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Association of vitamin D with sepsis incidence and mortality: a large population-based prospective cohort study

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Abstract

Background

The role of vitamin D on the risk and clinical outcomes of sepsis remains incompletely elucidated.

Objectives

This study aims to investigate the association between serum 25-hydroxyvitamin D [25(OH)D] concentrations and the risk of incident sepsis, and to evaluate its relationship with 28-day, 60-day, and 1-year mortality.

Methods

In this prospective cohort study, we analyzed data from the UK Biobank. The association between serum 25(OH)D concentrations and sepsis incidence was evaluated using Cox proportional hazards models, Kaplan–Meier survival curves, and restricted cubic spline analyses.

Results

Over a mean follow-up of 14 years, 15,452 incident sepsis cases were documented. A negative and nonlinear association was observed between serum 25(OH)D levels and sepsis risk. Compared with participants whose 25(OH)D levels were >20 ng/mL, those with levels <10 ng/mL exhibited an adjusted hazard ratio (HR) of 1.28 (1.22–1.34) for sepsis. This association was stronger among women and participants with a BMI <25 kg/m². Furthermore, participants with 25(OH)D <10 ng/mL had significantly higher mortality than those with 25(OH)D >20 ng/mL, with adjusted HRs of 1.14 (1.02–1.27) for 28-day mortality, 1.11 (1.01–1.23) for 60-day mortality, and 1.10 (1.02–1.19) for 1-year

mortality.

Conclusion

Lower serum 25(OH)D concentrations were associated with an increased incidence of sepsis and higher mortality.

Keywords: Vitamin D, sepsis, cohort study, UK Biobank

1. Introduction

Sepsis is defined as life-threatening organ dysfunction caused by a dysregulated host immune response to infection[1]. As a major global health challenge, sepsis is associated with high mortality and substantial healthcare burden. In 2021, approximately 166 million sepsis cases were reported worldwide resulting in 21.4 million related deaths and accounting for 31.5% of total global deaths[2]. Economically, patients with sepsis experience hospital stays that are approximately 75% longer than those of patients hospitalized for most other conditions, and their treatment costs are substantially higher than those of non-sepsis patients [3,4]. This economic burden is underscored by a systematic review estimating the average per-patient cost of sepsis treatment in high-income countries exceeds $32,000[5]. Therefore, the development of effective strategies for the prevention and treatment of sepsis is a critical clinical priority.

Sepsis incidence and progression are influenced by multiple risk factors, including advanced age, immunosuppression, seasonal variations (with higher rates in autumn and winter), and comorbid conditions such as diabetes, renal disease, congestive heart failure, cancer, and abnormal body weight[6–

[9]. Beyond these epidemiological factors, the host's intrinsic immune competence and capacity to regulate inflammation play a central role in determining both susceptibility to sepsis and clinical outcomes. The initial host response involves the recognition of pathogen-associated molecular patterns by innate immune cells through Toll-like receptor (TLR) pathways. TLR activation promotes the production of antimicrobial peptides, including cathelicidins, which are key components of the host's first-line defense against infection. Concurrently, TLR signaling induces a vigorous proinflammatory cytokine response, characterized by the release of cytokines such as tumor necrosis factor (TNF)-α and interleukin (IL)-6. While this inflammatory surge is essential for pathogen clearance, its excessive or dysregulated activation can result in collateral tissue injury, leading to systemic inflammation, endothelial dysfunction, and acute organ damage. In many patients, this hyperinflammatory phase is followed by a compensatory immunosuppressive state, which further impairs host defense and contributes to ongoing disease progression[10,11].

Vitamin D insufficiency is increasingly prevalent worldwide. Vitamin D deficiency (VDD), defined as a serum 25-hydroxyvitamin D [25(OH)D] level below 20 ng/mL, affects approximately 24.0% of the population in the United States and 40.4% in Europe[12,13]. Risk factors for low vitamin D status include advanced age, abnormal body weight (obesity or underweight), residence at higher latitudes, low levels of physical activity, limited sun exposure, the winter season, and low alcohol consumption[14,15]. Beyond its classical role in mineral and bone metabolism, vitamin D functions as a potent immunomodulatory hormone. Its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], exerts pleiotropic effects on both innate and adaptive immune responses, as well as on endothelial integrity[16]. Mechanistically, vitamin D directly enhances the expression of antimicrobial peptides such as cathelicidin, thereby bridging innate

immune recognition and effector functions. It also attenuates excessive inflammatory signaling by downregulating the production of pro-inflammatory cytokines, including TNF-α and IL-6, while promoting immune tolerance, in part through the induction of regulatory T cells. In addition, vitamin D supports the maintenance of endothelial barrier function, a critical frontier compromised during sepsis[17]. Accumulating evidence has linked vitamin D status to the incidence and severity of multiple immune-mediated diseases, including type 1 diabetes, systemic lupus erythematosus, and rheumatoid arthritis[12].

Given the central role of inflammatory dysregulation and immune dysfunction in sepsis pathogenesis [18,19], the immunomodulatory properties of vitamin D have been proposed as a potential contributor to this process. Moreover, VDD and sepsis share several overlapping risk factors, such as advanced age, abnormal body weight, and seasonal variation. Therefore, the potential association between vitamin D and sepsis warrants attention, though the exact relationship between the two remains to be fully elucidated. Several studies conducted in emergency and intensive care settings have reported inverse correlation between vitamin D levels and sepsis risk and sepsis-related mortality[20–24]. By contrast, a prospective cohort study of general ward patients with systemic inflammatory response syndrome reported no significant association between serum 25(OH)D levels and subsequent sepsis incidence or mortality[25].

To further elucidate this relationship, we conducted a prospective analysis of the associations between vitamin D status and sepsis incidence and mortality using data from the United Kingdom Biobank (UKB).

2. Materials and Methods

2.1. Data source and study population

The UKB is a large-scale, prospective cohort study that enrolled more than 500,000 participants aged 40-69 years between 2006 and 2010 across the United Kingdom. This population-based repository integrates extensive genetic, phenotypic, and environmental data through comprehensive baseline assessments, including touchscreen questionnaires, physical measurements, and biological sample collection. All participants provided written informed consent, and the study received approval from the North West Multi-center Research Ethics Committee[26,27].

For the present prospective analysis, participants with a pre-existing diagnosis of sepsis at baseline (n = 2,268) were excluded. We further excluded individuals with missing values on serum 25(OH)D concentrations (N=53,815) and comorbidities (N=1,546). The final analytic cohort included 444,509 participants to explore the correlation between 25(OH)D levels and incident sepsis (Figure. S1).

2.2. Ascertainment of exposure

Vitamin D level was assessed at baseline as serum 25(OH)D concentration. Serum 25(OH)D (ng/mL) was measured using a chemiluminescent immunoassay on a DiaSorin Liaison XL analyzer. This method demonstrates good analytical performance, with reported intra- and inter-assay coefficients of variation that ensure the reliability of the dataset used for epidemiological analyses[28].

VDD was defined as a serum 25(OH)D concentration below 20 ng/mL, and severe vitamin D deficiency (SVDD) was specified as levels under 10 ng/mL. In this study, participants were stratified according to

their serum 25(OH)D levels using the following sequential approach. (1) Participants were divided into a VDD group and a non-VDD group; (2) Based on these thresholds, participants were categorized into three groups: SVDD (<10 ng/mL), VDD (10 ~ 20 ng/mL), and vitamin D sufficiency (>20 ng/mL); (3) Participants were further classified into quartiles based on the distribution of 25(OH)D concentrations: Q1 (<13.0 ng/mL), Q2 (13.0 - 18.8 ng/mL), Q3 (18.8 - 25.0 ng/mL), and Q4 (≥25.0 ng/mL).

