Original Resarch

25-Hydroxyvitamin D Deficiency Elevates the Risk of COPD Incidence and Mortality: A Large Population-Based Prospective Cohort Study

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***Running Head*: 25(OH)D Deficiency and COPD Incidence**

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Abbreviations: COPD: chronic obstructive pulmonary disease; 25(OH)D: 25-hydroxyvitamin D; UKB: UK Biobank; BMI: body mass index; RCTs: randomized controlled trials; CVD: cardiovascular disease; CKD: chronic kidney disease; DM: diabetes mellitus; ICD-10: the International Classification of Diseases, Tenth Revision; FEV1/FVC: forced expiratory volume in one second/forced vital capacity; sCa: serum calcium; 95% CI: 95% confidence intervals; OR: odds ratio; HR: hazard ratio; LDL: low density lipoprotein; HDL: high density lipoprotein

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Abstract

Background: The association between 25(OH)D levels and chronic obstructive pulmonary disease (COPD) remains unclear. The study aims to investigate the association between 25(OH)D concentrations and the incidence and survival of COPD in the UK Biobank cohort.

Methods: We conducted a cross-sectional analysis using UK Biobank data from 328,855 participants with complete 25(OH)D records. This analysis examined the association between 25(OH)D levels and COPD prevalence via logistic regression. Additionally, we prospectively followed a cohort of 327,871 individuals without baseline COPD. We assessed the risk of incident COPD and survival outcomes in this cohort using multivariable-adjusted Cox proportional hazards models. Kaplan-Meier estimates were used to generate survival curves.

Results: The prevalence of COPD was significantly higher in individuals with 25(OH)D deficiency compared to those with normal level, as evidenced by adjusted OR(95% CI) of 1.266(1.206–1.330) for COPD. During the median follow-up period of 15 years (IQR: 14-16 years), the overall COPD incidence was 262.3 per 10,000 person years, with higher rates among those with 25(OH)D deficiency (345.2 per 10,000 person years) compared to normal levels (232.6 per 10,000 person years) ($p<0.001$).In fully adjusted models, 25(OH)D deficiency was significantly associated with increased COPD incidence[HR 1.874, 95% CI 1.659 to 2.117] and mortality [HR 1.598, 95% CI 1.406-1.816]. Subgroup analyses revealed stronger associations with COPD incidence among men, current smokers, and individuals not taking vitamin D supplements, as well as an increased COPD mortality risk among patients with depression (p for interaction <0.05).

Conclusions: Our study suggests that 25(OH)D deficiency is associated with COPD incidence and survival, providing a basis for preventive strategies and interventions.

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Introduction

Chronic obstructive pulmonary disease (COPD), characterized by progressive airflow obstruction, ranks as the third leading cause of death globally, affecting over 300 million people and imposing a substantial socioeconomic burden[1]. Traditional modifiable risk factors, such as tobacco smoke exposure, indoor and outdoor air pollution, and low body mass index (BMI), contribute to its onset, but emerging evidence implicates nutritional deficiencies, including vitamin D, in disease pathogenesis[2,3]. Vitamin D, primarily measured as serum 25-hydroxyvitamin D [25(OH)D], plays a critical role in immunomodulation and anti-inflammatory processes, potentially mitigating respiratory inflammation central to COPD [4,5]. Given COPD's preventable nature, identifying modifiable factors like low 25(OH)D levels could enable targeted interventions to reduce incidence and improve outcomes in high-risk populations.

25(OH)D deficiency is a pervasive public health issue, with European surveys reporting 25(OH)D levels below 50 nmol/L in 40.4% and below 30 nmol/L in 13.0% of the general population[6]. In COPD patients, deficiency prevalence reaches 40–70%, raising questions about whether it precedes and exacerbates disease or arises as a consequence[7]. Low 25(OH)D impairs lung epithelial integrity and promotes chronic inflammation, aligning with COPD's pathophysiology[8,9]. Cross-sectional studies often show inverse associations, but causality remains debated due to reverse causation risks, such as reduced outdoor activity in symptomatic patients limiting sun exposure, a key vitamin D source[10,11].Epidemiologic evidence on 25(OH)D and COPD incidence is inconsistent[12-15]. A meta-analysis of 18 studies (8 cohorts, 5 case-controls, and 5 RCTs) found no overall link between low 25(OH)D and COPD susceptibility[16]. In contrast, another pooling 21 studies (n=4,818 COPD cases) reported a protective effect of higher 25(OH)D[17]. Heterogeneity likely stems from variable assays, supplement use, and unadjusted confounders like latitude or BMI. Prospective designs are needed to clarify these discrepancies and inform whether 25(OH)D screening could identify at-risk individuals.

Beyond incidence, low 25(OH)D associates with heightened COPD mortality and comorbidities, complicating management. An L-shaped curve links 25(OH)D <50 nmol/L to

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elevated all-cause and cardiovascular disease (CVD) mortality, particularly in individuals with diabetes mellitus(DM)[18,19]. Prior studies consistently identify common comorbidities in COPD, such as cancer(40%–70%), hypertension(17%–65%), depression(20%–60%), CVD(20%–48%), and DM (10%–45%), which are associated with increased mortality[20-25]. While chronic kidney disease (CKD) and cirrhosis disrupt 25(OH)D metabolism, leading to deficiency rates of 40.7%-85.7% across CKD stage 3-5 and 93% in cirrhosis, respectively[22,26].

In COPD cohorts, comorbid depression poses significant challenges for identification and treatment, as its symptoms often overlap with those of COPD itself [27]. Among COPD patients, depression exacerbates physical disability, impairs quality of life, increases healthcare service utilization, promotes noncompliance with medical therapy, and elevates mortality risk [28]. Vitamin D deficiency has been implicated in the pathogenesis of depression through mechanisms such as neuroinflammation and serotonin dysregulation, while higher serum 25(OH)D levels and supplementation show potential benefits in mitigating depressive symptoms and reducing its development [29,30]. These interconnections highlight the need for further exploration of 25(OH)D's role in modulating depression-related outcomes in COPD patients, as investigated in the present study.

This study addresses these gaps using UK Biobank data. Primary objectives are 1) to evaluate 25(OH)D levels and COPD prevalence in a cross-sectional study; and 2) to examine associations with COPD incidence and mortality over 15 years in a prospective cohort. Additionally, subgroup analyses examined effect heterogeneity across demographics, nutrients supplement, and comorbidities to inform personalized strategies.

Method

Study design, setting and participants

Cross-Sectional Study

Participants were selected from the UK Biobank, a large-scale cohort study initiated between 2006 and 2010. This resource provides comprehensive genetic, lifestyle, environmental, and

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health-related data for 502,357 individuals aged 37–73 years recruited across England. For our cross-sectional analysis, we included 448,222 participants with complete data on 25(OH)D. After excluding those with missing data on body mass index (BMI; n=1,751), smoking status (n=2,244), alcohol consumption (n=462), coffee intake (n=789), family income (n=62,520), sun exposure (n=20,652), and serum calcium (n=30,949), a final sample of 328,855 individuals was available for analysis. Among the participants, 13,890 were diagnosed with COPD, while 314,965 were without the disease (Table S1).

Longitudinal Follow-Up

For the prospective analysis, we excluded 984 participants with a baseline diagnosis of COPD(prior to enrollment), yielding a cohort of 327,871 individuals without COPD (Figure 1). During the follow-up period, 12,906 individuals developed COPD, and 1,591 died from this disease by the end of follow-up (Table 1 & Table S2). This cohort was followed to assess the risk of incident COPD and COPD-related mortality.

Definitions

25(OH)D status definitions

The quantification of 25(OH)D status was ascertained through the measurement of serum 25(OH)D concentrations, utilizing chemiluminescence immunoassay (CLIA) techniques facilitated by the DiaSorin Ltd. LIASON XL instrument [31]. We classified vitamin D status using two established criteria, as follows:

Institute of Medicine (IOM) Cutoffs[32]:

Normal (Sufficiency): ≥50 nmol/L

Insufficiency: 30–50 nmol/L

Deficiency: <30 nmol/L

Endocrine Society Clinical Practice Guideline[33]:

Normal (Sufficiency): ≥30 ng/mL (≥75 nmol/L)

Insufficiency: 21–29 ng/mL (50-75 nmol/L)

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Deficiency: <20 ng/mL (<50 nmol/L)

Assessment of COPD with ICD-10 codes

The definition of COPD to the Global Initiative for Chronic Obstructive Lung Disease-2024 Report (GOLD 2024) is confirmed by the presence of non-fully reversible airflow obstruction (FEV1/FVC < 0.7 post-bronchodilation) mesured by spirometry[34]. We extracted data on events and mortality specifically associated with COPD using the International Classification of Diseases, Tenth Revision (ICD-10). As J40–J43 primarily encompass patients with chronic bronchitis and emphysema, who may not meet the spirometric criteria for COPD, these were excluded. Ultimately, we selected patients with ICD-10 code J44, which includes the following subcategories of COPD as:

(1) J44.0 (Chronic obstructive pulmonary disease with acute lower respiratory infection),

(2) J44.1 (Chronic obstructive pulmonary disease with acute exacerbation, unspecified),

(3) J44.8 (Other specified chronic obstructive pulmonary disease), and

(4) J44.9 (Chronic obstructive pulmonary disease, unspecified).

Pre-Existing COPD Definition

Pre-existing COPD was defined as a J44 diagnosis recorded prior to study enrollment (baseline date). This was determined by comparing the timestamp of the first COPD diagnosis code against the enrollment date for each participant. Individuals with a pre-enrollment diagnosis were classified as having pre-existing COPD and were excluded from the prospective incidence analysis to minimize immortal time bias (Figure 1).

COPD-Specific Death Ascertainment

Furthermore, COPD-specific deaths were ascertained from linked UKB death register data (Category 10093) using ICD-10 codes J44 (J44.0–J44.9) as the underlying or contributing cause

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of death.

