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AUTOIMMUNE DISEASES

Neonatal vitamin D levels and autoimmune disorders: a Danish population-based cohort study

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Abstract

To examine the associations of neonatal 25-hydroxyvitamin D (25(OH)D) and vitamin D-binding protein (DBP), and their corresponding genetic predictors, with the risk of nine autoimmune disorders. We conducted a population-based cohort study of a random sample of individuals born in Denmark between 1981 and 2005, sourced from the iPSYCH2012 study. We measured 25(OH)D and DBP concentrations in neonatal dried blood spots. We identified individuals diagnosed with selected autoimmune disorders (multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, type 1 diabetes mellitus, autoimmune thyroiditis, Graves' disease, celiac disease, Crohn's disease, and ulcerative colitis). Cox regression was employed to estimate hazard ratios (HRs) for any autoimmune disorder and for nine specific diagnoses, in relation to 25(OH)D, DBP, and their polygenic scores (PGSs). Among 20,404 eligible individuals, 757 (3.7%) developed an autoimmune disorder. Neither neonatal 25(OH)D nor DBP was associated with the risk of any autoimmune disorder, with HRs of 1.07 (95% CI, 0.99–1.15) and 0.99 (95% CI, 0.92–1.07) per standard deviation (SD) increase, respectively. Similarly, PGSs for 25(OH)D and DBP did not show an association with any autoimmune disorder, with HRs of 1.04 (95% CI, 0.97–1.12) and 0.98 (95% CI, 0.91–1.05) per SD increase, respectively. Findings were similar when exposures were analyzed in tertiles and across nine individual autoimmune disorders. Neonatal vitamin D is not associated with the risk of autoimmune disorders. Similarly, genetic predictors of vitamin D status, as reflected in PGSs for 25(OH)D and DBP, are not associated with the risk of autoimmune disorders.

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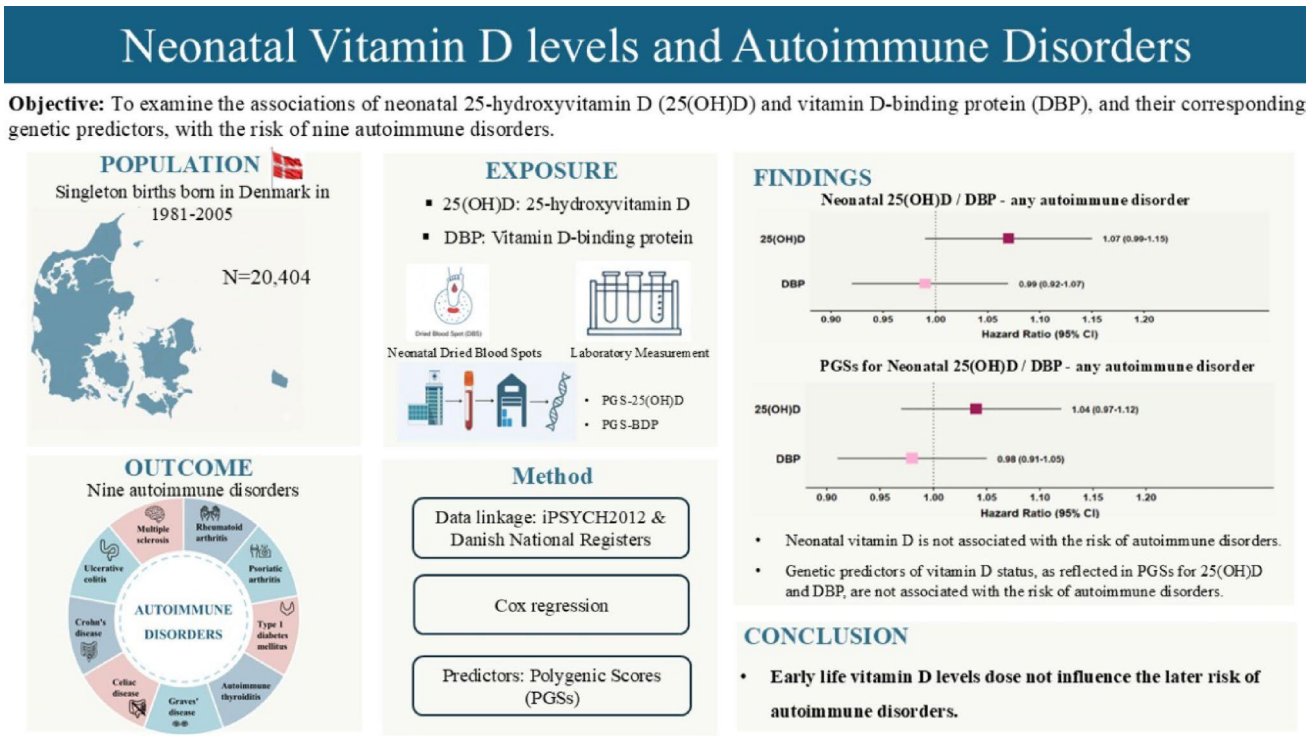
Graphical abstract