2.3. Assessment of Sepsis

The primary outcome was the incident sepsis, identified using the following International Classification of Diseases, 10th Revision (ICD-10) codes: A02.1, A39.2, A40, and A41[29]. To evaluate the association between vitamin D status and sepsis prognosis, we further examined all-cause mortality at 28 days, 60 days, and 1 year following sepsis diagnosis. Participants were followed from enrollment until the first occurrence of incident sepsis, death, loss to follow-up, or the end of the study period (October 1, 2023), whichever occurred first.

2.4. Assessment of covariates

The following covariates were included in our analysis: age-group (<65 years, ≥65 years), sex (male, female), ethnicity (White, non-white), Townsend deprivation index (continuous), education (college/university degree; A/AS levels or equivalent; O levels/General Certificate of Secondary Education or equivalent; National Vocational Qualification, Higher National Diploma, Higher National Certificate, or equivalent; other professional qualifications; not answered), household income (<18,000; 18,000–30,999; 31,000–51,999; 52,000–100,000; >100,000; not answered), employment status (employed, unemployed, not answered), drinking status (current, previous, never, not answered),

smoking status (current, previous, never, not answered), sleep (<7h/d, 7~8h/d, >8h), physical activity (continuous, MET-hours/week), body mass index (BMI) (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), total cholesterol (continuous, mmol/L), low-density lipoprotein cholesterol (LDL-C) (continuous, mmol/L), triglycerides (continuous, mmol/L), urate (continuous, μmol/L), creatinine (continuous, μmol/L), Hemoglobin A1c (HbA1c) (continuous, %), history of hypertension (HTN), cardiovascular disease (CVD), cancer , Type 2 diabetes (T2D) (yes, no), vitamin D supplementation (yes, no).

2.5. Statistical analysis

Baseline participant characteristics were summarized based on status of 25(OH)D levels. Continuous variables are presented as means (standard deviations) and were compared using analysis of variance (ANOVA) or Student's t tests, as appropriate. Categorical variables are expressed as counts (percentage) and were compared via chi-square test.

Kaplan-Meier survival curves were constructed to visualize sepsis incidence stratified by VDD status and vitamin D level. The association between serum 25(OH)D levels and sepsis risk was evaluated using Cox proportional hazards regression, with hazard ratios (HRs) estimated through a series of sequentially adjusted models. In addition to a crude unadjusted model, three multivariable models were fitted: Model 1 was adjusted age, sex, ethnicity. Model 2 additionally included Townsend deprivation index, education, household income, employment status, smoking status, drinking status, sleep, physical activity. Model 3 was further adjusted for BMI, total cholesterol, LDL-C, triglycerides, urate, creatinine, HbA1c, history of HTN, CVD, cancer, T2D. The proportional hazards assumption was verified using Schoenfeld residuals, and no material violations were detected. Furthermore, we examined the potential non-linear

dose–response relationship between serum 25(OH)D levels and sepsis incidence using restricted cubic spline (functions) within the fully adjusted Cox models, with knots placed at the 5th, 27.5th, 50th, 72.5th, and 95th percentiles of the vitamin D distribution.

We assessed the consistency of the primary association across subgroups, including age group (< 65 years, ≥ 65 years), sex (male, female), drinking status (current, previous, never), smoking status (current, previous, never), BMI (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), history of HTN, CVD (yes, no). Statistical interactions were evaluated by including product terms between vitamin D status and each stratification variable, with *P* values for interaction used to assess effect modification.

To assess the robustness of our primary findings, we performed several sensitivity analyses: (1) To minimize potential reverse causality, we repeated the analyses after sequentially excluding participants who developed sepsis within the first 1, 2, and 3 years of follow-up. (2) The analyses were repeated after excluding all individuals with any of the following baseline comorbidities: HTN, CVD, obesity (BMI ≥30 kg/m²), CKD, or T2D. (3) Participants with immunodeficiency, defined as those with HIV infection or agranulocytosis (absolute neutrophil count < 0.5 × 10⁹/L), were excluded from the analysis. (4) Participants who reported using vitamin D supplements at baseline were excluded to eliminate the influence of exogenous intake; (5) Vitamin D supplementation was further incorporated as a covariate in Model 4 to evaluate the independent association of serum vitamin levels with sepsis risk.

To examine the association between vitamin D status and survival among patients with sepsis, all-cause mortality at 28 days, 60 days and 1 year following sepsis diagnosis was assessed. Participants were

categorized into three predefined vitamin D groups based on serum 25(OH)D levels: <10 ng/mL, 10 ~ 20 ng/mL and >20 ng/mL. The association between vitamin D status and mortality risk was assessed using multivariable Cox proportional hazards models, with adjustment for the full set of covariates specified in Model 3. Results are presented as HRs with 95%CIs.

All statistical analyses were performed using R software (version 4.5.1), and a two-sided *P* value < 0.05 was considered statistical significant.

3. Results

3.1. Baseline characteristics

As shown in Table 1, the study cohort comprised 197,970 participants with sufficient vitamin D levels (>20 ng/mL), 186,941 with VDD (10 ~ 20 ng/mL), and 59,598 with SVDD (<10 ng/mL). Demographically, participants with lower serum 25(OH)D levels were younger, more likely to be male, and more frequently current smokers. Socioeconomically, they had higher educational attainment, but also higher rates of unemployment and higher body mass index, with a greater proportion classified as overweight or obese. Lower 25(OH)D levels were further associated with greater socioeconomic disadvantage, as reflected by a higher Townsend deprivation index and lower household income. In terms of lifestyle, participants with lower serum 25(OH)D concentrations were less likely to be current drinkers, reported more favorable sleep durations, and engaged in higher levels of physical activity. Biochemically, lower 25(OH)D levels were associated with elevated levels of triglycerides and HbA1c. Clinically, these participants had a higher prevalence of HTN, CVD and T2D. Baseline characteristics stratified by VDD and serum 25(OH)D quartiles are presented in Table S1 and Table S2, respectively.

3.2. Risk of incident sepsis associated with serum 25(OH)D levels

During a mean follow-up of 14 years, 15,452(3.46%) incident sepsis cases were recorded, with sepsis incidence increasing progressively across decreasing levels of serum 25(OH)D. Figure 1.A and Figure S2.A presents the Kaplan-Meier curves for incident sepsis stratified by VDD status and vitamin D levels. Participants with VDD experienced a significantly higher cumulative incidence of sepsis compared with those with sufficient vitamin D levels. Moreover, Kaplan-Meier curves from sensitivity analyses (Figure 1.B-D, Figure S2.B-D) demonstrated similar patterns, supporting the robustness of the primary findings.

In Cox regression analyses, participants with 25(OH)D levels <10 ng/mL exhibited the highest risk of sepsis across all models, showing progressively higher and statistically significant HRs [1.28 (1.22–1.34)] compared with the reference group (>20 ng/mL). An inverse association between serum 25(OH)D levels and sepsis risk was consistently observed across both the VDD and 25(OH)D quartiles (Table 2). In the fully adjusted Model 3, each 10 nmol/L (4ng/mL) increase in 25(OH)D concentration was associated with a 3% lower risk of sepsis [0.97 (0.97–0.98)].

Restricted cubic spline analyses revealed a nonlinear inverse dose-response relationship between 25(OH)D (ng/mL) and the risk of incident sepsis (Figure. 2, $P < 0.01$, P for nonlinearity < 0.01), with an inflection point at 18.72 ng/mL. Together, these analyses indicate that lower serum vitamin D levels are associated with a higher risk of incident sepsis, independent of measured confounders.