Covariates

We included certain factors that influence both the exposure (vitamin D status) and outcome (COPD prevalence/incidence/mortality) to minimize confounding as covariates. Specifically, we comprised 5 sociodemographic factors [age, sex, ethnicity, area (rural or urban) and family income], 6 lifestyles (BMI, smoking, alcohol, coffee, vitamin D supplement and time spend outdoor in summer and in winter), 5 blood factors [serum calcium (sCa) and 4 kinds of lipids (Triglycerides, Cholesterol, low density lipoprotein(LDL) and high density lipoprotein (HDL)], and 7 major comorbidities prevalent in COPD that may influence long-term mortality and vitamin D metabolism (hypertension, CVD, CKD, DM, cancer, cirrhosis, and depression).

Socioeconomic variables (e.g., age, sex, ethnicity, residence, income) were included as established COPD risk adjusters, which adjusted for these in vitamin D-COPD analyses[34]. Lifestyle factors (e.g., BMI, smoking, alcohol, coffee) reflect modifiable COPD triggers and 25(OH)D influencers[34,35]. For vitamin D metabolism, we incorporated supplementation, sun exposure, sCa, and lipids, given their roles in synthesis/regulation[36-38]. Comorbidities were selected based on their bidirectional links to both low 25(OH)D and COPD mortality (e.g., CKD/cirrhosis impair 25(OH)D activation; hypertension/diabetes/CHD/cancer/depression amplify systemic inflammation)[20-26].

Given that older adults are more susceptible to developing COPD, we stratified participants into two age groups: those younger than 65 years and those aged 65 years or older. As a baseline for adequate 25(OH)D3 production, it is noted that direct sunlight exposure for merely 15 minutes twice a week suffices; thus, we defined sun exposure of less than 0.5 hours per day as minimal outdoor activity. Participants were also categorized into six household income subgroups. sCa levels were classified into 3 groups: low (<2.2 mmol/L), normal (2.2–2.75 mmol/L), and high (>2.75 mmol/L). BMI were divided into 4 categories: Underweight (BMI<18.5kg/m^2), Normal (18.5-25kg/m^2), Overweight (25-30kg/m^2), Obesity (≥30kg/m^2).

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Statistical analyses

For all descriptive statistics, continuous variables were presented as means with standard deviations (SD) and categorical variables were presented as frequencies. To examine the group differences in baseline characteristics, an analysis of Student's t tests (or Mann–Whitney–Wilcoxon tests) was used for continuous variables where appropriate and the chi-squared or Fisher's exact test was used for categorical variables. A multivariate logistic regression analysis was performed to assess the association between categorized serum 25(OH)D levels and COPD prevalence. Multivariate Cox proportional hazards regression was assess the association between serum 25(OH)D levels and the incidence and mortality of total COPD events, adjusting for potential confounders. Additionally, Kaplan-Meier curves were estimated to depict event-free survival across different 25(OH)D categories, and the log-rank test was employed to compare differences between these curves. Non-adjusted hazard ratios and adjusted hazard ratios, along with their 95% confidence intervals (95% CI), are reported. Additionally, we performed stratified analyses based on 25(OH)D supplement use (yes/no), sex (male/female), age (≥65 years vs. <65 years), smoking status(never/previous/current) and statistically significant comorbidities (present/absent) in the fully adjusted model. A likelihood ratio test was performed to assess potential effect modification between 25(OH)D concentrations and stratification variables by comparing models with and without interaction terms.

Our analytical strategy employed a series of nested, progressively adjusted models to systematically control for potential confounders in examining the association between 25(OH)D status and COPD outcomes. Model 1 provided the unadjusted (crude) estimates. Model 2 adjusted for demographic factors (age, sex, ethnicity, area of residence [rural or urban] and family income). Model 3 incorporated additional factors related to lifestyle and dietary habits. (BMI, smoking status, alcohol intake, coffee intake, sCa, sun exposure, vitamin D supplementation and lipids [triglycerides, total cholesterol, LDL, and HDL]). Finally, Model 4 represented the fully adjusted analysis, including all clinically justified covariates plus

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comorbidities (hypertension, CVD, CKD, DM, cancer, cirrhosis, and depression). All primary results are based on Model 4.

Our statistical analyses utilized IBM SPSS Statistics (version 26.0), with forest plots created through GraphPad Prism (version 9.0). Significance was assigned to p-values below 0.05, adhering to rigorous hypothesis testing standards and ensuring statistical integrity with two-sided tests.

Results

Baseline characteristics of study participants

The demographics and baseline characteristics of the cross-sectional study data are summarized in Table S1.The mean serum 25(OH)D level in COPD patients (45.79±21.78 nmol/L) was lower than in healthy controls (48.91±21.00 nmol/L). Additionally, 25(OH)D deficiency was observed in 27.3% of COPD patients, compared to 20.32% in the healthy population (Table S1). Over a 15-year median follow-up period in a cohort of 327,871 participants (Table 1), the overall COPD incidence was 262.3 per 10,000 person years, with higher rates among those with 25(OH)D deficiency (345.2 per 100,000 person years) or insufficiency (251.8) compared to normal levels (232.6) ($p<0.001$). Furthermore, COPD-specific mortality rates were also observed higher in participants with 25(OH)D deficiency (10.68 per 100,000 person years than in those with normal levels(6.6 per 100,000 person years) Aditionally, the mortality rates among COPD patients with comorbid DM (27.61% vs. 19.19%), CHD (33.56% vs. 29.74%), cancer (38.31% vs. 34.74%), and depression (20.14% vs. 16.48%) were significantly higher in the deficiency group. These findings indicate a significant association between 25(OH)D status and COPD outcomes.

Cross-sectional analysis of the association between serum 25(OH)D concentrations and COPD prevalence

Table 2 summarizes the association between serum 25(OH)D levels and COPD prevalence,

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analyzed via logistic regression across four different models. Compared to normal 25(OH)D levels, both insufficient and deficient categories showed higher odds of COPD in a dose-dependent manner, with associations strengthening for deficiency. In the fully adjusted Model 4, ORs remained significant at 1.071 (95% CI: 1.026- 1.119, p=0.002) for 25(OH)D insufficiency and 1.266 (95% CI: 1.206–1.330, p<0.001) for 25(OH)D deficiency. Consistent with Endocrine Society diagnostic criteria, our analysis confirmed a significant link between 25(OH)D deficiency and elevated COPD prevalence (HR: 1.169; 95% CI: 1.097–1.245) (Table S3).

Figure 2 presents a forest plot illustrating the multivariable-adjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the associations between various coviriates and COPD prevalence from logistic regression analysis (fully adjusted Model 4). In addition to the association between 25(OH)D status and COPD prevalence, other notable associations included advanced age (≥65 years), male sex, urban residence, current-smoking status, and comorbidities such as hypertension and depression, while overweight status showed a protective effect.

Longitudinal association of serum 25(OH)D levels with COPD incidence and COPD-specific death

During a median follow-up of 15(IQR:14-16) years, 12906 cases of COPD were recorded in this prospective cohort study(Table S2). In the fully adjusted Model 4, compared to the normal group, the 25(OH)D deficiency and insufficiency groups exhibited an 87.4% (HR: 1.874; 95% CI: 1.659–2.117) and 35.8% (HR: 1.358; 95% CI: 1.207–1.527) increased risk of COPD incidence, respectively (Figure 3). According to the categorization in the Endocrine Society Clinical Practice Guideline, similar results were observed in the 25(OH)D deficiency group (HR: 1.724; 95% CI: 1.442-2.062) (Table S4).

Multivariable analysis across four different adjusted models demonstrated a dose-dependent association between serum 25(OH)D status and COPD-specific mortality. Compared to the sufficient group, fully adjusted models revealed a graded elevation in risk, with 25(OH)D-deficient individuals exhibiting a 59.8% increase (HR:1.598, 95% CI:1.406–1.816) and

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insufficient individuals showing a 32.7% higher risk (HR:1.327, 95% CI:1.171–1.504), as depicted in Figure 4A. Survival probability curves in Figure 4B further supported these findings, with the deficient group exhibiting significantly reduced survival over follow-up(log-rank p<0.001). Stratification by Endocrine Society criteria similarly confirmed these trends, with complete methodological details (HR: 1.654; 95% CI: 1.366-2.004) in Table S4.

Subgroup analysis

COPD prevalence and specific mortality show stronger association with male gender, advanced age and smokers[26494423, 37497381]. This aligns with our fingdings in Figure 2. Consequently, we conducted additional subgroup analyses (Tables S5–S6), stratified by gender, age, smoking status and vitamin D supplementation, to clarify the associations between 25(OH)D levels and risks of risks across these groups. 25(OH)D deficiency was more strongly associated with COPD incidence in men, current smokers, and those not taking vitamin D supplements (*p* for interaction <0.05). Male gender also played a significant role in the link between 25(OH)D deficiency and COPD mortality risk. COPD comorbidities such as DM, CVD, cancer, and depression showed significant differences between the 25(OH)D deficiency and normal groups. Therefore, we conducted subgroup analyses for these comorbidities. The results showed that depression subgroup indicates a stronger effect of 25(OH)D deficiency on increasing COPD mortality risk among patients with depression (*p* for interaction <0.05)(Table S7).

Discussion

In our cross-sectional study, we utilized a large sample from the UK Biobank, identified an association between 25(OH)D deficiency and a higher prevalence of COPD. Specifically, we observed that compared to individuals with normal 25(OH)D levels, those exhibiting deficiency group had a 26.6% increased prevalence of COPD. Subsequently, we designed a prospective study

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to evaluate the association between 25(OH)D deficiency and the risk of COPD incidence and survival. In our fully adjusted model, the group with 25(OH)D deletion exhibited a substantially higher COPD incidence [HR(95CI%): 1.874(1.659-2.117)] and comorbidity [HR(95CI%): 1.598(1.406-1.816)] compared to the control group. Subgroup analyses revealed stronger associations with COPD incidence among men, current smokers, and individuals not taking vitamin D supplements, as well as an increased COPD mortality risk among patients with depression (p for interaction <0.05).