Keywords Vitamin D · Autoimmune disorders · Cohort study · Epidemiology

Introduction

Vitamin D has been increasingly recognized for its influence on various biological processes, in addition to its canonical role in calcium-regulated bone health [1, 2]. There has been sustained interest in the association between vitamin D status and immune-related outcomes [3, 4]. Experimental studies have shown that vitamin D can regulate the immune response through its interactions with immune cells, such as T and B lymphocytes, and influence gene expressions involved in inflammatory pathways [5]. A recent large-scale randomized trial involving 25,871 participants demonstrated that vitamin D supplementation for 5 years can reduce the risk of autoimmune diseases by 22% [6].

In particular, there is strong evidence from epidemiological studies suggesting that vitamin D deficiency is linked to a higher risk of multiple sclerosis [7, 8]. Studies based on Mendelian randomization provide additional support for the hypothesis that low vitamin D status is a causal risk factor for multiple sclerosis [9–12]. Of interest, research indicates that the early life period, particularly during the prenatal and childhood years, represents a crucial window in which low levels of 25-hydroxyvitamin D (25(OH)D) may influence future disease risk [13, 14]. A Danish case-control study measuring 25(OH)D levels in neonatal dried blood spots found that lower 25(OH)D levels were associated with an increased risk of multiple sclerosis [8].

Apart from multiple sclerosis, evidence linking low vitamin D levels to the risk of other autoimmune disorders is either null or weak. Ecological studies on the cessation of vitamin D fortification of margarine found suggestive evidence of an increased risk of celiac disease after cessation [15]. Studies based on measured neonatal 25(OH)D concentrations found no association with rheumatoid arthritis [16] or type 1 diabetes mellitus [17]. To the best of our knowledge, the potential association between neonatal 25(OH)D status and the later development of other autoimmune conditions has not been examined.

Vitamin D-binding protein (DBP) is a circulating protein that transports vitamin D-related molecules and influences the half-life of 25(OH)D [18, 19]. One study suggested low maternal DBP concentration and an increased risk of type 1 diabetes mellitus in the offspring [20]. To the best of our knowledge, no study has examined neonatal DBP levels and their association with the risk of autoimmune disorders.

Based on the population-based subcohort within the Lundbeck Foundation Initiative for Integrative Psychiatric Research (iPSYCH)2012 study [21], we investigated the associations between neonatal 25(OH)D concentrations

and the risk of nine autoimmune disorders (multiple sclerosis, rheumatoid arthritis, psoriatic arthritis, type 1 diabetes mellitus, autoimmune thyroiditis, Graves' disease, celiac disease, Crohn's disease, and ulcerative colitis), both collectively and individually. We hypothesized that low neonatal 25(OH)D concentration would be associated with an increased risk of autoimmune disorders. As secondary hypotheses, we examined whether (a) low DBP concentration, and (b) low genetically predicted 25(OH)D and DBP concentrations, were associated with an increased risk of autoimmune disorders.

Methods

Setting

We conducted a cohort study using population data by linking the iPSYCH2012 study to Danish national registers. We reported the study in accordance with the Strengthening Reporting of Observational Studies in Epidemiology (STROBE) guidelines [22]. The study protocol was preregistered with the Open Science Framework. We utilized the unique personal identification number (CPR number) assigned to all residents and live-born children in Denmark. Detailed information regarding the iPSYCH2012 study has been published elsewhere [21]. Briefly, the iPSYCH2012 study was selected from the Danish Civil Registration System [23] of all singleton births born between May 1, 1981, and December 31, 2005, who were alive and residing in Denmark at the age of 1 year and had a known mother (the source population). The iPSYCH2012 case-cohort study comprises individuals diagnosed with major mental illnesses by the end of 2012 (not included in this study). Additionally, a random sample of 30,000 subjects from the Danish population born during the same period, referred to as the subcohort, was selected, with a sampling probability of 2.04%. Because the subcohort was selected randomly from the source population, some individuals may also have the disorders. Consequently, the subcohort is representative of the entire underlying source population.

Study population

We restricted our study to the 30,000 individuals in the iPSYCH2012 subcohort. We excluded 2,595 individuals with no genetic data, 4,534 with no data on neonatal levels of 25(OH)D or DBP, and 2,467 individuals of non-European ancestry (Fig. 1 for the flowchart). European ancestry was determined based on the offspring's genotype, as described by Privé et al. [24, 25]. In brief, the first 20 principal components were estimated from common single-nucleotide polymorphisms (minor allele frequency$\geq$0.01), and European ancestry was inferred using the leading principal components, and individuals with a logarithmic distance from the cluster center greater than 4.8 were excluded.