3.3. Subgroup analyses

Stratified analyses were performed by age group, sex, smoking status, alcohol consumption, BMI, and history of HTN, CVD to explore potential effect modifications. As shown in Table 3, sex (*P* for interaction = 0.012) and BMI (*P* for interaction = 0.044) significantly modified the association between serum 25(OH)D levels and incident sepsis risk. When comparing participants with serum 25(OH)D < 10 ng/mL to those with > 20 ng/mL, the HR (95% CI) for sepsis was 1.33 (1.23, 1.43) among females and 1.27 (1.19, 1.35) among males. Among individuals with BMI < 25 kg/m², the HR (95% CI) was 1.37 (1.24, 1.51), compared to 1.20 (1.11, 1.30) in those with obesity. Subgroup analyses of the associations based on VDD, serum 25(OH)D quartiles and sepsis incidence are presented in Table S3 and Table S4 respectively. Sex remained a significant effect modifier for the quartile-based 25(OH)D–sepsis association (*P* for interaction = 0.002), whereas no statistically significant interaction was observed for VDD status.

Overall, the association between lower serum 25(OH)D levels and a higher risk of incident sepsis was directionally consistent across all subgroups, including those defined by age group, sex, smoking status, alcohol consumption, BMI, and history of HTN or CVD.

3.4. Sensitivity analysis

Across multiple sensitivity analyses, the association between serum 25(OH)D levels and incident sepsis risk remained largely robust (Table S5-S7). This was confirmed by (1) sequentially excluding participants who developed sepsis within 1, 2, and 3 years of follow-up, (2) excluding those with pre-existing comorbidities at baseline, including T2D, HTN, CVD, CKD, or obesity (BMI ≥ 30kg/m^2); (3) Excluding participants with immunodeficiency, which was defined as HIV infection or agranulocytosis

(absolute neutrophil count < 0.5 × 10^9/L); (4) excluding vitamin D supplement users; and (5) further adjusting for vitamin D supplementation (Model 4), which did not materially alter the observed associations.

3.5. Risk of sepsis death associated with serum 25(OH)D levels

Sepsis-related mortality was defined as death from any cause within 28 days, 60 days, or 1 year following sepsis diagnosis. Baseline characteristics for patients who developed sepsis are shown in Table S8. In analyses evaluating the association between serum 25(OH)D levels and sepsis mortality (Table 4), the <10 ng/mL group exhibited significantly higher HRs for both 28-day, 60-day, and 1-year mortality compared to the reference group (>20 ng/mL). Following multivariable adjustment in Model 3, the HR (95% CI) was 1.14(1.02, 1.27) for 28-day mortality, 1.11(1.01, 1.23) for 60-day mortality, and 1.10 (1.02–1.19) for 1-year mortality. In contrast, no statistically significant difference in 28-day, 60-day, or 1-year mortality was observed for the 10 ~ 20 ng/mL group versus the reference.

4. Discussion

In this large, population-based prospective cohort study using data from the UKB, we investigated the association between baseline serum 25(OH)D concentrations and the risk and prognosis of sepsis. We observed a significant negative and nonlinear association between 25(OH)D levels and incident sepsis, which remained robust after comprehensive adjustment for demographic, socioeconomic, lifestyle, metabolic, and clinical confounders. This negative association was more pronounced among females and individuals with normal body weight (BMI < 25 kg/m^2). Moreover, participants with SVDD (< 10 ng/mL) faced a significantly elevated risk of both 28-day, 60-day and 1-year mortality following sepsis

diagnosis, compared with those with sufficient vitamin D status (> 20 ng/mL).

Our findings are consistent with and extend prior evidence linking vitamin D deficiency to sepsis susceptibility and adverse outcomes. A 2025 meta analysis encompassing 39 studies reported that 55% of adult sepsis patients had serum vitamin D levels below 30 ng/mL, demonstrating a significant association between VDD and both sepsis incidence and mortality[30]. These conclusions aligns with earlier meta-analyses[31]. However, existing evidence has been largely derived from small-scale, heterogeneous, and predominantly retrospective clinical studies, limiting causal inference and generalizability. In contrast, our study offers several important methodological and conceptual advances. Prior investigations—including a single-center retrospective cohort of intensive care unit patients by Guan et al.[32] and a small cross-sectional study by Bayat et al.[33] —were constrained by restricted sample sizes, short follow-up durations, and potential selection bias. By leveraging the UKB's large-scale, prospective design and long-term follow-up, our analysis enabled more reliable estimation of sepsis risk and short-term mortality across a broad, community-based population. The standardized assessment of serum 25(OH)D, substantial statistical power, and reduced susceptibility to reverse causation collectively strengthen the validity of our findings. Crucially, our results extend beyond confirming an inverse association by demonstrating a clear nonlinear dose–response relationship between serum 25(OH)D concentrations and sepsis risk. The consistency of this association across multiple sensitivity analyses and most subgroups, together with observed effect modification by sex and BMI, further underscores the biological and epidemiological plausibility of our findings. While a limited number of prospective studies have examined vitamin D and sepsis outcomes, these have largely been restricted to small-scale, single-center cohorts from emergency room or general ward settings[25,34,35]. To the best of our knowledge, our

study represents the first large-scale, population-based prospective analysis with long-term follow-up specifically designed to evaluate vitamin D status in relation to both sepsis incidence and mortality.

Vitamin D is metabolized in a two-step activation process. It is first hydroxylated in the liver to form 25(OH)D, which circulates as the primary biomarker of vitamin D status. Subsequent conversion in the kidneys produces $1,25(OH)_2D$. The biologically active $1,25(OH)_2D$ signals through the vitamin D receptors (VDR), widely expressed on monocytes, dendritic cells, and lymphocytes, to mediate immune regulation [36,37]. Notably, some VDR-expressing cells possess the capacity for intracrine synthesis of $1,25(OH)_2D$, facilitating localized (autocrine/paracrine) regulation that is crucial for fine-tuning immune responses[38–40]. The vitamin D/VDR signaling pathway induces the expression of antimicrobial peptides, most notably cathelicidin, which significantly enhances the innate immune response against a broad spectrum of pathogens[36,41–43]. In addition, $1,25(OH)_2D$ inhibits B-cell proliferation, immunoglobulin class switching, thereby tempering the adaptive antibody response[44,45]. It also shifts the T helper (Th) 1/Th2 balance by suppressing Th1 responses and the production of pro-inflammatory cytokines such as IL-12, interferon (IFN)-γ, IL-6, IL-8, TNF-α, IL-17, and IL-9, while promoting Th2 responses and the release of anti-inflammatory cytokines such as IL-4, IL-5, and IL-10[44,46]. Moreover, $1,25(OH)_2D$ enhances Treg cell development through both an indirect dendritic cell-mediated pathway and a direct effect on T cells[47]. Furthermore, the vitamin D/VDR pathway plays a critical role in regulating oxidative stress and preserving the integrity of vascular endothelial cells[48–50]. Collectively, these pathways represent potential mechanisms that provide biological plausibility for the observed association between vitamin D deficiency and increased sepsis risk and mortality.

In this study, higher serum 25(OH)D levels were associated with a stronger protective effect against sepsis among females and individuals with normal BMI. Regarding the sexual dimorphism, the stronger protective effect observed in females could be linked to the immunomodulatory influence of sex hormones, particularly estrogen[51]. Estrogen has been shown to upregulate the expression of VDR and enhance the conversion of 25(OH)D to its active form, $1,25(OH)_2D$, thereby amplifying vitamin D signaling pathways[52–54]. This synergistic interaction may result in a more robust anti-inflammatory and antimicrobial response in females than in males. The attenuation of the association between vitamin D status and sepsis risk among individuals with obesity may similarly reflect several biologically plausible mechanisms. First, vitamin D, as a fat-soluble compound, is sequestered in adipose tissue, reducing its bioavailability in the circulation and to target organs[55]. Second, obesity is characterized by a state of chronic low-grade inflammation and systemic oxidative stress, which may decrease the anti-inflammatory capacity of vitamin D[56]. Third, obesity has been shown to downregulate CYP2R1, a key enzyme in vitamin D activation[57,58]. Collectively, these mechanisms may diminish the physiological effectiveness of vitamin D in individuals with higher adiposity.

