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The associations of serum 25-hydroxyvitamin D levels and vitamin D supplement use with inflammation, mortality, and low back pain

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$1,25(OH)D_2$	1,25-dihydroxyvitamin D
25(OH)D	Serum 25-hydroxyvitamin D
BMI	Body Mass Index
CHD	Coronary Heart Disease
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CRP	C-Reactive Protein
CVD	Cardiovascular Diseases
CYP27B1	Vitamin D_3-1α-Hydroxylase
eGFR	Estimated Glomerular Filtration Rate
FDR	False Discovery Rate
FEV1	Forced Expiratory Volume In 1-Second
GPS	Glasgow Prognostic Score
HbA_{1c}	Haemoglobin A1C
HDL	High-Density Lipoprotein
HR	Hazard Ratio
HS_mGPS	High-Sensitive Modified Glasgow Prognostic Score
ICD-10	The 10^{th} Revision of The International Statistical Classification of Diseases
IQR	Interquartile Range
LBP	Low Back Pain
LDL	Low-Density Lipoprotein
LMR	Lymphocyte-To-Monocyte Ratio
mGPS	Modified Glasgow Prognostic Score
MR	Mortality Rate Per 1000 Person-Year
N	Absolute Number of Cases
NA	Not Applicable
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NIH	National Institute of Health
NLR	Neutrophil-To-Lymphocyte Ratio
NPS	Neutrophil-Platelet Score
OR	Odds Ratio
OTC	Over-The-Counter
PLR	Platelet-To-Lymphocyte Ratio
PNI	Prognostic Nutritional Index
RCS	Restricted Cubic Spline
RCT	Randomized Controlled Trial
Ref.	Reference
RR	Relative Risk
SAS	Statistical Analysis System
SII	Systemic Immune-Inflammation Index
SIR	Systemic Inflammatory Response
UK	United Kingdom
US	United States
UV-B	Ultraviolet B
VDR	Vitamin D Receptor
VIF	Variation Inflation Factors

1 Introduction

Vitamin D insufficiency and deficiency are highly prevalent in European countries among the general population (Amrein et al. 2020; Cashman et al. 2016; Zittermann et al. 2016). Although vitamin D is obtained from the diet and dietary supplements, the main source of vitamin D is its production in the skin under the influence of solar ultraviolet B (UV-B) radiation. Exposure of skin to UV-B radiation is limited in countries of the Northern hemisphere in all seasons except summer. For example, it is estimated that approximately 24%, 37%, and 40% of the population in the United States (US), Canada, and Europe have low vitamin D levels (serum 25-hydroxyvitamin D (25[OH]D) levels < 50 nmol/L), respectively (Amrein et al. 2020; Cashman 2020; Cashman et al. 2016; Sarafin et al. 2015).

Vitamin D, a pivotal secosteroid hormone, has engendered considerable attention due to its manifold roles in human health. It has been well recognized that vitamin D actions go far beyond the regulation of bone metabolism and calcium homeostasis. Vitamin D and its metabolites are carried into the circulation via binding to vitamin D receptor (VDR) after being hydroxylated by the key enzyme 25-hydroxyl vitamin D_3-1α-hydroxylase (CYP27B1) (Afzal et al. 2014a; Autier et al. 2014; Brown et al. 1999; Chiang et al. 2011; Feldman et al. 2014; Khammissa et al. 2018; Veldman et al. 2000; Yin and Agrawal 2014). The active vitamin D metabolite 1,25-dihydroxyvitamin D (1,25[OH]D_2) can bind to the VDR, which is expressed in numerous cells in the human body, including bone, muscle and immune cells (Brown et al. 1999; Veldman et al. 2000). Moreover, 1,25(OH)D_2 has been ascribed immunomodulatory effects by reduction of lymphocyte proliferation and inhibition of the production of pro-inflammatory cytokines (Di Rosa et al. 2011).

1.1 The association of vitamin D with all-cause mortality and cause-specific mortality

Up to the commencement of the study, accumulating evidence from epidemiological studies has shown that vitamin D deficiency (25[OH]D) levels < 30 nmol/L) (Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011) and vitamin D insufficiency (25[OH]D levels of 30 - <50 nmol/L) go along with increased all-cause mortality and cause-specific mortality including mortality from cancer, cardiovascular diseases (CVD), respiratory diseases (Durup et al. 2015; Schöttker

et al. 2013a; Schöttker et al. 2013b; Schöttker et al. 2014a; Schöttker et al. 2014b; Schöttker and Brenner 2015; Schöttker et al. 2019; Zittermann et al. 2013). In addition, Mendelian randomization study showed an inverse association of genetically predicted 25(OH)D levels with all-cause mortality, cancer mortality, and other forms of mortality, but not with CVD mortality (Afzal et al. 2014b). Moreover, results from meta-analyses of randomized controlled trials (RCTs) with vitamin D supplementation demonstrated lower cancer mortality and total mortality in the vitamin D group than in the placebo group (Autier et al. 2017; Bjelakovic et al. 2014; Keum et al. 2019).

Given the increasing importance of real-world evidence in determining the drug effectiveness outside of the strictly defined and controlled situations of RCTs, it is of great interest how the efficacy data of vitamin D supplementation obtained from well-defined and well-controlled clinical trial populations translate into effectiveness in real-world practice. Up to date, there have been two observational cohort studies with claims data, which have shown that vitamin D supplementation is associated with reduced COVID-19 related mortality in patients achieving serum 25(OH)D levels ≥ 75 nmol/L and is associated with improved survival of breast cancer patients (Madden et al. 2018; Oristrell et al. 2021). However, the outcomes of all-cause mortality and mortality due to any CVD, total cancer, or respiratory disease have not been addressed in population-based cohort studies so far.

1.2 The association of vitamin D with cancer site-specific mortality

Building upon the evidence from epidemiological studies showing that a low 25(OH)D concentration is associated with increased total cancer mortality (Lee et al. 2014; Schöttker et al. 2013b; Wong et al. 2015), as well as a Mendelian randomization study that further established the causal relationship (Afzal et al. 2014b), the investigation into the associations of vitamin D with mortality specific to distinct cancer types remains a focal point of interest.

Regarding the incidence of specific cancer types, meta-analyses of observational studies have concluded elevated risks of lung cancer, colorectal cancer, breast cancer, bladder carcinoma, liver cancer and lymphoma in participants who were vitamin D insufficient (Garland and Gorham 2017; Kim and Je 2014; Li et al. 2014; Zhang et al. 2015a; Zhang et al. 2015b; Zhang et al. 2021). With respect to

prognosis, sufficient 25(OH)D levels were found to be associated with better survival in patients with lung, colorectal, breast, and prostate cancer (Feng et al. 2017; Kim and Je 2014; Li et al. 2021; Li et al. 2014; Liu et al. 2017; Maalmi et al. 2018; Madden et al. 2018; Song et al. 2018; Toriola et al. 2014).

However, findings for associations between 25(OH)D levels and mortality due to specific cancer types are heterogeneous and mostly limited to the most common cancer sites (Muñoz and Grant 2022). This may be attributed, in part, to the requirement of a large sample size and numbers of deaths to establish significant associations. In addition, previous studies on the association between vitamin D supplement use and cancer site-specific mortality are very scarce and had limitations on sample size and proper adjustment for the most important confounding factors (Gnagnarella et al. 2021).

1.3 Interrelationship of vitamin D, biomarkers of systemic inflammatory response, and mortality

It has been suggested that a sufficient vitamin D status (25[OH]D ≥ 50 nmol/L) may protect from atherosclerosis and tumorigenesis through anti-inflammatory activities (Liu et al. 2018; Menezes et al. 2014). This has led to an interest in whether vitamin D sufficiency could prevent a systemic inflammatory response (SIR) to adverse health conditions. In the scientific literature, a SIR is the most frequently examined for cancer patients (Liu et al. 2018; Marques et al. 2021), but it has also been observed in patients with diabetes mellitus, CVD (Akash et al. 2013; Alfaddagh et al. 2020; Kawai et al. 2021; Lontchi-Yimagou et al. 2013), and patients who undergo any kind of surgeries or intensive care (Amrein et al. 2018; Smajic et al. 2018). The SIR is generally associated with poor prognosis (Ju et al. 2021; Li et al. 2017; Liu et al. 2018; Marques et al. 2021; Proctor et al. 2015). This leads to the hypothesis of whether the association of low vitamin D status with mortality might be explained by the anti-inflammatory effects of vitamin D, which could attenuate a SIR to various diseases or treatments of these diseases (Schöttker and Brenner 2015).

The SIR is characterized by changes in blood cell counts and acute-phase proteins such as C-reactive protein (CRP) (Gabay and Kushner 1999; Roxburgh and McMillan 2014; Tuomisto et al. 2019), which allows to broadly categorize the biomarkers of SIR in blood cell count and CRP-based markers. There

are two modified versions of Glasgow prognostic score (GPS) with different cut-off values for CRP and serum albumin in the calculation, known as modified GPS (mGPS) and high-sensitive mGPS (HS_mGPS) (Ando et al. 2021; Proctor et al. 2013). The blood cell count-based markers include the neutrophil-to-lymphocyte ratio (NLR), the platelet-to-lymphocyte ratio (PLR), the lymphocyte-to-monocyte ratio (LMR), the neutrophil-platelet score (NPS), the systemic immune-inflammation index (SII), and the prognostic nutritional index (PNI) (Chan et al. 2021; Guthrie et al. 2013; Marques et al. 2021; Roxburgh and McMillan 2010; Taniai et al. 2021; Wang and Wang 2019; Watt et al. 2015).

To date, observational studies from the general population have reported cross-sectional associations of vitamin D status with CRP, NLR, and PLR (Akbas et al. 2016; de Oliveira et al. 2017); and a Mendelian randomization analysis with data from the United Kingdom (UK) Biobank suggested that a low vitamin D status was causally related to increased CRP levels (Zhou and Hyppönen 2022). However, there are few studies on the associations of vitamin D status with other biomarkers of SIR (Marques et al. 2021), and the potential associations require further investigation.

1.4 The association of vitamin D with low back pain

In addition to investigating the association between vitamin D and mortality, attention was drawn to the nexus of vitamin D and its potential association with low back pain (LBP), rendering it another focal point of this dissertation. LBP is the most prevalent musculoskeletal disorder globally and has become the leading cause of years lived with disability (Wu et al. 2020). Recent estimates indicate that approximately 7.5% of the world's population experienced LBP in 2017, a number that is on the rise (Wu et al. 2020). The incidence of LBP has been increasing across all age groups since 1990, with a more pronounced increase among the middle-aged population (Institute for Health Metrics and Evaluation 2023). In developed countries, up to 90% of individuals may experience LBP at some point in their lives, leading to substantial medical and socioeconomic costs (Ge et al. 2022; Scott et al. 2010; Wu et al. 2020).

The integral role of vitamin D in maintaining musculoskeletal health, including facilitating calcium absorption, bone mineralization, and supporting muscle function, is widely acknowledged (Mendes et

al. 2022). Regarding pain management, studies have observed that individuals with various chronic pain conditions often exhibit lower serum levels of 25(OH)D (Hossein-nezhad and Holick 2013; Wu et al. 2018). For example, it was observed in a primary care clinic in Minneapolis, USA, that 93% of patients with musculoskeletal disorders had insufficient 25(OH)D levels ≤ 50 nmol/L (Plotnikoff and Quigley 2003). This has spurred interest in investigating whether vitamin D might be useful in LBP treatment and prevention. A meta-analysis of 28 observational studies observed a cross-sectional association of vitamin D deficiency with LBP (Zadro et al. 2017). However, most included cross-sectional observational studies had limitations, such as small sample sizes and inadequate adjustment for confounders (Zadro et al. 2017). No separate meta-analysis with longitudinal studies was conducted, as none were found in this systematic review (Zadro et al. 2017), leaving the association between 25(OH)D levels and LBP uncertain.

A Mendelian randomization study demonstrated an association between genetically predicted 25(OH)D levels and a reduced risk of LBP in the European population (Jiang et al. 2022). In contrast, a meta-analysis of eight small clinical trials involving vitamin D intervention did not show efficacy in treating LBP (Zadro et al. 2018). Notably, there is also a lack of real-world evidence from large datasets examining the longitudinal association of vitamin D supplement use with the onset of LBP.

1.5 Aims of the dissertation

In light of the contextual background, the aims of the dissertation were to investigate if vitamin D deficiency and insufficiency as well as self-reported regular intake of vitamin D supplement (in form of a vitamin D preparation or as part of a multivitamin product) are associated with a list of health outcomes in the real-world context using the large UK Biobank, a nationwide, population-based cohort from the UK (UK Biobank 2017). The specific objectives include:

i. To assess the association of vitamin D deficiency, insufficiency, and vitamin D supplement use with all-cause mortality and cause-specific mortality including CVD mortality, cancer mortality, and respiratory mortality. To achieve this aim, the prevalence and determinants of vitamin D deficiency and self-reported regular vitamin D supplement use were investigated first.

ii. To assess the association of vitamin D deficiency, insufficiency, and vitamin D supplement use with cancer site-specific mortality, including the most common but also rarer cancer sites.

iii. To explore interrelationships of vitamin D deficiency and insufficiency with biomarkers of SIR (including three CRP-based biomarkers and five white blood cell count-based biomarkers) and mortality outcomes (including all-cause mortality, CVD mortality, cancer mortality, and respiratory mortality).

iv. To assess the associations of vitamin D deficiency, insufficiency, and vitamin D supplement use with LBP, both cross-sectionally and longitudinally.

2 Material and Methods

2.1 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with all-cause mortality, CVD mortality, cancer mortality and respiratory disease mortality

This section is for the first aim of this dissertation that was to investigate whether the serum 25(OH)D levels and intake of vitamin D supplements are associated with reduced all-cause and cause-specific mortality including cancer mortality, CVD mortality and respiratory disease mortality in the large UK Biobank. Furthermore, this unique data source was also used to explore and compare the determinants of vitamin D deficiency and self-reported and regular vitamin D supplement use.

2.1.1 Study population

UK Biobank is a prospective cohort study with a large-scale biomedical database containing genetic and health information from approximately half a million UK participants aged between 40-69 years at the time of recruitment between 2006 and 2010 (UK Biobank 2017). Data was collected from the 22 assessment centers in England, Scotland, and Wales through a touchscreen questionnaire, a brief verbal interview, and a wide range of physical and medical assessments (UK Biobank 2017). Biological samples including blood, urine and other sample types (e.g., faeces, hairs, etc.) were collected at the initial assessment visit (Elliott and Peakman 2008). Health care outcomes and other follow-up data were obtained through linkages to health care records, i.e., the UK National Health Service (NHS), primary care, cancer screening data, and disease-specific registers, in addition to validation and subclassification methods developed by the UK Biobank (Sudlow et al. 2015). The study was conducted according to the guidelines of the Declaration of Helsinki, and was approved by the North West Haydock Research Ethics Committee (#16/NW/0274, 13 May 2016).

2.1.2 Mortality data

Mortality information, including causes and dates of death, was obtained from the NHS from baseline until 1 December 2020 for the UK Biobank participants. The 10th revision of the *International Statistical Classification of Diseases* (ICD-10) was used to define causes of death as follows: mortality due to CVD (I00-I99), cancer (C00-C97), and respiratory disease (J00-J99).

2.1.3 Serum 25-hydroxyvitamin D measurement

Serum 25(OH)D status was categorized based on the thresholds proposed by the Institute of Medicine in the US: vitamin D deficiency was defined as having a 25(OH)D concentration of less than 30 nmol/L, vitamin D insufficiency as 25(OH)D between 30 and less than 50 nmol/L, and sufficient vitamin D status as 25(OH)D of 50 nmol/L or higher (Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011). Quantification of 25(OH)D concentration in serum was carried out by chemiluminescence immunoassay on the DiaSorin Liaison XL platform manufactured by Diasorin S.p.A. (Fry et al. 2019). The results were further verified through the Randox International Quality Assessment Scheme Immunoassay Speciality I scheme, attesting to the robustness of the quality control measures implemented (Fry et al. 2019; Randox Laboratories 2021).

2.1.4 Vitamin D supplement use

Information on regular use of vitamin D and multivitamin supplements was obtained from the UK Biobank's baseline questionnaire from the question "Do you regularly take any of the following (You can select more than one answer)?" with the following answer categories: "Vitamin A/ Vitamin B/ Vitamin C/ Vitamin D/ Vitamin E/ Folic acid or Folate/ Multivitamins ± minerals/ None of the above/ Prefer not to answer" (Data Field 6155) (UK Biobank 2021). A comparison with the prescribed drugs reported at baseline revealed that 16.6% of those who reported regular vitamin D use in this question used it as a prescription drug and 83.3% as an over-the-counter (OTC) drug.

2.1.5 Covariate

Covariates in the study contained demographic and socio-economic factors, including, age, sex, skin color, the latitude of study center (per 1°), the calendar month of attending assessment centers (collected at recruitment); Townsend deprivation index at recruitment, household numbers, total household income before taxes in average, years of education; and lifestyle factors including time spent outdoors in summer, and winter, use of sunscreen/UV protection, ease of skin tanning, frequency of solarium/sunlamp use, summed minutes of activity per day, smoking, alcohol consumption, oily fish, processed meat, milk, spread types, bread type, frequency of visiting friend/family, and venturesome personality (collected from the touchpad questionnaire).

Biomarkers and healthcare-related factors were also used for adjustment in the analysis, including body mass index (BMI), waist circumference (collected from physical measures); the number of self-reported cancer and non-cancer illnesses, disability, overall health rating, the number of treatments/medications taken (collected from touchpad questionnaire); low dose aspirin, lipid-lowering drug, anti-depression drug intake, estimated glomerular filtration rate (eGFR), haemoglobin A_{1c} (HbA_{1c}), high-density lipoprotein (HDL) cholesterol, CRP (collected from biological samples); systolic blood pressure, diastolic blood pressure, forced expiratory volume in 1-second (FEV_1), handgrip strength (collected from physical measures); diabetes, stroke, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), osteoporosis, arthritis, gout, frequency of depressed mood in last 2 weeks, frequency of tiredness/lethargy in last 2 weeks, Parkinson, cancer, asthma, fractures in last 5 years, hypothyroidism, chronic fatigue syndrome, dementia, and hypertension (collected from verbal interviews).

2.1.6 In- and exclusion criteria

From n=502,490 individuals enrolled in the UK Biobank study at the initiation of the study, this study excluded n=7,293 participants without available information on the use of vitamin D or multivitamin supplements, and n=49,596 participants with no measurement of 25(OH)D concentration at baseline,

leaving n=445,601 participants for the analysis. After these exclusions, none of the study participants were without mortality follow-up data.

2.1.7 Statistical analyses

2.1.7.1 General remarks

This study used Statistical Analysis System (SAS) statistical software (version 9.4; SAS Institute, Incorporated, Cary, North Carolina, US) for all statistical analyses. Descriptive statistics were used for demographics and baseline information. This study calculated the person-time from the enrolment date to the date of death or the last follow-up (1 December 2020). Multiple imputation with 5 imputed datasets was conducted for missing values (exposure and outcome variables were not included) prior to performing regression analysis (Sterne et al. 2009). With few exceptions, covariates had less than 5% of missing values and none had more than 19.1% of missing values. The proportion of missing values for each variable used in the analyses can be calculated from the numbers shown in **Appendix 1**. The Markov chain Monte Carlo (MCMC) approach with a single chain was used for a dataset with arbitrary missing patterns, assuming multivariate normality (Yuan 2011). The SAS program PROC MIANALYZE was used for analyzing results from corresponding imputed datasets. Schoenfeld Residuals were used to test if the hazard ratio (HR) was constant over time for Cox proportional hazards regression models. A significance level of 0.05 was applied for all analyses.

2.1.7.2 Determinants of vitamin D deficiency and vitamin D supplement use

All available baseline variables of the UK Biobank were screened by my supervisor, a senior research scientist (PD Dr. Ben Schöttker) for vitamin D or health-related variables that could potentially be determinants of vitamin D deficiency and vitamin D supplement use and included in the analysis based on subject matter knowledge. A logistic regression model was fitted with vitamin D deficiency as the dependent variable (people with vitamin D sufficiency were the reference group and people with vitamin D insufficiency were excluded). Another logistic regression model was fitted with vitamin D supplement use as the dependent variable (those who did not take vitamin D supplements were the reference group and multivitamin users were excluded). All continuous variables were categorized in deciles. Irrelevant

variables were trimmed out by a stepwise backward elimination process. All variables with a weak ß coefficient < 0.0488 were removed if all categories had such a weak association (corresponds to an odds ratio (OR) between 1.0 and 1.05 or between 0.952 and 1.0). In the next step, variable categories (especially deciles of originally continuous variables) with a difference in ß coefficients < 0.0488 were combined.

To identify the determinants of vitamin D insufficiency, the established determinants of vitamin D deficiency were put in a logistic regression model and subjects with vitamin D deficiency were excluded. Likewise, to identify the determinants of multivitamin supplement use, the established determinants of vitamin D supplement use were put in a logistic regression model and vitamin D users were excluded.

2.1.7.3 Associations of vitamin D deficiency and insufficiency with mortality

Cox proportional hazards regression was employed to explore the potential associations of serum vitamin D deficiency and insufficiency with all-cause, CVD, cancer, and respiratory disease mortality. The set of determinants of vitamin D deficiency was used to control for confounding. The variables were allocated to five models, with increasing adjustments. Model 1 included age, sex, skin color, the latitude of the assessment center, and the calendar month of attending the assessment center. Model 2 further included socio-economic factors, model 3 lifestyle and vitamin D-specific factors, model 4 weight measures, and model 5 diseases, disease symptoms, biomarkers, and variables describing the general health status. The detailed list of the variables and their modelling (as categorical or linear variables) is shown in **Appendix 1**.

To determine optimal cut-offs for 25(OH)D levels in mortality prediction, dose-response curves were assessed using restricted cubic splines (RCS) with 5 knots located at the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles of 25(OH)D values and 75 nmol/L as the reference (Desquilbet and Mariotti 2010; Holick et al. 2011). Cox proportional hazards regression with the variables of model 5 for adjustment was used for the dose-response analysis.

2.1.7.4 Association of vitamin D supplement use with mortality

In analogy with the analyses for vitamin D deficiency and insufficiency, five Cox proportional hazards regression models were developed to explore the potential associations of vitamin D and multivitamin supplements use with all-cause, CVD, cancer, and respiratory disease mortality. The set of determinants of vitamin D supplement use was used to control for confounding and their modelling is shown in **Appendix 2**.

2.2 Associations of serum 25-hydroxyvitamin D levels and vitamin D supplement use with 18 cancer site-specific cancer

This section is dedicated to the second objective of the dissertation: assessing the association of vitamin D deficiency and insufficiency, as well as the use of vitamin D supplements, with mortality from 18 cancers, encompassing both common and less frequent cancers.

2.2.1 Study population

This study also utilized data from the UK Biobank, with the description of the UK Biobank and the statement of ethical approval provided in *Chapter 2.1.1*. The data were analyzed using a cohort study design.

2.2.2 Cancer mortality

Information on the dates and causes of death was obtained from the NHS for the time from the date of enrolment to 12 November 2021. This study identified the cancer site-specific mortality using the ICD-10. Specific cancers which caused at least 100 deaths in the study population were included as study outcomes of interest. Total cancer mortality was defined by the ICD-10 codes C00-C97.

2.2.3 Serum 25-hydroxyvitamin D measurement

The approaches used for measuring and validating serum 25(OH)D concentration were described in *Chapter 2.1.3.* Definitions of vitamin D deficiency and insufficiency remain the same as before.

2.2.4 Vitamin D supplement use

Acquisition of data of vitamin D supplement use was described in *Chapter 2.1.4*. Procedures remained the same.

2.2.5 Covariate

Variables that had been identified to be statistically and independently associated with vitamin D deficiency (n=48) or vitamin D supplement use (n=48) in previous analyses of the UK Biobank cohort were used for the model adjustment in this study (vitamin D/multivitamin use itself was excluded from the list of covariates). Details of their assessment methods have been described in *Chapter 2.2.5,* and the finding has also been published on the Journal of Internal Medicine (Sha et al. 2023).

2.2.6 In- and exclusion criteria

In 2022, at the inception of the study, a subset of participants had withdrawn from the UK Biobank, resulting in a remaining cohort of n=502,411. Of the n=502,411 baseline participants of the UK biobank, n=54,145 individuals whose serum 25(OH)D measurement was not available, and n=2,736 individuals with missing information about the use of vitamin D/multivitamin supplements were excluded. N=34,094 individuals who had been diagnosed with any cancer before study enrolment (except for the diagnosis of non-melanoma skin cancer [C44]) were furthermore excluded. Data on cancer diagnoses were extracted from both self-reported diagnoses in the questionnaire and the primary care records. Overall, n=411,436 participants were included in this analysis.

2.2.7 Statistical analyses

2.2.7.1 General remarks

General remarks, encompassing analytical software used, significance levels, methods for handling missing data, and testing for Cox proportional hazard regression assumptions, persist unchanged from the description provided in *Chapter 2.1.7.1*.

2.2.7.2 The association of vitamin D deficiency and insufficiency with total cancer mortality and cancer site-specific mortality

This study fitted cause-specific Cox proportional hazard models that considered the competing risk of dying of other causes than the cause of interest. HRs and 95% confidence intervals (CIs) were estimated for the associations of vitamin D status (sufficiency as reference) with cause-specific mortality from 18 cancers. Total cancer mortality was added as an outcome for comparison. Multivariable models were constructed and progressively adjusted. Same as *Chapter 2.1.7.3*, Covariates were increasingly allocated to five models by their attributes: model 1 included age, sex, skin color, the latitude of the assessment center, and the calendar month of blood draw. Model 2 further included socio-economic factors, model 3, lifestyle and vitamin D-specific factors, model 4, weight measures, and model 5, diseases, disease symptoms, biomarkers, medication use, and variables that describe the general health status (see legend of **Appendix 6** for the detailed list of the 48 model variables adjusted in the models).