Measures of 25(OH)D and DBP concentrations

The genotypes, along with 25(OH)D and DBP concentrations, were analyzed in dried blood spots collected from newborns during routine screening at birth from the Danish Newborn Screening Biobank [26]. This Biobank stores dried blood spots collected at birth from almost all infants born in Denmark since May 1, 1981 [26]. DNA genotyping was performed at the Broad Institute (Boston, MA, USA) using the Infinium PsychChip (version 1.0; Illumina, San Diego, CA, USA).

To measure 25(OH)D, we utilized previously established methods that leverage tandem mass spectrometry [27, 28]. The measurement was validated through both external and internal methods [27]. We assessed Standard Reference Material 972 serum from the National Institute of Standards and Technology (Gaithersburg, MD, USA) and achieved excellent accuracy, with results ranging from 92% to 105%. Our method could detect 25(OH)D concentrations as low as 5 nmol/L in protein extracts. All analyses focused on the total 25(OH)D, encompassing the combined levels of 25(OH)D2 and 25(OH)D3. Throughout the study, our laboratory

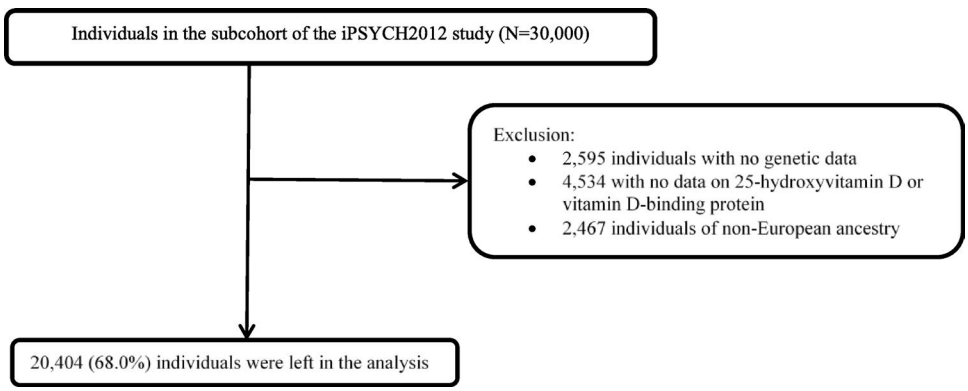


Fig. 1 Flowchart of the study population

participated in the Vitamin D External Assessment Scheme, which verified the precision of our assay platform.

To measure DBP, proteins were extracted from dried blood spots and analyzed using a multiplex immunoassay with U-plex plates from Meso-Scale Diagnostics (MSD), Maryland, USA. We used specific antibodies targeting DBP (HYB249–05 and HYB249–01), obtained from Statens Serum Institut Antibodies in Copenhagen, Denmark. The DBP detection limits were established at 2.07 µg/L for the lower threshold and 79.8 mg/L for the upper threshold. The intra-assay variation was recorded at 7.6%, while the inter-assay variation stood at 22.4%.

For both 25(OH)D and DBP levels, we accounted for plate and batch effects by regressing them out of the estimates using a mixed linear model. We then transformed the data using a rank-based inverse normal transformation [29].

Assessment of autoimmune disorders

Information on autoimmune diseases was extracted from the Danish National Patient Register, which has documented information on inpatient care since 1977, as well as on outpatient and emergency room visits since 1995 [30]. The International Classification of Diseases, Eighth Revision (ICD-8) was used from 1977 to 1993, and the Tenth Revision (ICD-10) from 1994 onwards. We obtained information on the nine most prevalent autoimmune diseases: Multiple sclerosis (ICD-8 code 340; ICD-10 code G35), rheumatoid arthritis (ICD-8 codes 712.09, 712.19, and 712.39; ICD-10 codes M05, M06, and M08 excluding M08.1), psoriatic arthritis (ICD-8 codes 696.00 and 696.09; ICD-10 codes L40.5, M07.0-M07.3, and M09.0), type 1 diabetes mellitus (ICD-8 code 250 before 1987 and 249 from 1987 to 1993; ICD-10 code E10 and O24.0), autoimmune thyroiditis (ICD-8 code 245.03; ICD-10 code E06.3), Graves' disease (ICD-8 code 242.00; ICD-10 code E05.0), celiac disease (ICD-8 codes 269.00 and 269.10; ICD-10 code K90.0), Crohn's disease (ICD-8 code 563.0; ICD-10 codes K50), and ulcerative colitis (ICD-8 code 563.19 and 569.04; ICD-10 codes K51) (See Table S1 in the Supplement).

Covariates

The following covariates were identified a priori based on causal diagrams using directed acyclic graphs and included in the models: child characteristics, including gender, calendar year of birth (1981–1985, 1986–1990, 1991–1995, 1996–2000, 2001–2005), and season of birth (winter, spring, summer, fall); and maternal characteristics, including age at delivery (<25, 25–29, 30–34, ≥35 years), parity, cohabiting status at delivery (married, cohabiting, single), and highest education attained (primary school, high school/vocational school, college/university).