The observed inverse association between vitamin D status and sepsis risk has motivated clinical investigations into the therapeutic potential of vitamin D supplementation for improving sepsis outcomes. A systematic review and meta-analysis of 5 studies (including 42,915 patients) suggested that vitamin D supplementation may be associated with reduced 28-day mortality, 90-day mortality, and in-hospital mortality; however, the overall certainty of evidence was low, limiting the strength of these conclusions[59].

Despite these observational trends, previous randomized controlled trials have consistently failed to

demonstrate a significant survival benefit. For instance, treatment with calcitriol did not reduce mortality compared to placebo[60]. Similarly, supplementation with cholecalciferol to boost vitamin D levels also failed to improve clinical endpoints in septic patients[61]. In critically ill populations, high-dose native vitamin D supplementation consistently failed to demonstrate a significant overall benefit on major clinical outcomes in two landmark trials: the VITdAL-ICU and VIOLET studies[62,63]. Collectively, these neutral findings highlight the immense complexity of translating observational associations into effective therapies. However, these broad failures may stem from the inclusion of patients with heterogeneous baseline levels, which potentially diluted the therapeutic effect. The ongoing VITDALIZE trial[64] addresses this by specifically targeting a subgroup with profound deficiency (25(OH)D < 12 ng/mL). This strategic shift fits well with our findings, as we observed that the heightened risk of sepsis and mortality was most pronounced in the < 10 ng/mL subgroup. This convergence suggests that previous trials may have missed the therapeutic window by not prioritizing those with severe depletion, a hypothesis that positions the baseline degree of deficiency as a critical determinant of future clinical success.

Several limitations should be considered when interpreting our findings. First, 25(OH)D was measured only at baseline, which does not capture longitudinal changes in vitamin D status changes during follow-up and may be influenced by potential confounding factors such as diet and seasonal variation. Second, causality cannot be established due to the observational nature of the design, despite the substantial sample size and prolonged follow-up. Although we performed comprehensive adjustments for covariates, the possibility of residual or unmeasured confounding cannot be entirely excluded. Third, the generalizability of our results is constrained by the predominantly White ancestry of the UKB population.

Furthermore, the lack of granular clinical data in the UKB posed specific challenges. Data on parathyroid hormone levels and the use of bisphosphonates were unavailable, preventing an assessment of their potential impact on vitamin D metabolism and sepsis susceptibility. Additionally, while sepsis events were identified through diagnostic codes, the absence of concurrent clinical parameters (e.g., blood pressure, urine output, or lactate levels) precluded the classification of sepsis severity (e.g., septic shock) or refined clinical phenotypes. Finally, our analysis focused solely on incident sepsis; the inherent constraints of the dataset did not allow for a reliable identification of recurrent sepsis. Given that recurrent sepsis is a significant clinical challenge often linked to long-term immune dysfunction, its relationship with vitamin D status remains an important area for future investigation using more detailed clinical registries.

5. Conclusion

A negative and nonlinear association was observed between serum 25(OH)D levels and incident sepsis, with participants in the SVDD group (<10 ng/mL) exhibiting an adjusted HR of 1.28 (1.22–1.34) compared to those with levels >20 ng/mL. This relationship was more pronounced among females and individuals with BMI <25 kg/m². Furthermore, SVDD was significantly associated with higher mortality, with adjusted HRs of 1.14 (1.02–1.27) for 28-day mortality, 1.11 (1.01–1.23) for 60-day mortality, and 1.10 (1.02–1.19) for 1-year mortality. Together, these findings suggest that SVDD may represent an independent risk factor for both sepsis incidence and mortality. Further randomized controlled trials are warranted to determine whether vitamin D supplementation can modify sepsis risk and improve clinical outcomes.

Abbreviations：

1,25(OH)$_2$D, 1,25-dihydroxyvitamin D;

25(OH)D, 25-dihydroxyvitamin D;

BMI, body mass index;

CVD, cardiovascular disease;

HbA1c, Hemoglobin A1c;

HR, hazard ratio;

HTN, hypertension;

ICD-10, International Classification of Diseases, 10th Revision;

IFN, interferon;

IL, interleukin;

LDL-C, low-density lipoprotein cholesterol;

SVDD, severe vitamin D deficiency;

T2D, Type 2 diabetes;

Th, T helper;

TLR, Toll-like receptor;

TNF, tumor necrosis factor;

UKB, UK Biobank;

VDD, vitamin D deficiency;

VDR, vitamin D receptor;

Declarations

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Availability of data and materials: The dataset supporting the conclusions of this article is available from the UK Biobank (https://www.ukbiobank.ac.uk/). Analytic methods will be made available to other researchers upon request.

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Reference

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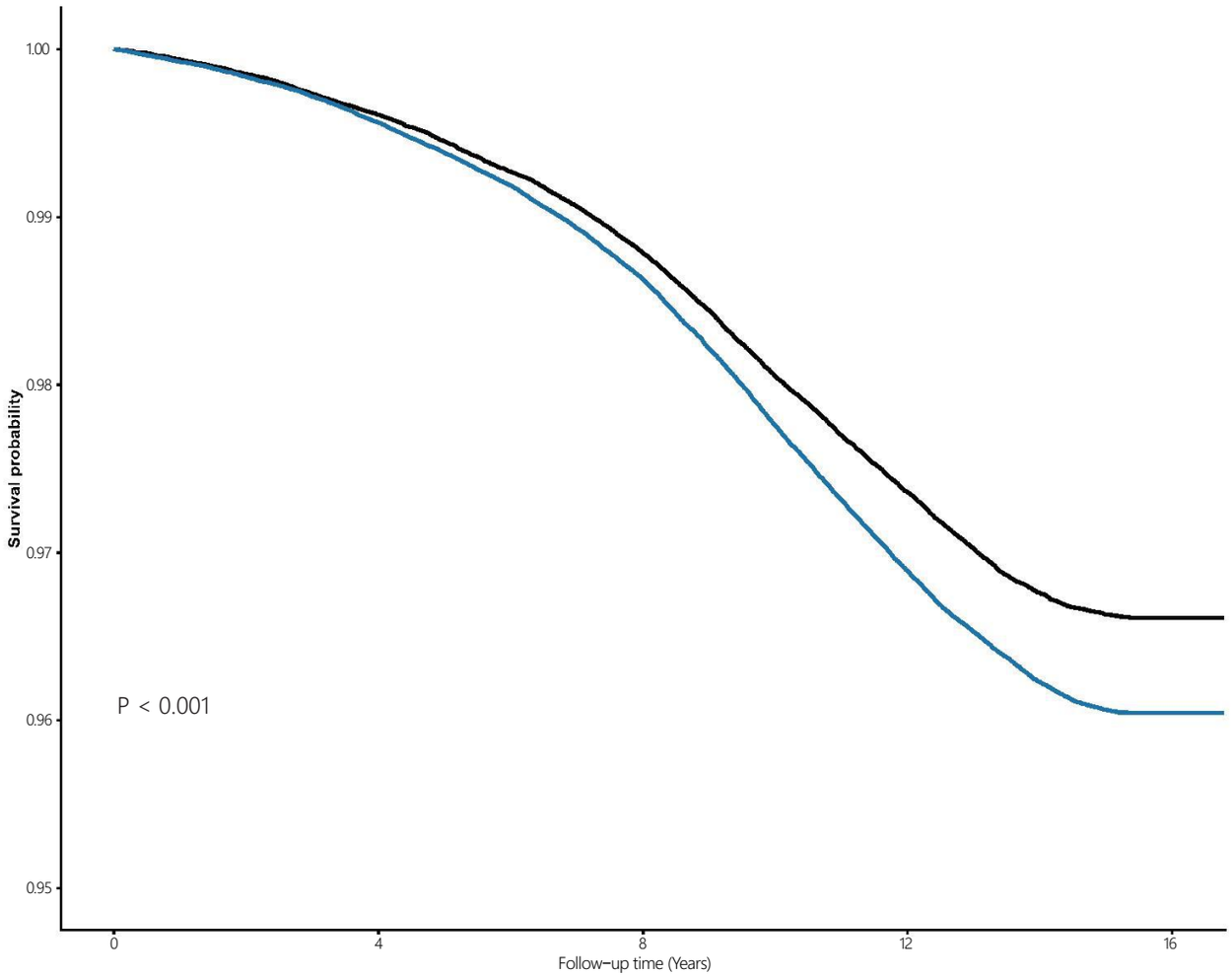
Figure legends

