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Original Research Article

High-dose vitamin D3 supplementation in pregnancy and risk of neurodevelopmental disorders in the children at age 10: A randomized clinical trial

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A B S T R A C T

Background: Vitamin D deficiency in pregnancy may increase the risk of autism and attention deficit hyperactivity disorder (ADHD).
Objective: The objective of this study was to estimate the effect of vitamin D3 supplementation in pregnancy on risk of autism and ADHD.
Design: This randomized clinical trial was part of the COpenhagen Prospective Study on Neuro-PSYCHiatric Development (COPYCH) project nested within the Copenhagen Prospective Studies on Asthma in Childhood 2010 (COPSAC2010) cohort comprising a population-based sample of 700 healthy mother-child pairs enrolled at week 24 of pregnancy. Maternal 25-hydroxy-vitamin D (25(OH)D) was measured at inclusion and 623 mothers were randomized 1:1 to either high-dose (2800 IU/d) or standard dose (400 IU/d) vitamin D3 until 1 wk postpartum (315 received high-dose, 308 standard dose). At age 10, diagnoses and symptom load of autism and ADHD, respectively, were established using the Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version.
Results: The psychopathologic evaluation was completed by 591 children aged 10 y, and 16 children (2.7%) were diagnosed with autism and 65 (11.0%) with ADHD. Hereof, 496 children participated in the vitamin D3 trial (246 received high-dose, 250 standard dose). Of these, 12 children (2.4%) were diagnosed with autism and 58 (11.7%) with ADHD. *Higher maternal preintervention 25(OH)D levels were associated with a decreased risk of autism [odd ratio (OR) per 10 nmol/L: 0.76 (0.59,0.97); P = 0.034], lower autistic symptom load [β per 10 nmol/L: −0.03 (−0.05,0.00); P = 0.024), and decreased risk of ADHD diagnosis (OR per 10 nmol/L: 0.88 (0.78,0.99); P = 0.033].* High-dose vitamin D3 supplementation was not associated with risk of autism or ADHD.
Conclusions: *Higher maternal preintervention 25(OH)D was associated with a decreased risk of autism, lower autistic symptom load, and decreased risk of ADHD diagnosis, but* high-dose vitamin D3 supplementation in pregnancy had no effect on risk of autism and ADHD.
This trial was registered at clinicaltrials.gov as *NCT00856947*.

Keywords: ADHD, Autism, neurodevelopment, supplementation, vitamin D

Abbreviations: ADHD, *attention deficit hyperactivity disorder*; *ADHD-RS*, *ADHD-Rating Scale*; *COPSAC*, Copenhagen Prospective Studies on Asthma in Childhood; COPSAC2010, Copenhagen Prospective Studies on Asthma in Childhood 2010; COPSYCH, COpenhagen Prospective Study on Neuro-PSYCHiatric Development; ICD-10, the International Classification of Disorders 10th Revision; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version; n-3 long-chain PUFA, omega-3 long-chain polyunsaturated acids; RCT, randomized clinical trial; *SRS-2*, *Social Responsiveness Scale 2*; 25(OH)D, 25-hydroxy-vitamin D.

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Introduction

During fetal development, the brain undergoes rapid growth and development. Early environmental exposures during this vulnerable phase may have long-term consequences including affected risk of common neurodevelopmental disorders, such as autism and attention deficit hyperactivity disorder (ADHD) [1,2].

The prevalence of vitamin D deficiency in pregnancy has globally been estimated to be present in >50% of pregnant women [3]. Animal models have shown that vitamin D is crucial for the developing brain, as it contributes to functions including modulation of neurotransmission and neuroprotection [4,5]. Because the fetus relies on vitamin D passing from the mother through the placenta, maternal vitamin D deficiency may potentially affect fetal brain development [6].

Previous observational studies have reported that maternal vitamin D deficiency in pregnancy is associated with the risk of autism and ADHD in the offspring, however, results are ambiguous, and potentially confounded by diet, lifestyle, and season [7–15]. Further, lower gestational vitamin D levels have been shown to increase the severity of traits and symptoms of autism and ADHD in childhood in some studies [7,8,16–19], but not in others [20–23]. However, no randomized clinical trials (RCTs) of vitamin D supplementation in pregnancy have investigated the effect on neurodevelopmental disorders.

Based on a hypothesized protective effect of higher serum vitamin D in pregnancy, we investigated the effect of high-dose compared with standard dose of vitamin D3 supplementation in an RCT during the third trimester of pregnancy on the risk of autism and ADHD and corresponding symptom load evaluated clinically at age 10 as part of the *COpenhagen Prospective Study on Neuro-PSYCHiatric Development (COPSYCH) project* [24].

Methods

Study design

The *COPSYCH project is nested within the* Copenhagen Prospective Studies on Asthma in Childhood 2010 (*COPSAC2010) cohort comprising 700 mother-child pairs enrolled at wk 24 of pregnancy. Pregnant women living in Zealand (Latitude 55° N), Denmark, were recruited by a written invitation sent out after their first pregnancy visit at the general physician. Women not fluent in Danish, with an intake of >600 IU vitamin D3 per day, and/or with any kidney, heart, or endocrine disorder were excluded. From the COPSAC2010 cohort, 623 pregnant women were included in the vitamin D3 trial. The offspring were followed prospectively and deeply phenotyped at the COPSAC unit through 14 visits until age 10* [25]. *At age 10, the children underwent an extensive neuropsychiatric evaluation. Children with a birth weight < 1500 g or a gestational age < 28 wk were excluded from the analyses* [1,2]. *For further details see* Supplementary Material.