This study also assessed the dose-response curves of 25(OH)D levels with total cancer mortality and cancer site-specific mortality using RCS curve with five knots located at the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles of 25(OH)D values, with 25(OH)D of 75 nmol/L as the reference (Desquilbet and Mariotti 2010; Holick et al. 2011). Cox proportional hazards regression model 5 was used for the dose-response analyses.

2.2.7.3 The association of vitamin D supplements with total cancer mortality and cancer site-specific mortality

Likewise in the analysis of vitamin D status, five cause-specific Cox proportional hazards models were also developed to examine the association between vitamin D supplement use and total as well as cancer site-specific mortality. The covariates in these five models were replaced by the set of determinants of vitamin D supplement use (see legend of **Appendix 10**).

2.2.7.4 Subgroup analyses by sex

All analyses were additionally carried out stratified by sex.

2.2.7.5 Sensitivity analyses

Several sensitivity analyses to validate the study findings were performed.

i. First, false discovery rate (FDR) was used to determine statistical significance, taking into account the number of statistical tests conducted for a specific analysis (analyses for total cancer mortality not included).
ii. Second, to account for seasonality in serum 25(OH)D concentrations (Hyppönen and Power 2007), 25(OH)D levels based on the calendar month of blood draw were standardized. As the results from this approach were comparable to the main analyses, in which the calendar month of blood draw was adjusted for in the models, these data are not shown.
iii. Third, to check the potential impact of the duration of follow-up time on the strength of the associations of vitamin D status/vitamin D intake and cancer mortality outcomes (Grant 2012), the associations with follow-up periods limited to 5 and 10 years were also assessed. The covariates of model 5 were used for all sensitivity analyses.

2.3 Interrelationships of 25-hydroxyvitamin D levels, biomarkers of systemic inflammatory responses and mortality

For the third aim of this dissertation, analyses were conducted on the interrelationships of low vitamin D status, nine biomarkers of systemic inflammatory response (CRP, mGPS, HS_mGPS, NLR, PLR, LMR, SII, PNI, and NPS), and all-cause and cause-specific mortality in the extensive UK Biobank cohort study.

2.3.1 Study population

The description of the UK Biobank and the statement of ethical approval were provided in *Chapter 2.1.1*. The data were analyzed using a cohort study design.

2.3.2 Serum 25-hydroxyvitamin D measurement

The approaches used for measuring and validating serum 25(OH)D concentration were described in *Chapter 2.1.3*. Cut-offs used for defining vitamin D deficiency, insufficiency and sufficiency remain the same.

2.3.3 Biomarkers of systemic inflammatory response

The serum CRP level (mg/L) was determined using immunoturbidimetric high-sensitivity analysis on a Beckman Coulter AU5800. The serum albumin level was measured by bromocresol green analysis on the same apparatus (UK Biobank 2022e; UK Biobank 2022f). The Beckman Coulter LH750 Hematology Analyzer was used to measure peripheral blood samples taken within 24 hours of the blood draw and 31 parameters including neutrophil, lymphocyte, monocyte, and platelet counts were obtained (Nøst et al. 2021; UK Biobank 2022a; UK Biobank 2022b; UK Biobank 2022c; UK Biobank 2022d). The equations to obtain the nine biomarkers of SIR used in this research project are shown in **Table 1** (Chan et al. 2021; Guthrie et al. 2013; Marques et al. 2021; Roxburgh and McMillan 2010; Taniai et al. 2021; Wang and Wang 2019; Watt et al. 2015).

Table 1. Equations for biomarkers of systemic inflammatory markers

Biomarkers		**Equation**
CRP based	CRP	Measured value, mg/L
	mGPS	0: CRP ≤ 10 mg/L and albumin ≥ 35 g/L 1: CRP > 10 mg/L and albumin ≥ 35 g/L 2: CRP > 10 mg/L and albumin < 35 g/L
	HS_mGPS	0: CRP ≤ 3 mg/L and albumin ≥ 35 g/L 1: CRP > 3 mg/L and albumin ≥ 35 g/L 2: CRP > 3 mg/L and albumin < 35 g/L
Blood cell count based	NLR	Neutrophil count / lymphocyte count
	PLR	Platelet count / neutrophil count
	LMR	Lymphocyte count / monocyte count
	SII	Platelet count × neutrophil count / lymphocyte count
	PNI	Serum albumin (g/L) + 0.005×1000×lymphocyte count (10^9/L)
	NPS	0: Neutrophils ≤ 7.5 x10^9/L and Platelets ≤ 400 x10^9/L 1: Neutrophils > 7.5 x10^9/L or Platelets > 400 x10^9/L 2: Neutrophils > 7.5 x10^9/L and Platelets > 400 x10^9/L

Abbreviations: CRP: C-reactive protein; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

2.3.4 Mortality data

Acquisition of mortality data including all-cause mortality, mortality due to CVD, cancer, and respiratory diseases was described in *Chapter 2.1.2*.

2.3.5 Covariate

This study developed models based on the 49 baseline characteristics identified as statistically significant and independently associated with vitamin D deficiency in the previous analysis of the UK Biobank data (see **Appendix 14**). The methods of the assessment of these covariates were described previously in *Chapter 2.1.5* (Sha et al. 2023). I included 47 out of these 49 covariates because of the exclusion of vitamin D/multivitamin use and CRP (which were highly related to the main variables of interest in the study). In the end, 51 covariates were included because a history of cancer (except non-melanoma skin cancer), inflammatory bowel disease, periodontitis, and pulmonary embolism were furthermore added due to their importance in SIR research and mortality outcomes.

2.3.6 In- and exclusion criteria

Of the n=502,411 baseline participants of the UK biobank, I excluded n=54,145 individuals whose serum 25(OH)D measurement was not available, and n=50,529 individuals who did not have information on any biomarkers of SIR at baseline, leaving n=397,737 participants included in this study.

2.3.7 Statistical analyses

2.3.7.1 General remarks

General remarks, encompassing analytical software used, significance levels, methods for handling missing data, and testing for Cox proportional hazard regression assumptions, persist unchanged from the description provided in *Chapter 2.1.7.1*.

2.3.7.2 Disadvantageous levels of biomarkers of systemic inflammatory response and their association with mortality

No established cut-off values for the dichotomization of the continuous biomarkers NLR, PLR, SII, LMR, and PNI are available in the literature. To obtain such cut-offs, RCS curves with age and sex-adjusted Cox proportional hazard regression models with 5 knots located at the 10^{th}, 25^{th}, 50^{th}, 75^{th}, and 90^{th} percentiles were firstly drawn using the SAS macro of Desquilbet and Mariotti (Desquilbet and Mariotti 2010). To choose a cut-off to dichotomize each biomarker, one of the 5 knots of the RCS curve at which the association with all-cause mortality had a turning point towards higher/lower HR were selected. The definition of a turning point was that the new direction needed to manifest at this point and not start at it. Thus, the chosen cut-off was usually one knot after the knot at which the new direction started. The rationale for this definition of a turning point was to obtain strong effect estimates in the exposed group of the dichotomized biomarker variable. If a dose-response association was u-shaped, only a knot at the end of the biomarker distribution (low or high levels), which is known to be associated with mortality from the literature, was chosen. Although a cut-off of 3 mg/L in general population samples is available from the literature for high-sensitive CRP, out of reasons of consistency, the method above to find the best suitable cut-off for this data set was applied. An exception was only made for the PLR, which did not show the expected dose-response relationship with mortality (see *Result Chapter 3.3.2*). Due to low numbers of patients with 2 points in the mGPS, HS_mGPS, and NPS, patients with 1 or 2 points were merged into the category of disadvantageous levels to obtain dichotomized variables for these scores.

The obtained cut-offs were subsequently used to assess HR and 95% CI for the associations of all nine biomarkers of SIR with all-cause, CVD, cancer, and respiratory disease mortality Cox proportional hazard regression models, with progressive adjustment of age, sex, BMI, waist circumference, and vitamin D status. This analysis was carried out for the total population and stratified by age (< 65 / ≥ 65 years) and sex.

2.3.7.3 Association of vitamin D status with biomarkers of systemic inflammatory response

The dichotomized biomarkers of SIR were used as dependent variables in logistic regression models to assess their association with vitamin D status (independent variable with three categories: deficiency, insufficiency, and sufficient vitamin D). To account for the high number of statistical tests in this analysis, the FDR was applied to determine statistical significance (FDR < 0.05). This analysis was also carried out for the total population and stratified by age (< 65 / ≥ 65 years) and sex.

Overall, five models were developed with increasing adjustments as described in *Chapter 2.1.7.3*. Model 1 includes age, sex, skin color, the latitude of the study center, and the calendar month of the blood draw. Model 2 adds socio-economic factors, model 3 lifestyle factors, model 4 body weight measures, and model 5 diseases, symptoms, and aspects of the general health status (for details about all 51 covariates summed up under these labels, see **Appendix 14** and legend of **Table 10**). Model 4 is the main model because the covariates in model 5 could be potential intermediates from a clinical perspective. Variation inflation factors (VIF) were used to test if there was multicollinearity across the 51 variables of model 5 (UCLA 2023). The median VIF of all the covariates and their categories was 1.5 and it ranged from 1.0 to 7.2. Thus, no factor had a VIF > 10, which would raise concerns regarding multicollinearity (UCLA 2023).

2.3.7.4 Association of vitamin D status with mortality

With the main model 4, Cox proportional hazards regression was used to assess the associations of vitamin D status with all-cause, CVD, cancer, and respiratory disease mortality. To address whether these associations of vitamin D status with mortality are independent of biomarkers of SIR, these were added one by one as covariates to the model. In addition, the same analysis was conducted with the continuous serum 25(OH)D concentration variable among subjects with vitamin D deficiency because this is a highly clinically relevant subpopulation with an approximately linear inverse relationship between 25(OH)D levels and mortality outcomes (Fan et al. 2020; Zhou and Hyppönen 2022). No subgroup analyses by age and sex were performed because it is known from previous analyses of the

UK Biobank that the associations of vitamin D status and mortality do not differ much by age and sex (Sha et al. 2023).

2.3.7.5 Mediation analysis

With the assumption of causality, the proportion of the total effect of vitamin D deficiency and vitamin D insufficiency on the mortality outcomes were quantified, which is mediated through biomarkers of SIR. The SAS macro of L. Valeri and T. J. VanderWeele for causal mediation analysis with adaptions for time-to-event analyses was used for the analyses (Localio et al. 2020; Valeri and Vanderweele 2013; VanderWeele 2015). The covariates of model 4 were used to adjust the Cox proportional hazards regression models of the mediation analyses.

2.4 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with low back pain

This section is dedicated to the fourth objective of this dissertation, which aimed to conduct a investigation into the associations of 25(OH)D status and the use of vitamin D supplements with LBP, both in a cross-sectional and longitudinal design.

2.4.1 Study population

The description of the UK Biobank and the statement of ethical approval were described in *Chapter 2.1.1*.

2.4.2 Serum 25-hydroxyvitamin D measurement

The approaches used for measuring and validating serum 25(OH)D concentration were described in *Chapter 2.1.3*. Cut-offs used for defining vitamin D deficiency, insufficiency and sufficiency remain the same.

2.4.3 Vitamin D supplement use

Acquisition of data of vitamin D supplement use was described in *Chapter 2.1.4*. Procedures remained the same.

2.4.4 Low back pain

The date and diagnosis of LBP information from primary care records were collected up to the date of the last data extraction from the NHS primary care dataset (September 2017) (UK Biobank 2019). The diagnosis of LBP was collected by the ICD-10 code M54.5 before the baseline visit for cross-sectional analyses, and during the follow-up period for longitudinal analyses. In cross-sectional analyses, the self-reported back pain from the questionnaire assessment of the UK Biobank via the query "Pain type(s) experienced in last month", with one of the options being "Back pain" (Data-Field 6159) was furthermore checked (UK Biobank 2023). By combining diagnosed LBP from primary care records with self-reported information about back pain experienced in the last month, an exposure variable of physician-diagnosed LBP with acute symptoms at baseline was created for cross-sectional analysis.

2.4.5 Covariate

The covariates incorporated in this study differed from those utilized for the first three objectives of the dissertation. Based on the previous analyses that identified a large number of variables statistically significantly associated with vitamin D deficiency, or vitamin D supplement use (described in *Chapter 2.1.5*) (Sha et al. 2023). These encompassed a broad spectrum, including not only sociodemographic factors, lifestyle factors, BMI, biomarkers, diseases and health-related factors, but also vitamin D-specific considerations such as the geographic latitude of the assessment center and seasonality (i.e., the calendar month of attending assessment centers and blood draw) (Sha et al. 2023). Adherence to a healthy life-style and the season of assessment are also relevant for LBP and are crucial aspects to adjust for (Ciaffi et al. 2021; Hyppönen and Power 2007; Knezevic et al. 2021; Roggio and Musumeci 2022). The covariates included in the final full models were selected from these determinants of vitamin D deficiency or vitamin D supplement use, along with two additional factors specific to LBP: a history of other musculoskeletal diseases before baseline enrollment (ICD-10: M00-M53, M55-M99) and injuries

to the abdomen, lower back, lumbar spine, and pelvis prior to baseline (ICD-10: S30-S39) from primary care data (Knezevic et al. 2021). The statistical method for the covariate selection is outlined in *Chapter 2.4.7.2*. The final list of covariates adjusted for in the models is shown in **Table 14** and the baseline distribution of all the covariates is shown in **Appendix 21**.

2.4.6 In- and exclusion criteria

To ascertain LBP diagnoses, linkage of the UK Biobank cohort to the NHS primary care data was required. While 98% of the UK population is registered with the NHS, at the time of the analyses, the primary care data had not been linked to the IT system supplier EMIS practice (EMIS 2021; Sudlow et al. 2015; UK Biobank 2019). Among the total study population of n=502,411 UK Biobank participants, linkage with NHS primary care data was feasible for n=225,014 study participants (**Figure 1**). Furthermore, it was necessary to exclude subjects with potentially undiagnosed LBP at baseline. In the baseline questionnaire, subjects were asked about symptoms of back pain in the last month. In a cross-sectional analysis, a comparison was made for individuals with physician-diagnosed LBP and acute symptoms at baseline, and subjects without any back pain. To establish this population, the following exclusion criteria was applied (**Figure 1**):

- Individuals with a history of dorsalgia diagnoses other than LBP in the primary care data (diagnosed using the ICD-10: M54.0-54.4, 54.6-54.9) before the baseline assessment (n=19,763).

- Self-reported back pain in the last month in the questionnaire (n=45,920) or missing information about this question (n=282) unless LBP was diagnosed in the primary care data.

- History of LBP diagnosis in the primary care data but no current symptoms reported in the question about LBP in the last month (n=6,847).

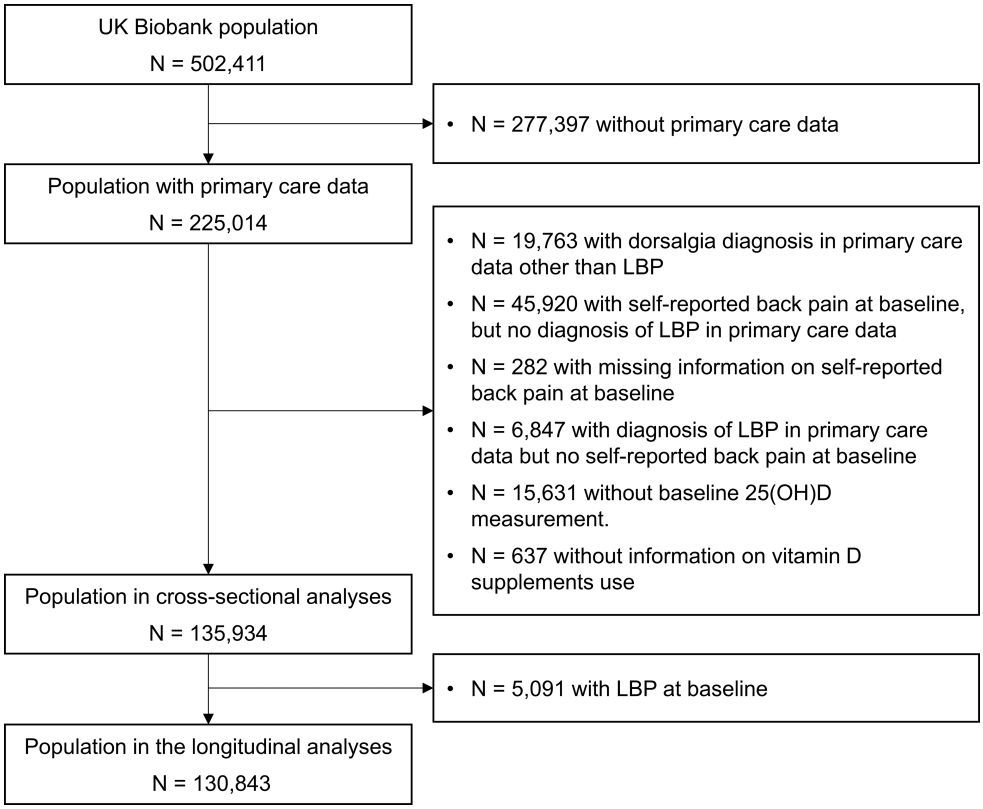

Figure 1. Flow-chart of the study population

Abbreviations: 25(OH)D, 25-hydroxyvitamin D; LBP, low back pain

2.4.7 Statistical analyses

2.4.7.1 General remarks

Statistical software, methods for handling of missing values, and methods for testing proportional hazards assumption in longitudinal analyses remain the same as described in *Chapter 2.1.7.1*.

In this analysis, two-sided statistical tests were employed, with a predetermined p-value < 0.003125 indicating statistical significance due to correction for multiple testing for 16 tests by the Bonferroni method (Miller 1981). The 16 tests are for the four exposures (i.e., vitamin D deficiency, vitamin D insufficiency, vitamin D supplement use and multivitamin use) tested for an association with LBP in both cross-sectional and longitudinal analysis in two models: age- and sex-adjusted model as well as the full model (4*2*2 = 16 tests).

2.4.7.2 Covariates

The set of potentially relevant covariates described in *Chapter 2.4.5* was reduced by a stepwise backward elimination with a stay criterion of $p<0.05$ using LBP at baseline as the dependent variable in a logistic regression model. Age and sex were forced into the model regardless of statistical significance. Furthermore, VIFs were used to examine the presence of multicollinearity among the variables incorporated in the final models (UCLA 2023).

2.4.7.3 Association of vitamin D status with low back pain

Logistic regression and Cox proportional hazard regression were applied to assess the cross-sectional and longitudinal association of 25(OH)D status with LBP, respectively. In both cross-sectional and longitudinal analyses, two distinct models were applied. The first model was adjusted for age and sex. The full model comprised the variables obtained by the covariate selection described in *Chapter 2.4.7.2* (see **Table 14** for final list of all covariates).

Furthermore, dose-response patterns of 25(OH)D concentrations in association with LBP were assessed using the same models, employing RCS curves characterized by five knots positioned at the 5^{th}, 25^{th}, 50^{th}, 75^{th}, and 95^{th} percentiles of the actual value of serum 25(OH)D. A 25(OH)D level of 75 nmol/L was used as a point of reference (Desquilbet and Mariotti 2010; Holick et al. 2011).

2.4.7.4 The association of vitamin D supplement use with low back pain

Similar to the analysis of 25(OH)D levels, logistic regression and Cox proportional hazards regression were used again to investigate the cross-sectional and longitudinal association of vitamin D supplement use with LBP, respectively.

2.4.7.5 Subgroup analyses

All analyses were further stratified based on age (<65/≥65 years old), sex (female/male), with/without a history of depression, and with/without a history of other musculoskeletal diseases.

3 Results

3.1 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with all-cause mortality, CVD mortality, cancer mortality and respiratory disease mortality

3.1.1 Description of the population included

A total of 445,601 participants were selected for the analyses with the total cohort. Included study participants were between 38 and 73 years old, with a mean age of 56.5 years (**Table 2**). There were slightly more female than male participants (53.6%). The majority of participants were overweight (BMI 25- <30 kg/m²; 42.4%) or obese (BMI ≥30 kg/m^2; 24.3%), never smokers (54.9%), and consumed alcohol at least once per week (69.5%). Furthermore, approximately 1 out of 5 study participants consumed alcohol daily or almost daily and reported ≤ 1 hour of physical activity per day. The prevalence of hypertension, diabetes mellitus, and coronary heart disease was 26.9%, 5.0%, and 4.7%, respectively, and the median number of chronic diseases per person was 2 (range: 0-29).

Table 2. Baseline characteristics of the study population (N=445,601)

Variables	Data
Sex, n (%)	
Male	206,597 (46.4%)
Female	239,004 (53.6%)
Age (years)	
Mean (SD)	56.5 (8.1)
Median (min:max)	58 (38: 73)
Body mass index (kg/m^2) n (%)	
< 18.5	2,285 (0.5%)
18.5 - <20	8,193 (1.9%)
20 - < 25	137,462 (31.0%)
25 - < 30	188,152 (42.4%)
30 - < 35	77,292 (17.4%)
35 - < 40	22,023 (5.0%)
≥ 40	8,519 (1.9%)
Smoking, n (%)	
Never	244,534 (54.9%)
Former, occasionally	51,089 (11.5%)
Former, regularly	103,488 (23.2%)

Variables	Data
Current, occasionally	12,177 (2.7%)
Current, regularly	34,169 (7.7%)
Alcohol consumption, n (%)	
Never	35,108 (7.9%)
Special occasions only	51,091 (11.5%)
1-3 times / month	49,683 (11.2%)
1-2 times / week	115,596 (26.0%)
3-4 times / week	103,356 (23.2%)
Daily or almost daily	90,393 (20.3%)
Total physical activity per day, n (%)	
≤ 1 h	67,824 (18.7%)
> 1 - 2 h	147,275 (40.7%)
> 2h	146,501 (40.5%)
Hypertension, n (%)	119,939 (26.9%)
Diabetes, n (%)	22,268 (5.0%)
Coronary heart disease, n (%)	20,847 (4.7%)
No. of self-reported chronic diseases, Median (min:max)	2.0 (0:29)
25(OH)D levels, Mean (SD)	48.7 (21.1)
Vitamin D status, n (%)	
Vitamin D deficiency (25(OH)D < 30 nmol/L)	93,435 (21.0%)
Vitamin D insufficiency (25(OH)D 30 - < 50 nmol/L)	152,963 (34.3%)
Vitamin D sufficiency (25(OH)D ≥ 50 nmol/L)	199,203 (44.7%)
Vitamin D / multivitamin supplements use, n (%)	
No	335,634 (75.3%)
Yes, vitamin D preparations regularly	19,185 (4.3%)
Yes, multivitamin (± minerals) preparations regularly	90,782 (20.4%)

Abbreviations: 25(OH)D: 25-hydroxyvitamin D, IQR: interquartile range.

The majority of the study participants had either vitamin D deficiency (21.0%) or insufficiency (34.3%). Only 4.3% specifically reported taking regularly vitamin D preparations and a further 20.4% reported using multivitamin (± minerals) preparations regularly. With median 25(OH)D levels of 57.5 nmol/L and 53.4 nmol/L, users of vitamin D supplements and users of multivitamin preparations had significantly higher median 25(OH)D levels than non-users of such supplements (44.3 nmol/L). The distribution of the 25(OH)D levels in these three groups is illustrated in **Figure 2**. Multivariate logistic regression models revealed that the odds of being vitamin D deficient were reduced by 74%, 84% and 89% if multivitamin, OTC vitamin D, or prescribed vitamin D preparations were used, respectively (**Table 3**). The odds of having vitamin D insufficiency (30 nmol/L ≤ 25[OH]D ≤ 50 nmol/L) of subjects using multivitamin preparations, OTC vitamin D, or prescribed vitamin D were 45%, 56% and 56% lower, respectively, compared to non-users of any vitamin preparations.

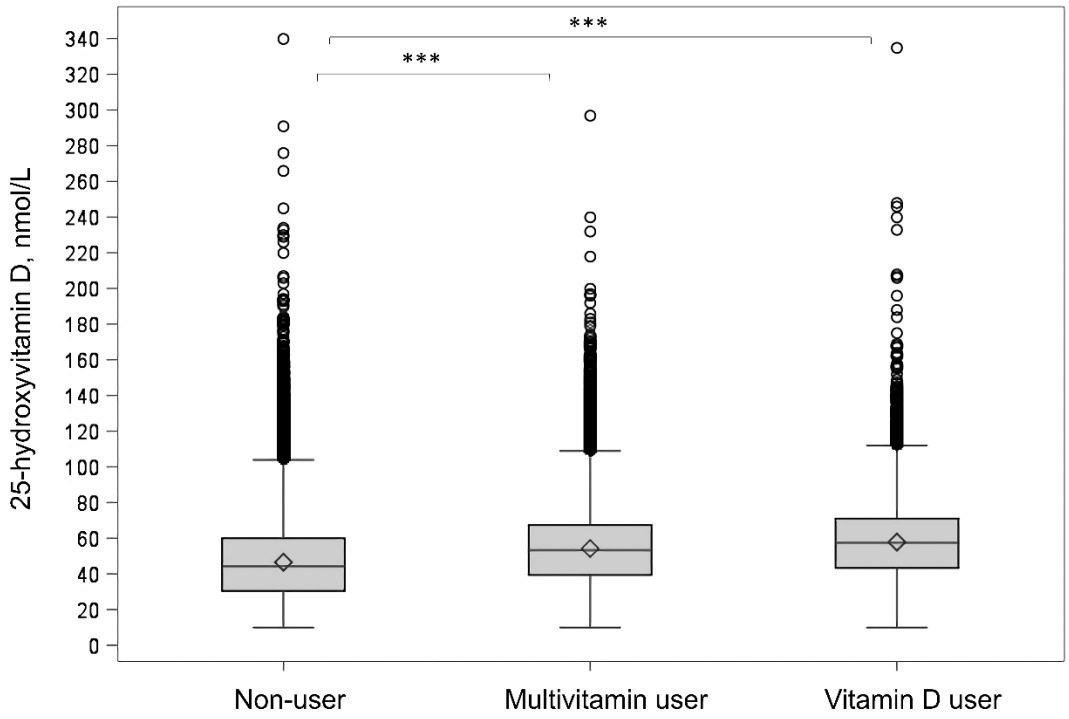

Figure 2. Box plots of 25-hydroxyvitamin D levels of study participants who regularly use vitamin D preparations, multivitamin preparations, and none of the aforementioned in 445,601 UK Biobank participants

***p < 0.0001 at the significance level of 5% (Wilcoxon rank–sum test).

Table 3. Associations of vitamin supplement use with vitamin D deficiency and insufficiency in 445,601 UK Biobank participants

Regular vitamin intake, n (%)	**N (%)**	**Association with vitamin D deficiency (n=93,435) OR (95%CI) [a]**	**Association with vitamin D insufficiency (n=152,963) OR (95%CI) [b]**
None	335,634 (75.3)	Ref	Ref
Multivitamins ± minerals	90,782 (20.4)	0.26 (0.25-0.27)	0.55 (0.54-0.56)
OTC vitamin D	15,985 (3.6)	0.16 (0.15-0.17)	0.44 (0.42-0.45)
Prescribed vitamin D	3,200 (0.7)	0.11 (0.09-0.13)	0.44 (0.40-0.48)

Abbreviations: CI: confidence interval, OR: odds ratio, OTC: over the counter, Ref: reference.