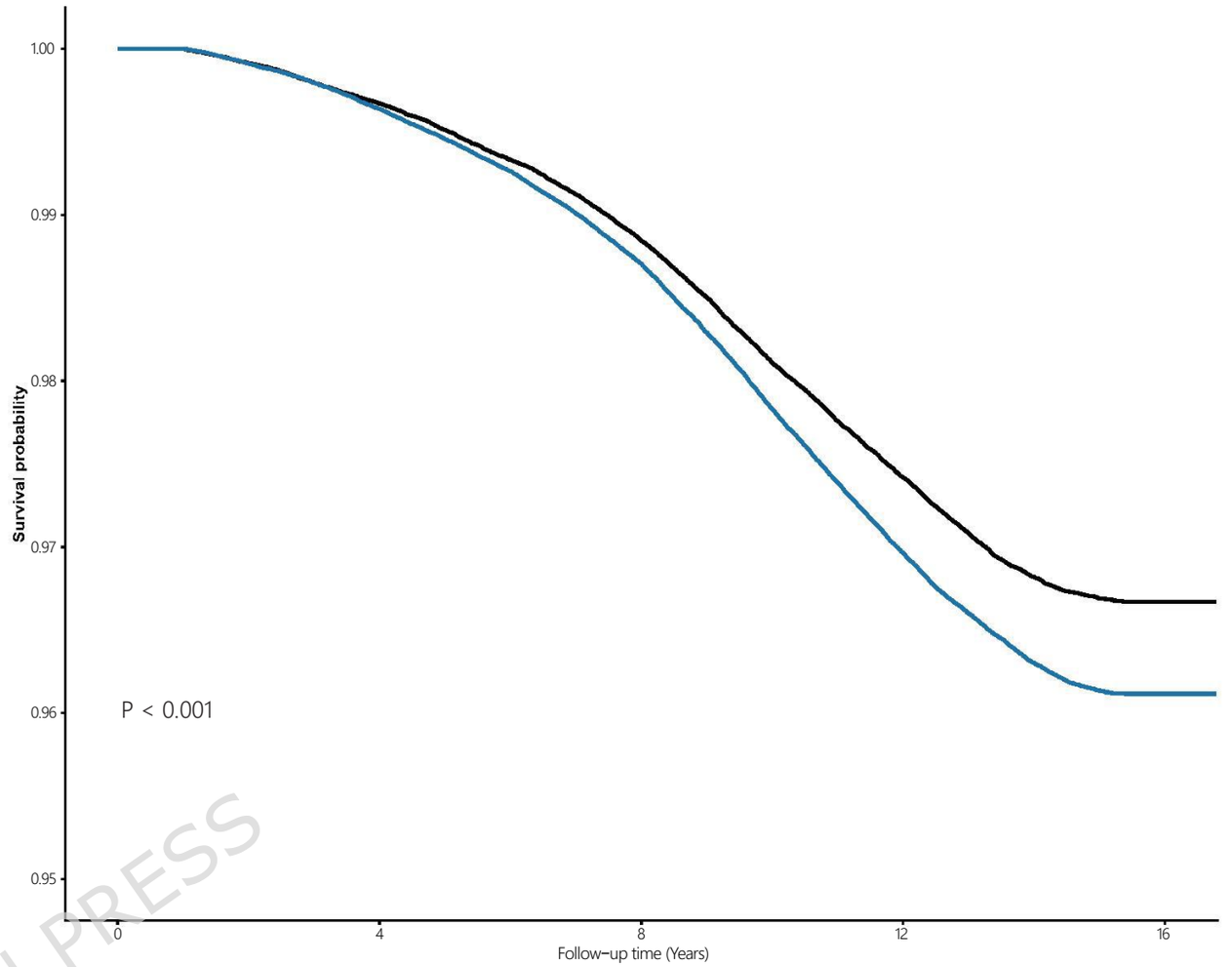
Figure.1 Kaplan-Meier curves for incident sepsis across Vitamin D deficiency status (A: All participants, B-D: excluding participants who developed sepsis within 1, 2, and 3 years of follow-up).

Figure.2 Association of serum Vitamin D levels with incident sepsis by restricted cubic splines. Data was adjusted for agegroup (< 65 years, ≥ 65 years), sex (male, female), ethnicity (White and non-white), Townsend deprivation index (continuous), education (College or university degree, A/AS levels or equivalent or O levels/General Certificate of Secondary Education or Certificate of Secondary Education or equivalent, National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent or other professional qualifications, not answer), household income (less than 18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, not answer), employment status (employed, unemployed and not answer), drinking status (current, previous, never, and not answer), smoking status (current, previous, never, and not answer), sleep (<7h/d, 7~8h/d, >8h), physical activity (continuous, MET-hours/week), BMI (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), total cholesterol (continuous, mmol/L), LDL-C (continuous, mmol/L), triglycerides (continuous, mmol/L), urate (continuous, μmol/L), creatinine (continuous, μmol/L), HbA1c (continuous, %), history of HTN, CVD, cancer ,T2D (yes, no, not answer).

MET: Metabolic Equivalent of Task; BMI: Body mass index; LDL-C: Low-density lipoprotein-cholesterol; HbA1c: Hemoglobin A1c; CVD: Cardiovascular disease; HTN: Hypertension; T2D: Type 2 diabetes.