25(OH)D insufficiency and deficiency exhibit substantial variability across diverse demographic groups, including differences in age, sex, malnutrition or malabsorption, as well as environmental factors such as seasonal variations in sunlight exposure and geographic latitude[39]. In our study, the prevalence of reduced 25(OH)D levels was 60.57% among individuals with COPD and 54.91% among those without COPD, which is consistent with prior research reporting rates ranging from 8.7% to 69%.[40-42]. In the cross-sectional study, the overall prevalence of COPD was 4.25% (13,890/328,855), which is lower than the 10.3% reported in the GOLD 2024 guidelines, but higher than the 2.7% prevalence rate reported in the 2021 GBD report[43]. Still, several factors explain the lower baseline COPD rate compared to population estimates: (1) Case definition specificity: Our narrow ICD-10 J44.x criteria exclude chronic bronchitis and emphysema without spirometric confirmation, enhancing specificity but reducing prevalence. (2) Cohort Smoking Profile: UK Biobank's ~89% never- and former-smokers yield a lower COPD burden than in higher-smoking populations. (3) Healthy Volunteer Bias: Participants are healthier and of higher socioeconomic status, likely lowering prevalence and attenuating effects. During a median follow-up of 15(IQR:14-16) years, the overall COPD incidence was 262.3 per 10,000 person years, which is highly consistent with prior UK Biobank analyses using similar definitions and follow-up lengths[35]. Thus, the longitudinal disease occurrence in our cohort is not unusually low. These rates fall largely within the range of reported global age-standardized incidence rates (ASIR), which averaged 197.37 per 100,000 people worldwide and reached highest in Nepal(310.58) [44].

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Our study shown the hazard ratio of 25(OH)D deficiency was 1.27 for COPD risk, which aligned with previous studies ranging from 1.23 to 2.00[35,45,46]. A large cohort of 18507 participants followed for over 20 years confirmed a prospective link between lower 25(OH)D and an elevated COPD risk, while it limited to white individuals in low-sun-exposure areas and delayed 25(OH)D measurements[45]. Similarly, Zhu Z *et al.* analyzed UK biobank data, finding that the lowest 25(OH)D quintile(<31.7nmol/L) conferred a 23% higher COPD risk (HR:1.23, 95%CI:1.15-1.32) compared to the fourth quintile[35]. Our findings align with Zhu et al. in associating lower 25(OH)D with higher COPD incidence and meaningfully extend prior findings: (1) Clinically actionable 25(OH)D thresholds: Unlike population-based quintiles, we used IOM and Endocrine Society cutoffs to distinguish insufficiency and deficiency, facilitating direct clinical application in screening, supplementation, and risk stratification. (2) Complementary cross-sectional and prospective analyses: To resolve prior cross-sectional inconsistencies, we combined prevalence and incidence assessments, linking 25(OH)D <50 nmol/L to higher COPD onset and worse survival for a more comprehensive temporal view. (3) Specific COPD case definition: We restricted cases to ICD-10 J44.0–J44.9, excluding chronic bronchitis and emphysema codes that may lack diagnostic confirmation, thereby minimizing misclassification and bolstering association validity. (4) Comprehensive confounder and comorbidity adjustment: We adjusted for expanded factors affecting vitamin D and COPD (e.g., sun exposure, supplementation, lipids, CKD, cirrhosis, depression), with associations remaining stable in sensitivity analyses. (5) Mortality analysis stratified by comorbidities: We advanced prior studies by evaluating COPD survival in comorbid subgroups, highlighting depression as a mortality modifier and identifying a high-risk group overlooked previously (p for interaction <0.05).

We further elucidated the impact of 25(OH)D on COPD survival. Participants with insufficiency and deficiency faced 32.7% (HR,1.33; 95CI%,1.17-1.50) and 59.8% (HR,1.60; 95CI%,1.41-1.82) higher COPD-specific mortality risks, respectively, versus nomal levels. UK Biobank data indicated higher 25(OH)D reduced all-cause mortality(17%), CVD(23%) and cancer(11%) mortality, though COPD-specific effects were unexamined[47]. Zhu Z *et al.* reported

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a 38% higher risk overall COPD death in the lowest quintile[35]. COPD Comorbidities independently elevate death risk [48-50]. Our models comprehensively adjusted for these factors, revealing persistent associations, including an increased COPD mortality risk among depressed patients (p for interaction <0.05). This finding is consistent with evidence of higher mortality among COPD patients with depression [51,52].

The association between 25(OH)D levels and COPD outcomes may be underestimated or overestimated when using quintiles. To address this, we employed both the U.S. Institute of Medicine (IOM) and Endocrine Society criteria to assess 25(OH)D status and identify deficiency. Our findings consistently show that 25(OH)D deficiency and insufficiency (per IOM cut-offs) or deficiency alone (per Endocrine Society guidelines) increase risks of COPD incidence and mortality[32,33].These aligned results suggest that 25(OH)D levels below 50nmol/L are a significant risk factor for both COPD risk and survival.

This study has several limitations that should be consideration when interpreting the findings. First, participants were younger than in prior studies, potentially limiting generalizability, as younger cohorts may have distinct risk profiles and disease trajectories compared to older, more COPD-prone groups. Future research should span broader age ranges to capture life-stage variations. Second, the prospective analysis lacked symptom scores and lung function data for COPD patients, restricting insights into 25(OH)D's ffects on clinical outcomes and severity. Since severe cases comprising only 0.8% of events, 25(OH)D deficiency linked more to mild-to-moderate but not severe COPD incidence. Further research should examine the role of 25(OH)D across severity levels. Third, subgroup analysis by vitamin D supplementation(used by only 3.9% of participants) showed significant association between 25(OH)D deficiency/insufficiency and COPD incidence in those not taking it. This small sample precludes firm conclusions on supplementation's protective effects. Intervention trials, such as RCTs, are needed to test causality and efficacy. Fourth, season variations strongly influence 25(OH)D levels (particularly in the UK), but our dataset lacked measurement of season data, hindering adjustments. Future studies should account for seasonality to improve accuracy. Fifth, the prospective study excluded baseline COPD

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patients to confirm vitamin D deficiency's link to increased COPD risk. Future research should be carried to assess potential reverse causality. Overall, these limitations underscore the value of more robust, comprehensive studies to address these gaps. Nonetheless, our work offers preliminary insights into the 25(OH)D-COPD relationship.

Conclusion

In conclusion, our findings suggest a higher prevalence of 25(OH)D deficiency among individuals with COPD compared to those with insufficiency and sufficiency. Using two criteria to assess 25(OH)D status, we observed potential associations between levels below 50nmol/L and elevated risks of COPD incidence and specific mortality. Depression comorbidity showed strong association with mortality risk.These results warrant cautious interpretation; future research, including large-scale RCTs, is needed to evaluate supplementation efficacy and causal links.

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Declarations

Ethics Approval and consent to participate

This study was performed in accordance with the Declaration of Helsinki. This human study was approved by UK National Health Service, National Research Ethics Service North West, the National Information Governance Board for Health and Social Care in England and Wales, and the Community Health Index Advisory Group in Scotland - approval: 106397. All adult participants provided written informed consent to participate in this study.

Availability of data and materials

All data are publicly available in the UKB repository (https://www.ukbiobank.ac.uk/).

Competing interests

The authors declare that they have no competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' contributions

ZY contributed in conceptualization, formal analysis, funding acquisition, investigation, methodology, project administration, software,writing-original draft and writing-review& editing. ZSJ contributed in funding acquisition, methodology, software and writing-original draft. ZC contributed in data curation, formal analysis, investigation and methodology. ZJZ contributed in resources, supervision, validation and writing-review& editing.TQ contributed in conceptualization, project administration, resources, supervision, visulization, writing-review& editing. All authors read and approved the final manuscript.

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Table 1. Baseline Characteristics of Participants based on 25(OH)D level over 15 years of follow-up

Characteristic	All	25(OH)D levels			*p* value
	Means±SD N(%)	Deficiency	Insufficiency	Normal	
All subjects	327871	67500	113232	147139	
Age, yr					<0.001
<65	53.77±7.02	52.74±6.94	53.67±7.00	54.35±7.02	
	270328(82.45)	58449(86.59)	94118(83.12)	117761(80.03)	
≥65	66.89±1.48	66.89±1.48	66.91±1.48	66.87±1.48	
	57543(17.55)	9051(13.41)	19114(16.88)	29378(19.97)	
Sex					0.330
Male	161493(49.26)	33251(49.26)	57273(50.58)	74856(50.87)	
Female	166378(50.74)	34249(50.74)	55959(49.42)	72283(49.13)	
Ethnicity					<0.001
White	312962(95.46)	59924(88.78)	108285(95.63)	144753(98.38)	
Non-white	14156(4.32)	7342(10.88)	4689(4.14)	2125(1.44)	
BMI[b], kg/m²					<0.001
Underweight	17.65±0.79	17.59±0.77	17.66±0.81	17.67±0.79	
	1511(0.46)	386(0.57)	441(0.39)	684(0.46)	
Normal	22.83±1.52	22.76±1.56	22.87±1.5	22.83±1.51	
	106480(32.48)	18794(27.84)	33277(29.39)	54409(36.98)	
Overweight	27.24±1.40	27.34±1.42	27.29±1.41	27.17±1.39	
	141248(43.08)	26672(39.51)	49322(43.56)	65254(44.35)	
Obesity	33.84±3.84	34.64±4.5	33.86±3.75	33.16±3.19	