Statistical analysis

Each participant was followed from birth until the earliest occurrence of an autoimmune disorder, emigration, death, or December 31, 2021. The onset of individual autoimmune disease was defined as the date of the participant's first hospital visit for that specific disease. For the analysis of the broader category of any of the nine autoimmune disorders (henceforth referred to as any autoimmune disorder), the onset time was considered as the date of the earliest diagnosed autoimmune disorder.

We assessed 25(OH)D concentrations as continuous variables (per standard deviation (SD) increase) and as tertiles. To explore the absolute risk of autoimmune disorders in relation to 25(OH)D concentrations, we examined cumulative incidence curves for the 25(OH)D tertiles. The cumulative incidence curves were smoothed using the Epanechnikov kernel [31]. To estimate hazard ratios (HRs) and their corresponding 95% confidence intervals (95% CIs) for any diagnosis and for each of the nine autoimmune diagnoses, we conducted Cox proportional hazards regression analyses. The age of the individuals served as the underlying time scale. Covariates with missing values were included as a separate category [32]. To account for multiple comparisons, we applied a Bonferroni-corrected P-value of 0.005, corresponding to an α of 0.05 and 10 tests per any diagnosis and per specific autoimmune disorder. Statistical analyses were conducted using STATA 18.0 (StataCorp, College Station, TX, USA).

We conducted two secondary analyses: First, as variations in DBP levels can directly influence 25(OH)D levels, we explored the risk of autoimmune disorders by neonatal DBP levels, both per SD increase and by tertiles. Second, polygenic scores (PGSs) can predict variance in 25(OH)D and DBP concentrations across the lifespan [33, 34]. We generated individual-level PGSs for 25(OH)D and DBP and examined whether these scores were associated with register-based autoimmune disorders. We derived the PGSs by weighting the effect size of multiple risk alleles obtained from genome-wide association studies (GWAS) [35], using the LDpred2-auto approach [36]. Briefly, GWAS summary statistics were harmonized with the target genotype data, and LDpred2-auto was applied to estimate linkage disequilibrium-adjusted single-nucleotide polymorphism (SNP) effect sizes. Individual PGSs were calculated as the weighted sum of risk alleles across the genome using the posterior effect sizes estimated by LDpred2-auto. We standardized the PGSs using the mean and SD of each PGS: (observed value - mean)/SD, yielding a mean of 0 and a SD

of 1. For the secondary analysis, we further adjusted for the first 10 principal components [24, 25].

Ethical considerations: According to Danish legislation, materials from the Danish Neonatal Screening Biobank can be used for research, provided approval is obtained from both the Biobank and the relevant Scientific Ethical Committee [37]. This study has been approved by the Danish Data Protection Agency and the Danish Health Data Authority [37]. Under Danish law, informed consent is not required for register-based studies that utilize anonymized data [38].

Results

A total of 20,404 individuals were included in the analysis, of whom 50.9% were male. The characteristics of the study population and incidence rate of any autoimmune disorder by characteristics are presented in Table 1. The median (interquartile range) was 22.2 (14.0–31.7) nmol/L for 25(OH)D and 2.0 (1.2–3.0) mg/L for DBP. At the end of follow-up, participants had a mean (SD) age of 27.7 (4.7) years. Over a maximum follow-up of 40.7 years (interquartile range, 28.4–33.9 years), 757 individuals developed an autoimmune disorder, with a cumulative incidence of 7.1% (95% CI, 6.3–7.9%). The most common autoimmune diagnosis was type 1 diabetes mellitus ($n = 162$), followed by ulcerative colitis ($n = 158$), Crohn's disease ($n = 123$), and rheumatoid arthritis ($n = 111$).

Primary analysis of neonatal 25(OH)D and autoimmune disorders

Estimates of HRs for any autoimmune disorder and for the nine specific autoimmune disorders per SD increase in neonatal 25(OH)D are presented in Fig. 2. Neonatal 25(OH)D was not associated with the risk of any autoimmune disorder (HR = 1.07; 95% CI, 0.99–1.15). Findings were similar across the nine autoimmune disorders, with HRs ranging from 0.92 (95% CI, 0.67–1.27) for psoriatic arthritis to 1.23 (95% CI, 0.94–1.61) for autoimmune thyroiditis.