A





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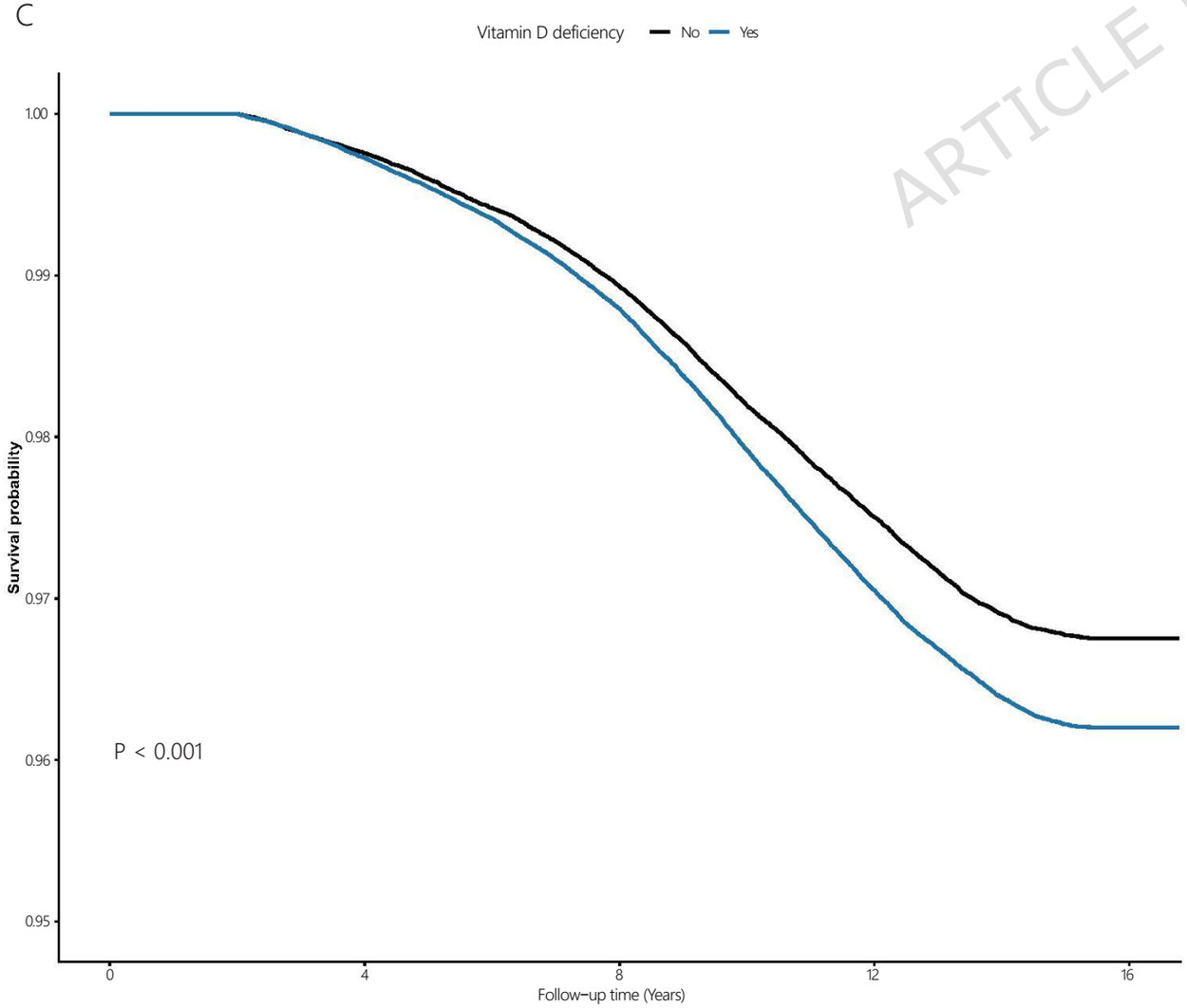

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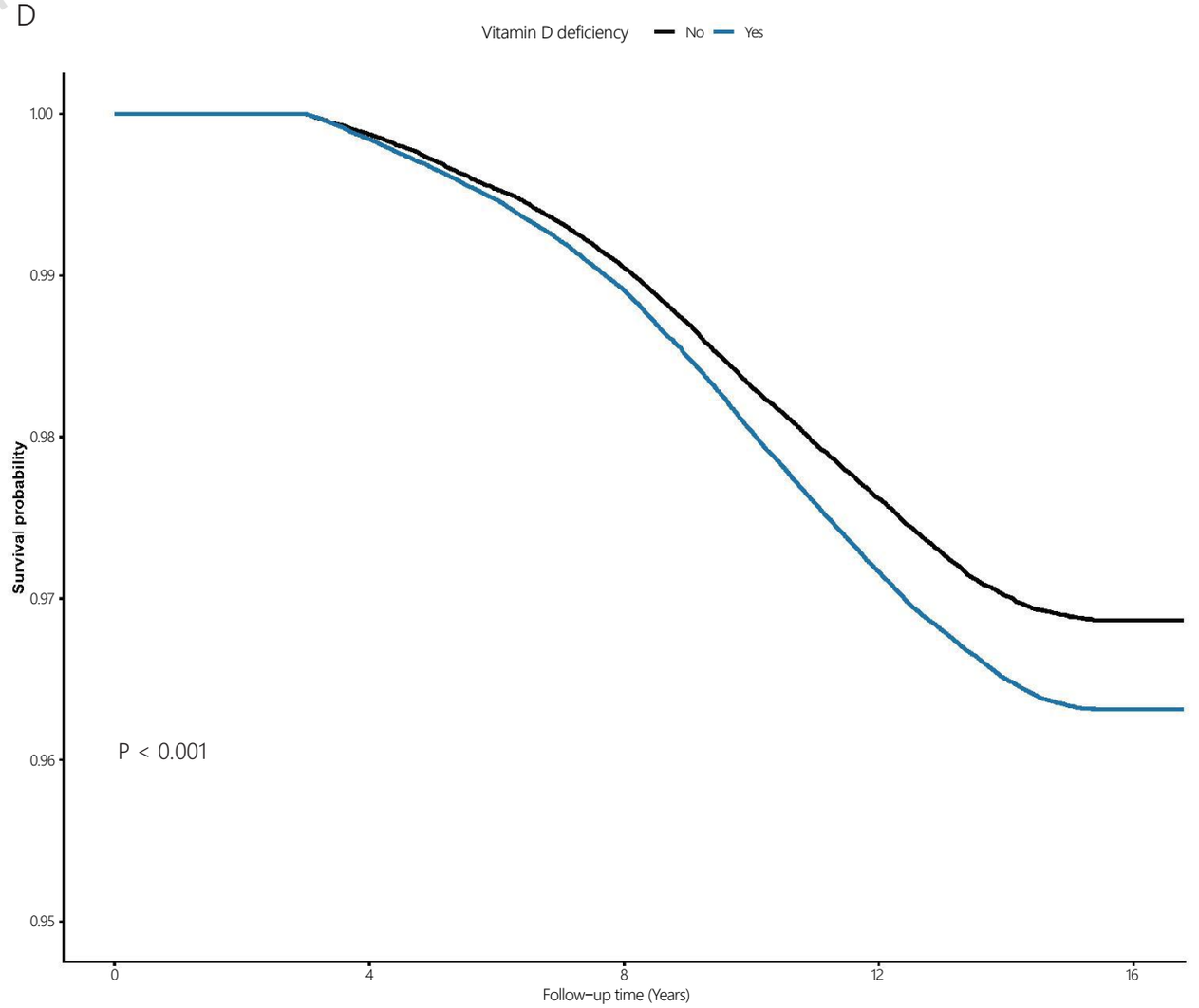