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	78632(23.98)	21648(32.07)	30192(26.66)	26792(18.21)	
Smoking status					<0.001
Never	178649(54.49)	35986(53.31)	62372(55.08)	80291(54.57)	
Previous	115151(35.12)	21282(31.53)	39445(34.84)	54424(36.99)	
Current	34071(10.39)	10232(15.16)	11415(10.08)	12424(8.44)	
Alcohol intake					<0.001
Yes	305215(93.09)	60399(89.48)	105531(93.2)	139285(94.66)	
No	22656(6.91)	7101(10.52)	7701(6.8)	7854(5.34)	
Coffee intake					<0.001
Yes	257536(78.55)	51463(76.24)	88953(78.56)	117120(79.6)	
No	70335(21.45)	16037(23.76)	24279(21.44)	30019(20.4)	
Time spent outdoor, hours					<0.001
In summer					
Yes	327185(99.79)	67200(99.56)	112991(99.79)	146994(99.9)	
No	686(0.21)	300(0.44)	241(0.21)	145(0.1)	
In winter					<0.001
Yes	317243(96.76)	64451(95.48)	109504(96.71)	143288(97.38)	
No	10628(3.24)	3049(4.52)	3728(3.29)	3851(2.62)	
Family income, pounds					<0.001
<18,000	70863(21.61)	17093(25.32)	23979(21.18)	29791(20.25)	
18,000-30,999	82590(25.19)	16151(23.93)	28074(24.79)	38365(26.07)	
31,000-51,999	86766(26.46)	17442(25.84)	30237(26.7)	39087(26.56)	
52,000-100,000	69069(21.07)	13537(20.05)	24382(21.53)	31150(21.17)	

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>100,000	18583(5.67)	3277(4.85)	6560(5.79)	8746(5.94)	
sCa^c, mmol/L					<0.001
Low	2.16±0.05 6582(2.01)	2.16±0.04 1951(2.89)	2.16±0.06 2347(2.07)	2.16±0.06 2284(1.55)	
Normal	2.38±0.09 320719(97.82)	2.37±0.09 65411(96.91)	2.38±0.09 110645(97.72)	2.39±0.09 144663(98.32)	
High	2.84±0.11 570(0.17)	2.84±0.1 138(0.20)	2.84±0.1 240(0.21)	2.84±0.12 192(0.13)	
Comorbidities, n (%)					
Hypertension	101187(30.86)	21617(32.03)	35067(30.97)	44503(30.25)	<0.001
CVD	33298(10.16)	7293(10.8)	11457(10.12)	14548(9.89)	<0.001
CKD	13810(4.21)	2903(4.3)	4701(4.15)	6206(4.22)	0.309
DM	28146(8.58)	8179(12.12)	10203(9.01)	9764(6.64)	<0.001
Cancer	65005(19.83)	12238(18.13)	21664(19.13)	31103(21.14)	<0.001
Cirrhosis	1513(0.46)	469(0.69)	510(0.45)	534(0.36)	<0.001
Depression	19908(6.07)	4874(7.22)	6748(5.96)	8286(5.63)	<0.001
Comorbidities in COPD, n (%)					
COPD /person-years (per 100,000 person years)	12906(262.3)	3495(345.2)	4277(251.8)	5134(232.6)	<0.001
COPD-Death /person-years (per 100,000 person years)	1591(3.07)	560(10.68)	523(8.25)	508(6.60)	<0.001

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Hypertension	8324(64.50)	2251(64.41)	2801(65.49)	3272(63.73)	0.205
CVD	4036(31.27)	1173(33.56)	1336(31.24)	1527(29.74)	0.001
CKD	1723(13.35)	448(12.82)	597(13.96)	678(13.21)	0.314
DM	3013(23.35)	965(27.61)	1063(24.85)	985(19.19)	＜0.001
Cancer	4716(36.54)	1967(38.31)	1535(35.89)	1214(34.74)	0.002
Cirrhosis	206(1.60)	68(1.95)	71(1.66)	67(1.31)	0.061
Depression	2279(17.66)	704(20.14)	729(17.04)	846(16.48)	＜0.001

Abbreviations: SD, standard deviation; BMI, Body mass index; sCa, serum calcium; Vit D,25(OH)D; CVD, cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus;

[a] Statistical significance was set at 2-sided $P \leq 0.05$.

[b] Underweight : BMI<18.5kg/m^2; Normal :18.5-25kg/m^2; Overweight: 25-30kg/m^2; Obesity: BMI≥30kg/m^2.

[c]sCa categorized as 3 groups: Low: <2.2 mmol/L; Normal:2.2-2.75 mmol/L; High:＞2.75 mmol/L.

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Table 2. Association of 25(OH)D level with COPD prevalence

25(OH)D, nmol/L	OR	95%CI	*p* value
Model 1[a]			＜0.001
Normal	Ref		
Insufficiency	1.100	1.057-1.144	＜0.001
Deficiency	1.536	1.472-1.603	＜0.001
Model 2[b]			＜0.001
Normal	Ref		
Insufficiency	1.158	1.112-1.205	＜0.001
Deficiency	1.757	1.682-1.835	＜0.001
Model 3[c]			＜0.001
Normal	Ref		
Insufficiency	1.069	1.024-1.115	0.002
Deficiency	1.286	1.227-1.349	＜0.001
Model 4[d]			＜0.001
Normal	Ref		
Insufficiency	1.071	1.026-1.119	0.002
Deficiency	1.266	1.206-1.330	＜0.001

Abbreviations: OR, Odds Ratio; 95%CI, 95% Confidence Interval.

a Calculated by means of a Logistic regression analysis with no adjustment.

b Adjusted by age, sex, ethnicity and area(rural or urban) and family income.

c Adjusted for model 2 plus BMI, lifestyle (coffee take, alcohol take, smoking status, sCa, sun exposure and vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL).

d Adjusted for model 3 plus comorbidities (hypertension, CVD, CKD, DM, cancer, cirrhosis, and depression).

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Figure1. Flowchart of COPD Cohort Study

A comprehensive analysis was conducted using data from 502,357 participants enrolled in the UK Biobank between 2006 and 2010. Individuals with missing serum 25(OH)D levels were excluded (n=54,135), yielding 448,222 participants with complete vitamin D data. Further exclusions were applied for missing values in key covariates, totaling n=119,367: BMI (n=1,751), smoking status (n=2,244), alcohol intake (n=462), coffee intake (n=789), family income (n=62,520), sun exposure (n=20,652), and serum calcium (n=30,949). This resulted in a final population of 328,855 eligible for the cross-sectional analysis of baseline characteristics, stratified by COPD status (COPD vs. non-COPD). For the prospective analysis, 984 participants with pre-existing COPD at baseline were additionally excluded, leaving 327,871 individuals for follow-up over a median of 15 years (IQR: 14–16 years).

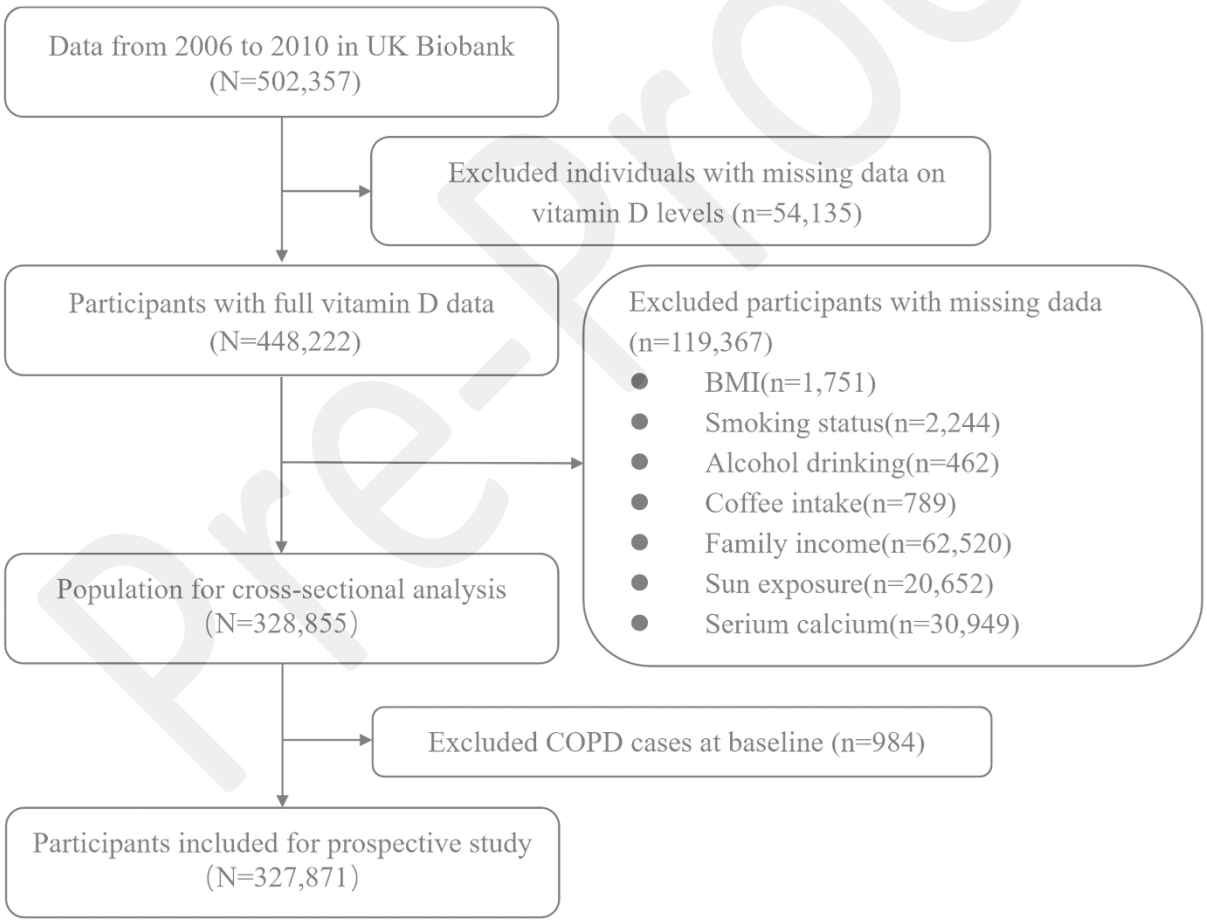

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Figure2. Forest plot of 25(OH)D Status, Covariates, and COPD Prevalence

Forest plot of multivariable-adjusted odds ratios (ORs) and 95% CIs from logistic regression in fully adjusted model, showing the primary exposure 25(OH)D status and key covariates in relation to COPD prevalence.