The study was conducted according to the guiding principles of the Declaration of Helsinki and was approved by the Local Ethics Committee (H-B-2009-014, COPSAC2010: H-B-2008-093), and the Danish Data Protection Agency (COPSAC2010: 2015-41-3696). All study participants provided informed consent.

Vitamin D intervention

The pregnant women were randomly assigned (1:1) to a daily vitamin D3 supplementation of 2400 IU or placebo starting from the first visit at the COPSAC research unit at week 24 of pregnancy until 1 wk postpartum. The vitamin D3 intervention was performed between 4 March, 2009, and 17 November, 2010. An external investigator with no additional involvement in the RCT performed the randomization by a computer-generated list of random numbers. All included women were instructed to continue consuming a daily vitamin D3 supplementation of 400 IU throughout pregnancy as recommended by the Danish National Board of Health. Total supplementation was therefore 2800 IU/d vitamin D3 in the intervention (high-dose) group and 400 IU/d in the control (standard dose) group. Mothers were asked to return capsules after the intervention period to estimate the adherence. The study was double-blinded until the youngest child had reached the age of 3 y, with the exception of medical emergency (3 cases of early unblinding). From this age information on treatment group was available to all parents. In a factorial 2×2 design, pregnant women were simultaneously randomly assigned to a daily fish oil (n-3 long-chain PUFA) supplement of 2400 mg or olive oil capsules (ClinicalTrials.gov: NCT00798226) [25].

Serum measures of 25-hydroxy-vitamin D

Maternal serum 25-hydroxy-vitamin D (25(OH)D) levels were measured before and after intervention at wk 24 of pregnancy and 1 wk postpartum, respectively. Child serum 25(OH)D concentrations were measured at 6 mo and 6 y [26].

The COPSYCH 10-y visit

The COPSYCH 10-y clinical visit was a post hoc follow-up of the vitamin D3 RCT (*clinicaltrials.gov identifier: NCT00856947*). The visit was carried out over 2 d and included an extensive evaluation of psychopathology, neurocognition, and brain structure and function using magnetic resonance imaging [24]. Examinations were performed between January 2019 and December 2021. Categorical psychopathology was established by the use of semi-structured clinical diagnostic interview Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version (K-SADS-PL) [27]. All K-SADS-PL interviews were administered by trained medical doctors, nurses, and psychologists and were video recorded to enable supervision by a psychologist (JRJM) and for external validation diagnostic conferences with a clinical professor of child and adolescent psychiatry (NB) both specialists in child and adolescent psychiatry to reach consensus on diagnostics [24]. Clinician verified symptom load of psychopathology (*symptoms component scores), were established based on number of symptoms endorsed for each disorder assessed by the K-SADS-PL. Autistic and ADHD symptoms component scores were defined as the first component (describing 41% and 46%, respectively, of the variation in data) from a multiple correspondence analysis of the registered autistic and ADHD symptoms (R package: FactoMineR)* [28]. *Further, parent-rated severity of ADHD symptoms and autistic traits were obtained with the ADHD-Rating Scale (ADHD-RS) and Social Responsiveness Scale 2 (SRS-2), respectively* [29–31]. Research diagnoses based on all sources of clinical information were assigned according to the International Classification of Disorders 10th Revision (ICD-10) [32]. ICD-10 diagnostic codes of autism assigned at the COPSYCH visit included the DF84.0, DF84.5, and DF84.8 diagnostic codes, and of ADHD DF90.0, DF90.8, and DF98.8.

Statistical Analysis

We estimated the effect of maternal preintervention and postintervention serum 25(OH)D as well as child serum 25(OH)D at age 6 mo and 6 y on diagnosis of autism and ADHD and continuous autistic and ADHD symptoms component scores reflecting symptom load by

logistic and linear regression analyses. The covariate adjusted association between maternal preintervention 25(OH)D and autistic symptom load was visualized in a partial residual plot. Covariates were included based on known risk factors for autism, ADHD, and known influencers of serum 25(OH)D (See Supplementary Methods). In analyses regarding maternal and child serum 25(OH)D and risk of autism and ADHD, we included all individuals attending the COPSYCH 10-y visit regardless of participation in the vitamin D3 trial.

Among COPSYCH participants included in the vitamin D3 trial, we estimated the effect of high-dose compared with standard dose of vitamin D3 on the prevalence of autism and ADHD diagnoses and symptom load by logistic and linear regression analyses. *We tested for* interactions between preintervention serum 25(OH)D levels and the vitamin D3 intervention on psychopathologic outcomes by adding cross products to the models and performed analyses stratified according to maternal preintervention serum 25(OH)D at wk 24 of pregnancy to assess the intervention effect according to early pregnancy 25(OH)D levels. Analyses were performed both crude and adjusted for preintervention pregnancy wk 24 25(OH)D levels, season of birth, child sex, and n-3 long-chain PUFA intervention. *In all analyses, we investigated for interaction with sex due to pre-existing studies suggesting sex differences in the effect of vitamin D on risk of psychopathology* [18,20,33].