Table 1 Descriptive characteristics of the study population ($n = 20,404$)

Baseline characteristics	*N* (%)	Any autoimmune disorders	
		Events	Incidence rate (per 10,000 PY)
Maternal age			
<25	4,258 (20.9)	198	15.38
25–29	7,978 (39.1)	283	12.64
30–34	5,885 (28.8)	207	13.36
≥35	2,283 (11.2)	69	11.82
Primiparous			
No	11,175 (54.8)	409	13.24
Yes	9,229 (45.2)	348	13.53
Maternal cohabiting status			
Married couple	9,852 (48.3)	341	13.14
Cohabiting couple	6,575 (32.2)	215	12.61
Single	1,227 (6.0)	48	14.59
Unknown	2,750 (13.5)	153	14.87
Maternal highest education attained			
Primary school	6,031 (29.6)	264	14.67
High school or vocational school	8,637 (42.3)	315	13.65
College or university	5,121 (25.1)	152	11.32
Unknown	615 (3.0)	26	12.35
Gender			
Female	10,025 (49.1)	463	16.65
Male	10,379 (50.9)	294	10.21
Birth year			
1981–1985	3,665 (18.0)	192	14.18
1986–1990	4,532 (22.2)	218	14.77
1991–1995	3,838 (18.8)	156	14.35
1996–2000	4,212 (20.6)	119	12.08
2000–2005	4,157 (20.4)	72	9.50
Season			
Winter (December to February)	4,885 (23.9)	187	13.82
Spring (March to May)	5,122 (25.1)	207	14.41
Summer (June to August)	5,419 (26.6)	197	13.20
Autumn (September to November)	4,978 (24.4)	166	12.05

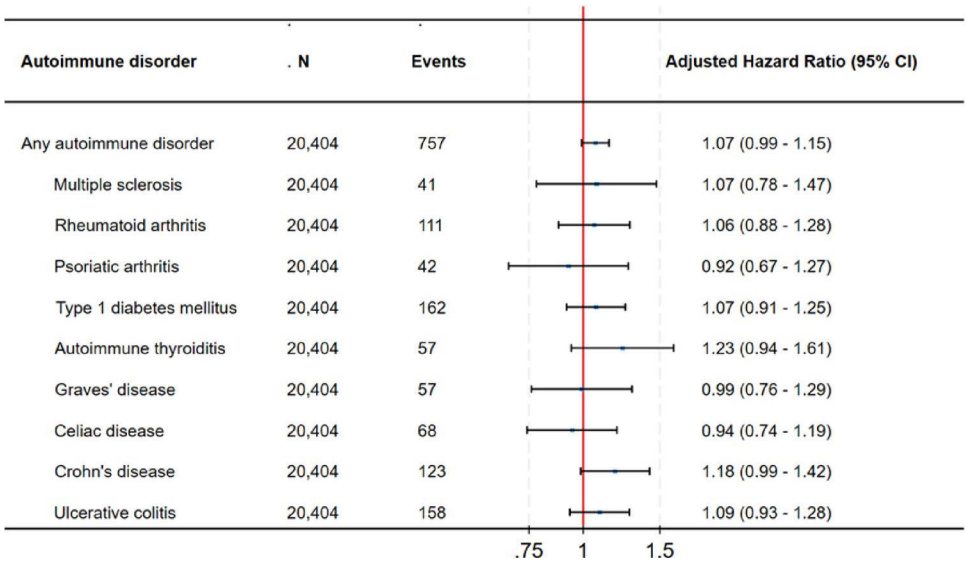


Fig. 2 Adjusted hazard ratios for autoimmune disorders according to a one standard deviation increase in neonatal 25(OH)D. All estimates are adjusted for gender, birth year, season, maternal age, maternal cohabiting status, and maternal high-est educational attainment

We further examined 25(OH)D in tertiles to assess potential non-linear associations. Higher neonatal 25(OH)D concentrations (second and third tertiles vs. the lowest tertile) were associated with a slightly higher cumulative incidence of any autoimmune disorder. However, the associations across tertiles varied for the nine individual autoimmune disorders (Fig. 3). Compared with the lowest tertile, the adjusted HRs for any autoimmune disorder were 1.13 (95% CI, 0.94–1.35, $p=0.183$) for the second tertile and 1.23 (95% CI, 1.03–1.47, $p=0.022$) for the highest tertile. Similarly, a higher risk of Crohn's disease was observed in the highest tertile (HR = 1.60; 95% CI, 1.03–2.49, $p=0.035$) (Fig. 4). However, none of these associations remained statistically significant after Bonferroni correction (threshold $p<0.005$).

Secondary analyses assessed neonatal DBP and genetic predictors of 25(OH)D and DBP in relation to autoimmune disorders

With respect to DBP, no association was observed with any autoimmune disorder (HR = 0.99; 95% CI, 0.92–1.07 per SD increase). The HRs ranged from 0.78 (95% CI, 0.60–1.02) for Graves' disease to 1.17 (95% CI, 0.90–1.52) for autoimmune thyroiditis (Figure S1). When DBP was analyzed in tertiles, the cumulative incidence of any autoimmune disorder and the nine specific disorders is shown in Figure S2, and the HRs in Figure S3. All 95% CIs included 1, indicating no statistically significant associations, except for individuals in the second tertile, who showed a reduced risk of autoimmune thyroiditis (HR = 0.31; 95% CI: 0.13–0.72, $p=0.006$). However, this finding was based on only seven cases, and there was no dose-response relationship across tertiles. Furthermore, after applying the Bonferroni correction for multiple comparisons, the association was no longer statistically significant.