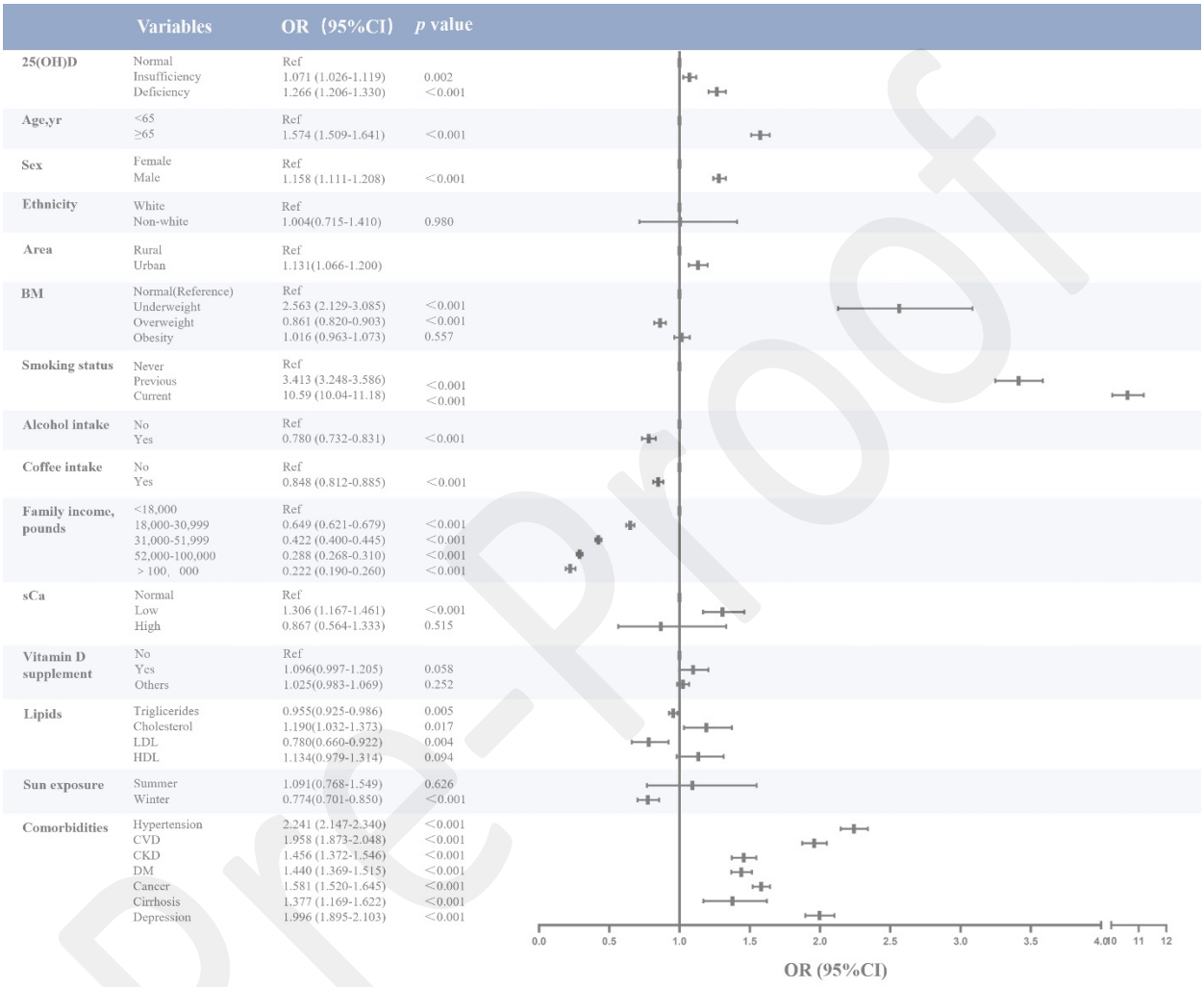

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Figure 3. Forest plot and cumulative risk of COPD incidence

Multiple cox regression model (A) and cumulative risk curves (B) was established to present the associations between 25(OH)D levels and the incidence of COPD. The tick marks for censored subjects are shown as black dots in this illustration.