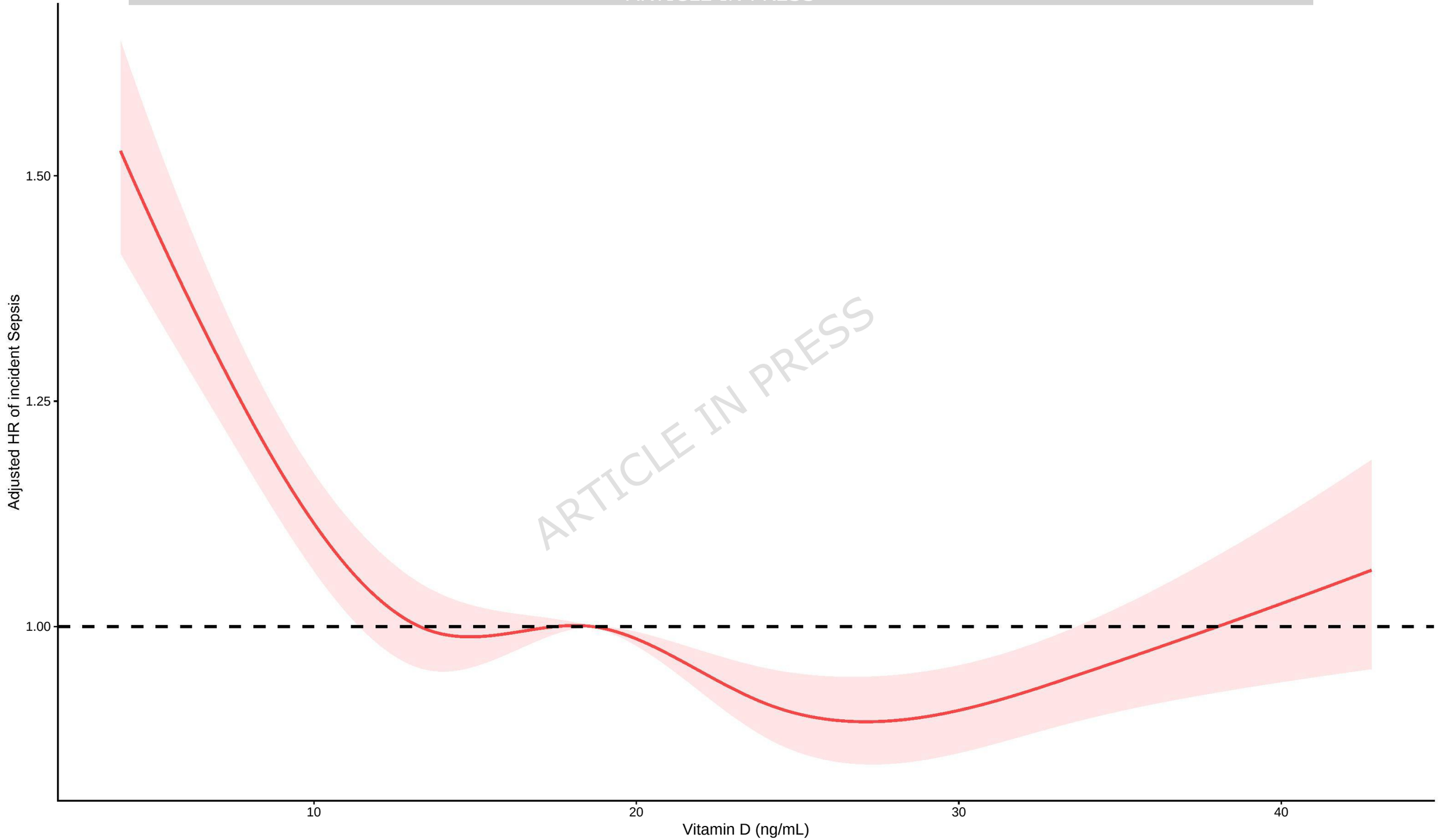

Table.1 Baseline characteristics according to serum 25(OH)D levels in the UK Biobank study

Characteristics	>20ng/mL	10~20 ng/mL	< 10 ng/mL	*P* value
N	197,970	186,941	59,598	
Age (Year)[a]	57 (8)	56 (8)	55 (8)	<0.001
Agegroup[b]				<0.001
<65	155,279 (78.4)	153,218(82.0)	51,194 (85.9)	
≥65	42,691 (21.6)	33,723 (18.0)	8,404 (14.1)	
Male (%)	91,441 (46.2)	86,933 (46.5)	27,943 (46.9)	0.007
White (%)	194,024 (98.0)	175,942(94.1)	50,340 (84.5)	<0.001
Townsend deprivation index	-1.75 (2.83)	-1.20 (3.12)	-0.30 (3.45)	<0.001
College or university degree (%)	59,698 (30.2)	63,872 (34.2)	21,154 (35.5)	<0.001
Household Income (%)				<0.001
Less than 18,000	35,179 (17.8)	36,015 (19.3)	14,367 (24.1)	
18,000 to 30,999	44,191 (22.3)	40,143 (21.5)	12,193 (20.5)	
31,000 to 51999	44,657 (22.6)	42,358 (22.7)	12,724 (21.3)	
52,000 to 100,000	35,162 (17.8)	33,728 (18.0)	9,477 (15.9)	
greater than 100,000	9,821 (5.0)	8,871 (4.7)	2,222 (3.7)	
Employed (%)	184,413 (93.2)	171,504(91.7)	51,840 (87.0)	<0.001
Smoke (%)				<0.001
Current	16,425 (8.3)	19,856 (10.6)	10,007 (16.8)	
Previous	72,448 (36.6)	63,712 (34.1)	17,831 (29.9)	
Never	108,376 (54.7)	102,726(55.0)	31,490 (52.8)	
Drinking status (%)				<0.001
Current	186,222 (94.1)	171,641(91.8)	51,286 (86.1)	
Previous	5,878 (3.0)	6,868 (3.7)	3,141 (5.3)	
Never	5,718 (2.9)	8,225 (4.4)	5,035 (8.4)	
Sleep (%)				<0.001
7~8h/d	137,442 (69.4)	125,171(67.0)	36,938 (62.0)	
<7h/d	47,809 (24.1)	50,231 (26.9)	18,733 (31.4)	
>8h/d	12,719 (6.4)	11,539 (6.2)	3,927 (6.6)	
MET (hours/week)	45.30 (41.91)	38.71 (37.85)	33.99 (34.54)	<0.001
BMI (%)				<0.001
<25	75,122 (37.9)	55,560 (29.7)	16,838 (28.3)	
25~30	86,828 (43.9)	79,602 (42.6)	23,005 (38.6)	
≥30	36,020 (18.2)	51,779 (27.7)	19,755 (33.1)	
LDL-C(mmol/L)	3.43 (0.77)	3.52 (0.79)	3.51 (0.80)	<0.001
Urate(μmol/L)	306.12 (78.52)	311.34(80.74)	311.69(84.82)	<0.001
Triglycerides (mmol/L)	1.56 (0.84)	1.80 (1.05)	1.95 (1.20)	<0.001
Creatinine (μmol/L)	72.97 (16.99)	72.32 (18.65)	71.11 (20.47)	<0.001
HbA1C (%)	3.45 (0.50)	3.51 (0.62)	3.59 (0.80)	<0.001
CVD (%)	10,962 (5.5)	11,085 (5.9)	4,286 (7.2)	<0.001
HTN (%)	51,368 (25.9)	52,287 (28.0)	17,718 (29.7)	<0.001
T2D (%)	8,019 (4.1)	10,613 (5.7)	4,839 (8.1)	<0.001
Cancer (%)	15,436 (7.8)	13,701 (7.3)	4,103 (6.9)	<0.001
Incident sepsis	6,336 (3.2)	6,524 (3.5)	2,592 (4.3)	<0.001
Follow-up period (Year)	14.10 (2.22)	14.05 (2.31)	13.85 (2.64)	<0.001

MET: Metabolic Equivalent of Task; BMI: Body mass index; LDL-C: Low-density lipoprotein-cholesterol; HbA1c: Hemoglobin A1c; CVD: Cardiovascular disease; HTN: Hypertension; T2D: Type 2 diabetes.

a. ANOVA test was used to compare the continuous variables among different groups.

b. Chi-square test was used to compare the categorical variables among different groups.

Table.2 Risk of incident sepsis associated with serum 25(OH)D levels

Characteristics	Crude model	model 1	model 2	model 3
25(OH)D(ng/mL)				
>20	1.00	1.00	1.00	1.00
10~20	1.10(1.06,1.14)	1.16(1.12,1.20)	1.11(1.07,1.15)	1.06(1.03,1.10)
<10	1.39(1.33,1.46)	1.57(1.50,1.64)	1.37(1.31,1.44)	1.28(1.22,1.34)
P for trend	<0.001	<0.001	<0.001	<0.001
Vitamin D deficiency				
No	1.00	1.00	1.00	1.00
Yes	1.17(1.13, 1.21)	1.25(1.21, 1.29)	1.17(1.13, 1.21)	1.11(1.07, 1.14)
25(OH)D quartiles				
Q1	1.00	1.00	1.00	1.00
Q2	0.84(0.81, 0.88)	0.80(0.76, 0.83)	0.86(0.82, 0.90)	0.89(0.85, 0.93)
Q3	0.80(0.77, 0.84)	0.73(0.70, 0.76)	0.81(0.77, 0.85)	0.86(0.82, 0.90)
Q4	0.78(0.75, 0.82)	0.70(0.67, 0.74)	0.79(0.75, 0.82)	0.85(0.81, 0.89)
P for trend	<0.001	<0.001	<0.001	<0.001
10 nmol/L (4 ng/mL) increment	0.96(0.95, 0.97)	0.94(0.93, 0.95)	0.96(0.95, 0.97)	0.97(0.97, 0.98)

25(OH)D quartiles: Q1 (<13.0 ng/mL), Q2 (13.0 - 18.8 ng/mL), Q3 (18.8 - 25.0 ng/mL), and Q4 (≥25.0 ng/mL).