To corroborate identified associations to K-SADS-PL diagnostic outcomes, we investigated the effect of maternal as well as child circulating 25(OH)D and the effect of the vitamin D3 intervention on the severity of parent-reported autistic traits and ADHD symptoms.

In all analyses, statistical significance was set as <0.05, 2-sided. Owing to the relatively few individuals with missing information, missing data were not imputed. We have not controlled for multiple testing because analyses were performed based on a strong hypothesis generated from existing research. Statistical analyses were performed using R statistical software version R4.2.1 (the R Foundation, Vienna). For complete overview of included exposure and outcome measures see Supplementary Figure 1.

Results

Baseline characteristics

From the total COPSAC cohort including 700 mother-child pairs, 591 children were included in the COPSYCH 10-y visit and eligible for analyses on maternal and child serum 25(OH)D levels. For baseline characteristics of the COPSYCH 10-y visit see Supplementary Table 1.

From the total COPSAC cohort, a subgroup of 496 children participated both in the vitamin D3 trial and in the COPSYCH 10-y visit and were eligible for primary analyses on the intervention effect: 246 received high dose and 250 standard dose of vitamin D3 (Figure 1).

There were no significant differences in serum 25(OH)D at baseline or in season of birth between the intervention and the placebo group. Before the intervention, 51.4 % of mothers had levels of serum 25(OH)D $\geq$75nmol/L. Demographics are provided in Table 1. See the Supplementary Material for additional descriptive tables stratified according to outcome measures (Supplementary Tables 2–5).

In total, 74% of the mothers adhered to the intervention, which was defined as an intake of $\geq$80% of the prescribed capsules [34,35]. The safety profile of the RCT has been reported previously [35].

Serum 25(OH)D and risk of autism and ADHD

Of the total 591 individuals included in the COPSYCH visit, 16 children (2.7%) were diagnosed with autism and 65 (11.0%) with ADHD. Clinically rated symptoms of autism were present in 49 individuals (8.3%) and of ADHD in 170 (28.8%). *Adjusted analyses showed that higher maternal preintervention 25(OH)D level was associated with a decreased risk of autism [odds ratio (OR) per 10 nmol/L 0.76 (0.59,0.97); P = 0.034)], lower autistic symptom load [β per 10 nmol/L −0.03 (−0.05,0.00); P = 0.024], and lower risk of ADHD diagnosis [OR per 10 nmol/L 0.88 (0.78,0.99); P = 0.033], but not ADHD symptom load [β per 10 nmol/L −0.02 (−0.04,0.00), P = 0.122]* (see Supplementary Table 6). *See Figure 2 for visualization of the effect of maternal preintervention 25(OH)D on autistic symptom load. Beta coefficients for all variables in adjusted models are provided in the* Supplementary Tables 7–10. *We did not observe sex differences (P-interactions > 0.05).*

Maternal post-intervention serum 25(OH)D level or child level age 6 mo or 6 y were not associated with autism or ADHD (Supplementary Table 11).

High-dose vitamin D3 supplementation and risk of autism and ADHD

In the high-dose vitamin D3 supplementation group, 5 (2.0%) children were compared with 7 (2.8%) children in the standard dose group diagnosed with autism at age 10. Clinically rated symptoms of autism were present in 15 (6.1%) in the high-dose group compared with 25 (10%) in the standard dose group, ADHD diagnosis in 27 (11%) compared with 31 (12.4%), and clinically rated symptoms of ADHD in 67 (27.2%) compared with 76 (30.4%).

Vitamin D3 treatment group was not significantly associated with risk of autism (crude OR: 0.72; 95% CI: 0.21,2.29; P = 0.580), symptom load of autism (crude β: −0.08; 95% CI: −0.19, 0.03; P = 0.142), ADHD diagnosis (crude OR: 0.87; 95% CI: 0.50,1.51; P = 0.622), or symptom load of ADHD (crude β: −0.06; 95% CI: −0.18,0.07; P = 0.375) and there was no interaction with sex (Table 2). Results were unchanged after adjustments.

Within the high-dose vitamin D3 supplementation group, no children of mothers with preintervention 25(OH)D levels ≥75 nmol/L at wk 24 (n = 128) were diagnosed with autism when compared to 5 children of mothers with 25(OH)D <75 nmol/L (n = 116), and there was a significant interaction between preintervention 25(OH)D concentrations and the vitamin D3 intervention on autism risk (interaction term coefficient = 0.97, crude P-interaction = 0.030). Barnard's exact test inferred a significant protective effect of the vitamin D3 intervention on risk of autism within mothers with preintervention 25(OH)D levels ≥75 nmol/L; OR = 0, P = 0.044. There was no significant interaction between preintervention 25(OH)D levels and the vitamin D3 intervention on autistic symptom load (crude P-interaction = 0.261), ADHD diagnosis (crude P-interaction = 0.687), or ADHD symptom load (crude P-interaction = 0.703). (See Supplementary Methods, Supplementary Figure 2, and Supplementary Figure 3)

A threshold analysis (moving average) suggested a U-shape effect of the high-dose vitamin D3 intervention with a protective effect on autistic symptom load in cases of maternal preintervention 25(OH)D concentrations within the normal to high range of serum 25(OH)D (approximately 55–110 nmol/L) (Figure 3).