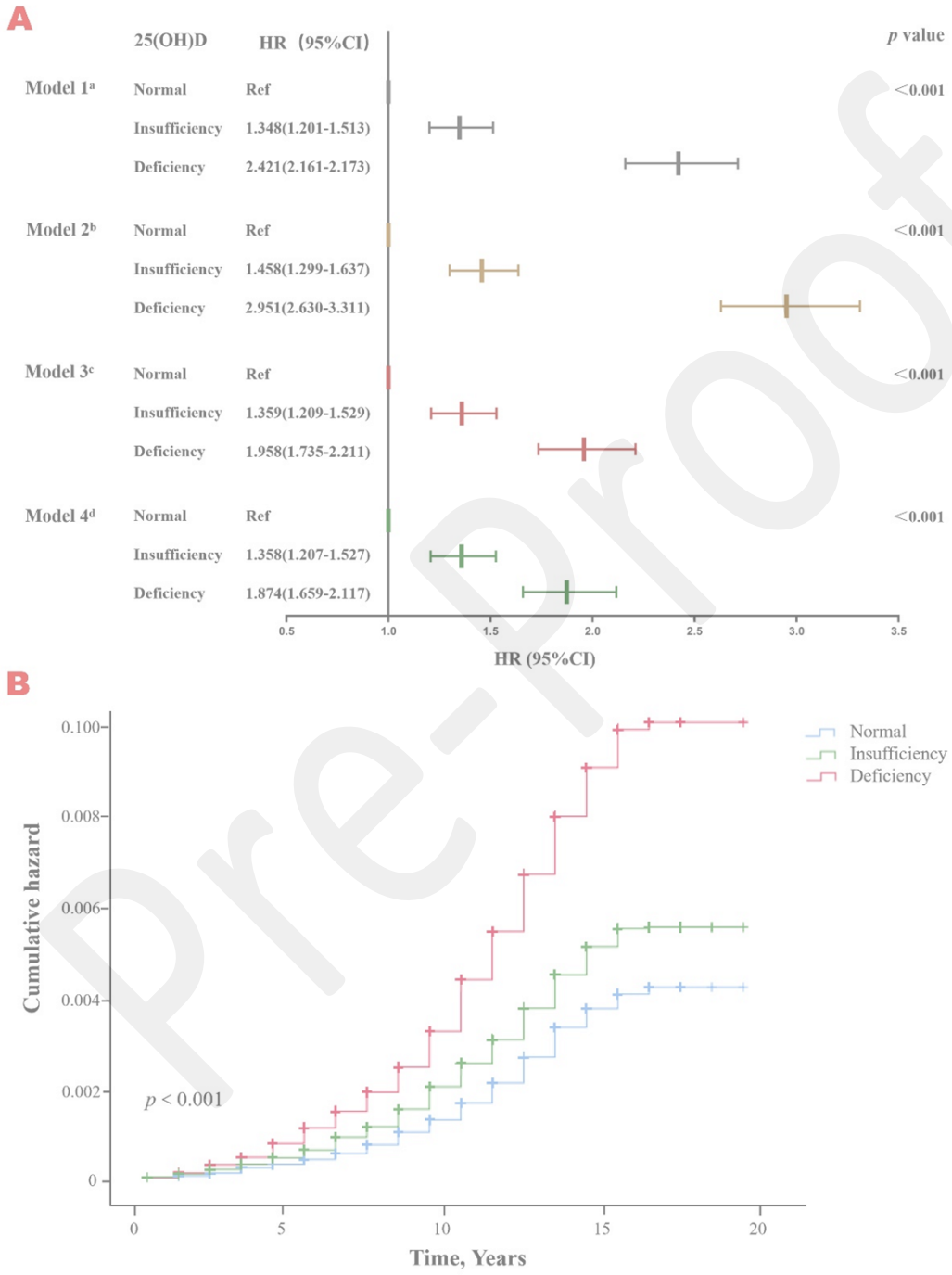

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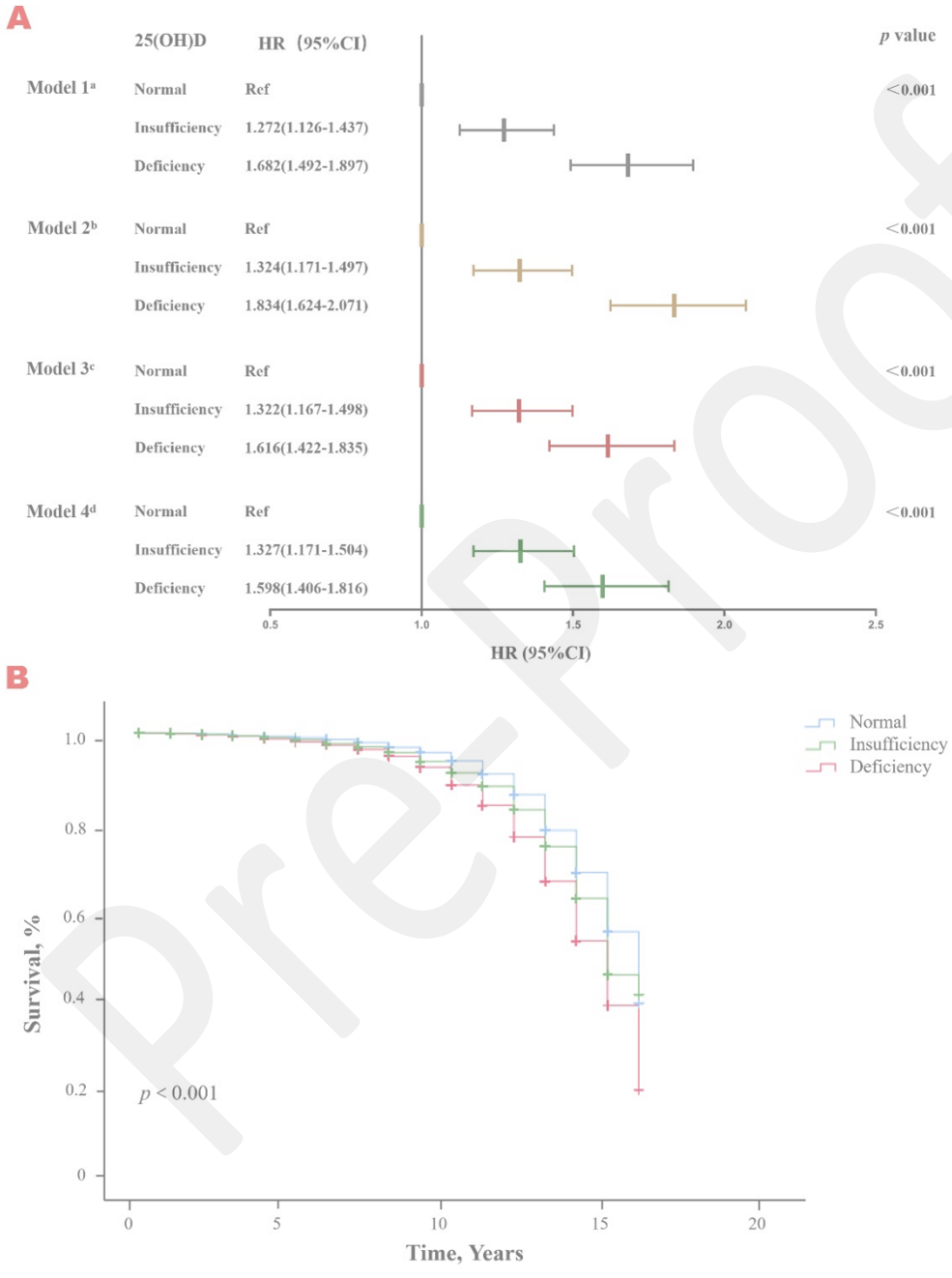
Figure4. Forest plot and Kaplan Meier Estimate for COPD Survival

Multiple cox regression model (A) and survival curves (B) were performed to present the associations between 25(OH)D and COPD-specific mortality. The tick marks for censored subjects are shown as black dots in this illustration.



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Online Supplement

Table S1. Baseline Characteristics of UK Biobank Participants based on COPD diagnosis

Characteristic	Total (N=328855)		COPD (N=13890)		Control (N=314965)		*p* value
	Means±SD	N(%)	Means±SD	N(%)	Means±SD	N(%)	
Age, yr	56.08±8.12		61.09±6.43		55.86±8.12		<0.001
<65	53.77±7.02	270923(82.38)	57.73±5.68	8871(63.87)	53.64±7.02	262052(83.2)	
≥65	66.88±1.48	57932(17.62)	67.01±1.50	5019(36.13)	66.87±1.48	52913(16.8)	
Sex							<0.001
Male		162045(49.28)		8073(58.12)		153972(48.89)	
Female		166810(50.72)		5817(41.88)		160993(51.11)	
BMI[b], kg/m^2	27.35±4.73		28.44±5.60		27.31±4.68		<0.001
Underweight	17.64±0.79	1523(0.46)	17.44±0.94	176(1.27)	17.67±0.77	1347(0.43)	
Normal	22.83±1.52	106676(32.44)	22.67±1.64	3647(26.26)	22.83±1.51	103029(32.71)	
Overweight	27.24±1.40	141585(43.05)	27.37±1.41	5380(38.73)	27.24±1.40	136205(43.24)	
Obesity	33.84±3.85	79071(24.04)	34.57±4.39	4687(33.74)	33.79±3.81	74384(23.62)	
Smoking status							<0.001
Never		178845(54.38)		2361(17.00)		176484(56.03)	
Previous		115692(35.18)		6568(47.29)		109124(34.65)	
Current		34318(10.44)		4961(35.72)		29357(9.32)	
Alcohol intake							<0.001
Yes		306032(93.06)		12378(89.11)		314965(93.23)	
No		22823(6.94)		1512(10.89)		293654(6.77)	
Coffee intake							<0.001
Yes		258237(78.53)		10472(75.39)		247765(78.66)	
No		70618(21.47)		3418(24.61)		67200(21.34)	
Time spent outdoor, hours							
In summer							0.019
Yes		328164(99.79)		13848(99.7)		314316(99.79)	
No		691(0.21)		42(0.3)		649(0.21)	
In winter							<0.001
Yes		318172(96.75)		13338(96.03)		304834(96.78)	
No		10683(3.25)		552(3.97)		10131(3.22)	
Family income, pounds							<0.001
<18,000		71477(21.74)		6814(49.06)		64663(20.53)	
18,000-30,999		82815(25.18)		3886(27.98)		78929(25.06)	
31,000-51,999		86861(26.41)		2104(15.15)		84757(26.91)	

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52,000-100,000		69110(21.02)		917(6.6)	68193(21.65)	
>100,000		18592(5.65)		169(1.22)	18423(5.85)	
sCa[c], mmol/L	2.38±0.09		2.37±0.1		2.38±0.09	<0.001
Low	2.16±0.05	6618(2.01)	2.15±0.07	416(2.99)	2.16±0.05	6202(1.97)
Normal	2.38±0.09	321667(97.81)	2.38±0.09	13449(96.83)	2.38±0.09	308218(97.86)
High	2.84±0.11	570(0.17)	2.85±0.14	25(0.18)	2.84±0.11	545(0.17)
25(OH)D[d], **nmol/L**	48.77±21.05		45.79±21.78		48.91±21.00	<0.001
Deficiency	22.31±5.07	67797(20.62)	21.40±5.26	3792(27.3)	22.37±5.06	64005(20.32)
Insufficiency	40.02±574	113576(34.54)	39.70±5.73	4621(33.27)	40.03±5.74	108955(34.59)
Sufficiency	67.68±14.57	147482(44.84)	67.82±15.08	5477(39.43)	67.67±14.55	142005(45.09)
Comorbidities, n (%)						<0.001
Hypertension		101872(30.98)		9009(64.86)	92863(29.48)	
CVD		33722(10.25)		4460(32.11)	29262(9.29)	
CKD		13934(4.24)		1847(13.3)	12087(3.84)	
DM		28446(8.65)		3313(23.85)	25133(7.98)	
Cancer		65356(19.87)		5067(36.48)	60289(19.14)	
Cirrhosis		1520(0.46)		213(1.53)	1307(0.41)	
Depression		20110(6.12)		2481(17.86)	17629(5.60)	

Abbreviations: SD, standard deviation; BMI, Body mass index; sCa,serum calcium; 25(OH)D,25-hydroxyvitamin D; CVD, cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus;

[a] Statistical significance was set at 2-sided $P \leq 0.05$.

[b] BMI is calculated as weight in kilograms divided by height in meters squared. Underweight : BMI<18.5kg/m^2; Normal :18.5-25kg/m^2; Overweight: 25-30kg/m^2; Obesity: BMI≥30kg/m^2.

[c]sCa categorized as 3 groups: Low: <2.2 mmol/L; Normal:2.2-2.75 mmol/L; High:＞2.75 mmol/L.

[d]25(OH)D was divided in to 3 categories. Deficiency: <30 nmol/L; Insufficiency: 30-50 nmol/L; Sufficiency: ≥50 nmol/L.

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Table S2. Baseline Characteristics of UK Biobank Participants developing COPD within 15 years of follow-up

Characteristic	Total (N=327871)		COPD (N=12906)		Control (N=314965)		*p* value
	Means±SD	N(%)	Means±SD	N(%)	Means±SD	N(%)	
Age, yr	56.07±8.12	327871(100)	61.04±6.44	12906(3.94)	55.86±8.12	314965(96.06)	<0.001
<65	53.77±7.02	270328(82.45)	57.70±5.69	8276(64.13)	53.64±7.02	262052(83.2)	
≥65	66.89±1.48	57543(17.55)	67.01±1.50	4630(35.87)	66.88±1.48	52913(16.8)	
Sex							<0.001
Male		161493(49.26)		7521(58.28)		153972(48.89)	
Female		166378(50.74)		5385(41.72)		160993(51.11)	
BMI[b], kg/m^2	27.35±4.72		28.34±5.54		27.31±4.68		<0.001
Underweight	17.65±0.79	1511(0.46)	17.46±0.94	164(1.27)	17.67±0.77	1347(0.43)	
Normal	22.83±1.52	106480(32.48)	22.68±1.63	3451(26.74)	22.84±1.51	103029(32.71)	
Overweight	27.24±1.40	141248(43.08)	27.37±1.41	5043(39.07)	27.24±1.40	136205(43.24)	
Obesity	33.84±3.84	78632(23.98)	34.51±4.35	4248(32.91)	33.80±3.81	74384(23.62)	
Ethnicity							<0.001
White		312962(95.46)		12584(97.51)		300378(95.37)	
Non-white		14156(4.32)		288(2.23)		13868(4.40)	
Smoking status							<0.001
Never		178649(54.49)		2165(16.78)		176484(56.03)	
Previous		115151(35.12)		6027(46.70)		109124(34.65)	
Current		34071(10.39)		4714(36.53)		29357(9.32)	
Alcohol intake							<0.001
Yes		305215(93.09)		11561(89.58)		314965(93.23)	
No		22656(6.91)		1345(10.42)		293654(6.77)	
Coffee intake							<0.001
Yes		257536(78.55)		9771(75.71)		247765(78.66)	
No		70335(21.45)		3135(24.29)		67200(21.34)	
Time spent outdoor, hours							
In summer							0.019
Yes		327185(99.79)		12869(99.71)		314316(99.79)	
No		686(0.21)		37(0.29)		649(0.21)	