With respect to the PGSs for 25(OH)D and DBP, no association was observed between genetically predicted 25(OH)D (HR = 1.04; 95% CI, 0.97–1.12) or DBP (HR = 0.98; 95% CI, 0.91–1.05) and the risk of any autoimmune disorder (Figure S4–S5).

Discussion

In this large, population-based cohort study of 20,404 individuals, neonatal 25(OH)D concentrations were not associated with the development of subsequent autoimmune disorders, either overall or for nine individual autoimmune disorders. Similarly, neonatal DBP levels and individual-level PGSs for 25(OH)D and DBP showed no evidence of association with autoimmune disorders.

Experimental studies have demonstrated that vitamin D acts as an immunomodulator, influencing both innate and adaptive immune functions, as well as regulating insulin secretion in pancreatic β-cells [5]. Consequently, it is biologically plausible that vitamin D deficiency may contribute to the development of autoimmune disorders. A recent randomized trial involving 25,871 participants demonstrated that, compared to those who received placebo, those who received vitamin D supplements (2000 IU/day) had a reduced risk of autoimmune diseases (a 22% reduction) [6].

Clinical trials have suggested that vitamin D supplementation may reduce the risk of developing multiple sclerosis [7–9]. This is further supported by several Mendelian randomization studies, which indicate a causal association between higher vitamin D levels and a lower risk of developing multiple sclerosis [10–12]. In contrast, our study

