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Short report

Maternal vitamin D deficiency and the risk of autism spectrum disorders: population-based study

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Background
Maternal vitamin D deficiency may increase risk of autism spectrum disorder (ASD), but direct evidence is lacking.

Aims
To clarify the relationship between maternal vitamin D deficiency and offspring risk of ASD with and without intellectual disability.

Method
Using a register-based total population study (*N*=509 639), we calculated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) of ASD with and without intellectual disability in relation to lifetime diagnoses of maternal vitamin D deficiency. Although rare, such deficiency was associated with offspring risk of ASD with, but not without, intellectual disability (aORs 2.51, 95% CI 1.22–5.16 and 1.28, 0.68–2.42). Relationships were stronger in non-immigrant children.

Conclusions
If reflecting associations for prenatal hypovitaminosis, these findings imply gestational vitamin D substitution as a means of ASD prevention.

Declaration of interest
None.

Autism spectrum disorders (ASDs) are developmental disorders associated with a high individual and societal burden, but their aetiology is poorly understood. Environmental and genetic factors appear equally important,[1] although ASD with and without intellectual disability may in part have different origins.[2,3]

In high-latitude countries such as Sweden, children of mothers with dark complexion are at particularly elevated risk of ASD with intellectual disability.[3] Because such women often have very low vitamin D levels due to melanin absorption of UVB radiation, maternal vitamin D deficiency has been suggested to contribute to ASD risk in offspring.[4,5] Indeed, experimentally induced vitamin D deficiency in pregnant dams is reported to affect foetal neurodevelopment and behaviour in adult offspring in rats,[4] and a recent study demonstrated lower neonatal vitamin D levels in children with ASD compared with their siblings.[6]

Early life vitamin D deficiency is thus a possible risk factor for ASD, but direct support of an association is lacking.[4] Maternal hypovitaminosis D is treatable, thus investigation of the matter is warranted. We report here on the relationship between secondary care diagnosis of lifetime maternal vitamin D deficiency and offspring risk of ASD with and without intellectual disability, while addressing the influence of ethnicity. We use data from the Stockholm Youth Cohort (SYC), which allow for detailed case ascertainment in the total population of young people in Stockholm, Sweden.

Method

We conducted a cohort study using the SYC, comprising all Swedish-born individuals aged 4–17 years who were resident for at least 4 years in Stockholm County between 2001 and 2011 and had complete covariate data (*N*=509 639).[7] Prospectively recorded data on probands and their relatives were retrieved from registers as previously described.[7]

We identified cases from several national and regional registers, using a validated approach covering all known pathways of ASD diagnosis and care in Stockholm County.[7] The National Patient Register contains the dates and discharge diagnoses of all in-patient (since 1973) and specialist out-patient care (since 2001) in Sweden.[7] Using this source, we defined exposure as a lifetime-recorded diagnosis of unspecified vitamin D deficiency (ICD-10 E55.9 or ICD-9 268.9), corresponding to a serum 25-hydroxyvitamin D level of less than 25 nmol/L (with clinical manifestations such as osteomalacia, muscle aches and weakness), in the biological mother.

We considered other parental characteristics described below (also see Table 1) as potential confounders or mediators based on their associations with ASD and vitamin D deficiency.[5,8,9]

Statistical analysis

All analyses were conducted using SAS 9.4. We first calculated frequencies and means of case status and other characteristics according to lifetime maternal vitamin D deficiency, with Pearson's chi-square tests to compute the difference between proportions and *t*-tests to test the difference between means. Using logistic regression models, we then derived odds ratios (ORs) and their 95% confidence intervals (CIs) for all ASDs, and dichotomised into ASD with or without intellectual disability, in relation to the exposure. Cluster robust standard errors accounted for non-independence within family clusters. We first estimated associations adjusting only for gender and year of birth, and then after additional adjustment for parental ages, income, education, and lifetime histories of diagnosed affective disorders, non-affective psychosis, ASD, attention deficit/hyperactivity disorder, intellectual disability, epilepsy and prescriptions for anticonvulsants. We then included maternal country of birth in a third model. Lastly, we evaluated whether lifetime maternal vitamin D deficiency was differently associated with ASD among children with and without maternal histories of migration. We calculated chi-square tests as a test for homogeneity of associations

Table 1 Study population characteristics in relation to lifetime maternal history of diagnosed vitamin D deficiency

Characteristic	Maternal history of vitamin D deficiency		*P*	All
	No	Yes		
Individuals, *n* (%)	509 092 (99.9)	547 (0.1)		509 639 (100.0)
Cases of ASD with intellectual disability, *n* (%)	2463 (0.5)	13 (2.4)	<0.0001	2476 (0.5)
Cases of ASD without intellectual disability, *n* (%)	7396 (1.4)	10 (1.8)	0.46	7406 (1.4)
Male (%)	51.3	52.6	0.51	51.3
Maternal age, years: mean	29.9	28.5	<0.0001	29.9
Paternal age, years: mean	32.8	34.0	<0.0001	32.8
Maternal country of birth (%)				
Sweden	76.3	19.2	<0.0001	76.2
Europe	8.3	4.6	0.002	8.3
Outside Europe	12.8	38.9	<0.0001	12.9
Sub-Saharan Africa	2.6	37.3	<0.0001	2.6
Lowest quintile of disposable family income (%)	14.8	35.6	<0.0001	14.8
Elementary maternal education (%)	15.6	43.1	<0.0001	15.6
Elementary paternal education (%)	16.8	32.7	<0.0001	16.8
Born small for gestational age (%)	2.5	3.7	0.09	2.5
Premature birth (<37 weeks, %)	5.9	6.2	0.07	5.9
Maternal history of neuropsychiatric disorder (%)[a]	2.4	9.3	<0.0001	2.4
Paternal history of neuropsychiatric disorder (%)[a]	2.0	2.0	0.98	2.0
Maternal history of affective disorder (%)[b]	15.4	36.8	<0.0001	15.4
Paternal history of affective disorder (%)[b]	8.1	10.8	0.02	8.1
Maternal history of epilepsy (%)	1.0	1.5	0.25	1.0
Paternal history of epilepsy (%)	1.0	0.7	0.52	1.0