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In winter						<0.001
Yes		317243(96.76)		12409(96.15)	304834(96.78)	
No		10628(3.24)		497(3.85)	10131(3.22)	
Family income, pounds						<0.001
<18,000		70863(21.61)		6200(48.04)	64663(20.53)	
18,000-30,999		82590(25.19)		3661(28.37)	78929(25.06)	
31,000-51,999		86766(26.46)		2009(15.57)	84757(26.91)	
52,000-100,000		69069(21.07)		876(6.79)	68193(21.65)	
>100,000		18583(5.67)		160(1.24)	18423(5.85)	
sCa[c], mmol/L	2.38±0.09		2.37±0.10		2.38±0.09	<0.001
Low	2.16±0.05	6582(2.01)	2.15±0.07	380(2.94)	2.16±0.05	6202(1.97)
Normal	2.38±0.09	320719(97.82)	2.38±0.09	12501(96.86)	2.38±0.09	308218(97.86)
High	2.84±0.11	570(0.17)	2.86±0.14	25(0.19)	2.84±0.11	545(0.17)
25(OH)D[d], **nmol/L**	48.79±21.05		46.00±21.85		48.91±21	<0.001
Deficiency	22.32±5.07	67500(20.59)	21.45±5.25	3495(27.08)	22.37±5.06	64005(20.32)
Insufficiency	40.02±5.74	113232(34.54)	39.76±5.74	4277(33.14)	40.03±5.74	108955(34.59)
Sufficiency	67.68±14.57	147139(44.88)	67.91±15.19	5134(39.78)	67.68±14.55	142005(45.09)
Comorbidities[e], n (%)						<0.001
Hypertension		101187(30.86)		8324(64.5)	92863(29.48)	
CVD		33298(10.16)		4036(31.27)	29262(9.29)	
CKD		13810(4.21)		1723(13.35)	12087(3.84)	
DM		28146(8.58)		3013(23.35)	25133(7.98)	
Cancer		65005(19.83)		4716(36.54)	60289(19.14)	
Cirrhosis		1513(0.46)		206(1.60)	1307(0.41)	
Depression		19908(6.07)		2279(17.66)	17629(5.60)	

Abbreviations: SD, standard deviation; BMI, Body mass index; sCa,serum calcium; 25(OH)D,25-hydroxyvitamin D; CVD, cardiovascular disease; CKD, chronic kidney disease; DM, diabetes mellitus;

[a] Statistical significance was set at 2-sided $P \leq 0.05$.

[b] BMI is calculated as weight in kilograms divided by height in meters squared. Underweight : BMI<18.5kg/m^2; Normal :18.5-25kg/m^2; Overweight: 25-30kg/m^2; Obesity: BMI≥30kg/m^2.

[c]sCa categorized as 3 groups: Low: <2.2 mmol/L; Normal:2.2-2.75 mmol/L; High:＞2.75 mmol/L

[d]25(OH)D was divided in to 3 categories. Deficiency: <30 nmol/L; Insufficiency: 30-50 nmol/L; Sufficiency: ≥50 nmol/L.

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Table S3. Association of 25(OH)D level with COPD prevalence by Endocrine Society Clinical Practice Guideline

25(OH)D, nmol/L	OR	95%CI	*p* value
Model 1[a]			＜0.001
Normal	Ref		
Insufficiency	0.987	0.927-1.050	0.674
Deficiency	1.249	1.178-1.323	＜0.001
Model 2[b]			＜0.001
Normal	Ref		
Insufficiency	0.997	0.936-1.061	0.916
Deficiency	1.360	1.283-1.442	＜0.001
Model 3[c]			＜0.001
Normal	Ref		
Insufficiency	1.019	0.955-1.087	0.568
Deficiency	1.164	1.094-1.239	＜0.001
Model 4[d]			
Normal	Ref		
Insufficiency	1.031	0.965-1.102	0.365
Deficiency	1.169	1.097-1.245	＜0.001

Abbreviations: OR, Odds Ratio; 95%CI, 95% Confidence Interval.
a Calculated by means of a Logistic regression analysis with no adjustment.
b Adjusted by age, sex, ethnicity, area(rural or urban) and family income.
c Adjusted for model 2 plus BMI, lifestyle (coffee take, alcohol take, smoking status, sCa, sun exposure and vitamin D supplement) and lipids(Triglycerides, Cholesterol, LDL and HDL).
d Adjusted for model 3 plus comorbidities (hypertension, CVD, CKD, DM, cancer, cirrhosis, and depression).

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Table S4. Association of vitamin D level with COPD risk and COPD-specific mortality by Endocrine Society Clinical Practice Guideline

Vit D, nmol/L	Model 1[a] HR (95%CI)	*p* value	Model 2[b] HR (95%CI)	*p* value	Model 3[c] HR (95%CI)	*p* value	Model 4[d] HR (95%CI)	*p* value
COPD incidence								
Normal	Ref		Ref		Ref		Ref	
Insufficiency	1.015(0.839-1.228)	0.878	1.031(0.852-1.247)	0.756	1.125(0.930-1.363)	0.226	1.146(0.947-1.388)	0.162
Deficiency	1.766(1.484-2.103)	<0.001	2.006(1.684-2.389)	<0.001	1.734(1.451-2.073)	<0.001	1.724(1.442-2.062)	<0.001
COPD-specific mortality								
Normal	Ref		Ref		Ref		Ref	
Insufficiency	1.095(0.894-1.342)	0.379	1.109(0.891-1.337)	0.398	1.198(0.977-1.470)	0.083	1.198(0.977-1.470)	0.083
Deficiency	1.558(1.293-1.878)	<0.001	1.647(1.366-1.986)	<0.001	1.654(1.366-2.004)	<0.001	1.654(1.366-2.004)	<0.001

Abbreviations: HR, Hazard Ratio; 95%CI, 95% Confidence Interval.

[a] Calculated by means of a Cox proportional hazards analysis with no adjustment.

[b] Adjusted by age, sex, ethnic and area(rural or urban)and family income.

[c] Adjusted for model 2 plus BMI, lifestyle (coffee take, alcohol take, smoking status, sCa, sun exposure and vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL).

[d] Adjusted for model 3 plus underlying diseases (hypertension, CVD, CKD, DM, cancer, cirrhosis, and depression).

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Table S5. Stratified Analysis of Association between 25(OH)D level and COPD incidence

		cut-offs of the US-American Institute of Medicine[a]			Endocrine Society Clinical Practice Guideline[b]		
		HR (95%CI)	***p* value**	***p* for interaction**	**HR (95%CI)**	***p* value**	***p* for interaction**
Total population	Normal	Ref			Ref		
	Insufficiency	1.358(1.207-1.527)	<0.001		1.146(0.947-1.388)	0.162	
	Deficiency	1.874(1.659-2.117)	<0.001		1.724(1.442-2.062)	<0.001	
	No			0.032			0.038
Vitamin D supplement	Normal	Ref			Ref		
	Insufficiency	1.322(1.146-1.525)	<0.001		1.055(0.829-1.342)	0.663	
	Deficiency	1.867(1.617-2.155)	<0.001		1.611(1.290-2.011)	<0.001	
	Yes						
	Normal	Ref			Ref		
	Insufficiency	0.824(0.425-1.600)	0.568		0.943(0.470-1.892)	0.869	
	Deficiency	2.073(0.098-4.163)	0.440		0.739(0.377-1.449)	0.379	
Gender	Male			0.013			0.001
	Normal	Ref			Ref		
	Insufficiency	1.399(1.205-1.601)	<0.001		1.116(0.889-1.402)	0.342	
	Deficiency	1.919(1.652-2.230)	<0.001		1.720(1.390-2.127)	<0.001	
	Female						
	Normal	Ref			Ref		
	Insufficiency	1.291(1.045-1.593)	0.018		1.196(0.838-1.706)	0.324	
	Deficiency	1.743(1.410-2.154)	<0.001		1.700(1.218-2.373)	0.002	
Age	⩾65years			0.473			0.436
	Normal	Ref			Ref		
	Insufficiency	1.248(1.055-1.476)	0.010		1.012(0.787-1.302)	0.926	
	Deficiency	1.933(1.618-2.310)	<0.001		1.496(1.179-1.899)	0.001	
	＜65years						
	Normal	Ref			Ref		
	Insufficiency	1.462(1.238-1.727)	<0.001		1.329(0.989-1.786)	0.059	
	Deficiency	1.855(1.567-2.197)	<0.001		2.021(1.535-2.661)	<0.001	
	Never			0.020			0.112
	Normal	Ref			Ref		
	Insufficiency	1.112(0.988-1.252)	0.079		1.027(0.884-1.194)	0.724	
	Deficiency	1.062(0.963-1.171)	0.231		1.101(0.951-1.275)	0.197	

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Smoking status	Precious				
	Normal	Ref		Ref	
	Insufficiency	1.056(0.995-1.120)	0.072	1.016(0.930-1.109)	0.729
	Deficiency	1.238(1.151-1.331)	<0.001	1.135(1.042-1.236)	0.004
	Current				
	Normal	Ref		Ref	
	Insufficiency	1.053(0.980-1.133)	0.159	0.994(0.887-1.115)	0.923
	Deficiency	1.257(1.173-1.347)	<0.001	1.133(1.020-1.260)	0.020

Abbreviations: HR, Hazard Ratio; 95%CI, 95% Confidence Interval.