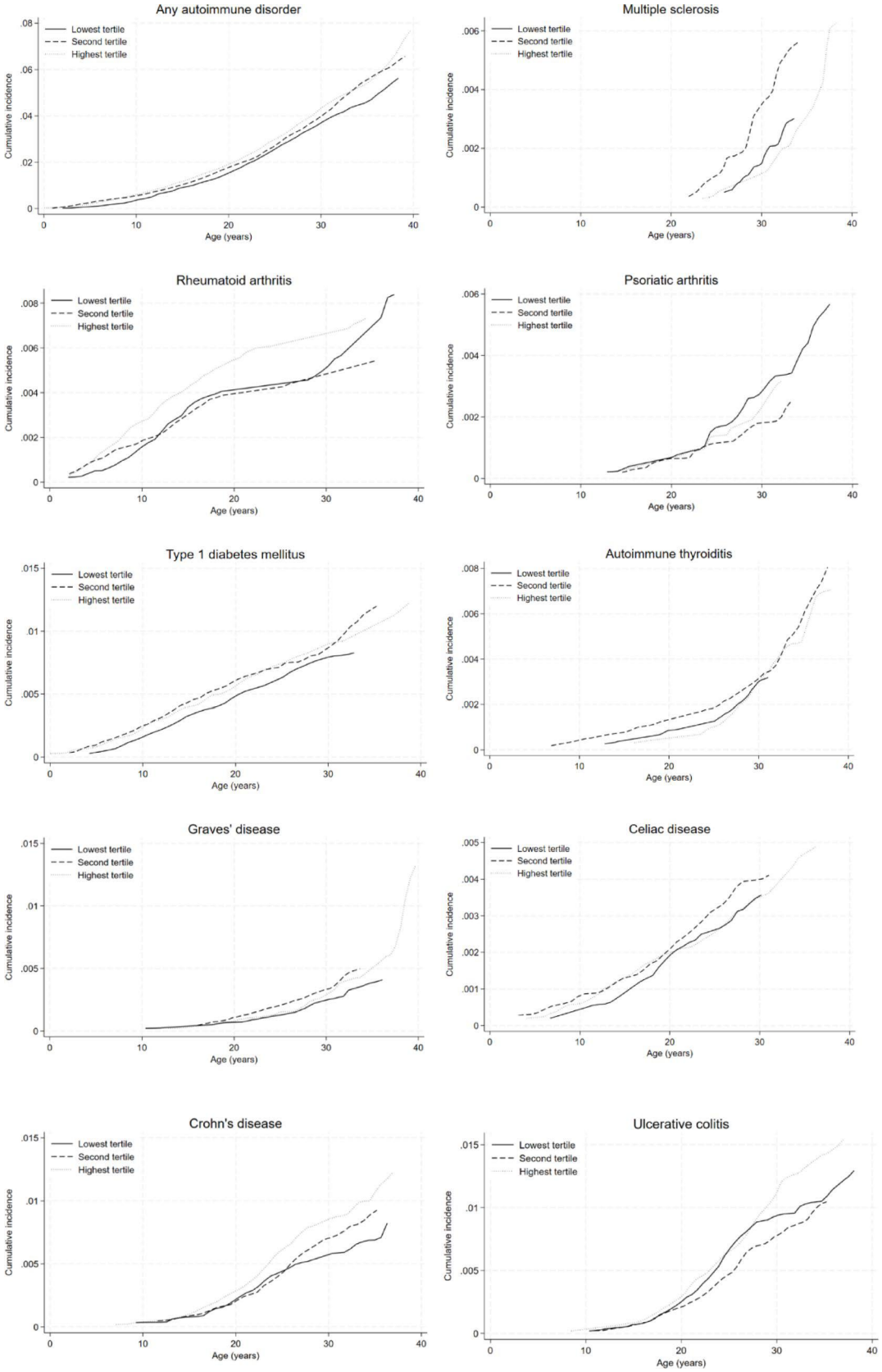


Fig. 3 Cumulative incidence curves according to tertiles of neonatal 25(OH)D

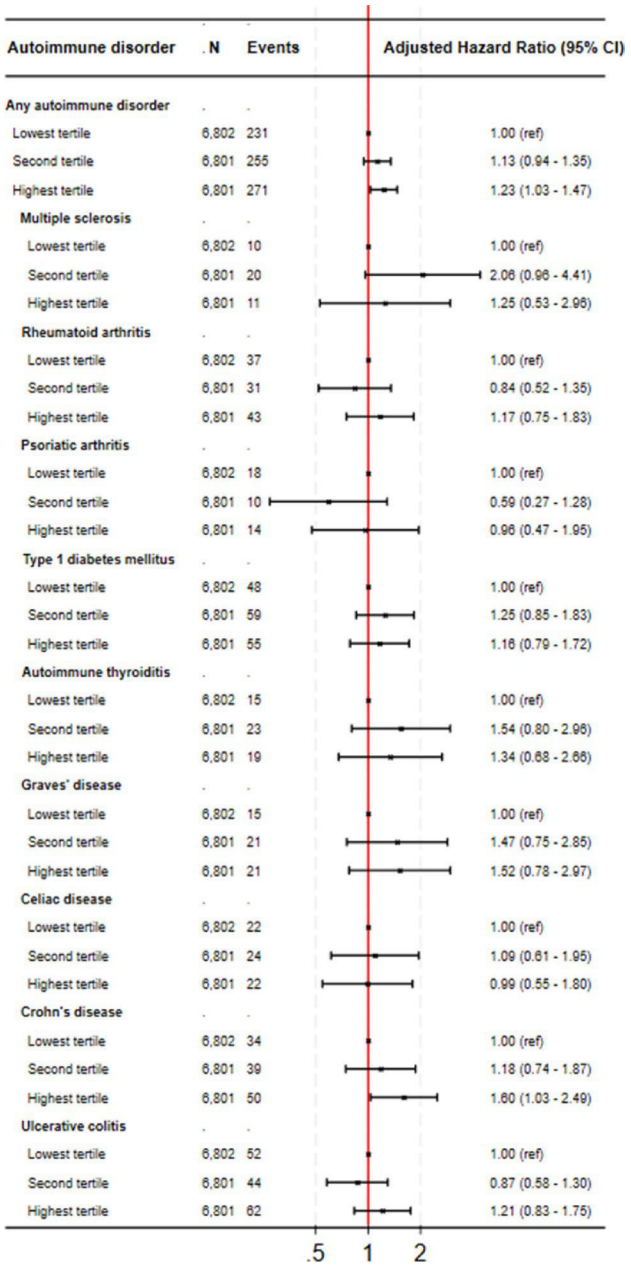


Fig. 4 Adjusted hazard ratios for autoimmune disorders according to tertiles of neonatal 25(OH)D. All estimates are adjusted for gender, birth year, season, maternal age, maternal cohabiting status, and maternal high-est educational attainment

found no association between neonatal 25(OH)D concentrations and the risk of multiple sclerosis. Our null findings for neonatal DBP and for PGSs related to vitamin D metabolism further support this observation. Our results also differ from a Danish matched case–control study, which reported a 30% reduced risk of multiple sclerosis (OR = 0.70, 95% CI 0.57–0.84) per 25 nmol/L increase in 25(OH)D [8]. The discrepant findings may reflect methodological differences between the studies, including differences in case ascertainment, diagnostic criteria, study design, and follow-up duration. The previous study identified multiple sclerosis cases through the Danish Multiple Sclerosis Registry with onset before or in 2012, whereas our study relied on register-based diagnoses and follow-up through 2021. Moreover, as multiple sclerosis typically develops between 20 and 40 years of age [39], our cohort, with a mean (SD) age at the end of follow-up 27.7 (7.4) years, may still be too young for complete case ascertainment. This limitation also applies to other autoimmune disorders with a later onset, such as rheumatoid arthritis, psoriatic arthritis, and autoimmune thyroiditis. In our study, we did not observe any beneficial effects for these disorders either. It is possible that any potential protective effect of vitamin D, if any, is age-dependent, particularly for autoimmune conditions that tend to develop later in adulthood.