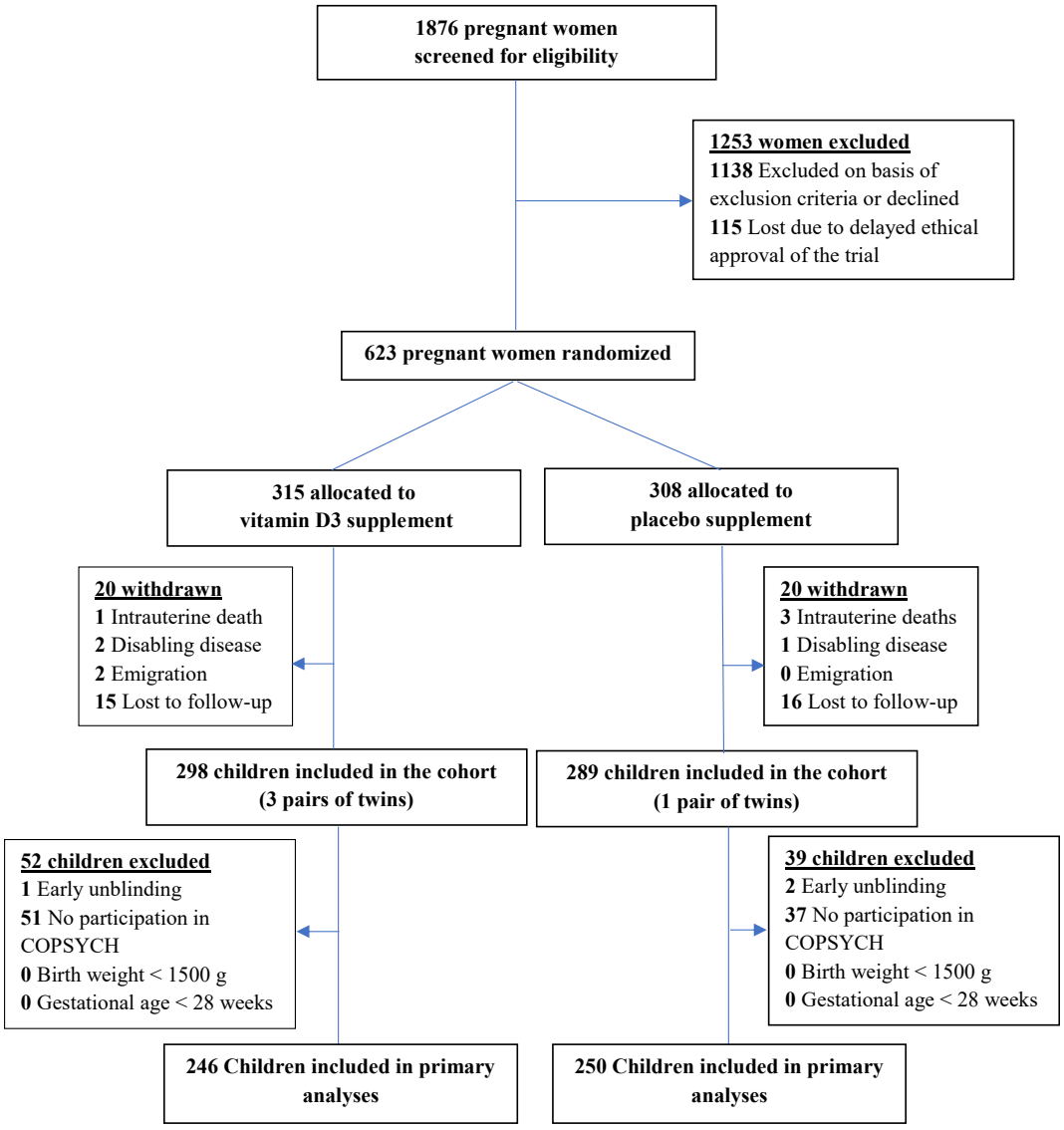

Figure 1. CONSORT participant flow diagram.

Vitamin D and parent-rated autistic traits severity and ADHD symptoms

No significant associations were found between the vitamin D3 supplementation, maternal pre- or post-intervention or child serum 25(OH)D and parent-rated severity of autistic traits measured by SRS-2 or ADHD symptoms measured by ADHD-RS [Supplementary Table 12 (vitamin D3 intervention), Table 13 (maternal 25(OH)D), and Table 14 (child 25(OH)D)]. However, estimates suggested lower SRS-total scores with increasing maternal preintervention 25(OH)D and child 6-mo 25(OH)D levels.

Sensitivity analyses

The association between maternal preintervention *25(OH)D and risk of ADHD disappeared after* additional adjustment for maternal ADHD PRS (OR, 0.94 (0.83,1.07); $P = 0.366$). *The association between higher maternal preintervention 25(OH)D and decreased autistic symptom load did replicate using alternative statistical models, however, results were nonsignificant. (see* Supplementary Methods *and* Supplementary Tables 15–16*).*

Discussion

In this RCT, investigating the effect of high-dose (2800 IU/d) compared with standard dose (400IU/d) of vitamin D3 from pregnancy wk 24 until 1 wk after birth, we found no overall protective effect on risk of autism, ADHD, or symptom loads. *Higher maternal pre-intervention 25(OH)D was associated with a decreased risk of autism, lower autistic symptom load, and decreased risk of ADHD.*