Calculated by means of a Cox proportional hazards analysis with adjustment by Model 4 included age, sex, ethnic, area, BMI,lifestyle (coffee take, alcohol take, smoking status, sCa, sun exposure, vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL),family income and comorbidities

[a] 25(OH) D sufficiency≥20ng/mL(50nmol/L); Vitamin D insufficiency between12-20ng/mL(30-50nmol/L) and Vitamin D deficiency＜12ng/mL(30nmol/L)

[b] 25(OH) D sufficiency≥30ng/mL(75nmol/L); Vitamin D insufficiency between21-29ng/mL(50-75nmol/L) and Vitamin D deficiency＜20ng/mL(50nmol/L)

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Table S6. Stratified Analysis of Association between 25(OH) D level and COPD-specific death

		cut-offs of the US-American Institute of Medicine[a]			Endocrine Society Clinical Practice Guideline[b]		
		HR (95%CI)	***p* value**	***p* for interaction**	**HR (95%CI)**	***p* value**	***p* for interaction**
Total population	Normal	Ref			Ref		
	Insufficiency	1.327(1.171-1.504)	<0.001		1.198(0.977-1.470)	0.083	
	Deficiency	1.598(1.406-1.816)	<0.001		1.654(1.366-2.004)	<0.001	
Vitamin D supplement	No			0.131			0.342
	Normal	Ref			Ref		
	Insufficiency	1.303(1.119-1.516)	0.001		1.194(0.923-1.546)	0.178	
	Deficiency	1.641(1.412-1.908)	<0.001		1.663(1.311-2.109)	<0.001	
	Yes						
	Normal	Ref			Ref		
	Insufficiency	1.215(0.573-2.573)	0.612		1.017(0.474-2.181)	0.966	
	Deficiency	1.658(0.745-3.687)	0.215		1.406(0.640-3.087)	0.396	
Gender	Male			0.001			0.001
	Normal	Ref			Ref		
	Insufficiency	1.289(1.106-1.503)	<0.001		1.160(0.908-1.481)	0.236	
	Deficiency	1.572(1.341-1.842)	0.001		1.570(1.249-1.973)	<0.001	
	Female						
	Normal	Ref			Ref		
	Insufficiency	1.381(1.108-1.721)	0.004		1.261(0.864-1.840)	0.229	
	Deficiency	1.564(1.254-1.951)	<0.001		1.754(1.229-2.503)	0.002	
Age	≥65years			0.305			0.248
	Normal	Ref			Ref		
	Insufficiency	1.293(1.083-1.544)	0.005		1.156(0.878-1.520)	0.302	
	Deficiency	1.630(1.354-1.963)	<0.001		1.594(1.227-2.070)	<0.001	
	<65years						
	Normal	Ref			Ref		
	Insufficiency	1.355(1.133-1.621)	<0.001		1.328(0.973-1.812)	0.074	
	Deficiency	1.587(1.326-1.898)	<0.001		1.803(1.354-2.402)	<0.001	
	Never			0.161			0.430
	Normal	Ref			Ref		
	Insufficiency	1.499(0.942-2.388)	0.088		0.947(0.455-1.973)	0.885	

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Smoking status	Deficiency	2.254(1.368-3.715)	0.001	1.681(0.849-3.329)	0.136
	Precious				
	Normal	Ref		Ref	
	Insufficiency	1.382(1.170-1.632)	<0.001	1.045(0.807-1.354)	0.737
	Deficiency	1.759(1.479-2.091)	<0.001	1.655(1.296-2.114)	<0.001
	Current				
	Normal	Ref		Ref	
	Insufficiency	1.320(1.104-1.577)	0.002	1.352(0.992-1.843)	0.056
	Deficiency	2.065(1.721-2.477)	<0.001	1.913(1.435-2.549)	<0.001

Abbreviations: HR, Hazard Ratio; 95%CI, 95% Confidence Interval.

Calculated by means of a Cox proportional hazards analysis with adjustment by Model 4 included age, sex, ethnicity, area, BMI,lifestyle (coffee take, alcohol take, smoking status, serum calcium, sun exposure, vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL),family income and comorbidities.

[a] 25(OH) D sufficiency≥20ng/mL(50nmol/L); insufficiency between12-20ng/mL(30-50nmol/L) and deficiency＜12ng/mL(30nmol/L)

[b] 25(OH) D sufficiency≥30ng/mL(75nmol/L); insufficiency between21-29ng/mL(50-75nmol/L) and deficiency＜20ng/mL(50nmol/L)

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Table S7. Association of vitamin D level with COPD-specific death in Patients with COPD Comorbidities

Vit D, nmol/L	cut-offs of the US-American Institute of Medicine[a]			Endocrine Society Clinical Practice Guideline[b]		
	HR (95%CI)	*p* value	*p* for interaction	HR (95%CI)	*p* value	*p* for interaction
Total participants						
Normal	Ref			Ref		
Insufficiency	1.327(1.171-1.504)	<0.001		1.198(0.977-1.470)	0.083	
Deficiency	1.598(1.406-1.816)	<0.001		1.654(1.366-2.004)	<0.001	
DM			0.080			0.057
Normal	Ref			Ref		
Insufficiency	1.011(0.791-1.293)	0.928		1.424(0.892-2.276)	0.139	
Deficiency	1.416(1.106-1.812)	<0.001		1.567(1.005-2.443)	0.048	
Depression			0.047			0.042
Normal	Ref			Ref		
Insufficiency	1.881(1.404-2.519)	<0.001		1.925(1.121-3.307)	0.018	
Deficiency	1.924(1.430-2.590)	<0.001		3.097(1.867-5.138)	<0.001	
CHD			0.349			0.202
Normal	Ref			Ref		
Insufficiency	1.213(1.002-1.467)	0.047		1.132(0.834-1.532)	0.428	
Deficiency	1.632(1.340-1.987)	<0.001		1.512(1.315-2.014)	0.005	
Cancer			0.348			0.447
Normal	Ref			Ref		
Insufficiency	1.300(1.092-1.547)	0.003		1.216(0.920-1.608)	0.169	
Deficiency	1.657(1.379-1.990)	<0.001		1.665(1.280-2.165)	<0.001	

Abbreviations: HR, Hazard Ratio; 95%CI, 95% Confidence Interval.
Calculated by means of a Cox proportional hazards analysis with adjustment by Model 4 included age, sex, ethnicity, area, BMI,lifestyle (coffee take, alcohol take, smoking status, serum calcium, sun exposure, vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL),family income and comorbidities.
[a] Vitamin D sufficiency≥20ng/mL(50nmol/L); Vitamin D insufficiency between12-20ng/mL(30-50nmol/L) and Vitamin D deficiency＜12ng/mL(30nmol/L)
[b] Vitamin D sufficiency≥30ng/mL(75nmol/L); Vitamin D insufficiency between21-29ng/mL(50-75nmol/L) and Vitamin D deficiency＜20ng/mL(50nmol/L)

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Table S8. Association of vitamin D level with COPD outcomes using age, BMI, sCa as continuous variables and categorical variables

		cut-offs of the US-American Institute of Medicine[a]				Endocrine Society Clinical Practice Guideline[b]			
		categorical variables		continuous variables		categorical variables		continuous variables	
		HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value	HR (95%CI)	*p* value
COPD prevalence	Normal	Ref		Ref		Ref		Ref	
	Insufficiency	1.071(1.026-1.119)	0.002	1.083(1.037-1.132)	<0.001	1.031(0.965-1.102)	0.365	1.018(0.953-1.088)	0.592
	Deficiency	1.266(1.206-1.330)	<0.001	1.277(1.216-1.342)	<0.001	1.169(1.097-1.245)	<0.001	1.186(1.112-1.264)	<0.001
COPD incidence	Normal	Ref		Ref		Ref		Ref	
	Insufficiency	1.358(1.207-1.527)	<0.001	1.278(1.221-1.338)	<0.001	1.146(0.947-1.388)	0.162	1.002(0.941-1.067)	0.950
	Deficiency	1.874(1.659-2.117)	<0.001	1.915(1.816-2.217)	<0.001	1.724(1.442-2.062)	<0.001	1.744(1.677-1.816)	<0.001
specific mortality	Normal	Ref		Ref		Ref		Ref	
	Insufficiency	1.327(1.171-1.504)	<0.001	1.376(1.223-1.548)	<0.001	1.198(0.977-1.470)	0.083	1.122(0.927-1.358)	0.239
	Deficiency	1.598(1.406-1.816)	<0.001	1.665(1.475-2.011)	<0.001	1.654(1.366-2.004)	<0.001	1.768(1.478-2.116)	<0.001

Abbreviations: HR, Hazard Ratio; 95%CI, 95% Confidence Interval.
Calculated by means of a Cox proportional hazards analysis with adjustment by Model 4 included age, sex, ethnicity, area, BMI,lifestyle (coffee take, alcohol take, smoking status, sCa, sun exposure, vitamin D supplement), lipids(Triglycerides, Cholesterol, LDL and HDL),family income and comorbidities.

[a] 25(OH) D sufficiency≥20ng/mL(50nmol/L); insufficiency between12-20ng/mL(30-50nmol/L) and deficiency＜12ng/mL(30nmol/L)

[b] 25(OH) D sufficiency≥30ng/mL(75nmol/L); insufficiency between21-29ng/mL(50-75nmol/L) and deficiency＜20ng/mL(50nmol/L

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