[a] Result of multivariate logistic regression model including all other 48 determinants of vitamin D deficiency and insufficiency levels as shown in the Appendix 1. Subjects with vitamin D insufficiency were excluded.

[b] Result of multivariate logistic regression model including all other 48 determinants of vitamin D deficiency and insufficiency levels as shown in the Appendix 1. Subjects with vitamin D deficiency were excluded.

3.1.2 Determinants of vitamin D deficiency and vitamin D supplement use

Overall, 49 independent determinants of vitamin D deficiency were identified, of which 44 were also significantly associated with vitamin D insufficiency (**Appendix 1**). Also, there were 49 determinants of vitamin D supplement use identified, and 42 of them were associated with multivitamin use (**Appendix 2**). A comparison of the determinants of vitamin D deficiency, vitamin D insufficiency, vitamin D supplement use, and multivitamin use showed many overlaps but the directions of the associations were often different (**Table 4**).

Table 4. Overview on the determinants of vitamin D deficiency, vitamin D insufficiency, vitamin D and multivitamin supplements use in 445,601 UK Biobank participants

Vitamin D status/Supplement use	**Direction of the association with**			
	Vitamin D deficiency [a]	**Vitamin D insufficiency** [a]	**Vitamin D supplements use** [b]	**Multivitamin supplements use** [b]
SOCIO-DEMOGRAPHIC/ -ECONOMIC FACTORS				
Age	-	-	+	0
Male sex	-	-	-	-
Education	+	+	0	0
Townsend deprivation index	+	+	+	0
No. of individuals in household	+	+	-	-
Annual household income	-	-	+	+
LIFE-STYLE FACTORS				
Smoking	+	+	-	-
Alcohol consumption	-	-	-	-
Venturesome personality	0	0	+	+
Total physical activity	-	-	+	+
Visiting friends/family	-	-	-	-
Oily fish consumption	-	-	+	+
Cereal consumption	-	-	0	0
Processed meat intake	-	0	-	-
Milk consumption	-	-	-	-
Butter consumption	+	+	-	-
Wholegrain bread consumption	-	0	+	+
DISEASES & SYMPTOMS				
Cancer	0	0	+	0
Hypertension	0	0	-	-
Diabetes	-	-	-	-
Stroke	+	0	-	-
CHD	+	+	-	-
COPD	+	+	-	-

Vitamin D status/Supplement use	Direction of the association with			
	Vitamin D deficiency [a]	Vitamin D insufficiency [a]	Vitamin D supplements use [b]	Multivitamin supplements use [b]
Asthma	0	0	-	-
Osteoporosis	-	-	+	-
Fracture in last 5 years	0	0	+	0
Arthritis	-	-	-	-
Gout	+	+	-	-
Parkinson	+	+	-	-
Depressed mood	+	+	+	+
Tiredness/lethargy	+	+	+	+
Chronic fatigue syndrome	0	0	+	+
Hypothyroidism	0	0	-	-
Dementia	0	0	+	+
BIOMARKERS				
Obesity vs. high-normal weight BMI	+	+	-	0
Waist circumference	+	+	-	-
eGFR	-	-	-	-
HbA_{1c}	+	+	0	0
HDL cholesterol	-	-	0	0
Systolic blood pressure	+	+	0	0
Diastolic blood pressure	+	+	0	0
C-reactive protein	-	-	-	0
FEV1	-	-	0	0
Hand grip strength	-	0	0	0
GENERAL HEALTH AND DRUG USE				
No. of chronic diseases	+	+	0	0
Disability	+	0	-	-
Poor general self-reported health	+	+	-	-
No of drugs	-	-	+	+
Low-dose aspirin use	0	0	-	0
Lipid-lowering drugs use	0	0	-	-
Anti-depressants use	0	0	-	-
VITAMIN D SPECIFIC FACTORS				
Latitude of study center	+	+	-	-
Month of attending the study center	-	-	-	-
Regular vitamin D intake	-	-	N/A	N/A
Time spent outdoors in summer	-	-	-	-
Time spent outdoors in winter	+	+	0	0
Skin color brown/black	+	+	+	+
Skin tanning: never tan, always burn	+	+	-	-
Sun screen/UV protection use	-	-	+	+
Solarium/sunlamp use	-	-	+	+

Abbreviations: BMI: body mass index, HbA_{1c}, Haemoglobin A_{1c}, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, eGRF: estimated glomerular filtration rate, FEV1, forced expiratory volume 1, HDL, high-density lipoprotein; LDL, low-density lipoprotein.

[a] See Appendix 1 for details. +: positive association, -: inverse association, 0: no association.

[b] See Appendix 2 for details. +: positive association, -: inverse association, 0: no association.

3.1.3 Associations of 25-hydroxyvitamin D levels with mortality

Among all participants, 29,107 (6.5%) died during a median follow-up time of 11.8 years (interquartile range [IQR]: 11.0-12.5 years). The numbers of deaths attributable to CVD, cancer, and respiratory diseases were 5,943, 15,184, and 2,084 respectively. **Table 5** shows that both vitamin D deficiency and insufficiency were significantly associated with all-cause mortality and cause-specific mortality due to cancer, CVD, and respiratory diseases in all models although the HRs were attenuated with increasing adjustment from model 1 to 5. In model 5, compared to people with a sufficient 25(OH)D level, those with vitamin D deficiency and vitamin D insufficiency had 29% and 10% increased all-cause mortality, respectively. Compared to all-cause mortality, excess mortality in the vitamin D deficiency and insufficiency groups was higher for CVD mortality (36% and 15%, respectively) and respiratory disease mortality (61% and 31%, respectively) and lower for cancer mortality (15% and 4%, respectively).

Figure 3 shows RCS curves that visually present the dose-response associations of serum 25(OH)D concentration with all-cause mortality and cause-specific mortalities. We observed L-shaped functions with increased mortality for 25(OH)D < 30 nmol/L for all outcomes, supporting the results of Table 5 for vitamin D deficiency. Less strongly increased mortality was also observed for the vitamin D insufficiency range from 30-50 nmol/L for all outcomes except respiratory disease mortality, which could be extended to up to 60 nmol/L. For 25(OH)D levels > 60 nmol/L, the curves plateaued at the null effect value of HR=1. To check, whether there is a statistically significantly increased mortality in the 25(OH)D range 50-<60 nmol/L, we added this category to the analyses and the results are shown in **Appendix 3**. Increased CVD mortality (by 10%, $p<0.05$) and respiratory disease mortality (by 14%, $p>0.05$) were observed for subjects with 25(OH)D levels 50-<60 nmol/L compared to > 60 nmol/L. No significant increased all-cause or cancer mortality was observed in subjects with 25(OH)D levels of 50-<60 nmol/L.

Table 5. Associations of vitamin D deficiency and insufficiency with all-cause and cause-specific mortality in 445,601 UK Biobank participants

Vitamin D status	**Vitamin D deficiency (n=93,435)**	**Vitamin D insufficiency (n=152,963)**	**Vitamin D sufficiency (n=199,203)**
Mortality	**HR(95%CI)**	**HR(95%CI)**	**HR (95%CI)**
All-cause mortality (N_{deaths}=29,107)			
Model 1 [a]	1.92 (1.85, 2.00)	1.25 (1.21, 1.30)	Ref
Model 2 [b]	1.73 (1.66, 1.80)	1.21 (1.17, 1.25)	Ref
Model 3 [c]	1.45 (1.39, 1.51)	1.14 (1.10, 1.18)	Ref
Model 4 [d]	1.37 (1.31, 1.43)	1.11 (1.07, 1.15)	Ref
Model 5 [e]	1.29 (1.24, 1.33)	1.10 (1.06, 1.13)	Ref
CVD mortality (N_{deaths}=5,943)			
Model 1 [a]	2.46 (2.25, 2.68)	1.43 (1.32, 1.55)	Ref
Model 2 [b]	2.07 (1.89, 2.26)	1.36 (1.25, 1.47)	Ref
Model 3 [c]	1.64 (1.49, 1.81)	1.23 (1.14, 1.34)	Ref
Model 4 [d]	1.45 (1.32, 1.60)	1.15 (1.06, 1.24)	Ref
Model 5 [e]	1.36 (1.26, 1.46)	1.15 (1.08, 1.23)	Ref
Cancer mortality (N_{deaths}=15,184)			
Model 1 [a]	1.52 (1.43, 1.60)	1.14 (1.09, 1.19)	Ref
Model 2 [b]	1.43 (1.35, 1.51)	1.12 (1.07, 1.17)	Ref
Model 3 [c]	1.24 (1.17, 1.32)	1.07 (1.02, 1.12)	Ref
Model 4 [d]	1.20 (1.13, 1.27)	1.05 (1.00, 1.10)	Ref
Model 5 [e]	1.15 (1.10, 1.21)	1.04 (1.00, 1.08)	Ref
Respiratory disease mortality (N_{deaths}=2,084)			
Model 1 [a]	3.73 (3.19, 4.36)	1.78 (1.54, 2.05)	Ref
Model 2 [b]	2.90 (2.47, 3.40)	1.64 (1.42, 1.90)	Ref
Model 3 [c]	2.07 (1.75, 2.46)	1.46 (1.26, 1.69)	Ref
Model 4 [d]	2.00 (1.68, 2.37)	1.47 (1.27, 1.70)	Ref
Model 5 [e]	1.61 (1.42, 1.83)	1.31 (1.17, 1.46)	Ref

Abbreviations: CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, Ref: reference

[a] Model 1: Age, sex, skin colour, latitude of study center and calendar month of attending the assessment center.

[b] Model 2: Model 1 variables plus socio-economic factors (education, Townsend deprivation index, no of individuals in household, and household income).

[c] Model 3: Model 2 variables plus life-style factors (smoking, alcohol consumption, physical activity, frequency of visiting friends/family and consumption of oily fish, cereal, processed meat, milk, bread and spread), and vitamin D specific factors (time spend outdoors in summer and winter, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use).

[d] Model 4: Model 3 variables plus weight variables (body mass index and waist circumference).

[e] Model 5: Model 4 variables plus diseases and disease symptoms (diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, arthritis, gout, Parkinson, depressed mood, and tiredness/lethargy), biomarkers (estimated glomerular filtration rate, HbA_{1c}, HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein, forced expiratory volume in 1-second, and hand grip strength), and general health status (no. of drugs, no. of chronic diseases, disability, and general self-rated health).

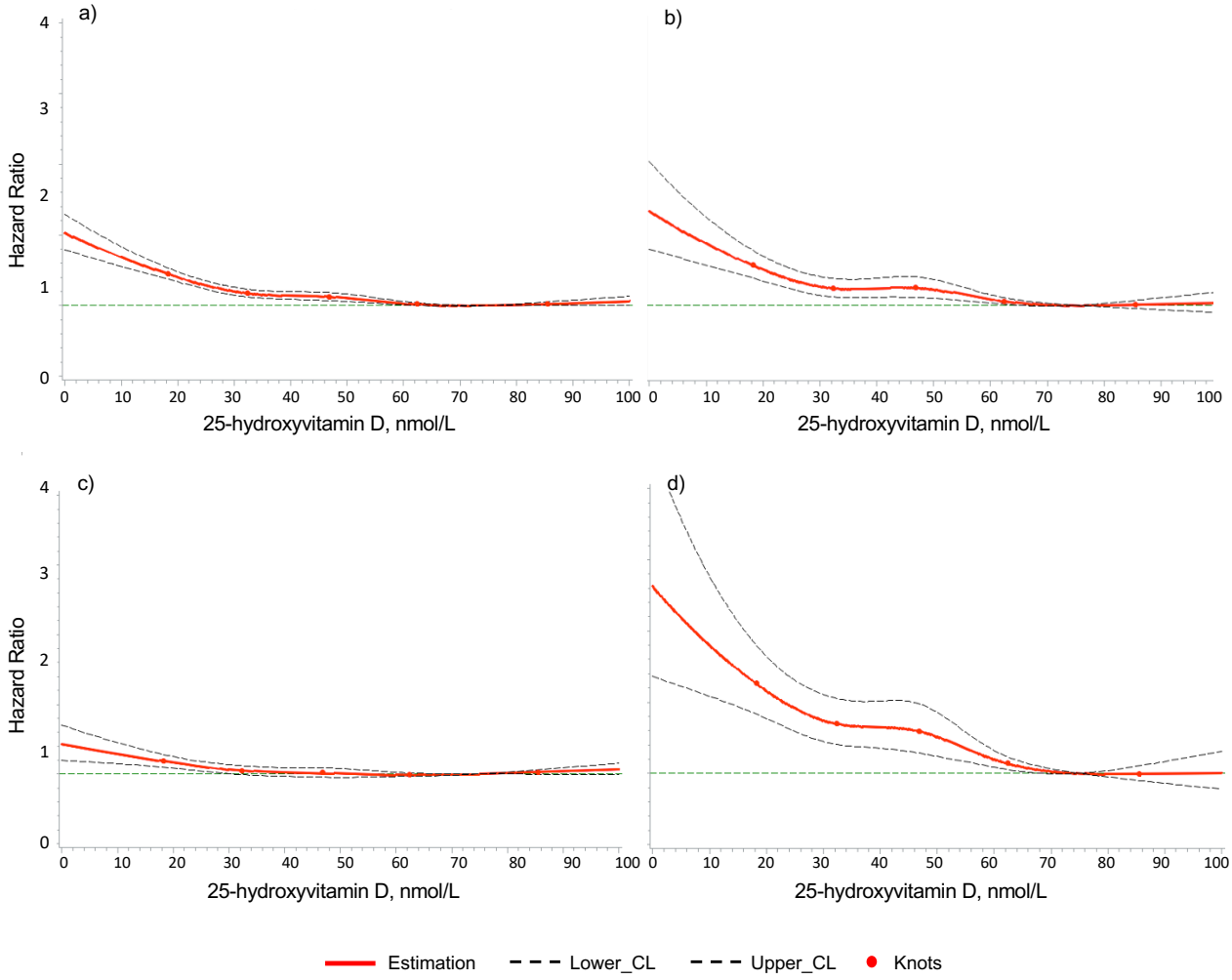

Figure 3. Adjusted dose-response relationship of serum 25-hydroxyvitamin D concentration with all-cause mortality (a), cardiovascular mortality (b), cancer mortality (c), respiratory mortality (d)

Note: 5 knots were used and located at the 5th, 25th, 50th, 75th, and 95th serum 25-hydroxyvitamin D percentile and the 75 nmol/L was used as the reference. Horizontal lines represent the hazard ratio of 1. Solid lines are estimates of hazard ratios and dashed lines are their 95% confidence intervals. Knots are represented by dots.

The models are adjusted for all covariates used in model 5 (see legend of Table 5).

3.1.4 Association of vitamin D supplement use with mortality

Table 6 shows the association of vitamin D and multivitamin supplements use with all-cause of mortality and cause-specific mortality. Self-reported vitamin D supplements intake (83% OTC drugs/17% prescribed) was not associated with any outcome in model 1-4 but after considering disease and general health status factors in model 5, vitamin D supplement users had 10% lower all-cause mortality, and 11% lower cancer mortality. The point estimate for CVD was in the same magnitude but 95% confidence intervals included the null value. The association with respiratory disease mortality was substantially stronger with 29% decreased mortality. Patterns for multivitamin use were different with not much change in the risk estimates with increasing adjustment from model 1 to 5. In the most comprehensively adjusted model 5, multivitamin use was statistically significantly associated with all-cause, CVD and respiratory disease mortality with 5%, 10%, and 17% reduced mortality, respectively, whereas there was no statistically significant association with cancer mortality.

Table 6. Associations of vitamin D supplement use and multivitamin use with all-cause and cause-specific mortality in 445,601 UK Biobank participants

Vitamin supplement use	Vitamin D users (n=19,185)	Multivitamin users (n=90,782)	Non-users (n=335,634)
Mortality	**HR(95%CI)**	**HR(95%CI)**	**HR (95%CI)**
All-cause mortality (N_{deaths}=29,107)			
Model 1 [a]	0.99 (0.94, 1.05)	0.91 (0.89, 0.94)	Ref
Model 2 [b]	0.98 (0.92, 1.03)	0.91 (0.89, 0.94)	Ref
Model 3 [c]	1.04 (0.98, 1.10)	0.97 (0.94, 1.00)	Ref
Model 4 [d]	1.05 (0.99, 1.11)	0.97 (0.94, 1.00)	Ref
Model 5 [e]	0.90 (0.85, 0.96)	0.95 (0.92, 0.98)	Ref
CVD mortality (N_{deaths}=5,943)			
Model 1 [a]	0.91 (0.79, 1.04)	0.83 (0.77, 0.89)	Ref
Model 2 [b]	0.89 (0.78, 1.01)	0.83 (0.77, 0.89)	Ref
Model 3 [c]	0.95 (0.83, 1.08)	0.89 (0.83, 0.95)	Ref
Model 4 [d]	0.99 (0.86, 1.13)	0.90 (0.84, 0.96)	Ref
Model 5 [e]	0.89 (0.78, 1.02)	0.90 (0.84, 0.97)	Ref
Cancer mortality (N_{deaths}=15,184)			
Model 1 [a]	0.94 (0.87, 1.01)	0.94 (0.90, 0.98)	Ref
Model 2 [b]	0.93 (0.86, 1.01)	0.94 (0.90, 0.98)	Ref
Model 3 [c]	0.97 (0.90, 1.05)	0.98 (0.94, 1.02)	Ref
Model 4 [d]	0.99 (0.91, 1.07)	0.99 (0.95, 1.03)	Ref
Model 5 [e]	0.89 (0.82, 0.97)	0.97 (0.93, 1.02)	Ref
Respiratory disease mortality (N_{deaths}=2,084)			
Model 1 [a]	1.00 (0.82, 1.23)	0.81 (0.72, 0.91)	Ref
Model 2 [b]	0.98 (0.79, 1.20)	0.82 (0.72, 0.92)	Ref
Model 3 [c]	1.11 (0.90, 1.36)	0.92 (0.82, 1.04)	Ref
Model 4 [d]	1.07 (0.87, 1.31)	0.92 (0.82, 1.04)	Ref
Model 5 [e]	0.71 (0.58, 0.89)	0.83 (0.74, 0.94)	Ref

Abbreviations: CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, Ref: reference

[a] Model 1: Age, sex, skin colour, latitude of study center and calendar month of attending the assessment center.

[b] Model 2: Model 1 variables plus socio-economic factors (Townsend deprivation index, no of individuals in household, and household income).

[c] Model 3: Model 2 variables plus life-style factors (smoking, alcohol consumption, physical activity, venturesome personality, frequency of visiting friends/family) and vitamin D specific factors (consumption of oily fish, processed meat, milk, bread, spread, time spend outdoors in summer, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use).

[d] Model 4: Model 3 variables plus weight variables (body mass index and waist circumference).

[e] Model 5: Model 4 variables plus diseases & disease symptoms (cancer, hypertension, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, osteoporosis, fractured in last 5 years, arthritis, gout, diabetes, hypothyroidism, chronic fatigue syndrome, tiredness/lethargy in last 2 weeks, dementia, Parkinson, and depressed mood), biomarkers (estimated glomerular filtration rate, C-reactive protein), general health status (disability, general self-rated health and no. of drugs), and medication intake (low dose aspirin, lipid-lowering drugs, and anti-depression drugs).

3.2 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with 18 cancer site-specific cancer

3.2.1 Description of the population included

The median age of the 411,436 study participants was 57 years (IQR: 50; 63) and slightly more females (52.9%) than males were included (**Table 7**). Participants were mostly overweight or obese (66.7% combined). Never-smokers (55.2%) slightly outnumbered ever-smokers. Aside from abstainers, 40.2% of participants consumed alcohol at a low level, and 29.1% consumed alcohol at higher levels. More than a quarter of participants reported having hypertension (26.6%), and approximately 5% reported diabetes mellitus (4.9%) and coronary heart disease (4.6%). The median number of chronic diseases per person was 1 (IQR: 0; 3). The median of 25(OH)D concentration was 46.8 (IQR: 32.4; 62.4) nmol/L and the majority of participants were with either vitamin D deficiency (21.1%) or insufficiency (34.4%). Only 4.1% of participants specifically reported using vitamin D supplementation regularly, and another 20.3% reported using multivitamin (± minerals) preparations regularly. The distribution of the complete list of baseline characteristics was shown in **Appendix 4**.

Table 7. Baseline characteristics of the study population (N=411,436)

Baseline characteristics	N (%) or Median (IQR)
Sex, n (%)	
Female	217,594 (52.9)
Male	193,842 (47.1)
Age (years), median (IQR)	57 (50; 63)
BMI, n (%)	
Underweight, < 18.5	2,061 (0.5)
Normal, 18.5 -< 25	134,323 (32.7)
Overweight: 25 - < 30	174,086 (42.5)
Obesity: ≥ 30	99,418 (24.2)
Smoking, n (%)	
Never	227,132 (55.2)
Ever (in the past or present)	184,168 (44.8)
Alcohol consumption [a], n (%)	
Abstainer	126,161 (30.7)
Low	165,309 (40.2)
Medium	69,839 (17.0)
High	49,663 (12.1)
Hypertension, n (%)	109,205 (26.6)
Diabetes, n (%)	20,316 (4.9)
CHD, n (%)	18,970 (4.6)
No. of chronic diseases, median (IQR)	1 (0; 3)
Serum 25(OH)D concentration (nmol/L), median (IQR)	46.8 (32.4; 62.4)
25(OH)D levels, n (%)	
< 30	86,638 (21.1)
30- < 50	141,429 (34.4)
≥ 50	183,369 (44.6)
Vitamin intake, n (%)	
None	310,731 (75.5)
Multivitamins +/-minerals	83,719 (20.3)
Vitamin D	16,986 (4.1)

Abbreviations: 25(OH)D: 25-hydroxyvitamin D, BMI: body mass index, CHD: coronary heart disease, IQR: interquartile range.

[a] Alcohol consumption: Low: Women > 0-19.99 grams of ethanol per day (g/d) or men > 0-39.99 g/d; Medium: Women 20-39.99 g/d or men 40-59.99 g/d; High: Women ≥ 40g/d or men ≥ 60 g/d.

3.2.2 Cancer site-specific mortality included in the study

During the median follow-up of 12.7 years (IQR: 12.0-13.4), 12,947 participants died of cancer. 18 cancer site-specific causes of mortality were included as the study outcomes, of which 14 occurred in both sexes (**Figure 4**). In both sexes combined, the highest mortality rate per 1000 person-years was

from lung cancer (0.47), followed by the ones from colorectal (0.25) and pancreatic cancer (0.21). The cancer site-specific mortality rates for women and men are shown distinctly in **Appendix 5**.