The present study overcomes important limitations of existing observational studies investigating the association between gestational serum 25(OH)D and risk of autism and ADHD in the offspring. First, the RCT design allows for an unbiased investigation of the effect of vitamin D3 supplementation in late pregnancy, a period characterized by rapid brain growth and neuronal development. This is of high importance due to the many known lifestyle factors influencing serum levels of vitamin D [36]. Second, this study was based on thorough clinical evaluations performed by uniformly trained nurses and medical doctors at the COPSAC research unit as opposed to parent-reported or registry-based outcomes more prone to bias [37,38]. Lastly,

Table 1
Baseline characterization of participants of the vitamin D3 RCT included in the COPSYCH project

Stratified by participation in the vitamin D3 RCT	All	Placebo	Vitamin D3
	n = 496	*n* = 250	*n* = 246
Diagnosis of autism, *n* (%)	12 (2.4)	7 (2.8)	5 (2.0)
Individuals presenting clinically rated symptoms of autism, *n* (%)	40 (8.1)	25 (10.0)	15 (6.1)
Diagnosis of ADHD, *n* (%)	58 (11.7)	31 (12.4)	27 (11.0)
Individuals presenting clinically rated symptoms of ADHD, *n* (%)	143 (28.8)	76 (30.4)	67 (27.2)
Long-chain n-3 PUFA supplementation, *n* (%)	249 (50.2)	122 (48.8)	127 (51.6)
Maternal preintervention 25(OH)D, nmol/L, [mean (SD)]	75.81 (25.66)	75.57 (25.44)	76.05 (25.92)
Maternal preintervention 25(OH)D, ≥75 nmol/L, *n* (%)	253 (51.4)	125 (50.4)	128 (52.5)
Maternal post-intervention 25(OH)D, nmol/L, [mean (SD)]	89.99 (38.09)	71.86 (31.54)	108.33 (35.31)
Maternal post-intervention 25(OH)D,≥75 nmol/L, *n* (%)	313 (64.0)	108 (43.9)	205 (84.4)
Maternal age at childbirth, y [mean (SD)]	32.33 (4.28)	31.98 (4.24)	32.69 (4.30)
Maternal pre-pregnancy weight, kg, [mean (SD)]	69.17 (13.57)	69.15 (13.18)	69.19 (13.99)
Parity			
1, *n* (%)	219 (44.2)	123 (49.2)	96 (39.0)
2, *n* (%)	198 (39.9)	91 (36.4)	107 (43.5)
≥3, *n* (%)	79 (15.9)	36 (14.4)	43 (17.5)
Alcohol intake in pregnancy, *n* (%)	81 (16.4)	39 (15.6)	42 (17.1)
Smoking third trimester, *n* (%)	17 (3.4)	11 (4.4)	6 (2.4)
Exclusive lactation, weeks (median [IQR])	17.43 [8.57, 21.57]	17.57 [8.93, 21.68]	17.43 [8.29, 21.39]
Maternal educational level (%)			
Low (Elementary school or college graduate)	41 (8.3)	24 (9.6)	17 (6.9)
Medium (Tradesman certification or bachelor's degree)	314 (63.3)	162 (64.8)	152 (61.8)
High (Master's degree or higher)	141 (28.4)	64 (25.6)	77 (31.3)
Household income (%)			
Low (< 100.000DKK[1])	44 (8.9)	23 (9.2)	21 (8.5)
Medium (100.000-200.000 DKK)	257 (51.8)	134 (53.6)	123 (50.0)
High (> 200.000 DKK)	195 (39.3)	93 (37.2)	102 (41.5)
Fathers age, y, [mean (SD)]	34.63 (5.19)	34.29 (5.20)	34.98 (5.17)
Gestational age, d [mean (SD)]	279.43 (10.86)	279.32 (10.25)	279.54 (11.46)
Season of birth			
Winter, *n* (%)	179 (36.1)	87 (34.8)	92 (37.4)
Spring, *n* (%)	97 (19.6)	50 (20.0)	47 (19.1)
Summer, *n* (%)	100 (20.2)	50 (20.0)	50 (20.3)
Fall, *n* (%)	120 (24.2)	63 (25.2)	57 (23.2)
Sex, male, *n* (%)	256 (51.6)	123 (49.2)	133 (54.1)
Race, White, *n* (%)	475 (95.8)	240 (96.0)	235 (95.5)

Abbreviations: ADHD, attention deficit hyperactivity disorder; RCT, randomized controlled trial; SD, standard deviation; IQR, interquartile range; N = number.
SI Conversion: vitamin D can be converted to ng/mL by dividing by 2.496.
Alcohol intake in pregnancy describes any intake of alcohol during pregnancy, yes/no.
Smoking in third trimester describes any smoking in third trimester of pregnancy, yes/no.
Information on race was obtained through parental interviews and was defined as either white or non-white.
[1] *DKK = 0.14 USD.*

consecutive follow-up and longitudinal deep phenotyping of the COPSAC2010 cohort allowed us to investigate the effects of serum 25(OH)D from the prenatal period until childhood controlling for potential confounders.