Vitamin D deficiency: 25(OH)D < 20ng/mL.

Model 1 was adjusted agegroup (< 65 years, ≥ 65 years), sex (male, female), ethnicity (White and non-white).

Model 2: Model 1+ Townsend deprivation index (continuous), education (College or university degree, A/AS levels or equivalent or O levels/General Certificate of Secondary Education or Certificate of Secondary Education or equivalent, National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent or other professional qualifications, not answer), household income (less than 18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, not answer), employment status (employed, unemployed and not answer), drinking status (current, previous, never, and not answer), smoking status (current, previous, never, and not answer), sleep (<7h/d, 7~8h/d, >8h), physical activity (continuous, MET-hours/week).

Model 3: Model 2+ BMI (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), total cholesterol (continuous, mmol/L), LDL-C (continuous, mmol/L), triglycerides (continuous, mmol/L), urate (continuous, μmol/L), creatinine (continuous, μmol/L), HbA1c (continuous, %), history of HTN, CVD, cancer ,T2D (yes, no).

MET: Metabolic Equivalent of Task; BMI: Body mass index; LDL-C: Low-density lipoprotein-cholesterol; HbA1c: Hemoglobin A1c; CVD: Cardiovascular disease; HTN: Hypertension; T2D: Type 2 diabetes.

Table.3 Association between serum 25(OH)D levels and the risk of incident sepsis stratified by subgroups

Characteristics	>20ng/mL	10~20 ng/mL	< 10 ng/mL	*P* for interaction
Agegroup				0.580
<65	1.00	1.07 (1.02, 1.12)	1.32 (1.24, 1.40)	
≥65	1.00	1.12 (1.06, 1.19)	1.38 (1.27, 1.51)	
Sex				0.012
Male	1.00	1.08 (1.03, 1.13)	1.27 (1.19, 1.35)	
Female	1.00	1.05 (1.00, 1.11)	1.33 (1.23, 1.43)	
Smoke				0.973
Current	1.00	1.11 (1.00, 1.23)	1.36 (1.21, 1.53)	
Previous	1.00	1.08 (1.02, 1.13)	1.26 (1.16, 1.36)	
Never	1.00	1.03 (0.98, 1.09)	1.23 (1.14, 1.32)	
Drinking status				0.784
Current	1.00	1.06 (1.02, 1.10)	1.26 (1.20, 1.33)	
Previous	1.00	1.14 (0.98, 1.33)	1.30 (1.08, 1.56)	
Never	1.00	1.02 (0.86, 1.20)	1.32 (1.08, 1.61)	
BMI				0.044
<25	1.00	1.06 (0.99, 1.14)	1.37 (1.24, 1.51)	
25-30	1.00	1.04 (0.98, 1.10)	1.26 (1.17, 1.37)	
≥30	1.00	1.05 (0.99, 1.12)	1.20 (1.11, 1.30)	
CVD				0.105
Yes	1.00	1.10 (1.00, 1.21)	1.42 (1.26, 1.61)	
No	1.00	1.06 (1.02, 1.10)	1.24 (1.18, 1.31)	
HTN				0.171
Yes	1.00	1.10 (1.05, 1.17)	1.29 (1.19, 1.38)	
No	1.00	1.03 (0.98, 1.08)	1.27 (1.19, 1.36)	

Hazard ratios were adjusted for agegroup (< 65 years, ≥ 65 years), sex (male, female), ethnicity (White and non-white), Townsend deprivation index (continuous), education (College or university degree, A/AS levels or equivalent or O levels/General Certificate of Secondary Education or Certificate of Secondary Education or equivalent, National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent or other professional qualifications, not answer), household income (less than 18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, not answer), employment status (employed, unemployed and not answer), drinking status (current, previous, never, and not answer), smoking status (current, previous, never, and not answer), sleep (<7h/d, 7~8h/d, >8h), physical activity (continuous, MET-hours/week), BMI (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), total cholesterol (continuous, mmol/L), LDL-C (continuous, mmol/L), triglycerides (continuous, mmol/L), urate (continuous, μmol/L), creatinine (continuous, μmol/L), HbA1c (continuous, %), history of HTN, CVD, cancer ,T2D (yes, no).

MET: Metabolic Equivalent of Task; BMI: Body mass index; LDL-C: Low-density lipoprotein-cholesterol; HbA1c: Hemoglobin A1c; CVD: Cardiovascular disease; HTN: Hypertension; T2D: Type 2 diabetes.

Table.4 Risk of sepsis death associated with serum 25(OH)D levels

Characteristics	25(OH)D(ng/mL)			
	>20	10~20	< 10	*P* for trend
28-Day Mortality				
Crude model	1.00	1.03(0.95, 1.12)	1.15(1.03, 1.27)	0.016
model 1	1.00	1.05(0.97, 1.14)	1.22(1.10, 1.36)	<0.001
model 2	1.00	1.03(0.94, 1.11)	1.13(1.01, 1.26)	0.051
model 3	1.00	1.04(0.96, 1.13)	1.14(1.02, 1.27)	0.030
60-Day Mortality				
Crude model	1.00	1.01(0.94, 1.09)	1.12(1.02, 1.22)	0.041
model 1	1.00	1.03(0.96, 1.11)	1.18(1.08, 1.30)	0.001
model 2	1.00	1.01(0.94, 1.08)	1.10(1.00, 1.21)	0.100
model 3	1.00	1.02(0.95, 1.10)	1.11(1.01, 1.23)	0.054
1-Year Mortality				
Crude model	1.00	0.99(0.94, 1.05)	1.08(1.01, 1.16)	0.086
model 1	1.00	1.01(0.96, 1.07)	1.15(1.06, 1.24)	0.002
model 2	1.00	1.00(0.94, 1.06)	1.09(1.01, 1.17)	0.079
model 3	1.00	1.01(0.96, 1.08)	1.10(1.02, 1.19)	0.026

Model 1 was adjusted agegroup (< 65 years, ≥ 65 years), sex (male, female), ethnicity (White and non-white).

Model 2: Model 1+ Townsend deprivation index (continuous), education (College or university degree, A/AS levels or equivalent or O levels/General Certificate of Secondary Education or Certificate of Secondary Education or equivalent, National Vocational Qualification or Higher National Diploma or Higher National Certificate or equivalent or other professional qualifications, not answer), household income (less than 18,000, 18,000 to 30,999, 31,000 to 51,999, 52,000 to 100,000, greater than 100,000, not answer), employment status (employed, unemployed and not answer), drinking status (current, previous, never, and not answer), smoking status (current, previous, never, and not answer), sleep (<7h/d, 7~8h/d, >8h), physical activity (continuous, MET-hours/week).

Model 3: Model 2+ BMI (< 25 kg/m^2, 25 kg/m^2~30 kg/m^2, ≥30 kg/m^2), total cholesterol (continuous, mmol/L), LDL-C (continuous, mmol/L), triglycerides (continuous, mmol/L), urate (continuous, μmol/L), creatinine (continuous, μmol/L), HbA1c (continuous, %), history of HTN, CVD, cancer ,T2D (yes, no).

MET: Metabolic Equivalent of Task; BMI: Body mass index; LDL-C: Low-density lipoprotein-cholesterol; HbA1c: Hemoglobin A1c; CVD: Cardiovascular disease; HTN: Hypertension; T2D: Type 2 diabetes.