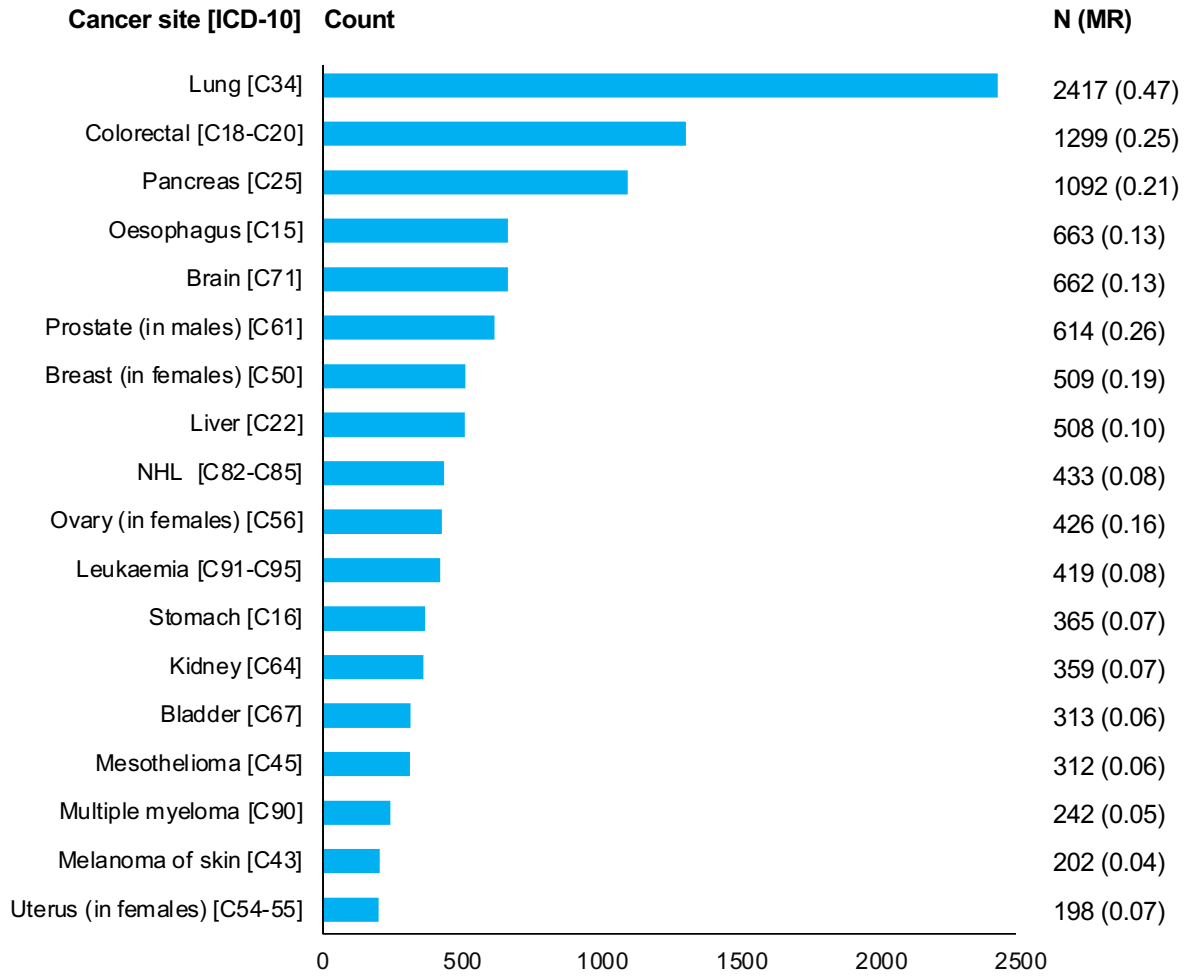

Figure 4. Cancer site-specific mortality rate in the UK Biobank in study participants free of cancer at baseline

Abbreviations: ICD-10, the 10th revision of the International Statistical Classification of Diseases; MR, mortality rate per 1000 person-year; N, absolute number of cases; NHL, non-Hodgkin lymphoma.

The MRs of breast cancer, ovarian cancer, and uterus cancer were calculated in females only.

The MR of prostate cancer was calculated for males only.

3.2.3 Association of 25-hydroxyvitamin D levels with cancer mortality

With few exceptions, the associations of vitamin D deficiency (25[OH]D < 30 nmol/L) with the cancer mortality outcomes were broadly attenuated with increasing adjustment of covariates from model 1-5 (**Appendix 6**). **Figure 5** plots the association between vitamin D status and total as well as cancer site-

specific mortality with the most comprehensively adjusted model (Model 5). Compared to vitamin D sufficiency, those with vitamin D deficiency had 15%, 42%, 27%, 24%, and 36% increased mortality due to total cancer, stomach cancer, colorectal cancer, lung cancer, and prostate cancer, respectively. Those with vitamin D insufficiency (30 nmol/L ≤ 25[OH]D < 50 nmol/L) also had 14% increased colorectal cancer mortality and 19% increased lung cancer mortality. Sensitivity analyses, limited follow-up times of 5 and 10 years, resulted in similar findings compared to those obtained with the entire 15 years of follow-up (**Appendix 7**).

Figure 6 shows RCS curves visualising the dose-response association of serum 25(OH)D concentration with mortality from total cancer, stomach cancer, colorectal cancer, and lung cancer in both sexes, as well as with prostate cancer mortality in men only. Almost linear associations of 25(OH)D levels with total cancer mortality and mortality due to these 4 specific cancer sites were observed in the range of 25(OH)D levels < 30 nmol/L. Only for lung cancer mortality, a slightly increased mortality was observed in higher 25(OH)D levels between 30 and 60 nmol/L compared to higher levels. For lung cancer mortality and mortality due to the other three specific cancers, the HR estimation line was very close to the null effect line of HR=1 at 25(OH)D levels > 60 nmol/L and > 50 nmol/L, respectively.

Sex-specific HRs for the association of vitamin D deficiency and insufficiency with total cancer and cancer site-specific mortality are presented in **Appendix 8** and **9**, respectively. The association of vitamin D deficiency with increased total cancer mortality and lung cancer mortality was more pronounced in males than in females. Additional sex-specific findings, which have not yet been observed in the total population, were: 1) an association of vitamin D deficiency with increased mortality from liver cancer in men, 2) an association of vitamin D deficiency with increased mortality from multiple myeloma in women, and 3) an association of vitamin D insufficiency with decreased mortality from multiple myeloma in men.

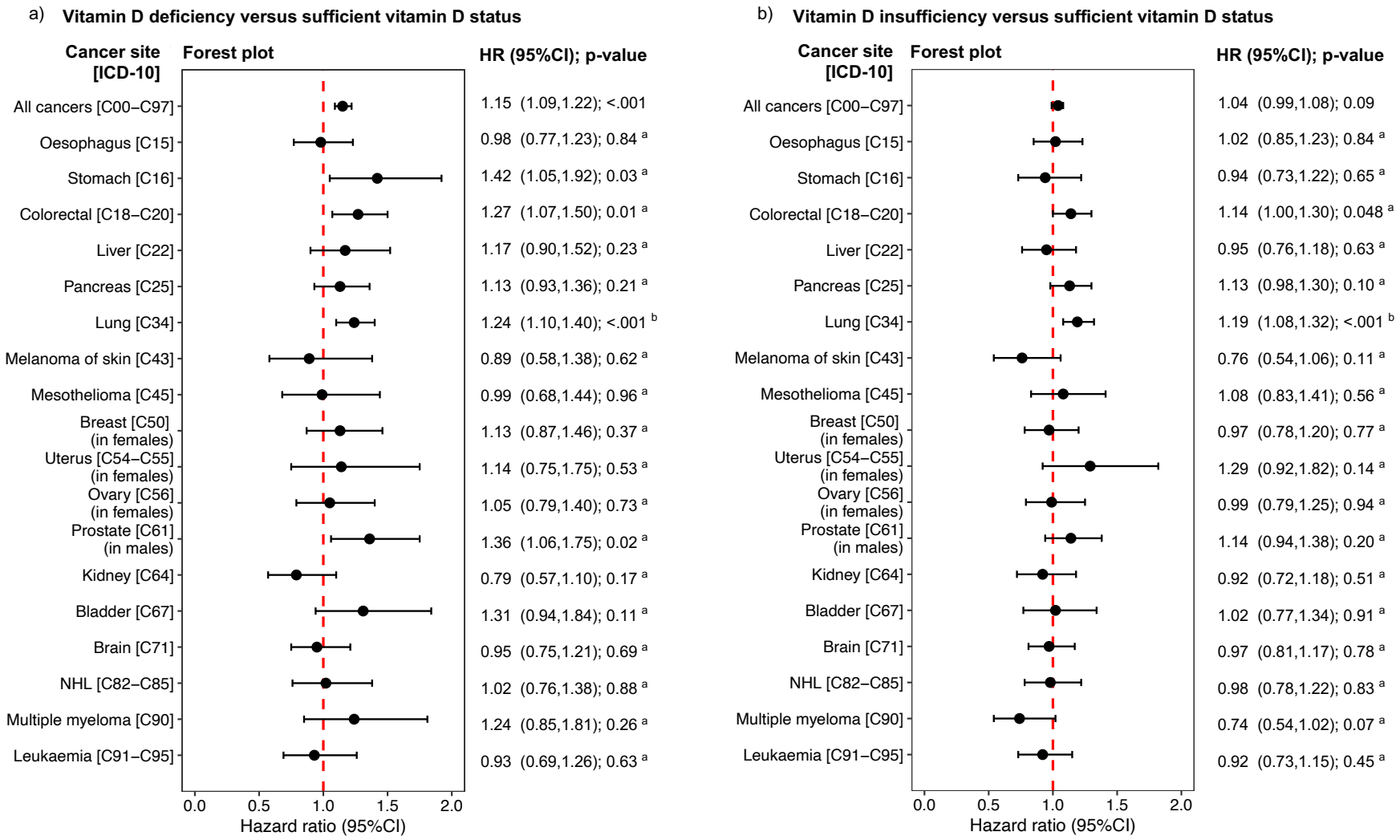

Figure 5. Association of vitamin D deficiency (a) and insufficiency (b) (compared to sufficient vitamin D status) with total cancer mortality and cancer mortality due to 18 cancer types in the UK Biobank

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma

Models adjusted for all covariates in model 5: age, sex, skin colour, latitude of study center and calendar month of blood draw, socio-economic factors (education, Townsend deprivation index, no of individuals in household and household income), life-style factors (smoking, alcohol consumption, physical activity, frequency of visiting friends/family and consumption of oily fish, cereal, processed meat, milk, bread, spread, time spend outdoors in summer and winter, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use), weight variables (body mass index and waist circumference), diseases and disease symptoms (diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, arthritis, gout, Parkinson, depressed mood, and tiredness/lethargy), biomarkers (estimated glomerular filtration rate, HbA1c, HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein, forced expiratory volume in 1-second, and hand grip strength), and general health status (no. of drugs, no. of chronic diseases, disability, and general self-rated health).

The number of deaths and mortality rate in each group of vitamin D status are shown in Appendix 6.

[a] Not statistically significant with false discovery rate of 5% considering the n=36 statistical tests of cancer site-specific mortality made for the analysis.

[b] Also statistically significant with false discovery rate of 5% considering the n=36 statistical tests of cancer site-specific mortality made for the analysis.

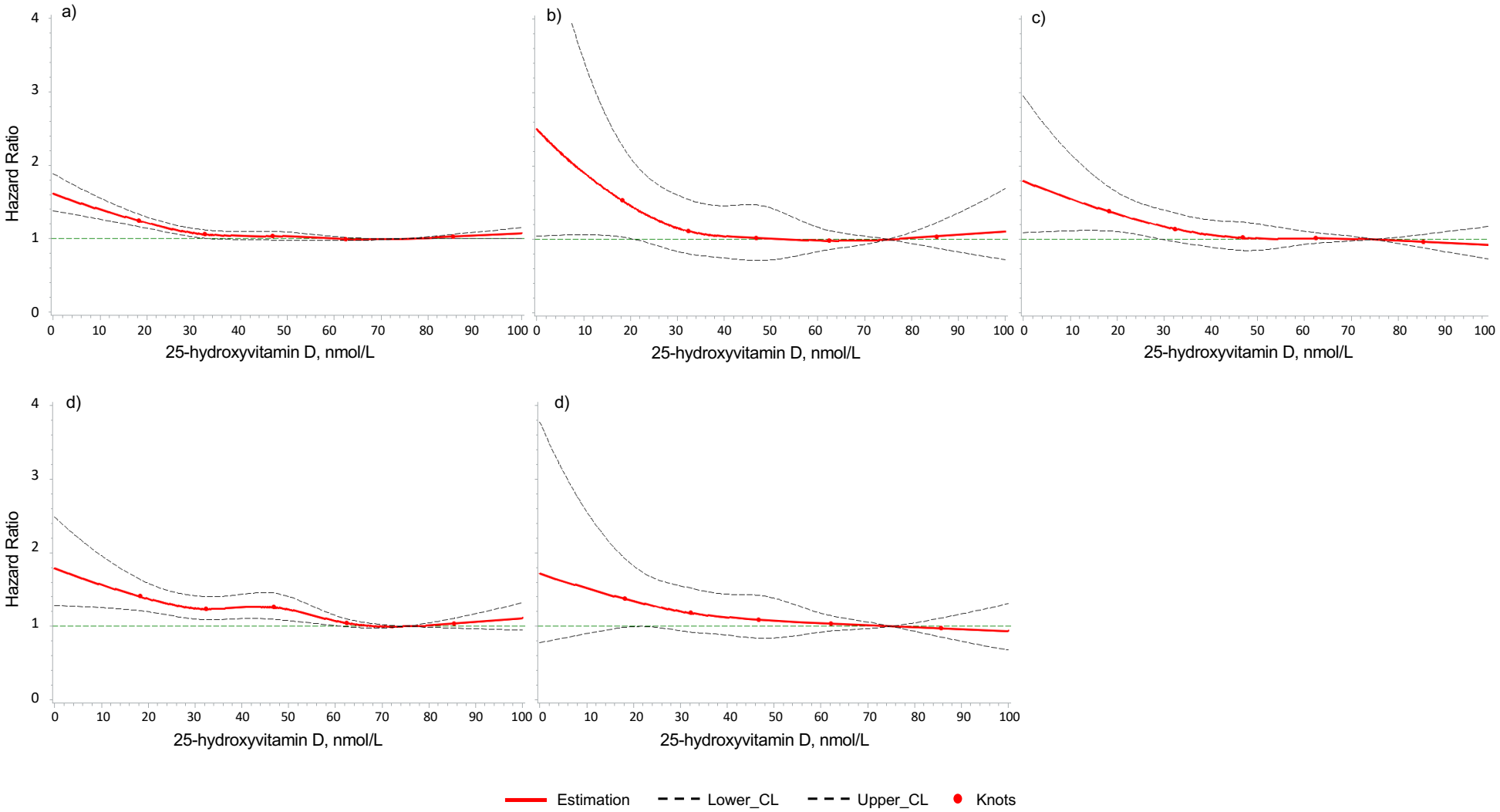

Figure 6. Adjusted dose-response relationship of serum 25-hydroxyvitamin D concentration with all-cancer mortality (a), stomach (b), colorectal (c), lung (d), and prostate cancer mortality (e)

Note: 5 knots were used and located at the 5th, 25th, 50th, 75th, and 95th serum 25-hydroxyvitamin D percentile and the 75 nmol/L was used as the reference. Horizontal lines represent the hazard ratio of 1. Solid lines are estimates of hazard ratios and dashed lines are their 95% confidence intervals. Knots are represented by dots.

The models are adjusted for all covariates used in model 5 (see legend of Figure 5).

3.2.4 Association of vitamin D supplement use with cancer mortality

Figure 7 shows the associations of vitamin D and multivitamin supplement use with total cancer and 18 cancer site-specific causes of death adjusted for all covariates in model 5 in the entire follow-up year. Compared to participants who neither used vitamin D nor multivitamins, self-reported regular use of vitamin D supplementation was associated with decreased total cancer mortality (HR, 95%CI: 0.85, 0.78-0.93), and significantly decreased lung cancer mortality (HR, 95%CI: 0.75, 0.60-0.95). Multivitamin use was also associated with 36% decreased mortality due to melanoma. Results from all models were presented in **Appendix 10**.

Sensitivity analyses, limited follow-up times of 5 and 10 years, resulted in similar findings compared to those with the entire 15 years of follow-up (**Appendix 11**). Subgroup analyses showed that female vitamin D supplement users were less likely to die from oesophagus cancer than non-users (**Appendix 12**). Furthermore, the use of multivitamin preparations was associated with higher mortality from non-Hodgkin lymphoma in males (**Appendix 13**).

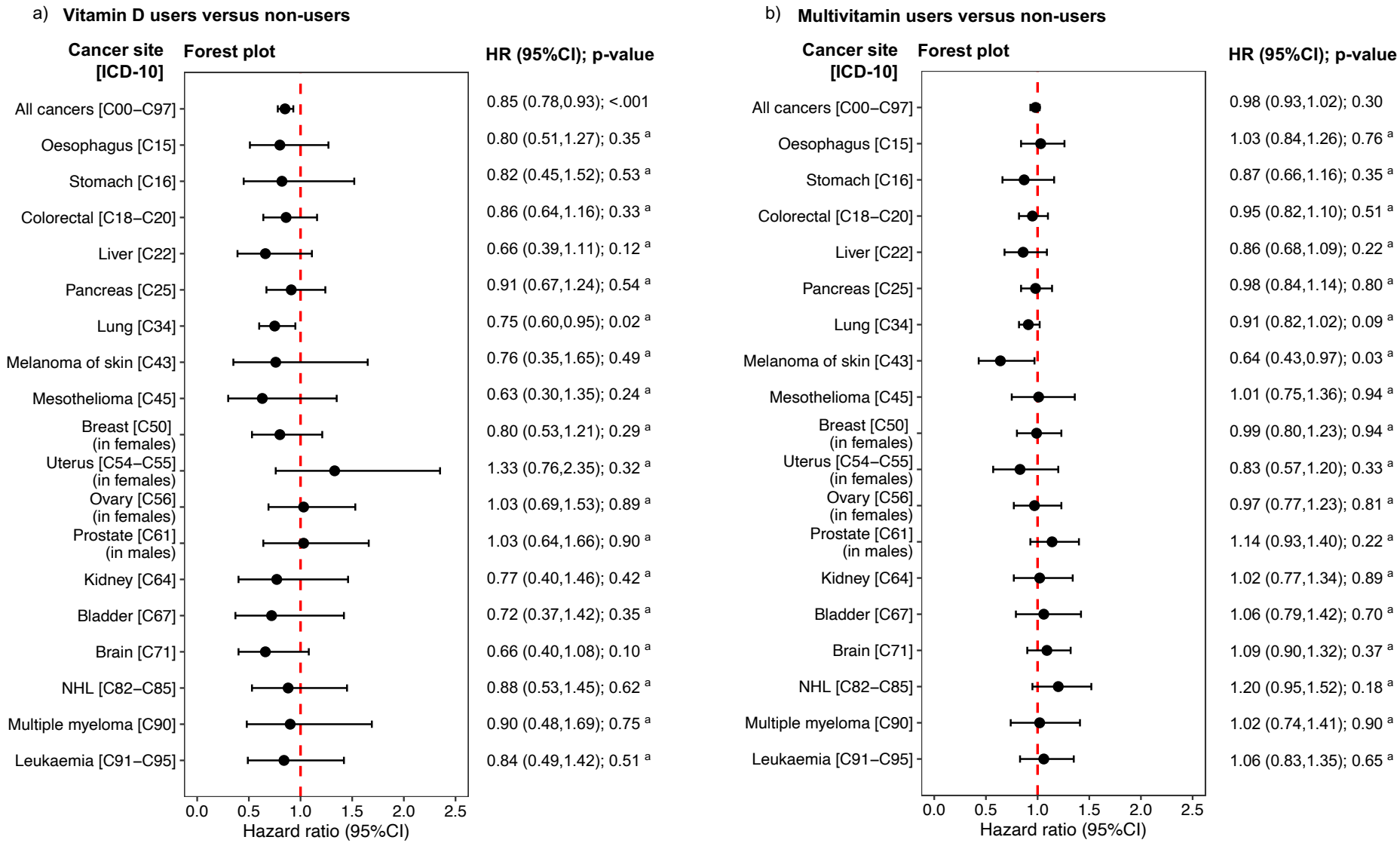

Figure 7. Association of vitamin D supplement use (a) and multivitamin use (b) with total cancer mortality and 18 types of cancer-specific mortality

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma

Models adjusted for all covariates in model 5: age, sex, skin colour, latitude of study center and calendar month of blood draw, socio-economic factors (Townsend deprivation index, no of individuals in household, and household income), life-style factors (smoking, alcohol consumption, physical activity, venturesome personality, frequency of visiting friends/family) and vitamin D specific factors (consumption of oily fish, processed meat, milk, bread, spread, time spend outdoors in summer, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use), weight variables (body mass index and waist circumference), diseases & disease symptoms (cancer, hypertension, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, osteoporosis, fractured in last 5 years, arthritis, gout, diabetes, hypothyroidism, chronic fatigue syndrome, tiredness/lethargy in last 2 weeks, dementia, Parkinson, and depressed mood), biomarkers (estimated glomerular filtration rate, C-reactive protein), general health status (disability, general self-rated health and no. of drugs), and medication intake (low dose aspirin, lipid-lowering drugs, and anti-depression drugs).

Note: The reference group is non-users of both vitamin D and multivitamin preparations. The number of deaths and mortality rate in each group of supplement use are shown in Appendix 10.

[a] Not statistically significant with false discovery rate of 5% considering the n=36 statistical tests of cancer site-specific mortality made for the analysis.

3.3 Interrelationship of 25-hydroxyvitamin D levels, biomarkers of systemic inflammatory response, and mortality

3.3.1 Description of the population included

Overall, 397,737 participants aged between 37 and 73 years (median, 58 years) were included in the study (**Table 8**). A little more than half of the participants were females (53.1%). The median serum 25(OH)D level was 46.8 nmol/L and thus, the majority of participants had either vitamin D deficiency (21.1%) or vitamin D insufficiency (34.4%). Most study participants scored 0 points for the mGPS (95.8%), HS_mGPS (77.4%), and NPS (96.1%), and only very few scored 2 points (less than 0.2%). **Appendix 14** describes all baseline characteristics used in the most comprehensively adjusted model.

Table 8. Baseline Characteristics of the Study Population (N= 397,737)

Variables	N_{total} (%) [a]	Median (IQR)
Sex		
Male	186,755 (46.9)	NA
Female	210,982 (53.1)	NA
Age (years)	397,737 (100.0)	58 (50;63)
BMI (kg/m²)	396,196 (100.0)	26.7 (24.1; 29.9)
Smoking		
Never	217,643 (54.8)	NA
Former	137,932 (34.8)	NA
Current	41,560 (10.4)	NA
Alcohol consumption[b]		
Abstainer	123,409 (31.0)	NA
Low	159,230 (40.0)	NA
Medium	67,419 (17.0)	NA
High	47,679 (12.0)	NA
Hypertension	107,411 (27.0)	NA
Diabetes	19,953 (5.1)	NA
CHD	18,739 (4.7)	NA
History of any cancer[c]	29,710 (7.5)	NA
25(OH)D levels (nmol/L)	397,737 (100.0)	46.8 (32.3; 62.4)
Vitamin D status[d]		
Vitamin D deficiency	83,929 (21.1)	NA
Vitamin D insufficiency	136,692 (34.4)	NA
Vitamin D sufficiency	177,116 (44.5)	NA
CRP based biomarkers of SIR		
CRP	397,737 (100.0)	1.3 (0.7; 2.8)
mGPS		

Variables	N_{total} (%) [a]	Median (IQR)
0	381,157 (95.8)	NA
1	16,496 (4.2)	NA
2	84 (<0.1)	NA
HS_mGPS		
0	307,861 (77.4)	NA
1	89,728 (22.6)	NA
2	148 (<0.1)	NA
Blood cell based biomarkers of SIR		
NLR	397,737 (100.0)	2.1 (1.7; 2.8)
PLR	397,737 (100.0)	132.3 (105.4; 166.5)
LMR	397,737 (100.0)	4.2 (3.2; 5.3)
SII	397,737 (100.0)	529.0 (392.2; 716.8)
PNI	397,737 (100.0)	54.7 (52.2; 57.4)
NPS		
0	382,192 (96.1)	NA
1	14,811 (3.7)	NA
2	734 (0.2)	NA

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; BMI: body mass index; CHD: coronary heart disease; CRP: C-reactive protein; HS_mGPS: High-sensitive mGPS; IQR: interquartile range; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NA: not applicable; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SD: standard deviation; SII: systemic immune-inflammation index; SIR, systemic inflammatory response.

[a] Data from one imputed data set. Does not include missing data.

[b] Alcohol consumption: Low: Women 0-19.99 grams of ethanol per day (g/d) or men 0-39.99 g/d; Medium: Women 20-39.99 g/d or men 40-59.99 g/d; High: Women ≥ 40g/d or men ≥ 60 g/d.

[c] Any cancer except non-melanoma skin cancer.

[d] Vitamin D deficiency: 25(OH)D < 30 nmol/L; Vitamin D insufficiency: 25(OH)D 30-50 nmol/L; Vitamin D sufficiency: 25(OH)D > 50 nmol/L.

3.3.2 Disadvantageous levels of biomarkers of systemic inflammatory response and their association with mortality

During a maximum of 15 years of follow-up (median, 12.7 years), n=29,548 study participants died. **Figure 8** presents the age and sex-adjusted dose-response curves of the biomarkers of SIR with all-cause mortality. As cut-off values for the disadvantageous level, the knot of the RCS curve for each biomarker were selected at which the association had a turning point towards higher/lower mortality. These were the knots at 2.75 mg/L (75^{th} percentile) for CRP, 2.78 (75^{th} percentile) for NLR, 237 (95^{th} percentile) for PLR, 2.56 (10^{th} percentile) for LMR, 717 (75^{th} percentile) for SII, and 50 (10^{th} percentile) for PNI. levels above the cut-offs for CRP, NLR, PLR, and SII were considered as disadvantageous, while levels below

the cut-offs for LMR and PNI were also considered disadvantageous. This is because the latter two biomarkers were found to be inversely associated with mortality, as expected. An exception was made for the PLR, which in contrast to the previous studies showed higher mortality at low PLR levels than at high PLR levels (Templeton et al. 2014). Furthermore, there was no clear turning point at higher levels between 150 and 300, which were used as cut-off values in the previous literature (Templeton et al. 2014). Thus, to be comparable with previous studies, the knot at the 95th percentile (PLR=237) was preferred.

The results show that disadvantageous levels of all biomarkers of SIR were strongly associated with increased all-cause mortality, CVD mortality, cancer mortality, and respiratory disease mortality in age and sex-adjusted models (**Table 9**). With further adjustment for BMI and waist circumference, the strength of the associations of CRP-based biomarkers of SIR with mortality was a little attenuated while this was not observed for the blood cell count-based biomarkers. After further adjustment for vitamin D status, the strength of the association between all biomarkers of SIR and mortality outcomes did not change to any relevant extent.