The study was limited by the low number of clinically evaluated cases of autism [39], which could explain why, we found no overall intervention effect. *A post hoc power calculation showed that the present study was underpowered (See* Supplementary Results*).* Additionally, we were unable to determine whether a higher dose initiated earlier in pregnancy or even pre-pregnancy would have caused an effect. Further, the observational result of the study was limited by missing information on parental mental health status—an important potential confounder considering both autism and ADHD are highly heritable (heritability estimate for autism 74–93% and for ADHD 70–80%) [1,2]. Analyses on the effect of maternal preintervention serum 25(OH)D adjusted for the mother's genetic risk of autism or ADHD removed the effect on ADHD (Supplementary Table 15). Lastly, the external validity of the present study is limited by the relatively high levels of maternal serum 25(OH)D when compared to global reports hereof [3].

Regardless of the intervention, but with the risk of lifestyle confounding, we observed that higher maternal preintervention 25(OH)D was associated with a reduced risk of autism and ADHD and lower clinically evaluated symptom load of autism but not ADHD. However, this association with autistic symptoms was not significant using parent-reported autistic traits. Higher maternal serum 25(OH)D in pregnancy has previously been associated with low risk of both autism and ADHD diagnosis [9,11,13,14]. The Generation R study reported an association between higher maternal gestational 25(OH)D and lower parent-rated autistic trait severity among offspring measured by SRS-2 in a large cohort comprising 2866 mother-child pairs [16]. In a smaller case-control study, higher gestational 25(OH)D was also associated with fewer autistic symptoms measured by childhood autism rating scale completed by health care professionals [7,40]. Finally, a large birth cohort study reported no association between gestational 25(OH)D and later parent-reported symptoms of ADHD [21].

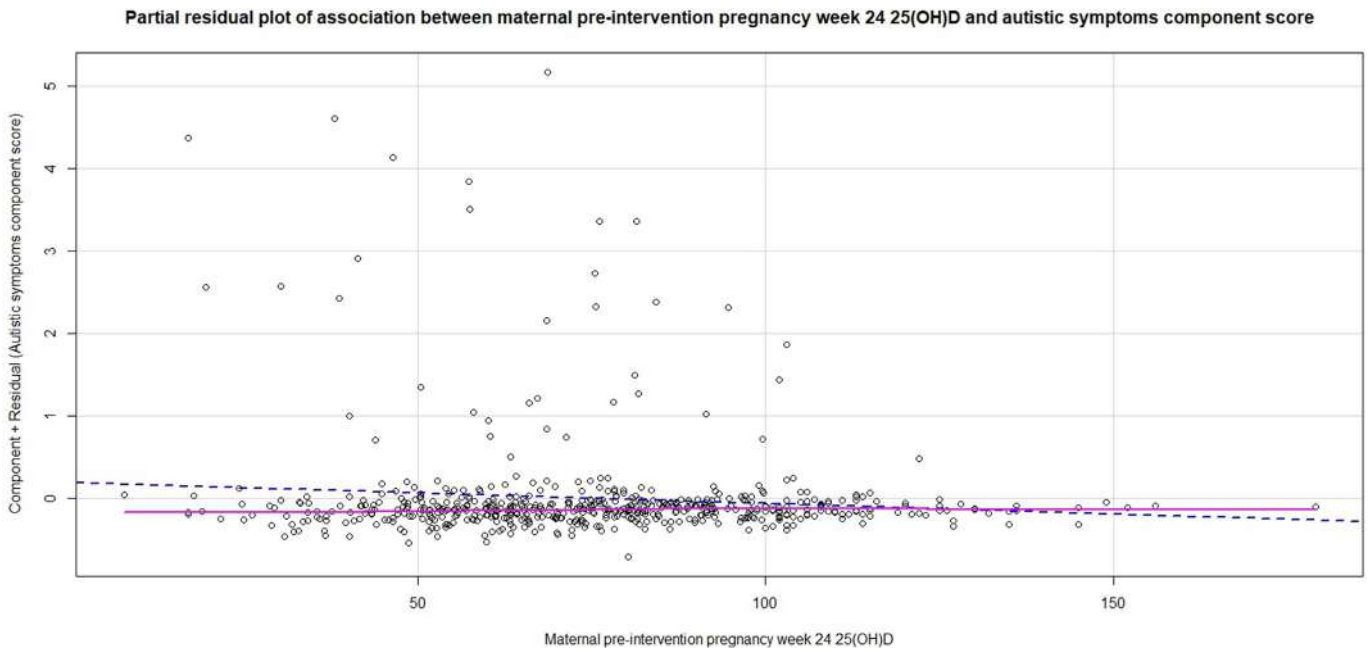

Figure 2. Partial residual plot of the covariate adjusted linear association between maternal preintervention pregnancy week 24 25(OH)D and autistic symptom load measured by Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version among 569 individuals. The linear fit is represented by the broken blue line and a smooth (loess) of the partial residuals by a solid magenta line (R package: crPlots). Adjusted for child sex, birth weight, gestational age, season of week 24 25(OH)D measurement, social circumstances, maternal smoking in third trimester of pregnancy, maternal pre-pregnancy weight, and fathers´ age. The study population included all individuals included in the COpenhagen Prospective Study on Neuro-PSYCHiatric Development 2010 cohort with available measurements of 25(OH)D in pregnancy week 24 and with offspring participating in the COpenhagen Prospective Study on Neuro-PSYCHiatric Development visit at age 10 regardless of participation in the vitamin D3 trial. 25(OH)D, 25-hydroxy-vitamin D.