a. Parental histories of neuropsychiatric disorder include any in-patient or secondary care out-patient record of diagnosed non-affective psychosis, bipolar disorder, attention-deficit hyperactivity disorder, ASD, or intellectual disability.
b. Parental histories of affective disorder include any in-patient or secondary care out-patient record of diagnosed affective disorder except for bipolar disorder.
ASD, autism spectrum disorder.

with ASD, respectively, with and without intellectual disability, and between Swedish-born children versus children of migrant mothers.

Results

By the end of follow-up in 31 December 2011, 9882 ASD cases were identified including 2476 with intellectual disability and 7406 without intellectual disability. Lifetime maternal vitamin D deficiency was rare according to secondary care diagnoses and recorded in only 547 individuals (0.1%). It was strongly associated with socioeconomic and medical parental characteristics (Table 1) including maternal psychiatric disorders, but not with preterm or small for gestational age births.

Diagnosed lifetime maternal vitamin D deficiency was associated with risk of ASD and, in particular, of ASD with intellectual disability (*P* for homogeneity 0.17) (Table 2), although there was some attenuation upon adjustment for parental characteristics. Associations varied with maternal migration status (*P* for homogeneity 0.05) as risks were more pronounced in native-born children (ORs being 7.08, 95% CI 2.96–16.94 and 2.15, 0.85–5.45 for ASD with and without intellectual disability, respectively).

Discussion

This study is, to our knowledge, the first population-based study to estimate the relationship between maternal vitamin D deficiency and the risk of ASD in a child. We found a positive association which was especially noticeable for ASD with intellectual disability, and for children of non-immigrant mothers.

Our findings should, however, be interpreted with caution. Although we had access to a large sample size, estimates of associations were based on low numbers. Second, maternal vitamin D status was identified from secondary care records, and therefore under-ascertained and perhaps differentially so with regard to ASD risk factors. Indeed, diagnosed maternal vitamin D deficiency co-occurred with such factors including parental psychiatric histories[10] (including depression, a proxy also for *in utero* exposure to antidepressants, shown to, rather than the underlying disorder, increase the risk of ASD),[11] immigration status[3] and disadvantageous social position.[8] Hence, residual confounding cannot be ruled out. Lastly, we used vitamin D deficiency recorded at any time as the exposure – and not timed to pregnancy, as no cases diagnosed before the birth of a child were identified. Therefore, reverse causality may be a

Table 2 Odds ratios (ORs) and 95% confidence intervals (CIs) for autism spectrum disorder (ASD), with and without comorbid intellectual disability, in relation to lifetime maternal history of diagnosed vitamin D deficiency

Vitamin D deficiency	Cases	OR (95% CI)[a]	OR (95% CI)[b]	OR (95% CI)[c]
All ASD				
No	9859	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	23	2.20 (1.35–3.58)	1.70 (1.03–2.79)	1.78 (1.08–2.92)
ASD with intellectual disability				
No	2463	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	13	5.08 (2.53–10.20)	3.55 (1.76–7.18)	2.51 (1.22–5.16)
ASD without intellectual disability				
No	7396	1.00 (ref)	1.00 (ref)	1.00 (ref)
Yes	10	1.23 (0.67–2.28)	0.99 (0.52–1.87)	1.28 (0.68–2.42)

a. Adjusted for year of birth and gender.
b. Additionally adjusted for disposable income, maternal and paternal age and level of education at birth, maternal and paternal lifetime histories of diagnosed affective disorders, non-affective psychosis, ASD, attention-deficit/hyperactivity disorder, intellectual disability, epilepsy and prescriptions for anticonvulsants.
c. Additionally adjusted for maternal country of birth.

concern. No cases of vitamin D deficiency were recorded before the birth of a child. However, given that vitamin D deficiency among pregnant women in Sweden is detected only when outright screened for,[12] many cases of deficiency are likely to manifest well before any official diagnosis is recorded.

Our finding of a stronger association between maternal hypovitaminosis D and ASD with intellectual disability than without intellectual disability is in line with migrant studies, demonstrating that offspring risk of severe forms of ASD – but not Asperger's syndrome or ASD without intellectual disability – is increased in migrant populations where vitamin D deficiency is highly prevalent.[3–6,8] There is also mounting evidence that environmental factors are more relevant (than genetic factors) for the development of lower-functioning ASD.[2] We, as well as others,[6] further observed heterogeneity in the associations between vitamin D deficiency and ASD between children with and without maternal migrant history. This discrepancy might be due to a limited range of exposure in children of immigrant mothers, as the majority of children and pregnant mothers with migrant background have neonatal/gestational vitamin D deficiency, according to recent Swedish reports.[6,11]

Causality cannot be inferred from our study. There are, however, biological underpinnings of a true association as experimental studies indicate critical roles of vitamin D in the development and functioning of the brain.[4]

In summary, our results support, but do not prove, the hypothesis that maternal vitamin D status is implicated in the aetiology of ASD with comorbid intellectual disability. As vitamin D deficiency in pregnancy is both prevalent and treatable, further investigation of this association is needed.

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