Subgroup analyses by age and sex are presented in **Appendix 15** and **16**, respectively. The associations of CRP-based biomarkers of SIR with all mortality outcomes were slightly stronger in subjects aged 40-64 years than in those aged 65-69 years. For blood count-based biomarkers, no consistent age difference was observed. Regarding sex differences, the CRP-based biomarkers of SIR showed stronger associations with all-cause, CVD and cancer mortality in males than in females, whereas the associations with respiratory disease mortality were comparable. The associations of blood cell count-based biomarkers of SIR with mortality outcomes were mostly comparable between the sexes for all mortality outcome.

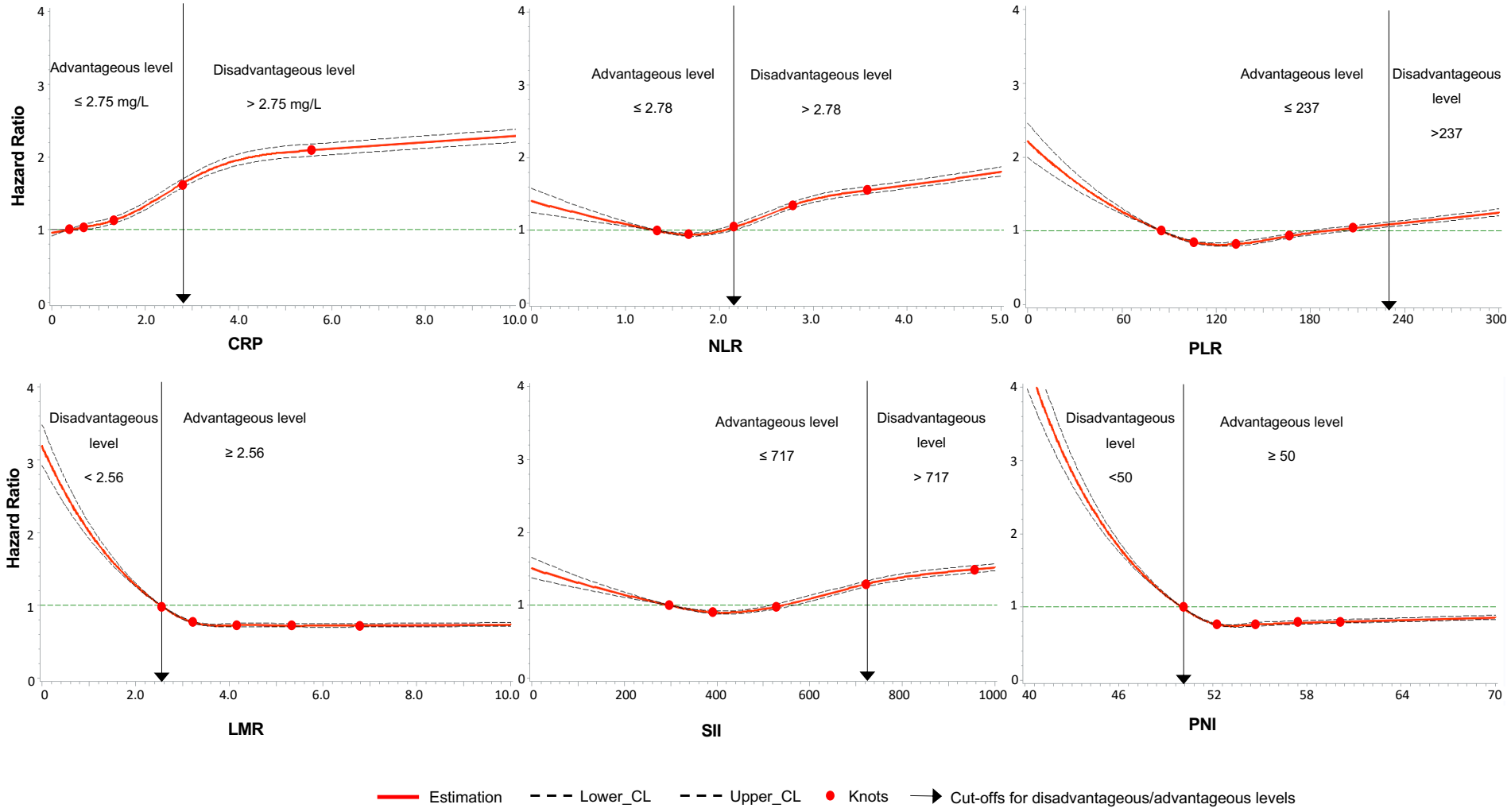

Figure 8. Age and sex adjusted dose–response relationships of biomarkers of systemic inflammatory response with all-cause mortality

Abbreviations: CRP, C-reactive protein; LMR, lymphocyte to monocyte ratio; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; PNI, prognostic nutritional index; SII, systemic immune inflammation index.

Note: Restricted cubic splines with 5 knots, located at the 10th, 25th, 50th, 75th, and 90th percentiles of the biomarkers, were used to create the figure. These knots are represented by dots. The Y-axis represents the adjusted hazard ratio for all-cause mortality. The X-axis represents the measurement values of the respective biomarker. Horizontal green lines represent the hazard ratio of 1. Solid lines are estimates of hazard ratios and the dashed lines represent their 95% confidence intervals.

Table 9. Associations of dichotomized biomarkers of systemic inflammatory response with all-cause and cause-specific mortality

Mortality	Biomarkers of systemic inflammatory response, HR (95%CI), N = 397,737								
	CRP > 2.75 mg/L	**mGPS** ≥ 1	**HS_mGPS** ≥ 1	**NLR** > 2.78	**PLR** > 237	**LMR** < 2.56	**SII** > 717	**PNI** < 50	**NPS** ≥ 1
All-cause mortality (N_{deaths}=29,548)									
Adjusted for age and sex	1.76 (1.72, 1.80)	2.18 (2.10, 2.27)	1.77 (1.73, 1.82)	1.48 (1.45, 1.52)	1.54 (1.48, 1.61)	1.54 (1.49, 1.58)	1.48 (1.45, 1.52)	1.52 (1.47, 1.56)	2.24 (2.14, 2.34)
Plus BMI and waist circumference	1.57 (1.54, 1.61)	1.91 (1.83, 1.99)	1.59 (1.55, 1.64)	1.47 (1.43, 1.51)	1.62 (1.55, 1.69)	1.52 (1.48, 1.57)	1.47 (1.43, 1.50)	1.51 (1.46, 1.55)	2.10 (2.01, 2.19)
Plus vitamin D status	1.56 (1.52, 1.60)	1.89 (1.81, 1.97)	1.58 (1.54, 1.62)	1.46 (1.42, 1.49)	1.61 (1.54, 1.68)	1.53 (1.48, 1.57)	1.45 (1.41, 1.48)	1.50 (1.46, 1.55)	2.04 (1.95, 2.13)
CVD mortality (N_{deaths}=6,091)									
Adjusted for age and sex	2.00 (1.90, 2.11)	2.28 (2.09, 2.5)	2.04 (1.93, 2.15)	1.68 (1.60, 1.77)	1.37 (1.24, 1.52)	1.68 (1.58, 1.78)	1.64 (1.55, 1.72)	1.51 (1.41, 1.62)	2.56 (2.34, 2.80)
Plus BMI and waist circumference	1.61 (1.53, 1.70)	1.79 (1.64, 1.96)	1.64 (1.55, 1.73)	1.67 (1.58, 1.75)	1.51 (1.36, 1.67)	1.66 (1.56, 1.77)	1.61 (1.53, 1.70)	1.50 (1.40, 1.60)	2.32 (2.12, 2.54)
Plus vitamin D status	1.60 (1.51, 1.69)	1.77 (1.62, 1.94)	1.62 (1.54, 1.71)	1.65 (1.57, 1.74)	1.50 (1.35, 1.66)	1.66 (1.56, 1.77)	1.59 (1.51, 1.68)	1.50 (1.40, 1.60)	2.24 (2.05, 2.46)
Cancer mortality (N_{deaths}=14,895)									
Adjusted for age and sex	1.62 (1.57, 1.67)	1.89 (1.78, 2.01)	1.62 (1.57, 1.68)	1.30 (1.26, 1.35)	1.51 (1.42, 1.61)	1.38 (1.32, 1.45)	1.34 (1.29, 1.39)	1.38 (1.32, 1.45)	1.77 (1.66, 1.9)
Plus BMI and waist circumference	1.52 (1.47, 1.58)	1.75 (1.65, 1.86)	1.53 (1.47, 1.58)	1.30 (1.26, 1.35)	1.56 (1.47, 1.66)	1.38 (1.32, 1.44)	1.33 (1.29, 1.38)	1.39 (1.32, 1.45)	1.70 (1.59, 1.82)
Plus vitamin D status	1.52 (1.46, 1.57)	1.74 (1.64, 1.85)	1.52 (1.46, 1.57)	1.29 (1.25, 1.34)	1.56 (1.46, 1.66)	1.38 (1.32, 1.44)	1.32 (1.28, 1.37)	1.38 (1.32, 1.45)	1.67 (1.57, 1.79)
Respiratory mortality (N_{deaths}=2,086)									
Adjusted for age and sex	2.73 (2.51, 2.98)	3.73 (3.30, 4.22)	2.75 (2.52, 2.99)	2.02 (1.85, 2.20)	2.15 (1.87, 2.48)	2.03 (1.83, 2.25)	2.25 (2.06, 2.45)	1.82 (1.63, 2.03)	4.75 (4.21, 5.37)
Plus BMI and waist circumference	2.63 (2.40, 2.88)	3.25 (2.87, 3.67)	2.61 (2.39, 2.86)	1.96 (1.79, 2.14)	2.16 (1.87, 2.49)	1.97 (1.78, 2.19)	2.19 (2.01, 2.39)	1.76 (1.57, 1.96)	4.35 (3.85, 4.92)
Plus vitamin D status	2.59 (2.37, 2.84)	3.19 (2.82, 3.62)	2.56 (2.34, 2.80)	1.93 (1.77, 2.10)	2.13 (1.85, 2.46)	1.98 (1.78, 2.19)	2.14 (1.96, 2.33)	1.76 (1.58, 1.96)	4.13 (3.65, 4.67)

Abbreviations: BMI: body mass index; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; HR: hazard ratio; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

3.3.3 Association of 25-hydroxyvitamin D levels with biomarkers of systemic inflammatory response

Table 10 shows the cross-sectional associations of vitamin D deficiency and insufficiency (compared to sufficient vitamin D status) with disadvantageous levels of biomarkers of SIR in logistic regression models. In Model 1-3, which did not adjust for body weight, both vitamin D deficiency and insufficiency were consistently associated with the disadvantageous level of all CRP-based biomarkers of SIR. With adjustment for waist circumference and BMI in main Model 4, the odds ratios (ORs) were attenuated and close to the null effect value of 1. Adding waist circumference only led to almost the same results (data not shown). When additionally adjusted for diseases in Model 5, all OR were < 1.0, which could be a sign of overadjustment.

This pattern was not observed for blood cell-based biomarkers of SIR. With exception of NPS, increasing adjustment did not lead to strong attenuations in the associations with vitamin D deficiency, which remained statistically significantly associated with all blood cell count-based biomarkers of SIR in main Model 4 and the most comprehensively adjusted Model 5. With one exception of a weak, but statistically significant association of SII with vitamin D insufficiency, the latter was not associated with the blood cell-based biomarkers of SIR in main Model 4.

Subgroup analyses for age and sex were conducted only for the comparison of vitamin D deficiency and sufficiency with the main Model 4. Regarding age, no large differences were observed between older (≥ 65 years) and younger (< 65 years) study participants but PLR, LMR, and PNI were only statistically significantly associated with vitamin D deficiency in the younger age group (**Appendix 17**). Regarding sex, results for women were comparable to those in the total population (**Appendix 18**). The same applied to most biomarkers of SIR among men. However, PLR and LMR were not statistically significantly associated with vitamin D deficiency among men. In contrast, a weak, but statistically significant association of vitamin D deficiency with HS_mGPS was detected among males (OR, 95%CI: 1.05, 1.01-1.09).

Table 10. Associations of vitamin D deficiency and insufficiency with disadvantageous levels of biomarkers of systemic inflammatory response in logistic regression models, N=397,737

Biomarkers of systemic inflammatory response		**Vitamin D Deficiency**	**Vitamin D Insufficiency**	**Vitamin D Sufficiency**
		OR (95%CI), FDR	OR (95%CI), FDR	OR (95%CI)
N_{total}		83,929	136,692	177,116
CRP based	**CRP**, $N_{case >2.75 mg/L}$ (%)	25,271 (30.1)	35,106 (25.7)	38,982 (22.0)
	Model 1[a]	**1.65 (1.62, 1.69), <.001**	**1.27 (1.25, 1.29), <.001**	Ref
	Model 2[b]	**1.60 (1.56, 1.63), <.001**	**1.27 (1.24, 1.29), <.001**	Ref
	Model 3[c]	**1.37 (1.34, 1.40), <.001**	**1.18 (1.16, 1.20), <.001**	Ref
	Model 4[d]	1.01 (0.99, 1.04), 0.271	**0.97 (0.96, 0.99), 0.007**	Ref
	Model 5[e]	**0.96 (0.94, 0.99), 0.005**	**0.96 (0.94, 0.98), <.001**	Ref
	mGPS, $N_{case \geq 1}$ (%)	4,659 (5.6)	5,598 (4.1)	6,323 (3.6)
	Model 1[a]	**1.65 (1.59, 1.73), <.001**	**1.17 (1.13, 1.22), <.001**	Ref
	Model 2[b]	**1.55 (1.48, 1.62), <.001**	**1.15 (1.11, 1.20), <.001**	Ref
	Model 3[c]	**1.28 (1.22, 1.34), <.001**	**1.06 (1.02, 1.10), 0.008**	Ref
	Model 4[d]	0.97 (0.93, 1.02), 0.233	**0.90 (0.87, 0.94), <.001**	Ref
	Model 5[e]	**0.92 (0.88, 0.97), 0.002**	**0.89 (0.86, 0.93), <.001**	Ref
	HS_mGPS, $N_{case \geq 1}$ (%)	23,179 (27.6)	31,694 (23.2)	35, 003 (19.8)
	Model 1[a]	**1.68 (1.64, 1.71), <.001**	**1.27 (1.25, 1.29), <.001**	Ref
	Model 2[b]	**1.62 (1.58, 1.65), <.001**	**1.26 (1.24, 1.29), <.001**	Ref
	Model 3[c]	**1.38 (1.35, 1.42), <.001**	**1.18 (1.16, 1.20), <.001**	Ref
	Model 4[d]	1.03 (1.00, 1.05), 0.059	**0.97 (0.95, 0.99), 0.006**	Ref
	Model 5[e]	0.97 (0.95, 1.00), 0.050	**0.96 (0.94, 0.98), <.001**	Ref
Blood cell based	**NPS**, $N_{case \geq 1}$ (%)	4,506 (5.4)	5,187 (3.8)	5,852 (3.3)
	Model 1[a]	**1.67 (1.60, 1.75), <.001**	**1.16 (1.11, 1.20), <.001**	Ref
	Model 2[b]	**1.54 (1.47, 1.61), <.001**	**1.13 (1.09, 1.17), <.001**	Ref
	Model 3[c]	**1.23 (1.17, 1.29), <.001**	1.04 (1.00, 1.08), 0.097	Ref
	Model 4[d]	**1.14 (1.09, 1.20), <.001**	0.99 (0.96, 1.04), 0.817	Ref
	Model 5[e]	**1.13 (1.07, 1.18), <.001**	1.01 (0.97, 1.06), 0.534	Ref
	NLR, $N_{case >2.78}$ (%)	22,111 (26.3)	33,797 (24.7)	43,264 (24.4)
	Model 1[a]	**1.17 (1.15, 1.20), <.001**	**1.03 (1.01, 1.05), 0.001**	Ref
	Model 2[b]	**1.13 (1.11, 1.16), <.001**	**1.02 (1.00, 1.04), 0.030**	Ref
	Model 3[c]	**1.08 (1.06, 1.10), <.001**	1.00 (0.98, 1.01), 0.770	Ref
	Model 4[d]	**1.09 (1.07, 1.12), <.001**	1.01 (0.99, 1.03), 0.291	Ref
	Model 5[e]	**1.11 (1.08, 1.13), <.001**	**1.03 (1.01, 1.05), 0.003**	Ref
	PLR, $N_{case >237}$ (%)	4,418 (5.3)	6,598 (4.8)	9, 009 (5.1)
	Model 1[a]	**1.07 (1.02, 1.11), 0.003**	**0.96 (0.93, 0.99), 0.013**	Ref
	Model 2[b]	1.04 (1.00, 1.08), 0.074	**0.95 (0.92, 0.98), 0.002**	Ref
	Model 3[c]	1.02 (0.98, 1.07), 0.406	**0.93 (0.90, 0.96), <.001**	Ref
	Model 4[d]	**1.13 (1.08, 1.18), <.001**	1.00 (0.96, 1.03), 0.880	Ref
	Model 5[e]	**1.17 (1.12, 1.22), <.001**	1.04 (1.00, 1.07), 0.060	Ref
	LMR, $N_{case <2.56}$ (%)	8,409 (10.0)	13,680 (10.0)	18,326 (10.4)

Biomarkers of systemic inflammatory response	**Vitamin D Deficiency**	**Vitamin D Insufficiency**	**Vitamin D Sufficiency**
	OR (95%CI), FDR	OR (95%CI), FDR	OR (95%CI)
Model 1[a]	**1.08 (1.04, 1.11), <.001**	1.00 (0.97, 1.02), 0.880	Ref
Model 2[b]	**1.05 (1.02, 1.08), 0.003**	0.99 (0.97, 1.02), 0.500	Ref
Model 3[c]	**1.04 (1.01, 1.07), 0.027**	0.98 (0.96, 1.01), 0.195	Ref
Model 4[d]	**1.05 (1.02, 1.09), 0.003**	0.99 (0.97, 1.02), 0.664	Ref
Model 5[e]	**1.06 (1.03, 1.10), 0.001**	1.01 (0.99, 1.04), 0.443	Ref
SII, $N_{case\ >717\ mg/L}$ (%)	23,213 (27.7)	33,921 (24.8)	42,207 (23.8)
Model 1[a]	**1.28 (1.26, 1.31), <.001**	**1.07 (1.05, 1.09), <.001**	Ref
Model 2[b]	**1.25 (1.22, 1.27), <.001**	**1.06 (1.04, 1.08), <.001**	Ref
Model 3[c]	**1.17 (1.15, 1.20), <.001**	**1.04 (1.02, 1.06), <.001**	Ref
Model 4[d]	**1.17 (1.14, 1.20), <.001**	**1.04 (1.02, 1.06), <.001**	Ref
Model 5[e]	**1.18 (1.15, 1.20), <.001**	**1.05 (1.04, 1.07), <.001**	Ref
PNI, $N_{case\ <50}$ (%)	8,320 (9.9)	13, 047 (9.5)	17,550 (9.9)
Model 1[a]	**1.14 (1.10, 1.17), <.001**	1.01 (0.99, 1.04), 0.391	Ref
Model 2[b]	**1.09 (1.06, 1.12), <.001**	0.99 (0.97, 1.02), 0.716	Ref
Model 3[c]	**1.07 (1.04, 1.10), <.001**	0.98 (0.96, 1.01), 0.186	Ref
Model 4[d]	**1.07 (1.04, 1.11), <.001**	0.99 (0.97, 1.02), 0.534	Ref
Model 5[e]	**1.10 (1.06, 1.14), <.001**	1.02 (0.99, 1.04), 0.218	Ref

Abbreviations: CI: confidence interval; CRP: C-reactive protein; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NA: not applicable; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; OR: odds ratio; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

Note: Numbers in **bold** indicate statistical significance of 0.05 level based on the nominal p-value.

[a] Model 1 is adjusted for age, sex, skin colour, latitude of study center and calendar month of attending the assessment center.

[b] Model 2 is adjusted for model 1 covariates plus socio-economic factors (education, Townsend deprivation index, no. of individuals in household, and household income).

[c] Model 3 is adjusted for model 2 covariates plus life-style factors (smoking, alcohol consumption, physical activity, frequency of visiting friends/family and consumption of oily fish, cereal, processed meat, milk, bread and spread), time spend outdoors in summer and winter, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use.

[d] Model 4 is adjusted for model 3 covariates plus weight variables (body mass index and waist circumference).

[e] Model 5 is adjusted for model 4 covariates plus diseases & symptoms (diabetes, stroke, cancer, coronary heart disease, chronic obstructive pulmonary disease, history of pulmonary embolism, inflammatory bowel disease, periodontitis, arthritis, osteoporosis, gout, Parkinson, depressed mood, and tiredness/lethargy), biomarkers (estimated glomerular filtration rate, HbA_{1c}, HDL cholesterol, systolic blood pressure, diastolic blood pressure, forced expiratory volume in 1-second, and hand grip strength), and general health status (no. of drugs, no of chronic diseases, disability, and general self-rated health).

3.3.4 Association of 25-hydroxyvitamin D levels with mortality

Individuals with vitamin D deficiency had 35%, 40%, 20%, and 66% statistically significantly increased all-cause mortality, CVD mortality, cancer mortality, and respiratory disease-related mortality, respectively, compared to people with sufficient vitamin D (**Table 11**). Furthermore, study participants with vitamin D insufficiency had statistically significant 9%, 12%, 5%, and 27% increased all-cause mortality, CVD, cancer, and respiratory mortality, respectively, compared to people with sufficient vitamin D. These effect estimates remained essentially unchanged when any biomarker of SIR was added to the model (the maximum HR difference was 0.03). The same pattern was observed when the continuous 25(OH)D level variable was used and the analysis was restricted to subjects with vitamin D deficiency (**Table 12**).

3.3.5 Mediation analysis

Appendix 19 and **20** present the results of the mediation analyses for vitamin D deficiency and vitamin D insufficiency, respectively. The total effects estimated for the association of vitamin D deficiency and insufficiency with the mortality outcomes were consistent with the findings shown in Table 5. The proportion mediated of the total effect of vitamin D deficiency on all-cause mortality ranged between -0.3% and 3.7% for the nine biomarkers of SIR, with a median of 1.1%. Median and range of the proportion mediated were similar for CVD mortality (median, 1.0%; range, -0.2% to 4.3%), cancer mortality (median, 1.3%; range, -0.3% to 3.9%), and respiratory disease mortality (median, 1.2%; range: -0.3% to 6.1%). The proportion mediated of the total effect of vitamin D insufficiency on the mortality outcomes was generally lower than for vitamin D deficiency. Across all biomarkers of SIR and mortality outcomes, it ranged from -3.3% to 3.6%, with a median of almost 0 (-0.25%).