Table 2
Vitamin D3 supplementation and K-SADS-PL evaluation of autism and ADHD

K-SADS-PL measure	*N* (N cases)	Odds ratio estimate (CI)	*N* (N cases)	Odds ratio estimate (CI) adjusted[1]
Autism	496 (12)	0.72 (0.21,2.29)	492 (12)	0.72 (0.21,2.32)
ADHD	496 (58)	0.87 (0.50,1.51)	492 (57)	0.87 (0.49,1.53)
K-SADS-PL measure	*N*	Beta estimate (CI)	*N*	Beta estimate (CI) adjusted[1]
Autistic symptoms component score	496	−0.08 (−0.19,0.03)	492	−0.08 (−0.19,0.03)
ADHD symptoms component score	496	−0.06 (−0.18,0.07)	492	−0.07 (−0.19,0.05)

ADHD, attention deficit hyperactivity disorder; CI, confidence interval; K-SADS-PL, Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children-Present and Lifetime Version; *N*, number.
ICD-10 diagnostic codes of Autism assigned at the COPSYCH visit included the DF84.0, DF84.5 and DF84.8 diagnostic codes, and of ADHD DF90.0, DF90.8 and DF98.8.
[1] Adjusted for week 24 vitamin D levels, season of birth, child sex, and the n-3 long-chain PUFA intervention.

The high-dose vitamin D3 supplementation during pregnancy did not show overall protection against child autism and ADHD diagnosis or symptom load. To our knowledge, no RCT has previously investigated the effect of vitamin D supplementation in pregnancy on risk of autism or ADHD. In a prospective study from 2016, vitamin D supplementation in pregnancy among mothers of children with autism decreased the recurrence rate of autism in newborn siblings from previously reported 20% to 5% [41]. These mothers were prescribed 5000 IU vitamin D3 per day during pregnancy as opposed to 2800 IU/day in the present study. In the study, newborns were also supplemented with 1000 IU/day vitamin D until the age of 3. A lower intervention dose of vitamin D3 in our RCT may therefore to some extent explain the discrepancy with our results.

Among mothers with early pregnancy serum 25(OH)D $\geq$*75 nmol/L*, we found that the high-dose vitamin D3 intervention may lower the risk of autism diagnosis. This may suggest that high 25(OH)D in early pregnancy is of particular importance for typical brain development. This is supported by a large registry-based study showing an association between lower maternal serum 25(OH)D in first and early second trimester of pregnancy and increased risk of autism diagnosis [11]. Furthermore, early pregnancy may represent a vulnerable phase because basics of the neural system are established already during the embryonic stage [42]. Hence, it is plausible that the vitamin D3 intervention in our study was introduced too late in pregnancy or that the intervention dose was too low to achieve an effect among mothers with vitamin D deficiency at randomization.

We performed a threshold analysis of the effect of the vitamin D3 supplementation on autistic symptom load according to maternal pre-intervention serum 25(OH)D. The analysis revealed a U-shaped association indicative of a protective effect of vitamin D3 intervention