Evidence for type 1 diabetes mellitus is more mixed. A meta-analysis involving more than 10,000 participants reported a U-shaped association between 25(OH)D and the risk of type 1 diabetes mellitus [40]. In addition, a clinical trial in Finland found an 80% reduction in type 1 diabetes mellitus at age one among children who received 25(OH)D supplementation during their first year of life [41]. However, this protective effect was not supported by a Mendelian randomization study of 443,734 Europeans, which found no evidence that genetically predicted 25(OH)D levels influence the risk of developing type 1 diabetes mellitus [42]. Our results align with previous Danish registry-based studies, which reported no association between neonatal vitamin D levels and type 1 diabetes mellitus [17]. Another study from the Norwegian Mother and Child (MoBa) cohort reported that cord blood 25(OH)D levels were marginally associated with a 15% reduced risk of type 1 diabetes mellitus (95% CI, 0.72–1.00) per 10 nmol/L increase among children carrying the vitamin D receptor rs11568820 G/G genotype but not AA/AG genotype [20]. This suggests that associations between neonatal vitamin D status and type 1 diabetes mellitus may be modified by genetic variation in vitamin D.

Strengths and limitations

Our study has several strengths. First, it used a large representative sample drawn from an entire population, with a follow-up period of up to 40 years. Second, we measured both 25(OH)D and DBP directly in the same neonatal dried blood spot extracts. Third, we incorporated both biomarkers and PGSs to assess genetically predicted levels of 25(OH)D and DBP. This approach increases the generalizability and reliability of our results. Fourth, we examined the risk of any autoimmune disorder and of nine specific autoimmune disorders to explore potential differences in the associations

between neonatal vitamin D levels and systemic versus organ-specific autoimmune conditions. Lastly, our analysis accounted for a wide range of potential confounding factors, including socioeconomic status and genetic influences.

Our study also has several limitations. First, we assessed 25(OH)D levels solely at birth, which may not accurately represent vitamin D status throughout an individual's early gestation or later post-natal, childhood and adult periods. Vitamin D levels can vary significantly over time and are affected by numerous factors, including latitude, season, diet, supplement use, and sunlight exposure. Likewise, the 25(OH)D PGS accounts for only a small portion of the total variance in these levels. Second, although we adjusted for a variety of confounding variables, we lacked comprehensive data on certain lifestyle factors, such as sun exposure, smoke exposure, diet, and vitamin D supplement intake, which means residual confounding cannot be wholly excluded. Third, autoimmune disorders were identified from hospital diagnoses recorded in the Danish National Patient Register. Consequently, the date of diagnosis reflects the time of clinical recognition rather than the true biological onset of disease, which may occur years earlier. Previous validation studies have demonstrated acceptable validity for several autoimmune disease diagnoses in the Danish National Patient Register, including multiple sclerosis and rheumatoid arthritis [43, 44]. However, diagnostic validity may vary across individual autoimmune disorders and case ascertainment algorithms, and some recorded diagnoses may represent provisional or rule-out diagnoses. Because any resulting outcome measurement error is unlikely to be related to neonatal 25(OH)D concentrations, DBP concentrations, or PRSs, misclassification would most likely be non-differential and therefore bias effect estimates toward the null. Fourth, despite a 40-year follow-up period, our cohort had a mean (SD) age of 27.7 (7.4) years at the end of follow-up and thus may still be too young for complete case ascertainment. Consequently, we cannot exclude a potential association between 25(OH)D and autoimmune disorders that typically present later in adulthood. Finally, despite having a sizeable sample, our ability to investigate less common autoimmune disorders, such as multiple sclerosis and psoriatic arthritis, is limited. As a result, the effect estimates are imprecise when analyzing 25(OH)D in tertiles.

Conclusions

Our findings suggest that neonatal vitamin D is not associated with the risk of autoimmune disorders. Likewise, genetic predisposition related to vitamin D metabolism, reflected by polygenic scores for 25(OH)D and DBP, showed no association with autoimmune disease risk. Replication in studies with longer follow-up is warranted to evaluate potential effects on late-onset autoimmune disorders. Studies with repeated measures of 25(OH)D across the lifespan may help clarify if vitamin D status other than during the neonatal period might influence the risk of autoimmune disorders.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s10654-026-01436-9.

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Author contributions H.T. Horsdal, J.J. McGrath, and X. Liu contributed to the study conception, design, and methodology. Data curation, visualization and analysis were performed by H.T. Horsdal. The first draft of the manuscript was written by H.T. Horsdal, J.J. McGrath, and X. Liu. All authors commented on previous versions of the manuscript and read and approved the final manuscript.

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Declarations

Competing interests The authors have no relevant financial or non-financial interests to disclose.

Ethical approval According to Danish legislation, materials from the Danish Neonatal Screening Biobank can be used for research, provided approval is obtained from both the Biobank and the relevant Scientific Ethical Committee. This study has been approved by the Danish Data Protection Agency and the Danish Health Data Authority. Under Danish law, informed consent is not required for register-based studies that utilize anonymized data.

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