Table 11. Associations of vitamin D deficiency and insufficiency with mortality outcomes when biomarkers of systemic inflammatory response are added to the main multivariate Cox proportional hazards regression model, N=397,737

	Vitamin D deficiency (n=83,929) vs. sufficient vitamin D status (n=177,116) HR (95%CI)									
Covariates / Mortality	**Model 4 [a]**	**Model 4 + CRP**	**Model 4 + mGPS**	**Model 4 + HS_mGPS**	**Model 4 + NLR**	**Model 4 + PLR**	**Model 4 + LMR**	**Model 4 + SII**	**Model 4 + PNI**	**Model 4 + NPS**
All-cause (N_{deaths}=19,545)	1.35 (1.30, 1.39)	1.35 (1.30, 1.39)	1.35 (1.30, 1.39)	1.34 (1.30, 1.39)	1.34 (1.29, 1.39)	1.34 (1.30, 1.39)	1.35 (1.30, 1.39)	1.33 (1.29, 1.38)	1.35 (1.30, 1.39)	1.34 (1.30, 1.39)
CVD (N_{deaths}=4,002)	1.40 (1.30, 1.51)	1.40 (1.30, 1.51)	1.41 (1.30, 1.51)	1.40 (1.30, 1.51)	1.39 (1.29, 1.50)	1.40 (1.30, 1.51)	1.40 (1.30, 1.51)	1.39 (1.29, 1.49)	1.40 (1.30, 1.51)	1.40 (1.30, 1.51)
Cancer (N_{deaths}=9,833)	1.20 (1.14, 1.26)	1.20 (1.14, 1.25)	1.20 (1.14, 1.26)	1.19 (1.14, 1.25)	1.19 (1.13, 1.25)	1.19 (1.14, 1.25)	1.20 (1.14, 1.25)	1.19 (1.13, 1.25)	1.19 (1.14, 1.25)	1.19 (1.14, 1.25)
Respiratory (N_{deaths}=1,374)	1.66 (1.47, 1.89)	1.66 (1.46, 1.88)	1.66 (1.47, 1.89)	1.65 (1.45, 1.87)	1.65 (1.45, 1.87)	1.66 (1.46, 1.88)	1.67 (1.47, 1.89)	1.63 (1.43, 1.85)	1.66 (1.47, 1.89)	1.65 (1.45, 1.87)
	Vitamin D insufficiency (n=136,692) vs. sufficient vitamin D status (n=177,116) HR (95%CI)									
Covariates / Mortality	**Model 4 [a]**	**Model 4 + CRP**	**Model 4 + mGPS**	**Model 4 + HS_mGPS**	**Model 4 + NLR**	**Model 4 + PLR**	**Model 4 + LMR**	**Model 4 + SII**	**Model 4 + PNI**	**Model 4 + NPS**
All-cause (N_{deaths}=21,812)	1.09 (1.06, 1.12)	1.09 (1.06, 1.13)	1.10 (1.07, 1.13)	1.09 (1.06, 1.13)	1.09 (1.06, 1.12)	1.09 (1.06, 1.13)	1.09 (1.06, 1.12)	1.09 (1.06, 1.12)	1.09 (1.06, 1.13)	1.09 (1.06, 1.13)
CVD (N_{deaths}=4,385)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.06, 1.20)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.05, 1.19)	1.12 (1.06, 1.20)
Cancer (N_{deaths}=11,414)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.10)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)	1.05 (1.01, 1.09)
Respiratory (N_{deaths}=1,425)	1.27 (1.14, 1.41)	1.27 (1.14, 1.41)	1.27 (1.14, 1.42)	1.27 (1.14, 1.41)	1.27 (1.14, 1.41)	1.27 (1.14, 1.42)	1.27 (1.14, 1.41)	1.26 (1.13, 1.41)	1.27 (1.14, 1.42)	1.28 (1.14, 1.42)

Abbreviations: CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease, HR: hazard ratio; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NA: not applicable; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

[a] The model is adjusted for covariates in Model 4 (see legend of Table 10)

Table 12. Hazard ratios for the association of 25-hydroxyvitamin D levels per 5 nmol/L with mortality outcomes among subjects with vitamin D deficiency with and without adjustment for biomarkers of systemic inflammatory response

	HR (95%CI) per 5 nmol/L increase of 25(OH)D levels in subjects with vitamin D deficiency (25(OH)D < 30 nmol/L), N=83,929									
Covariates / Mortality	**Model 4 [a]**	**Model 4 + CRP**	**Model 4 + mGPS**	**Model 4 + HS_mGPS**	**Model 4 + NLR**	**Model 4 + PLR**	**Model 4 + LMR**	**Model 4 + SII**	**Model 4 + PNI**	**Model 4 + NPS**
All-cause	0.87	0.87	0.87	0.87	0.87	0.88	0.88	0.88	0.87	0.87
(N_{deaths}= 7,736)	(0.85, 0.89)	(0.86, 0.89)	(0.85, 0.89)	(0.86, 0.89)	(0.86, 0.90)	(0.86, 0.90)	(0.86, 0.90)	(0.86, 0.90)	(0.85, 0.89)	(0.86, 0.90)
CVD	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86	0.86
(N_{deaths}= 1,706)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.90)	(0.82, 0.91)	(0.82, 0.90)	(0.82, 0.90)
Cancer	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91	0.91
(N_{deaths}= 3,481)	(0.88, 0.94)	(0.88, 0.94)	(0.88, 0.94)	(0.88, 0.95)	(0.88, 0.94)	(0.88, 0.95)	(0.88, 0.94)	(0.88, 0.95)	(0.88, 0.94)	(0.88, 0.94)
Respiratory	0.79	0.79	0.79	0.79	0.80	0.80	0.80	0.80	0.79	0.80
(N_{deaths}= 661)	(0.73, 0.86)	(0.74, 0.86)	(0.73, 0.86)	(0.73, 0.86)	(0.74, 0.86)	(0.74, 0.86)	(0.74, 0.86)	(0.74, 0.87)	(0.73, 0.86)	(0.74, 0.86)

Abbreviations: 25(OH)D: 25-hydroxyvitamin D; CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease, HR: hazard ratio; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NA: not applicable; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

[a] The model is adjusted for covariates in Model 4 (see legend of Table 10)

3.4 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with low back pain

3.4.1 Description of the population included

Table 13 presents the overview of baseline characteristics of the study population. The cross-sectional analyses in the study included n=135,934 participants with a median age of 58 years (IQR: 50-63). A slightly higher proportion of females (54%) was included compared to males. Approximately 65.4% of the studied population were overweight or obese. Individuals who had never smoked (56.6%) marginally outnumbered those who had smoked. Furthermore, a substantial proportion of participants reported experiencing hypertension (25.8%) and having had depression in their lifetime (10.8%). Less frequently reported comorbidities included diabetes (4.6%) and coronary heart disease (4.3%). The median chronic diseases per individual was 1 (IQR: 0-3). Over half of the participants (53.5%) had been diagnosed with musculoskeletal diseases by GPs in their lifetime, but only 2% had a lifetime history of an injury to the abdomen, lower back, lumbar spine, or pelvis.

Overall, 3.8% of the population had a GP diagnosis of LBP prior to baseline and reported suffering from LBP in the month before the study enrollment. Regarding vitamin D status, the median concentration of 25(OH)D was 46.3 (IQR: 32.0-61.9) nmol/L, and a significant portion of participants were identified as either vitamin D deficient (21.6%) or insufficient (34.5%). Regular use of vitamin D supplements was reported by only 4% of participants, though a further 19.7% reported regular use of multivitamin (± mineral) preparations.

Excluding the participants with LBP at baseline for the longitudinal analysis did not significantly alter the distribution of baseline characteristics. During the follow-up period, 3.3% of participants received their first LBP diagnosis.

Table 13. Baseline characteristics of study population – for low back pain study

Variables	Cross-sectional analysis (N= 135,934)	Longitudinal analysis [a] (N= 130,843)
	N (%)/Median	**N (%)/Median (IQR)**
Female sex, n (%)	73,427 (54.0)	70,690 (54.0)
Age (years), Median (IQR)	58 (50; 63)	58 (50; 63)
BMI, n (%)		
< 25	46,625 (34.3)	45,351 (34.6)
25 - < 30	57,440 (42.3)	55,317 (42.3)
≥30	31,368 (23.1)	29,703 (22.7)
Smoking, n (%)		
Never	76,907 (56.6)	74,471 (56.9)
Ever	58,990 (43.4)	56,337 (43.1)
Hypertension, n (%)	35,014 (25.8)	33,359 (25.5)
Diabetes, n (%)	6286 (4.6)	5957 (4.6)
CHD, n (%)	5797 (4.3)	5429 (4.2)
Lifetime history of depression, n (%)	14,614 (10.8)	13,842 (10.6)
No. of chronic diseases, Median (IQR)	1 (0; 3)	1 (0; 3)
Lifetime history of musculoskeletal diseases, n (%)	72,784 (53.5)	68,524 (52.4)
Lifetime history of injury to the abdomen, lower back, lumbar spine and pelvis, n (%)	2674 (2.0)	2384 (1.8)
Low back pain in the month before enrolment, n (%)	5091 (3.8)	NA
Low back pain during follow-up, n (%)	NA	4,288 (3.3)
25(OH)D concentration (nmol/L), Median (IQR)	46.3 (32; 61.9)	46.4 (32; 61.9)
Vitamin D status, n (%)		
Deficiency(<30nmol/L)	29,419 (21.6)	28,216 (21.6)
Insufficiency(30-<50nmol/L)	46,949 (34.5)	45,208 (34.6)
Sufficiency(≥50nmol/L)	59,566 (43.8)	57,419 (43.9)
Vitamin D intake, n (%)		
No	103,710 (76.3)	99,886 (76.3)
Multivitamins ± minerals	26,807 (19.7)	25,792 (19.7)
Vitamin D	5417 (4.0)	5165 (3.8)

Abbreviations: BMI: body mass index, CHD: coronary heart disease, 25(OH)D: 25-hydroxy-vitamin D, IQR: interquartile range, NA: Not applicable.

3.4.2 Covariates associated with low back pain at baseline

Two pools of variables were used to screen for factors statistically significantly associated with LBP at baseline and to be used for the full models. The first pool consisted of n=48 factors statistically significantly associated with vitamin D deficiency and the second pool included n=49 factors statistically significantly associated with vitamin D supplement use. The n=2 factors, specifically relevant for LBP (history of musculoskeletal diseases & injuries), were part of both variable pools. A

total of n=27 factors were selected by backwards selection from the pool of variables for vitamin D deficiency because they were statistically significantly associated with LBP. With respect to vitamin D supplement use, n=30 variables were selected from the pool of potential covariates because they showed a statistically significant association with LBP. These two sets of selected variables were subsequently used as the covariates for the full models for vitamin D status and vitamin D supplement use (**Table 14**). **Appendix 22** shows the associations of covariates selected from both variable pools with LBP at baseline. The median VIF of these factors in this model was 1.7, spanning from 1.0 to 6.1, which raises no concerns regarding multicollinearity as no VIF was > 10 (UCLA 2023).

Table 14. List of baseline characteristics adjusted for in the analyses on vitamin D status and vitamin D supplementation – for low back pain study

Variables	Covariate in the analyses on vitamin D status (n=27)	Covariate in the analyses on vitamin D supplementation (n=30)
SOCIO-DEMOGRAPHIC/-ECONOMIC FACTORS		
Age	Yes	Yes
Sex	Yes	Yes
Education	Yes	No
Annual household income	Yes	Yes
LIFE-STYLE FACTORS		
Smoking	Yes	Yes
Venturesome personality	No	Yes
Total physical activity	Yes	Yes
DISEASES & DISEASE SYMPTOMS		
Diabetes	Yes	Yes
Stroke	Yes	Yes
Coronary heart disease	Yes	Yes
Hypertension	No	Yes
Tiredness/lethargy in last 2 weeks	Yes	Yes
Depressed mood	Yes	Yes
History of depression	No	Yes
History of musculoskeletal disease	Yes	Yes
History of injury to abdomen, lower back, lumbar spine and pelvis	Yes	Yes
Cancer	No	Yes
BIOMARKERS		
Body mass index	Yes	Yes
Systolic blood pressure	Yes	No
Forced expiratory volume in 1-second	Yes	No
Hand grip strength	Yes	No
GENERAL HEALTH		
Disability	Yes	Yes
General self-reported health	Yes	Yes
No of chronic diseases	Yes	Yes

Variables	Covariate in the analyses on vitamin D status (n=27)	Covariate in the analyses on vitamin D supplementation (n=30)
No of drugs	Yes	Yes
Low-dose aspirin use	No	Yes
Lipid-lowering drugs use	No	Yes
Anti-depressants use	No	Yes
VITAMIN D SPECIFIC FACTORS		
Latitude of study center	Yes	Yes
Month of attending the study center	Yes	Yes
Time spent outdoors in summer	Yes	Yes
Skin color brown/black	Yes	Yes
Ease of skin tanning	Yes	Yes
Solarium/sunlamp use	Yes	Yes

3.4.3 Association of 25-hydroxyvitamin D levels with low back pain

Table 15 presents the cross-sectional and longitudinal associations of vitamin D deficiency and insufficiency (compared to vitamin D sufficiency) with LBP. Vitamin D insufficiency was not associated with LBP in any of the analyses. In the age- and sex-adjusted model, vitamin D deficiency was cross-sectionally associated with acute LBP (OR, 95%CI: 1.13, 1.05-1.22). However, this association was markedly weakened in the full model, which was adjusted for 27 covariates including BMI and diseases, resulting in an OR that was greatly attenuated and a CI that contained the null effect value, suggesting no significant association.

Throughout a median follow-up period of 8.5 years (IQR: 7.8-9.3 years; maximum: 10.8 years), 4,288 individuals received their first physician-diagnosed LBP. Contrary to the findings from the cross-sectional analysis, no longitudinal association was observed between vitamin D deficiency and LBP in the age- and sex-adjusted model. The relationship was even inverse in the fully adjusted model, which is not a biologically plausible direction because this would imply a decreased risk of LBP among individuals with vitamin D deficiency. As expected, this was a finding by chance because of multiple testing. After correcting the p-value for multiple testing, this inverse association was not statistically significant ($p>0.003125$).

In subgroup analyses by age, sex, history of depression and musculoskeletal disease, the associations of vitamin D deficiency with LBP were comparable to the findings from the total cohort (**Appendix 23**).

Table 15. Associations of vitamin D deficiency and insufficiency with low back pain, cross-sectionally and longitudinally.

	Vitamin D status							
	Deficiency			**Insufficiency**			**Sufficiency**	
	N_{case} (%)	OR/HR (95%CI)	*p*-value [a]	N_{case} (%)	OR/HR (95%CI)	*p*-value [a]	N_{case} (%)	OR/HR (95%CI)
Cross-sectional analyses								
Adjusted for age & sex	1203 (4.1)	1.13 (1.05, 1.22)	0.0008	1741 (3.7)	1.03 (0.96, 1.10)	0.42	2147 (3.6)	Ref
Adjusted for all covariates [b]	1203 (4.1)	0.95 (0.87, 1.03)	0.21	1741 (3.7)	0.97 (0.91, 1.04)	0.38	2147 (3.6)	Ref
Longitudinal analyses								
Adjusted for age & sex	874 (3.1)	0.93 (0.86, 1.01)	0.07	1533 (3.4)	1.03 (0.96, 1.10)	0.45	1881 (3.3)	Ref
Adjusted for all covariates [b]	874 (3.1)	0.87 (0.79, 0.95)	0.0032	1533 (3.4)	1.00 (0.93, 1.07)	0.96	1881 (3.3)	Ref

Abbreviations: CI: confidence interval, HR: hazard ratio, OR: odds ratio, Ref: reference.

[a] A *p*-value < 0.003125 indicates statistical significance after correction for multiple testing for 16 tests by the Bonferroni method.

[b] Model adjusted for n=27 variables listed in Table 14.

Figures 9a and 9b illustrate the dose-response relationship between serum 25(OH)D concentration and LBP in the cross-sectional and longitudinal analyses, respectively. Only the curves for the fully adjusted model are shown. In line with the findings mentioned earlier, the dose-response analyses exhibited no association cross-sectionally and a reduced risk of LBP longitudinally for 25(OH)D levels in the vitamin D deficiency range below 30 nmol/L.

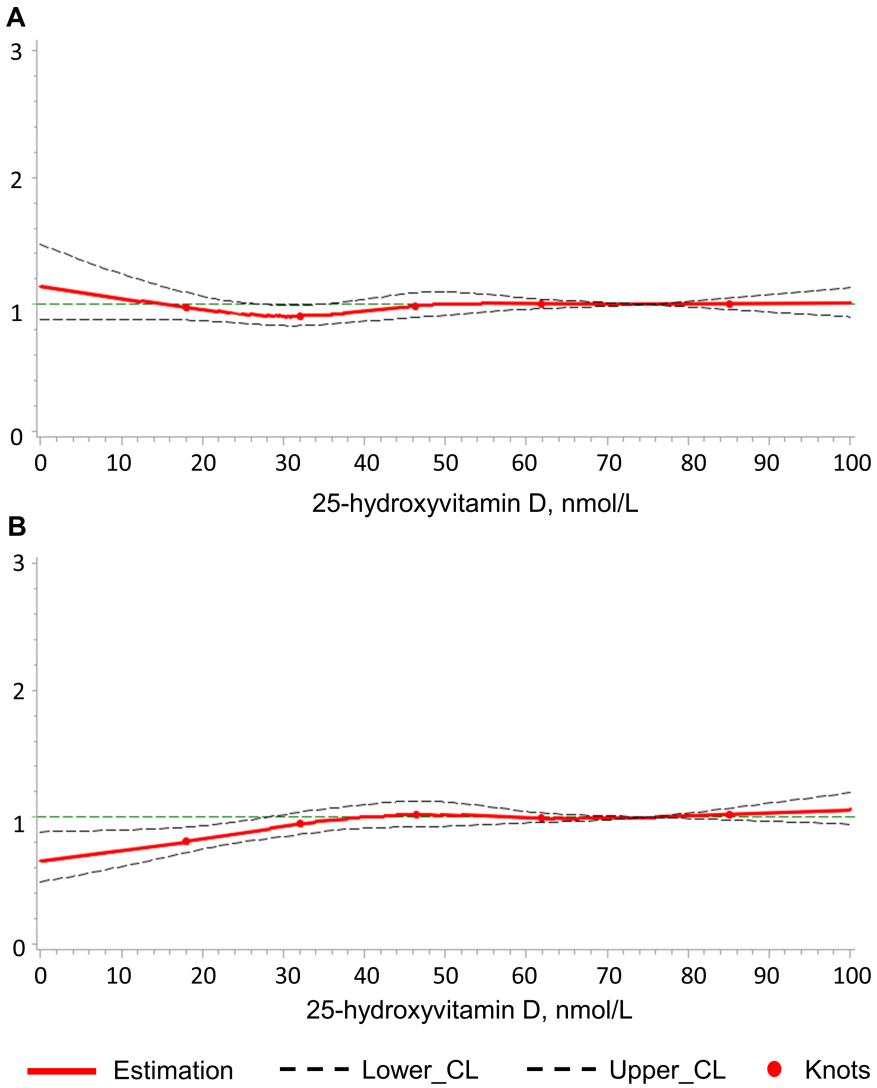

Figure 9. Dose–response relationships of 25-hydroxyvitamin D levels with low back pain, cross-sectionally (a) and longitudinally (b)

Logistic regression (a) and Cox proportional hazard regression (b) models, adjusted for 27 covariates (see Table 14), using restricted cubic splines with 5 knots positioned at the 5th, 25th, 50th, 75th, and 95th percentiles of the 25(OH)D level. The knots are depicted by dots. The horizontal green lines represent an odds ratio of 1 (a) or hazard ratio of 1 (b). The solid lines represent the estimated odds ratios or hazard ratios, and the dashed lines indicate their corresponding 95% confidence intervals.

3.4.4 Association of vitamin D supplement use with low back pain

In comparison to individuals who did not use either vitamin D or multivitamin supplements, those who used vitamin D had a higher likelihood of having LBP after adjusting for age and sex (OR, 95%CI: 1.29, 1.13-1.47) in the cross-sectional analysis (**Table 16**). This association disappeared after adjusting for all covariates. The longitudinal analyses did not show any associations of vitamin D and multivitamin supplement use with LBP.

Subgroup analyses by age, sex, history of depression and musculoskeletal disease revealed no heterogeneity in the results according to these factors (**Appendix 24**).

Table 16. Associations of vitamin D and multivitamin supplements use with low back pain, cross-sectionally and longitudinally

	Vitamin D users							
	Non-users		**Multivitamin users**			**Vitamin D users**		
	N_{case} (%)	OR/HR (95%CI)	N_{case} (%)	OR/HR (95%CI)	*p*-value [a]	N_{case} (%)	OR/HR (95%CI)	*p*-value [a]
Cross-sectional analyses								
Adjusted for age & sex	3824 (3.7)	Ref	1015 (3.8)	1.03 (0.96, 1.11)	0.42	252 (4.7)	1.29 (1.13, 1.47)	0.0001
Adjusted for all covariates [b]	3824 (3.7)	Ref	1015 (3.8)	0.97 (0.90, 1.05)	0.45	252 (4.7)	0.99 (0.86, 1.14)	0.87
Longitudinal analyses								
Adjusted for age & sex	3269 (3.3)	Ref	853 (3.3)	1.01 (0.94, 1.09)	0.69	166 (3.2)	0.99 (0.85, 1.16)	0.90
Adjusted for all covariates [b]	3269 (3.3)	Ref	853 (3.3)	0.99 (0.91, 1.07)	0.74	166 (3.2)	0.93 (0.80, 1.09)	0.38

Abbreviations: CI: confidence interval, HR: hazard ratio, OR: odds ratio, Ref: reference.

[a] A *p*-value < 0.003125 indicates statistical significance after correction for multiple testing for 16 tests by the Bonferroni method.

[b] Model adjusted for n=30 variables listed in Table 14.

4 Discussion

4.1 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with all-cause mortality, CVD mortality, cancer mortality and respiratory disease mortality

When pursuing the first aim of this dissertation, self-reported, regular vitamin D supplement use and multivitamin intake, as well as vitamin D deficiency and insufficiency measured in serum samples were observed to be consistently associated with all-cause mortality. Both vitamin D deficiency and insufficiency were associated with CVD mortality, cancer mortality, and respiratory disease mortality. The cut-off of 50 nmol/L of the 25(OH)D level worked well for all-cause mortality and cancer mortality, whereas 60 nmol/L might be the better cut-off for CVD and respiratory disease mortality. Furthermore, the broad picture emerged that self-reported vitamin D supplements and multivitamin use were also associated with cause-specific mortality outcomes but in a few analyses statistical significance was not reached. All analyses were comprehensively adjusted for 49 identified determinants of either vitamin D deficiency or vitamin D supplement use.

4.1.1 Associations of 25-hydroxyvitamin D levels with mortality

The observed associations of inadequate vitamin D serum status with mortality outcomes were congruent with previous findings from meta-analyses of cohort studies that observed inverse associations between 25(OH)D levels and all-cause mortality (Autier et al. 2014; Gaksch et al. 2017; Schöttker et al. 2013a; Schöttker et al. 2014a; Zittermann et al. 2012). Furthermore, large cohort studies from Denmark, Germany and a previous analysis with the UK Biobank demonstrated an inverse association of 25(OH)D levels with CVD, cancer and respiratory disease mortality (Afzal et al. 2014b; Fan et al. 2020; Schöttker et al. 2013b). This analysis has used the most comprehensive adjustment seen so far, which attenuated the strong association of vitamin D deficiency and insufficiency with the mortality outcomes but the associations remained statistically significant. This makes us confident that confounding is limited as far as possible and that the results are reliable.

4.1.2 Dose-response relationships of 25-hydroxyvitamin D levels with mortality

The identified L-shaped dose-response curves for 25(OH)D levels with all-cause and cause-specific mortality confirmed similar observations from previous cohort study analyses including one, which used the UK Biobank as well (Fan et al. 2020; Schöttker et al. 2013b; Zittermann et al. 2012). Our data suggest optimal 25(OH)D cut-offs for the outcomes of all-cause mortality, CVD mortality, cancer mortality and respiratory disease mortality of 50, 60, 30 and 60 nmol/L, respectively. In clinical practice, all-cause mortality will be the most relevant outcome for most patients and for this composite outcome, our results supported the cut-off for vitamin D insufficiency of 50 nmol/L suggested by the Institute of Medicine (Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011). Patients at increased risk to die from pre-existing cardiovascular or respiratory diseases may profit from aiming for a higher 25(OH)D level of at least 60 nmol/L.

4.1.3 Determinants of vitamin D deficiency and vitamin D supplement use

In addition, the large amount of data collected at baseline enabled us to systematically search for independent determinants of vitamin D deficiency, vitamin D insufficiency, vitamin D supplement use and multivitamin use including vitamin D relevant aspects rarely assessed in cohort studies, such as time spent outdoors during winter and summer, ease of kin tanning, and solarium/sunlamp use. This expands the number of known determinants of vitamin D deficiency/insufficiency substantially compared to previous, smaller studies, which usually found less than ten statistically significant determinants (Duarte et al. 2020; Giovannucci et al. 2006; Larose et al. 2014). Overall, 49 determinants were identified for vitamin D deficiency and vitamin D supplement use each in the UK Biobank of which most overlapped but not always had the same directions of the associations. Some differences are irrelevant such as that vitamin D deficiency is associated with systolic and diastolic blood pressure but vitamin D supplement use with hypertension. The high number of determinants and the large overlap in the determinants with often different directions of associations can be explained by the fact that both are associated with the general health status. However, in different directions: compared to subjects with self-reported excellent health status, subjects with self-reported poor health status had 77% higher odds to have vitamin D deficiency but 19% lower odds to be vitamin D supplement user.

4.1.4 Association of vitamin D supplement use with mortality

Meta-analyses of RCTs have shown that vitamin D supplementation is associated with lower risks of all-cause mortality, cancer mortality, and respiratory tract infections (Autier et al. 2017; Bjelakovic et al. 2014; Keum et al. 2019; Martineau et al. 2017). Nevertheless, this study aimed to assess whether these results from well-defined clinical trial settings could be translated into real-world evidence. Strikingly, the effectiveness of regular vitamin D supplement use for reducing all-cause mortality by 10% (HR 95%CI: 0.90, 0.85-0.96) was observed to be more pronounced compared to the efficacy of 6% all-cause mortality reduction by vitamin D_3 interventions reported from a meta-analysis of 38 RCTs (Relative risk [RR], 95%CI: 0.94, 0.91-0.98) (Bjelakovic et al. 2014). Regarding cancer mortality, a meta-analysis of 5 RCTs concluded that vitamin D supplementation could reduce cancer mortality by 13% (RR, 95%CI: 0.87, 0.79-0.96) (Keum et al. 2019), which is slightly higher than this observational study that observed 11% cancer mortality reduction (HR, 95%CI: 0.89, 0.82-0.97). Last, a strong reduction in respiratory mortality of 29% among vitamin D users was observed. As no meta-analysis of RCTs is available for this outcome, a comparison was made between the results and that available for the outcome “acute respiratory tract infection”. In the meta-analysis of Martineau et al., a 12% risk reduction (RR, 95%CI: 0.88, 0.81-0.96) of acute respiratory tract infections was observed as the pooled effect of 25 RCTs (Martineau et al. 2017). This study results suggest that this efficacy of vitamin D against acute respiratory tract infections may translate into even higher effectiveness with respect to respiratory disease mortality reduction in the real world.

4.1.5 Mechanisms for an effect of vitamin D on mortality

There are manifold mechanisms of how vitamin D supplementation could have an effect on all-cause mortality. The active form of vitamin D, $1,25(OH)D_2$ binds to the vitamin D receptor, which is expressed in various tissues (Holick 2007). The various biological responses do not only affect the musculoskeletal system such as calcium homeostasis, osteoblast differentiation, and matrix calcification, but also the immune (boosting of cellular innate and adaptive immunity), intestinal-digestive, respiratory, cardiovascular, and endocrine system (Aranow 2011; Autier and Gandini 2007; Bouillon et al. 2006; Brown et al. 1999; Di Rosa et al. 2011; Feldman et al. 2014; Gallagher 2021; Hansdottir and Monick

2011; Veldman et al. 2000), which may explain the observed reduced all-cause mortality and respiratory mortality among vitamin D users. Evidence from cellular studies and animal models might also explain why vitamin D use was associated with reduced cancer mortality. Vitamin D was shown to inhibit carcinogenesis and mitigate tumor development, as well as reduce the aggressiveness and metastatic tendency of tumors (Feldman et al. 2014; Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin and Calcium 2011).