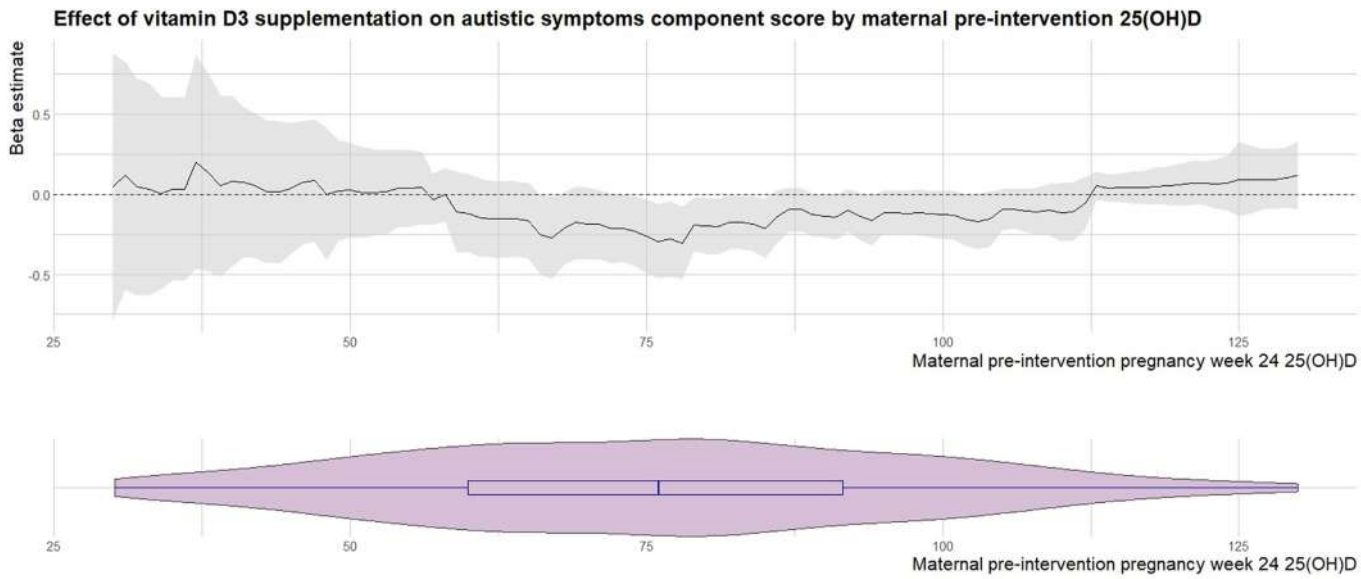

Figure 3. Threshold analysis of the effect of high-dose vitamin D3 supplementation on autistic symptom load measured by Kiddie-Schedule for Affective Disorders and Schizophrenia for School-Age Children - Present and Lifetime Version according to maternal preintervention serum 25(OH)D measured at pregnancy week 24.
Overall sample size was 492 individuals. The violin plot below shows the distribution of the measured maternal preintervention serum 25(OH)D. Linear regression was used to estimate the effect of the intervention according to maternal preintervention 25(OH)D within a moving window of ± 20 nmol/L. Black line marks the β estimate and gray area the corresponding 95% confidence interval. Estimates are unadjusted. 25(OH)D, 25-hydroxy-vitamin D.

among mothers with preintervention levels between ~55 and 110 nmol/L. U-shaped associations between vitamin D and bone health as well as aeroallergen sensitization have been described previously [43,44]. Further, a case-control study has also reported higher risk of schizophrenia among children with either low or high 25(OH)D measured in neonatal dried blood samples [45]. Future studies on vitamin D and autism should be aware of potential non-linear associations.

Two previous studies have reported sex differences in the relationship between early life vitamin D status and autism, where one study reported a protective association of higher neonatal vitamin D only among girls [20], whereas another study reported a protective association of higher gestational vitamin D among boys and an opposite association among girls [33]. In our study, there was no interaction between sex and the intervention for neither autism nor ADHD.

Neither the suggested protective effect on autism diagnosis of the vitamin D3 intervention within mothers with early pregnancy levels of 25(OH)D ≥75nmol/L nor the protective association of higher gestational serum 25(OH)D on autistic symptom load could be replicated using the parent-reported SRS-2. However, SRS-2 scores are influenced by factors not specific to autism such as developmental difficulties and behavioral problems. Thus, SRS scores may to some extent reflect parent-evaluated general impairment of the child instead of the severity of core autistic traits [38]. Therefore, compared to a clinician rating of autistic symptoms, the SRS-2 may be a more unspecific measure of autistic trait severity, which may have prevented us from replicating our findings.

Finally, we found no associations of maternal post-intervention serum 25(OH)D or child serum 25(OH)D at either age 6 mo or 6 y on risk of autism or ADHD, which contrasts a recent meta-analysis showing evidence of lower serum 25(OH)D in children and adolescents with autism [46]. However, all included studies were case-control and may be prone to bias from lifestyle factors such as picky eating patterns, less time spent outdoors, and medication influencing 25(OH)D levels [46], factors which would probably not be as influential in childhood measurements. A meta-analysis from 2018 also suggested an association between low childhood 25(OH)D status and risk of ADHD [15], but a Mendelian randomization study did not find evidence of a causal relationship [47].

In conclusion, *higher maternal preintervention 25(OH)D was associated with a decreased risk of autism, lower autistic symptom load, and decreased risk of ADHD diagnosis.* High-dose vitamin D3 supplementation from pregnancy wk 24 until 1 wk postpartum did not reduce the overall risk of autism and ADHD diagnosis or symptom load in the offspring at age 10 when compared to standard dose vitamin D3.

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Authors contributions

The authors' responsibilities were as follows –; KA: drafted the manuscript. All co-authors (JRMJ, AS, DH, RV, JBR, NB, AE, PM, NF, MH, BF, BYG, MAR, NB, JS, KB, BHE, BC): have provided important intellectual input and contributed considerably to the analyses and interpretation of the data. All authors: guarantee that the

accuracy and integrity of any part of the work have been appropriately investigated and resolved and all have approved the final version of the manuscript. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication. No honorarium, grant, or other form of payment was given to any of the authors to produce this manuscript, and all authors: read and approved the final manuscript.

Conflict of interest

BHE is part of the Advisory Board of Eli Lilly Denmark A/S, Janssen-Cilag, Lundbeck Pharma A/S, and Takeda Pharmaceutical Company Ltd; and has received lecture fees from Bristol-Myers Squibb, Boehringer Ingelheim, Otsuka Pharma Scandinavia AB, Eli Lilly Company, and Lundbeck Pharma A/S. BG has been the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS) (January 2009 – December 2021), which was partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. All grants are the property of the Mental Health Services in the Capital Region of Denmark and administrated by them. She has no other conflicts to disclose. All other authors report no conflicts of interest. *The funding agencies did not have any role in design and conduct of the study; collection, management, and interpretation of the data; or preparation, review, or approval of the manuscript. No pharmaceutical company was involved in the study.*

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Governance

We are aware of and comply with recognized codes of good research practice, including the Danish Code of Conduct for Research Integrity. We comply with national and international rules on the safety and rights of patients and healthy subjects, including Good Clinical Practice as defined in the EU's Directive on Good Clinical Practice, the International Conference on Harmonisation's (ICH) Good Clinical Practice guidelines and the Helsinki Declaration. Privacy is important to us which is why we follow national and international legislation on General Data Protection Regulation (GDPR), the Danish Act on Processing of Personal Data and the practice of the Danish Data Inspectorate.

Data availability

Data described in the manuscript, code book, and analytic code will be made available upon request pending approval by author Klaus Bønnelykke (kb@copsac.com) and a signed data access agreement.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.12.002.

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