28
60-79	241 (21.05)	229 (20.00)	1.08 (0.83-1.40)	0.58	1.02 (0.78-1.34)	0.89
≥80	224 (19.56)	229 (20.00)	Ref		Ref	
Deciles	**Cases n (%)**	**Controls n (%)**				
<10	101 (8.82)	113 (9.87)	0.99 (0.68-1.44)	0.97	0.85 (0.58-1.25)	0.41
10-19	125 (10.92)	115 (10.04)	1.23 (0.84-1.78)	0.29	1.18 (0.80-1.74)	0.40
20-29	94 (8.21)	115 (10.04)	0.90 (0.62-1.32)	0.59	0.87 (0.59-1.28)	0.48
30-39	95 (8.30)	114 (9.96)	0.89 (0.61-1.31)	0.57	0.83 (0.56-1.28)	0.35
40-49	131 (11.70)	115 (10.04)	1.28 (0.89-1.84)	0.19	1.26 (0.86-1.83)	0.23
50-59	134 (11.70)	115 (10.04)	1.28 (0.89-1.85)	0.18	1.33 (0.92-1.94)	0.13
60-69	107 (9.34)	114 (9.96)	1.03 (0.70-1.51)	0.88	1.02 (0.68-1.51)	0.93
70-79	134 (11.70)	115 (10.04)	1.32 (0.91-1.92)	0.14	1.29 (0.88-1.88)	0.20
80-89	120 (10.48)	114 (9.96)	1.18 (0.82-1.71)	0.37	1.26 (0.86-1.83)	0.22
90-100	104 (9.08)	115 (10.04)	Ref		Ref	

[a] Adjusted for paternal immigration status and gestational week of blood draw

only in mothers or offspring with a genetic mutation that alters one-carbon metabolism. This has been suggested in studies of gene variants such as methylene tetrahydrofolate reductase (MTHFR), folic acid, and neural tube defects (Etheredge et al., 2012). It is also possible that maternal vitamin B12 levels and offspring schizophrenia are dependent on the timing of assessment, and the present findings solely reflect early pregnancy levels.

Given prior findings, noted above, that elevated prenatal maternal homocysteine was related to an increased risk of schizophrenia in offspring, and that both vitamin B12 and folic acid deficiency are important causes of elevated homocysteine (Brown et al., 2007), this suggests that maternal folic acid deficiency should be investigated in relation to schizophrenia. Unfortunately, folic acid is not stable in the archived serum specimens in the Finnish Maternity cohort biobank, and in fact for most serum specimens stored long-term, and thus this vitamin could not be assayed in the present study.

The present findings are not concordant with previous studies from the Dutch Hunger Winter and Chinese famine studies showing associations with schizophrenia (Brown et al., 1996). However, vitamin B12 is but one micronutrient and those prior studies did not specifically measure levels of this vitamin during pregnancy. In other nested case-control studies drawn from the same Finnish birth cohort, maternal serum vitamin B12 levels in early pregnancy were associated with offspring childhood autism (Sourander et al., 2023) but not with offspring attention-deficit hyperactivity disorder (Sourander et al., 2021), suggesting that vitamin B12 might be a specific risk factor for childhood autism at least among these disorders.

The major strengths of the present study include a large nationwide representative sample, assessment of maternal vitamin B12 levels from prospectively collected maternal serum samples during pregnancy and the ability to control for several covariates. The main limitation was that the maternal vitamin B12 levels were measured only once during the first and early second trimesters of pregnancy, and thus we cannot rule out the possibility that vitamin B12 deficiency during later pregnancy is related to schizophrenia in offspring.

In the present study, we did not find any association between maternal vitamin B12 deficiency in early to mid-pregnancy and schizophrenia in offspring. Future studies with larger sample sizes and follow-up data measuring both genetic and environmental factors are required to elucidate whether maternal vitamin B12 deficiency plays a role in schizophrenia and the pathways through which this exposure may influence schizophrenia in offspring.

CRediT authorship contribution statement

Andre Sourander: Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing, Supervision. **Sanju Silwal:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Heljä-Marja Surcel:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Susanna Hinkka-Yli-Salomäki:** Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing. **Keely Cheslack-Postava:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **Subina Upadhyaya:** Writing – original draft, Writing – review & editing. **Ian W. McKeague:** Investigation, Methodology, Writing – original draft, Writing – review & editing. **Alan S. Brown:** Conceptualization, Investigation, Methodology, Project administration, Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare no conflict of interest.

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