4.1.6 Strengths and limitations

This investigation has strengths and limitations. This is the largest cohort study so far to examine the association between vitamin D status and mortality outcomes, and the first to address the associations of vitamin D supplement use with mortality in a large cohort of community-dwelling older adults. A strength of this dataset is that not only data on prescribed vitamin D but also on vitamin D from OTC (as a single ingredient or in multivitamin preparations) are available because the latter is much more frequent. The large range of 49 independent determinants of vitamin D deficiency and 49 of vitamin D supplement use included in the models, of which most overlapped, reduced confounding by the maximal possible extent. However, it should be noted that residual confounding cannot be completely excluded in observational studies. This study also has limitations. First, UK Biobank is not a representative sample of the UK's population with a certain "healthy volunteer" bias as only people living nearby the study centers were invited and a low response rate was achieved (5.5%) (Batty et al. 2020). Nonetheless, the scientific exposure-disease inference could be granted by the large size and heterogeneity of exposure measures and generalized to a wider population (Fry et al. 2017). Secondly, medication adherence data were not available and data on regular use of self-medication with vitamin D and multivitamin supplements was self-reported and assessed only at the baseline. Moreover, information on the chemical properties (e.g. vitamin D_2 or D_3) and dosage of vitamin D supplements were not available in the analysis. Thus, further investigations are required to add details on the effectiveness of vitamin D supplement use on mortality stratified by chemical entity and dose.

The results of this study from the UK Biobank are generalizable for European countries without widespread vitamin D food fortification. Results in countries with food fortification, a different extent of sun exposure, and a higher proportion of Non-White ethnicity may be different.

4.2 Associations of serum 25-hydroxyvitamin D levels and vitamin D supplement use with 18 cancer site-specific cancer

With the data of 411,436 UK Biobank participants, the association of vitamin D insufficiency and deficiency, as well as the association of vitamin D supplement use with total cancer mortality and the mortality specific to 18 different cancers in the general population were investigated. Compared to people with vitamin D sufficiency, increased total cancer mortality and increased mortality due to 4 of the 18 investigated cancer types in people with vitamin D deficiency were observed, including stomach cancer, colorectal cancer, lung cancer, and prostate cancer. Furthermore, increased colorectal and lung cancer mortality in people with vitamin D insufficiency were observed. Concordantly, the results show that users of vitamin D supplements had 15% lower total cancer mortality and 25% lower lung cancer mortality than non-users, respectively.

4.2.1 Association of 25-hydroxyvitamin D levels and with cancer site-specific mortality

This study shows a substantial variability among the 18 cancer sites with respect to the association of 25(OH)D levels with cancer mortality. In comparison with the observed 15% increased total cancer mortality among subjects with vitamin D deficiency in the UK Biobank, this study showed that the association of vitamin D deficiency with cancer mortality was stronger for mortality from some specific cancers. A 42%, 27%, 24%, and 36% increased mortality from stomach, colorectal, lung, and prostate cancer were observed, respectively. In contrast, other frequent types of cancer mortality were not associated with vitamin D deficiency, such as pancreas, oesophagus, brain, breast, and ovary cancer mortality. A similar pattern was observed for vitamin D insufficiency.

This finding is generally consistent with a recent observational study from the US-National Institute of Health (NIH), which measured 25(OH)D levels of 4,038 patients with cancers from any of the following

11 sites before cancer diagnoses were made: breast, prostate, colorectum, lung, bladder, hematopoietic cancer, pancreas, kidney, endometrium, upper gastrointestinal tract, and ovary (Weinstein et al. 2022). The NIH study found that the highest quintile of 25(OH)D was associated with 17% reduced total cancer mortality and 37% reduced lung cancer mortality, compared to the lowest quintile of 25(OH)D (Weinstein et al. 2022). This is in agreement with this study. In general, the evidence for an inverse association of 25(OH)D levels with lung cancer mortality is the strongest in all cancer types as it was also observed in meta-analyses of 3 to 4 cohort studies (Feng et al. 2017; Liu et al. 2017). However, the meta-analyses did not observe an association with lung cancer survival.

Regarding mortality from other cancer sites, there is supportive evidence for this study results from other existing studies that not only lung cancer mortality but also mortality from colorectal cancer and prostate cancer might be associated with 25(OH)D levels. Dose-response meta-analyses of observational studies concluded that high 25(OH)D levels were associated with decreased mortality from prostate and colorectal cancer (Maalmi et al. 2018; Song et al. 2018). Regarding stomach cancer mortality, there is a paucity of observational studies with large cohorts that investigate the association of 25(OH)D levels with stomach cancer mortality and the existing evidence is conflicting (Khayatzadeh et al. 2015; Shah et al. 2021). However, it is noteworthy that the meta-analyses comprising studies that measured 25(OH)D levels both before and after cancer diagnosis (Khayatzadeh et al. 2015; Maalmi et al. 2018; Song et al. 2018), with the latter studies having the limitation that the 25(OH)D levels could be influenced by the cancer treatment. Thus, further studies with pre-diagnosis 25(OH)D measurements are still needed to explore these associations, especially for stomach cancer for which no other large studies are available so far (Khayatzadeh et al. 2015; Muñoz and Grant 2022; Shah et al. 2021).

4.2.2 Dose-response relationships of 25-hydroxyvitamin D levels with mortality from stomach, colorectal, lung, and prostate cancer

The patterns of the dose-response curves observed in this study for mortality from total cancer, stomach, colorectal, and prostate cancer were analogous to the observation from previous studies that showed increased total cancer mortality for 25(OH)D levels < 30 nmol/L (Schöttker et al. 2013b; Sha et al. 2023). For lung cancer mortality, the curve further showed a continued slight decrease from 30 to 60

nmol/L, which was similar to the result previously observed for respiratory disease mortality (refer to **Figure 3**). Lung cancer and chronic obstructive pulmonary disease are closely linked at a molecular level and share the same underlying predispositions (Durham and Adcock 2015), which might explain the similar dose-response relationships with 25(OH)D levels.

4.2.3 Association of vitamin D supplement use with cancer mortality

Consistent with the findings on vitamin D status, self-reported vitamin D supplement use was observed to be associated with 15% and 25% reductions in total cancer mortality and lung cancer mortality, respectively. The observed association of vitamin D supplement use with total cancer mortality is supported by evidence from meta-analyses of RCTs (Keum et al. 2019; Kuznia et al. 2023), which focused on RCTs with daily vitamin D_3 intake and observed an up to 12% reduction in cancer mortality. In contrast, use of large bolus doses of vitamin D_3 once per months or even rarer seem not to be effective (Kuznia et al. 2023). Regarding lung cancer, existing observational studies, investigating the association of vitamin D use with lung cancer mortality, are limited and remain conflicted potentially due to disparities in vitamin D sources analyzed (e.g., dietary-derived vitamin D, OTC or prescription vitamin D supplement use), confounding factors adjusted in the analyses, and the study populations (Gnagnarella et al. 2021). A US-American study, which analyzed 456 patients with early-stage non-small cell lung cancer, observed a joint effect of surgery season and dietary vitamin D intake on the survival of early-stage lung cancer with the longest survival time observed among study participants with high vitamin D intake and surgery in summer (Zhou et al. 2005). In contrast, data from UK Clinical Practice Research Datalink (CPRD) including 21,932 women did not show an association of vitamin D prescriptions with improved survival from lung cancer (Jeffreys et al. 2015).

Regarding findings from RCTs, results are contradictory for lung cancer survival which may be in part due to potential limitations, such as the lack of restriction for vitamin D-deficient populations (Pilz et al. 2022). This can be best seen in the RCT of Akiba et al., which did not detect an effect of vitamin D supplementation on survival in patients with non-small cell lung cancer but in a subgroup of early-stage adenocarcinoma patients with vitamin D deficiency at baseline (Akiba et al. 2018).

4.2.4 Potential biological mechanisms for the effect of vitamin D on cancer mortality

There are numerous possible mechanisms proposed in the scientific literature that can explain the potential effect of vitamin D on cancer prognosis. Vitamin D may modulate the entire tumorigenesis process, encompassing the initiation, progression, and metastasis, as well as the intricate cellular and microenvironmental interplay (Giammanco et al. 2015; Jeon and Shin 2018). In the early stages of tumorigenesis, vitamin D may thwart genetic mutations by inducing anti-inflammatory, antioxidant, and DNA damage repair mechanisms (Giammanco et al. 2015; Jeon and Shin 2018; Nair-Shalliker et al. 2012). Secondly, vitamin D may inhibit cancer progressions such as metastasis and angiogenesis through reducing cellular invasiveness, as well as modulating a range of cell activities including proliferation, differentiation, apoptosis, autophagy, as well as epithelial-mesenchymal transition (Gaudet et al. 2022; Giammanco et al. 2015; Jeon and Shin 2018; Nakagawa et al. 2004; Nakagawa et al. 2005). Furthermore, from a perspective of molecular metabolism, vitamin D may regulate numerous genes via direct binding to the vitamin D receptor and the subsequent modulation of key cellular proteins (Norton and O'Connell 2012). This includes the epidermal growth factor receptor, which is one of the most commonly mutated proteins found in non-small cell lung cancer, and a range of downstream members of intracellular signalling pathways that promote neoplasm growth and metastasis (Norton and O'Connell 2012; Shaurova et al. 2020).

4.2.5 Public health implications & needs for future research

In view of the above, there is increasing evidence for the need to maintain adequate 25(OH)D levels to reduce cancer mortality in the general population, especially for lung cancer. As lung cancer is often diagnosed at advanced stages, supplementing vitamin D among those with vitamin D insufficiency or deficiency before lung cancer is diagnosed might be a promising approach to reduce the burden of the disease. This could enhance the immune function in the lung and other organs already at early, pre-diagnostic lung cancer stages and inhibit tumour growth (Hansdottir and Monick 2011; Jeon and Shin 2018; Nakagawa et al. 2005). The hypothesis that vitamin D therapy needs to be initiated early to reduce cancer mortality is supported by the recently published systematic review of RCTs with individual patient data, which showed that those who initiated vitamin D_3 therapy before being diagnosed with

cancer benefited from daily vitamin D_3 supplementation by 12% lower cancer mortality (HR [95% CI]: 0.88 [0.79; 0.99]), whereas those who initiated vitamin D_3 therapy up to 5 years after the cancer diagnosis did not have improved survival (HR [95% CI]: 1.17 [0.86; 1.59]) (Kuznia et al. 2023).

In addition to the well-known benefits of sufficient 25(OH)D levels for bone health and a risk reduction for upper respiratory infections (Muñoz and Grant 2022; Pham et al. 2019; Segheto et al. 2021), this study suggests that it might also reduce premature mortality from some other cancers than lung cancer, such as stomach, colorectal, and prostate cancer mortality. Furthermore, large observational studies are required to corroborate the findings for these cancer sites. Additionally, further RCTs are needed with cancer survival as the primary outcome, which should focus on subjects with low 25(OH)D levels at baseline. Especially for lung cancer survival, such an RCT may be promising and feasible due to the high mortality rate for this cancer.

4.2.6 Strengths and limitations

Certainly, a strength of this study is the large sample size of the UK Biobank which allowed to examine the association of vitamin D status and vitamin D supplement use with mortality due to a large number of specific cancers, including less common cancer types, for the first time. As the same cohort and the same statistical methods were used across the 18 cancer types, the strengths of the associations of vitamin D deficiency and vitamin D supplement use with mortality due to these cancer types can be directly compared. However, despite the large size of the UK Biobank, the absence of statistically significant results for rarer cancer types should not be interpreted as an absence of these associations because the statistical power could still have been too low to detect them. Further studies with large case numbers of less common cancer types are still needed and meta-analyses of such studies with the currently provided results from the UK Biobank could potentially provide statistically significant findings. Other strengths of the UK Biobank, including the availability of information on the use of vitamin D supplements as OTC drugs, and the adjustment of 48 covariates to reduce confounding have been illustrated in *Chapter 4.1.6*.

This study also has limitations. Firstly, the well-known 'healthy volunteer' bias, limitations on drug adherence and detailed drug specifications, as well as constraints on other ethical generalizations, were discussed in *Chapter 4.1.6*. Moreover, due to the large number of statistical tests conducted in the subgroup analyses, statistically significant findings should only be interpreted as hypotheses that need to be tested in further studies. Of note, none of the statistical findings in the subgroup analyses were also statistically significant when the FDR was used.

4.3 Interrelationship of 25-hydroxyvitamin D levels, biomarkers of systemic inflammatory response, and mortality

With data from almost 400,000 individuals from the UK Biobank, strong cross-sectional associations of vitamin D deficiency with disadvantageous levels of all blood cell count-based biomarkers of SIR but not with the CRP-based biomarkers were observed. With exception of the SII, no biomarker of SIR was associated with vitamin D insufficiency.

Vitamin D deficiency, vitamin D insufficiency, and disadvantageous levels of all biomarkers of SIR were strongly associated with increased all-cause mortality, CVD, cancer, and respiratory disease mortality. After adjusting for each other, neither the association of vitamin D status with mortality nor the association of biomarkers of SIR with mortality were attenuated. In support of this finding, mediation analysis showed that the proportions of the total effects of vitamin D deficiency and insufficiency on all mortality outcomes mediated through biomarkers of SIR were close to 0% for most of the associations tested. The largest mediation proportion observed for all-cause mortality was 3.7% by the SII. This speaks against the hypothesis that biomarkers of SIR are on the pathway between vitamin D status and mortality outcomes.

4.3.1 Association of 25-hydroxyvitamin D levels with CRP-based biomarkers of systemic inflammatory responses

The results from the main model with adjustment of BMI and waist circumference showed that vitamin D deficiency was not associated with CRP-based biomarkers of SIR. In contrast, a cross-sectional

association has been frequently observed in other observational studies. The England Longitudinal of Ageing (ELSA) study reported an association of vitamin D deficiency with elevated levels of CRP (≥ 3 mg/L) (de Oliveira et al. 2017). Cohort studies with hospital patients also observed an inverse association between 25(OH)D and CRP levels (Hernández-Álvarez et al. 2019; Kruit and Zanen 2016). Moreover, a Mendelian randomization study with the UK Biobank population showed that genetically predicted serum 25(OH)D levels ≤ 25 nmol/L were inversely associated with serum CRP levels (Zhou and Hyppönen 2022). However, findings from meta-analyses of RCTs speak against a causal association between vitamin D supplementation and CRP in the general population. A meta-analysis of 24 RCTs did not find such an association (Mazidi et al. 2018). However, if meta-analyses of RCTs are restricted to populations with specific diseases, such as diabetes, abnormal glucose homeostasis, and psychiatric disorders, statistically significant inverse associations between vitamin D supplementation and CRP were observed (Dashti et al. 2021; Jamilian et al. 2019; Yu et al. 2018).

Taken together, this speaks for a causal association of vitamin D and CRP in specific, diseased populations, in which CRP levels are increased due to the diseases. However, this does not apply to general population cohorts like the UK Biobank, in which the association of vitamin D deficiency and CRP is confounded by body weight. One reason why the Mendelian randomization study in the UK Biobank observed an association (Zhou and Hyppönen 2022), and this study did not, may be as follows: the authors only observed an association of genetically predicted serum 25(OH)D levels and CRP in subjects with 25(OH)D levels ≤ 25 nmol/L but not at higher 25(OH)D levels. Subjects with 25(OH)D levels ≤ 25 nmol/L likely have a high disease burden because such low 25(OH)D levels are usually observed among patients with diseases.

4.3.2 Association of 25-hydroxyvitamin D levels with blood cell count-based biomarkers of systemic inflammatory responses

To my knowledge, this study is the first population-based cohort reporting that vitamin D deficiency is cross-sectionally associated with blood cell count-based biomarkers of SIR. The results of this study could be only compared to previous observational studies with diseased populations, which investigated NLR and PLR. Akbas et al. showed that PLR and NLR are increased in subjects with vitamin D

insufficiency in 4,120 hospitalized patients (Akbas et al. 2016). Furthermore, a low vitamin D status was associated with higher NLR in patients with prediabetes/diabetes, and patients admitted to intensive care units with SARS-CoV-2 Infection (Pimentel et al. 2021; Wang et al. 2021). Furthermore, there has been a first placebo-controlled trial including 106 patients hospitalized with COVID-19 that showed vitamin D supplements decreased NLR within 2 months (Maghbooli et al. 2021).

4.3.3 Can the association of vitamin D deficiency and mortality be explained by a systemic inflammatory response to adverse health conditions?

The study showed a cross-sectional association of vitamin D deficiency with disadvantageous levels of blood cell count-based biomarkers of SIR. In theory, such an association could be due to different reasons, such as 1) A disease could have caused both, inflammation and vitamin D deficiency, 2) Vitamin D deficiency could have caused the inflammation, and 3) the inflammation could have caused the vitamin D deficiency. Unfortunately, no causal interferences are possible with this observational study and the question, which, if any, of these explanations might apply cannot be answered with certainty based on the results of the study.

Nevertheless, the research question can be approached, of whether the associations of vitamin D and biomarkers of SIR with mortality are independent, with the study design. By putting them in the same Cox regression model, no attenuations of the HRs with mortality of neither biomarkers of SIR nor vitamin D status were observed. This finding was further supported by the mediation analysis, which observed very low proportions of the total effects of vitamin D deficiency and insufficiency on all mortality outcomes mediated through biomarkers of SIR. Taken together, this study does not support the hypothesis that biomarkers of SIR are on the pathway from vitamin D deficiency to mortality in the general population. However, this might be different in patient populations with high inflammation, such as individuals with cancer, diabetes mellitus, or acute cardiovascular disease (Akash et al. 2013; Alfaddagh et al. 2020; Kawai et al. 2021; Liu et al. 2018; Lontchi-Yimagou et al. 2013; Marques et al. 2021). Such disease-specific cohort studies are still needed to confirm the findings.

4.3.4 Strengths and limitations

This study has strengths and limitations. This is the largest cohort study with the most comprehensive list of biomarkers of SIR to date to examine the association between vitamin D status and biomarkers of SIR. The consistent findings for CRP-based and blood cell count-based biomarkers of SIR, as well as the correction for multiple testing limits the risk of chance findings for a single biomarker. Another strength of the study is the availability of a long-term mortality follow-up (> 10 years) and adjustment for 51 potential confounders in vitamin D analyses including rarely assessed factors such as time spent outdoors in summer. The limitation of the study including the well-known "healthy volunteer" bias in the UK Biobank and constraints on other ethical generalizations of the study findings were described in *Chapter 4.1.6*.

4.4 Associations of 25-hydroxyvitamin D levels and vitamin D supplement use with low back pain

This study used the data from over 130,000 participants in the large population-based UK Biobank cohort to investigate both the cross-sectional and longitudinal association of 25(OH)D status and vitamin D supplement use with LBP. Age- and sex-adjusted analyses indicated statistically significant associations between vitamin D deficiency and LBP, and between vitamin D supplement use and LBP in cross-sectional analyses. However, both associations disappeared after comprehensive adjustment for potential confounders. In the longitudinal analysis of vitamin D deficiency and LBP, no association with statistical significance was observed in the fully adjusted model. Neither vitamin D insufficiency nor multivitamin use were associated with LBP in any analysis.

The current evidence on the association of 25(OH)D levels with LBP predominately comes from studies with a cross-sectional design. A meta-analysis of 19 cross-sectional studies and 9 case-control studies by Zadro et al. concluded that vitamin D deficiency was associated with LBP (Zadro et al. 2017). However, most included studies had sample sizes (mostly < 1000 participants) and exhibited high heterogeneity.

A few years after the literature search date for the systematic review in March 2017, a large cross-sectional study involving 17,038 individuals from the Korean National Health and Nutrition Examination Survey was published. This survey observed an inverse association between vitamin D insufficiency and chronic LBP (OR, 95% CI: 0.77, 0.69-0.85) (Park et al. 2023) but interpreted it as a lack of an association because there is not biological explanation for such an inverse association. This conclusion also aligns with the findings from the UK Biobank and the sole other prospective study available in the literature. Heuch et al. analyzed the 25(OH)D levels of 1,683 incident LBP cases and 3,137 controls from a Norwegian community-based cohort in a nested case-control design and found no association (OR per 10 nmol/L 25(OH)D increase, 95% CI: 1.01, 0.97-1.06) (Heuch et al. 2017).

To the best of the knowledge, this study is the first to explore the association of vitamin D supplement use with LBP in a large prospective cohort study. Consistent with the findings for vitamin D status in blood samples, the results for vitamin D supplement use did not observe any association with LBP in fully adjusted models. In line with this observation, a meta-analysis of eight clinical studies by Zadro et al. showed that vitamin D supplementation was not effective in the treatment of LBP when compared with a placebo, no intervention, or other treatments (Zadro et al. 2018).

Although the role of vitamin D in LBP is plausible due to potential anti-inflammatory effects (Helde-Frankling and Björkhem-Bergman 2017) and a general role in maintaining musculoskeletal health (Mendes et al. 2022), the causes of LBP are likely too complex to be significantly influenced by vitamin D supplement use alone. LBP may arise from various factors, such as a sedentary lifestyle, psychosocial issues, injuries, comorbidities, occupational reasons, and genetic predisposition (Knezevic et al. 2021). Future investigations could explore whether vitamin D exerts an impact on distinct etiologies of LBP.

4.4.1 Strengths and limitations

This study has strengths and limitations. The large sample size is a strength, providing high statistical power to detect even weak associations. Furthermore, this is the first cohort study to investigate the longitudinal association of 25(OH)D levels and vitamin D supplement use with LBP, whereas almost all previous studies had a cross-sectional design, which could not differentiate the time sequence of

events between vitamin D deficiency/initiation of vitamin D supplement use and LBP. Another strength is obtaining information on vitamin D supplement use from both prescription and OTC medications, as vitamin D supplements are mostly obtained OTC. Furthermore, the question in the interview at baseline about LBP symptoms in the past months ascertains that the study population used for the longitudinal analysis was free of subjects with LBP, allowing investigation of true incident cases. In addition, the analyses adjusted for a large number of covariates, thereby minimizing confounding concerns. However, it is important to note that residual confounding cannot be completely disregarded given the nature of observational studies.

A recognized limitation of the UK Biobank is the "healthy volunteer" bias and the limitation on population generalization of the study findings were described in *Chapter 4.1.6*. Moreover, the UK Biobank dataset's partial linkage with primary care records led to the exclusion of approximately 55% of initial cohort participants during the participant selection process. Nonetheless, the distribution of baseline characteristics for the remaining participants in the study was strikingly comparable to that of the complete cohort (data not shown). A notable limitation is that both the 25(OH)D concentration and the regular use of vitamin D supplement use were ascertained only at the baseline. Potential changes in exposure during follow-up might have hindered observing exposure – outcome associations. However, the proportional hazards assumption was met in all longitudinal analyses, speaking for constant hazards over time and a very limited impact of this limitation on the results. Furthermore, broadly consistent findings between cross-sectional and longitudinal analyses mitigate the impact of this aspect.

4.5 Conclusion

With the data of the large, population-based UK Biobank cohort, this dissertation aims to scrutinize whether serum 25(OH)D levels and the use of vitamin D supplements are associated with various mortality outcomes, encompassing all-cause mortality, CVD mortality, respiratory mortality, total cancer mortality, and mortality specific to distinct cancer sites. Furthermore, the investigation extended to examine the interrelationship of vitamin D, biomarkers of SIR, and mortality outcomes, along with the potential association between vitamin D and LBP, a prevalent musculoskeletal disorder.

With respect to the association of vitamin D with mortality outcomes, the findings showed that the intake of self-reported, regular vitamin D supplements (mostly as OTC drug), multivitamin preparations (which almost always include vitamin D), and vitamin D deficiency and insufficiency measured in serum samples, were consistently associated with all-cause mortality. With the exception of an 11% decreased CVD mortality risk by vitamin D supplementation, which was not statistically significant, both vitamin D deficiency and vitamin D supplement use were statistically significantly associated with the major causes of death (cancer, CVD and respiratory diseases). All analyses were comprehensively adjusted for 49 identified determinants of either vitamin D deficiency or vitamin D supplement use but this can never be a guarantee for the absence of confounding in observational studies. However, the results are supported by previous results from meta-analyses of RCTs and Mendelian randomization studies, which are not prone to confounding. Taken this evidence together, a recommendation for clinical practice could be that 25(OH)D levels should be routinely tested by GPs and supplementing vitamin D in adequate doses could be favourable for those with 25(OH)D levels below 50 nmol/L.

Moreover, substantial differences in the strength of the association of vitamin D status and vitamin D supplement use with mortality from the 18 cancer sites were evident. Statistically significant associations of vitamin D deficiency with increased total cancer mortality as well as stomach, colorectal, lung, and prostate cancer specific mortality were observed. In line with the findings for vitamin D status, vitamin D supplement use was observed to be associated with 15% reduced total cancer mortality and 25% decreased lung cancer mortality. The results also suggest a potential of vitamin D supplementation for maintaining sufficient 25(OH)D levels as a measure to reduce lung cancer mortality. RCTs focusing on people with low 25(OH)D levels are required to test this hypothesis.

In consideration of the interrelationship of vitamin D, biomarkers of systemic inflammatory responses and mortality, this expansive cohort study observed cross-sectional associations of vitamin D deficiency with disadvantageous levels of blood cell count-based biomarkers of SIR. However, the strong associations of low vitamin D status with all-cause and cause-specific mortality were not attenuated when biomarkers of SIR were added to the model, and vice versa. In causal mediation analysis, the proportions of total effects of vitamin D deficiency and insufficiency on the mortality outcomes

mediated by biomarkers of SIR were mostly close to 0%. Taken together, the results suggest that low vitamin D status and disadvantageous levels of biomarkers of SIR are independently associated with all-cause and cause-specific mortality. Future studies should thoroughly evaluate these associations in a cohort of patients with specific diseases that can cause a SIR (e.g., cancer). For clinical practice, the potential of clinical interventions against both vitamin D deficiency and the underlying causes of systemic inflammation in people with both conditions should be explored.

For the final objective of this dissertation, contrary to the initial hypothesis, there was no increased risk of LBP among subjects with low 25(OH)D levels. Furthermore, there was no statistically significant reduction in the risk of LBP among users of vitamin D supplements. Therefore, the findings provide no evidence supporting a role for vitamin D status in the etiology of LBP.

Overall, this dissertation with extensive analyses from the UK Biobank cohort, showed associations between vitamin D status and vitamin D supplement use with biomarkers of SIR and multiple mortality outcomes. Despite the absence of an association of vitamin D exposure and LBP, the results for mortality underscore the importance of maintaining adequate 25(OH)D levels in the general population. It reinforces the recommendation for general practitioners to regularly assess 25(OH)D concentrations and advocate appropriate vitamin D supplementation for individuals identified as vitamin D deficient.

5 Summary

5.1 English summary

Vitamin D insufficiency and deficiency are highly prevalent in the general population of European countries. Meta-analyses of observational studies and randomized controlled trials (RCT) generally concur that the effect of vitamin D extends well beyond bone health. However, it is imperative to underscore the persisting limitations in many current studies, particularly the paucity of real-world evidence. This dissertation aimed to investigate the associations of vitamin D deficiency (defined by serum 25-hydroxyvitamin D levels (25(OH)D) < 30 nmol/L), insufficiency (25(OH)D 30 - < 50 nmol/L) and self-reported regular intake of vitamin D supplements with a range of mortality outcomes and low back pain (LBP). Furthermore, it aimed to explore whether the associations of vitamin D exposures with mortality outcomes are mediated by biomarkers of systemic inflammatory responses (SIR) to diseases (e.g. cancer). Data from the large, prospective United Kingdom (UK) Biobank were used to address these aims.

Of the included 445,601 participants, 4.3% and 20.4% of the participants reported regularly taking vitamin D or multivitamin supplements, respectively. The majority of the population had either vitamin D deficiency (21.0%) or insufficiency (34.3%). Overall, 49 independent determinants of vitamin D deficiency and also 49 independent determinants of vitamin D supplement use were detected. Cox regression models adjusting for all of these determinants showed that both vitamin D deficiency and insufficiency were strongly associated with all-cause mortality, cardiovascular disease (CVD) mortality, cancer mortality and respiratory disease mortality. Furthermore, self-reported vitamin D supplement use was significantly associated with 10%, 11%, and 29% lower all-cause mortality, cancer, and respiratory disease mortality compared non-users, respectively. An 11% decreased CVD mortality risk by vitamin D supplementation was not statistically significant. Compared to RCTs or meta-analyses of RCTs, the efficacy of vitamin D supplements in reducing mortality in this real-world evidence study was at least as good as observed in RCTs.

In the investigation for the association of vitamin D status and vitamin D supplement use with mortality from 18 cancers, vitamin D deficiency was observed to be associated with significantly increased mortality from 4 cancers: stomach, colorectal, lung, and prostate cancer. Vitamin D insufficiency was

associated with increased colorectal and lung cancer mortality. Compared to non-users, vitamin D use was associated with lower lung cancer mortality. The findings indicate that vitamin D supplement use for maintaining sufficient 25(OH)D levels may be a potential approach to reduce lung cancer mortality. Furthermore, it was observed that vitamin D deficiency was associated with disadvantageous levels of all the investigated 6 blood cell count-based biomarkers of SIR, but not with the 3 C-reactive protein-based biomarkers of SIR. Although both vitamin D deficiency and all blood cell count-based biomarkers of SIR were significantly associated with all mortality outcomes the strength of these associations was unaltered if vitamin D deficiency and biomarkers of SIR were put in the same model. Thus, vitamin D deficiency and a SIR are independently associated with all-cause and cause-specific mortality and there is no evidence for the hypothesis that systemic inflammation is on the pathway from vitamin D deficiency to mortality.

In another objective of the dissertation, I addressed the hypothesis that a low vitamin D status plays a role in LBP. Vitamin D deficiency and vitamin D supplement use were cross-sectionally associated with LBP in age- and sex-adjusted models, but these associations were not evident in comprehensively adjusted models. In longitudinal analyses, both vitamin D deficiency and vitamin D supplement use were not associated with LBP in any model after correction for multiple testing. This speaks against a role of vitamin D in the etiology of LBP.

In summary, this dissertation used data from the large UK Biobank and showed associations of vitamin D status and vitamin D supplement use with blood cell count based biomarkers of SIR, all-cause mortality, and cause-specific mortality (due to CVD, respiratory disease, total cancer as well as lung cancer), whereas the findings provide no evidence to support their association with LBP. The independent association of vitamin D deficiency and biomarkers of SIR with the mortality outcomes indicate that clinical interventions against both vitamin D deficiency and causes of systemic inflammation are needed if both conditions are present. Regarding vitamin D deficiency, routine testing of 25(OH)D concentrations by general practitioners and the appropriate intake of vitamin D supplement for those identified as vitamin D deficient or insufficient (25(OH)D < 50 nmol/L) is being recommended.

5.2 Deutsche Zusammenfassung

Vitamin-D-Mangelzustände sind in der Allgemeinbevölkerung europäischer Länder weit verbreitet. Metaanalysen von Beobachtungsstudien und randomisierten kontrollierten Studien (RCT) stimmen im Allgemeinen darin überein, dass die Wirkung von Vitamin D weit über die Knochengesundheit hinausgeht. Es besteht jedoch ein Mangel an *real-world evidence*-Studien. Ziel dieser Dissertation war es, die Zusammenhänge zwischen Vitamin-D-Mangel (definiert durch Serum-25-Hydroxyvitamin-D-Spiegel (25(OH)D) < 30 nmol/L), -Insuffizienz (25(OH)D 30 - < 50 nmol/L) und Eigenangaben zu regelmäßiger Einnahme von Vitamin-D-Nahrungsergänzungsmitteln (NEM) mit der Mortalität und Schmerzen im unteren Rückenbereich zu erheben. Darüber hinaus sollte untersucht werden, ob die Zusammenhänge zwischen der Vitamin-D-Exposition und Mortalität durch systemische Entzündungsreaktionen (SER) auf Krankheiten (z. B. Krebs) erklärt werden können. Um diese Ziele zu erreichen, wurden Daten der großen, prospektive UK Biobank ausgewertet.

Von den eingeschlossenen 445.601 Teilnehmern gaben 4,3 % bzw. 20,4 % der Teilnehmer an, regelmäßig Vitamin D bzw. Multivitaminpräparate einzunehmen. Der Großteil der Teilnehmer hatte entweder einen Vitamin-D-Mangel (21,0 %) oder eine Vitamin-D-Insuffizienz (34,3 %). Insgesamt wurden 49 unabhängige Determinanten des Vitamin-D-Mangels und auch 49 unabhängige Determinanten der Einnahme von Vitamin-D-NEM ermittelt. Cox-Regressionsmodelle, die für alle diese Determinanten adjustiert waren, zeigten, dass sowohl Vitamin-D-Mangel als auch -Insuffizienz stark mit der Gesamtmortalität, der Mortalität durch Herz-Kreislauf-Erkrankungen, der Krebsmortalität und der Mortalität durch Atemwegserkrankungen assoziiert waren. Studienteilnehmer, die Vitamin-D-NEM regelmäßig einnahmen, wiesen eine um 10 % niedrigere Gesamtmortalität, eine um 11% niedrigere kardiovaskuläre Mortalität, eine um 11 % niedrigere Krebsmortalität und eine um 29 % niedrigere Mortalität aufgrund von Atemwegserkrankungen auf als Probanden, die keine Vitamin-D-NEM einnahmen. Lediglich der Zusammenhang mit der kardiovaskulären Mortalität war nicht statistisch signifikant. Die Wirksamkeit von Vitamin-D-NEM hinsichtlich einer Mortalitätsreduktion in der Allgemeinbevölkerung war damit in dieser *real-world evidence*-Studie ähnlich hoch wie in RCTs oder Meta-Analysen von RCTs.

Bei der Untersuchung des Zusammenhangs zwischen dem Vitamin-D-Status und der Einnahme von Vitamin-D-NEM mit der Sterblichkeit aufgrund von 18 Krebsarten wurde beobachtet, dass ein Vitamin-

D-Mangel mit einer signifikant erhöhten Sterblichkeit bei 4 Krebsarten einhergeht: Magen-, Darm-, Lungen- und Prostatakrebs. Zudem war die Einnahme von Vitamin D-NEM war mit einer geringeren Lungenkrebssterblichkeit assoziiert.

Darüber hinaus wurde beobachtet, dass ein Vitamin-D-Mangel mit ungünstigen Werten aller untersuchten 6 blutbildbasierten Biomarker für SER assoziiert war, nicht jedoch mit den 3 auf dem C-reaktiven Protein-basierenden Biomarkern für SER. Obwohl sowohl ein Vitamin-D-Mangel als auch die Biomarker für SER signifikant mit allen Mortalitätsendpunkten assoziiert waren, blieb die Stärke dieser Assoziationen unverändert, wenn Vitamin-D-Mangel und die Biomarker für SER in dasselbe Modell einbezogen wurden. Somit gibt es keine Belege für die Hypothese, dass eine SER auf dem kausalen Weg vom Vitamin-D-Mangel zur Mortalität liegt.

Des Weiteren beschäftigte ich mich mit der Hypothese, ob ein niedriger Vitamin-D-Status eine Rolle bei Schmerzen im unteren Rücken spielt. Ein Vitamin-D-Mangel und die Einnahme von Vitamin-D-NEM waren in alters- und geschlechtsadjustierten Modellen querschnittlich mit diesen Rückenschmerzen assoziiert, jedoch in umfassend adjustierten Modellen waren diese Assoziationen nicht erkennbar. In Längsschnittanalysen waren sowohl der Vitamin-D-Mangel als auch die Einnahme von Vitamin-D-NEM in keinem Modell mit Schmerzen im unteren Rücken assoziiert. Dies spricht gegen eine Rolle von Vitamin D in der Ätiologie von Rückenschmerzen.

Zusammenfassend verwendete diese Dissertation Daten der großen UK Biobank und fand Assoziationen zwischen dem Vitamin-D-Status und der Einnahme von Vitamin-D-NEM mit blutbildbasierten Biomarkern für SER, der Gesamtmortalität und der ursachenspezifischer Mortalität auf (aufgrund von Herz-Kreislauf-Erkrankungen, Atemwegserkrankungen und Krebserkrankungen - insbesondere Lungenkrebs), wohingegen keine Assoziationen mit Schmerzen im unteren Rückenbereich gefunden wurden. Die unabhängigen Assoziationen von Vitamin-D-Mangel und Biomarkern für SER mit der Mortalität implizieren, dass klinische Interventionen sowohl gegen den Vitamin-D-Mangel als auch gegen die Ursachen von systemischen Entzündungen benötigt werden, wenn beide Konditionen vorliegen. Im Hinblick auf den Vitamin-D-Mangel wird eine routinemäßige Prüfung der 25(OH)D-Konzentration durch Allgemeinmediziner und die Einnahme von geeigneten Vitamin-D-NEM für Personen mit Vitamin-D-Mangel oder -Insuffizienz (25(OH)D < 50 nmol/L) empfohlen.

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7 Own publications and contributions

This dissertation uses data from the UK Biobank study. Three accepted publications and one submitted paper resulted from this dissertation. In these four papers, my involvement spanned literature review, comprehensive data analyses, interpretation of results, and the writing of manuscripts associated with this dissertation (the details are shown below). Substantial contributions from my supervisor were significantly noted in the management of the original database, and extensive revisions of the manuscripts prior publication. Additionally, co-authors provided meticulous comments on the methodology, the interpretation of the results and the discussion in each of the publications.

All the findings, including texts, tables, figures, and appendix presented in this dissertation, have been or will be published in peer-reviewed journals with high impact factors through the following four papers:

1. Sha, S., Nguyen, T. M. N., Kuznia, S., Niedermaier, T., Zhu, A., Brenner, H. and Schöttker, B. (2023). **Real-world evidence for the effectiveness of vitamin D supplementation in reduction of total and cause-specific mortality**. J Intern Med *293 (3)*, 384-397, doi: 10.1111/joim.13578.

2. Sha, S., Chen, L. J., Brenner, H. and Schöttker, B. (2023). **Associations of 25-hydroxyvitamin D status and vitamin D supplement use with mortality due to 18 frequent cancer types in the UK Biobank cohort**. Eur J Cancer *191*, 113241, doi: 10.1016/j.ejca.2023.113241.

3. Sha, S., Gwenzi, T., Chen, L. J., Brenner, H. and Schöttker, B. (2023). **About the associations of vitamin D deficiency and biomarkers of systemic inflammatory response with all-cause and cause-specific mortality in a general population sample of almost 400,000 UK Biobank participants**. Eur J Epidemiol *38 (9)*, 957-971, doi: 10.1007/s10654-023-01023-2.

4. Sha, S., Chen, L. J., Brenner, H. and Schöttker, B. (202X). **Serum 25-hydroxyvitamin D status and vitamin D supplement use are not associated with low back pain in the large UK Biobank cohort**. [submitted to journal]

In this dissertation, Chapter 1.1, 2.1, 3.1, 4.1, part of the Chapter 1 and 4.5 are derived from **the first Publication (#1)**. I contributed 90% of the literature review, 90% of data analyses, 80% of the

interpretation of results and 70% of drafting and refinement the manuscript. My supervisor, PD Dr. Ben Schöttker, made significant contributions to the revision of the manuscript and played a crucial role in proposing the methodology for variable selection.

Chapters 1.2, 2.2, 3.2, 4.2, as well as part of the Chapter 1 and 4.5 in this dissertation originate from **the second publication (#2)**. The limitation on the perspective of population generalization described in Chapter 4.1.6 is derived from this publication as well and this aspect is for all the findings in the dissertation. My own contributions to this publication include 100% of the literature review, 100% of dataset creation, 100% of the data analyses, 80% of the interpretation of results and writing of the manuscript. The manuscript was revised by my supervisor PD Dr. Ben Schöttker.

Chapters 1.3, 2.3, 3.3, 4.3, as well as part of the Chapter 1 and 4.5 of this dissertation stem from **the third publication (#3)**. My contributions to this publication encompass 100% of the literature review, 100% of dataset creation, 100% of the data analyses, and 80% of the interpretation of results and manuscript writing. The manuscript underwent revision by my supervisor, PD Dr. Ben Schöttker, who provided substantial suggestions.

Chapters 1.4, 2.4, 3.4, 4.4, and part of the Chapter 4.5 of this dissertation are grounded on **the fourth paper (#4)**. My contributions to this work encompass the entirety of the literature review, dataset creation, and data analyses, as well as 80% of the interpretation of results and manuscript writing. The manuscript underwent meticulous revision overseen by my supervisor, PD Dr. Ben Schöttker.

Further own and co-authored publications:

Chen LJ, Sha S, Brenner H, Schöttker B. **Longitudinal associations of polypharmacy and frailty with major cardiovascular events and mortality among more than half a million middle-aged participants of the UK Biobank** [under review]

Chen LJ, Sha S, Stocker H, Brenner H, Schöttker B. **Unraveling the Link between Vitamin D Status, Supplementation, and Dementia Outcomes in Over 250,000 UK Biobank Participants** [under review]

Huang, S., Sha, S., Du, W., Zhang, H., Wu, X., Jiang, C., Zhao, Y. and Yang, J. (2021). **The association between living environmental factors and adolescents' body weight: a cross-sectional study**. BMC Pediatr *21 (1)*, 572, doi: 10.1186/s12887-021-03054-8.

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Zhang, W., Usman, Y., Iriawan, R. W., Lusiana, M., Sha, S., Kelly, M. and Rao, C. (2019). **Evaluating the quality of evidence for diagnosing ischemic heart disease from verbal autopsy in Indonesia**. World J Cardiol *11 (10)*, 244-255, doi: 10.4330/wjc.v11.i10.244.

Oral presentations at scientific conferences:

- **Joint International Symposium-Vitamin D in Prevention and Therapy and Biologic Effects of Light**

  4th-6th May, 2022, Homburg, Germany

  "25 hydroxyvitamin D level and vitamin D supplement use and mortality"

- **SCIENCE@DKFZ**

  5th December, 2022, Heidelberg, Germany

  "Real-world evidence of vitamin D supplement in reducing all-cause mortality and cause-specific mortality"

Spotlight poster presentations at scientific conference:

- **The 38th International Conference of Pharmacoepidemiology 2022**

  24th-28thAugust, 2022, Copenhagen, Danmark

  "Real-world evidence of vitamin D supplement in reducing all-cause mortality and cause-specific mortality"

Media Release:

15th August, 2023

- Independent – Vitamin D intake 'may reduce cancer mortality in the population by 15%'
- Evening Standard - Vitamin D intake 'may reduce cancer mortality in the population by 15%'
- Daily Mail - Vitamin D intake `may reduce cancer mortality in the population by 15%´

Appendix

Appendix 1. Determinants of vitamin D deficiency and insufficiency levels in 445,601 UK Biobank participants

Determinants	N (%) or Mean (SD)	Association with vitamin D deficiency (n=93,435)[a]	Association with vitamin D insufficiency (n=152,963)[b]
		OR (95%CI)	OR (95%CI)
SOCIO-DEMOGRAPHIC/-ECONOMIC FACTORS			
Age (years), mean (SD)	56.5 (8.1)	0.97 (0.97-0.97)	0.99 (0.99-0.99)
Sex, n (%)			
Female	239,004 (53.6)	Ref	Ref
Male	206,597 (46.4)	0.84 (0.81-0.88)	0.77 (0.75-0.79)
Education (years), mean (SD)	3.3 (2.2)	1.08 (1.08-1.09)	1.04 (1.04-1.05)
Townsend deprivation index (points),	-1.3 (3.1)	1.25 (1.24-1.27)	1.11 (1.10-1.12)
No. of individuals in household, n (%)			
1	81,587 (18.4)	1.49 (1.44-1.53)	1.24 (1.21-1.26)
2	206,612 (46.7)	Ref	Ref
3-4	130,508 (29.5)	1.24 (1.20-1.27)	1.11 (1.09-1.13)
≥ 5	23,889 (5.4)	1.43 (1.36-1.50)	1.16 (1.12-1.21)
Annual household income (£), n (%)			
< 18,000	85,757 (22.4)	Ref	Ref
18,000 - < 52,000	196,860 (51.5)	0.90 (0.87-0.93)	0.97 (0.94-0.99)
52,000 - < 100,000	78,653 (20.6)	0.78 (0.74-0.82)	0.92 (0.89-0.94)
≥ 100,000	21,006 (5.5)	0.63 (0.60-0.68)	0.84 (0.80-0.87)
LIFESTYLE FACTORS			
Smoking, n (%)			
Never	244,534 (54.9)	Ref	Ref
Occasionally	63,266 (14.2)	1.28 (1.20-1.36)	1.09 (1.05-1.15)
Regularly	137,657 (30.9)	2.05 (1.97-2.13)	1.31 (1.27-1.35)
Alcohol consumption (g ethanol/d), n			
Abstainer	137,490 (30.9)	Ref	Ref
Women 0 - < 20 / men 0 - < 40	178,300 (40.1)	0.69 (0.67-0.71)	0.85 (0.83-0.86)
Women 20 - < 40 / men 40 - < 60	75,695 (17.0)	0.63 (0.61-0.66)	0.80 (0.78-0.82)
Women ≥ 40 / men ≥ 60	53,620 (12.0)	0.73 (0.70-0.75)	0.80 (0.78-0.83)
Total physical activity (hours/day), n			
≤ 1	67,824 (18.8)	Ref	Ref
≤ 2	147,275 (40.7)	0.85 (0.82-0.87)	0.93 (0.91-0.95)
> 2	146,501 (40.5)	0.66 (0.64-0.68)	0.80 (0.78-0.82)
Visiting friends/family, n (%)			
Almost daily	37,198 (8.4)	Ref	Ref
2-4 times/week	59,778 (13.5)	0.91 (0.87-0.95)	0.98 (0.95-1.02)
Once/week	158,310 (35.7)	0.80 (0.76-0.83)	0.90 (0.88-0.93)
Once every few months/rare	187,696 (42.4)	0.75 (0.72-0.78)	0.89 (0.86-0.92)
Oily fish consumption, n (%)			
Never/ less than once a week	195,569 (44.1)	Ref	Ref
At least once a week	247,530 (55.9)	0.73 (0.72-0.75)	0.93 (0.92-0.95)

Determinants	N (%) or Mean (SD)	Association with vitamin D deficiency (n=93,435)[a]	Association with vitamin D insufficiency (n=152,963)[b]
		OR (95%CI)	OR (95%CI)
Cereal consumption (bowls/week), n			
Never	75,863 (17.1)	Ref	Ref
< 7	198,135 (44.6)	0.88 (0.86-0.91)	0.96 (0.93-0.98)
≥ 7	170,097 (38.3)	0.72 (0.70-0.74)	0.87 (0.85-0.89)
Processed meat intake, n (%)			
Never/ less than once a week	176,446 (39.7)	Ref	Ref
At least once a week	268,206 (60.3)	0.94 (0.91-0.96)	1.01 (0.99-1.02)
Milk consumption, n (%)			
Never/rarely	14,593 (3.3)	Ref	Ref
Occasionally/regularly	430,688 (96.7)	0.89 (0.84-0.95)	0.95 (0.91-0.99)
Spread consumption, n (%)			
Never/rarely	48,214 (10.8)	Ref	Ref
Butter	160,710 (36.1)	1.14 (1.10-1.19)	1.12 (1.09-1.15)
Margarine/others	235,904 (53.0)	0.76 (0.73-0.78)	1.00 (0.97-1.02)
Preferred bread type, n (%)			
White	113,460 (27.6)	Ref	Ref
Wholemeal/wholegrain/brown	297,933 (72.4)	0.93 (0.91-0.96)	1.00 (0.98-1.02)
DISEASES & DISEASE SYMPTOMS			
Diabetes, n (%)			
No	423,235 (95.0)	Ref	Ref
Yes	22,268 (5.0)	0.85 (0.79-0.92)	0.89 (0.84-0.94)
Stroke, n (%)			
No	439,517 (98.7)	Ref	Ref
Yes	5,985 (1.3)	1.16 (1.06-1.27)	1.04 (0.97-1.11)
CHD, n (%)			
No	424,655 (95.3)	Ref	Ref
Yes	20,847 (4.7)	1.12 (1.06-1.18)	1.08 (1.04-1.12)
COPD, n (%)			
No	444,014 (99.7)	Ref	Ref
Yes	1,488 (0.3)	1.49 (1.25-1.78)	1.29 (1.13-1.48)
Osteoporosis, n (%)			
No	434,538 (97.5)	Ref	Ref
Yes	10,964 (2.5)	0.27 (0.25-0.29)	0.41 (0.39-0.43)
Arthritis, n (%)			
No	399,020 (89.6)	Ref	Ref
Yes	46,482 (10.4)	0.80 (0.77-0.83)	0.92 (0.90-0.94)
Gout, n (%)			
No	438,319 (98.4)	Ref	Ref
Yes	7,183 (1.6)	1.21 (1.11-1.31)	1.10 (1.04-1.17)
Parkinson, n (%)			
No	444,732 (99.8)	Ref	Ref
Yes	770 (0.2)	1.49 (1.20-1.85)	1.22 (1.03-1.43)

Determinants	N (%) or Mean (SD)	Association with vitamin D deficiency (n=93,435)[a]	Association with vitamin D insufficiency (n=152,963)[b]
		OR (95%CI)	OR (95%CI)
Depressed mood in last 2 weeks, n (%)			
≤ half the days	404,547 (95.1)	Ref	Ref
> half the days	21,027 (4.9)	1.12 (1.06-1.18)	1.06 (1.02-1.10)
Tiredness/lethargy in last 2 weeks, n			
≤ half the days	377,364 (87.4)	Ref	Ref
> half the days	54,417 (12.6)	1.18 (1.14-1.22)	1.12 (1.09-1.15)
BIOMARKERS			
BMI (kg/m^2), n (%)			
Underweight, < 18.5	2,285 (0.5)	1.78 (1.55-2.05)	1.23 (1.11-1.38)
Low normal weight, 18.5 - <20	8,193 (1.9)	1.30 (1.21-1.41)	1.05 (0.99-1.11)
High normal weight, 20 - < 25	137,462 (31.0)	Ref	Ref
Overweight/obesity class I: 25 - <	265,444 (59.8)	1.15 (1.12-1.19)	1.10 (1.07-1.12)
Obesity class II: 35 - < 40	22,023 (5.0)	1.38 (1.30-1.46)	1.20 (1.15-1.25)
Obesity class III: ≥ 40	8,519 (1.9)	1.63 (1.48-1.79)	1.14 (1.06-1.22)
Waist circumference (cm), mean (SD)	90.3 (13.5)	1.40 (1.37-1.43)	1.33 (1.31-1.34)
eGFR (ml/min/1,73 m^2), n (%)			
≥ 90	264,798 (59.5)	Ref	Ref
< 90	180,262 (40.5)	0.71 (0.69-0.73)	0.84 (0.82-0.85)
HbA_{1c}			
< 6	388,635 (92.0)	Ref	Ref
6 - < 6.5	17,492 (4.1)	1.31 (1.24-1.40)	1.14 (1.09-1.19)
6.5 - < 7	6,205 (1.5)	1.41 (1.28-1.55)	1.19 (1.11-1.28)
7 - < 8	5,973 (1.4)	1.60 (1.44-1.78)	1.24 (1.14-1.34)
≥ 8	4,365 (1.0)	2.22 (1.97-2.51)	1.46 (1.33-1.61)
HDL cholesterol (mg/L), n (%)			
< 40	51,481 (12.6)	Ref	Ref
≥ 40	355,779 (87.4)	0.89 (0.86-0.92)	0.94 (0.92-0.97)
SBP (mmHg), n (%)			
< 140	236,953 (53.2)	Ref	Ref
140 - < 160	140,544 (31.5)	1.07 (1.05-1.10)	1.03 (1.01-1.05)
160 - < 180	53,997 (12.1)	1.14 (1.09-1.18)	1.06 (1.04-1.09)
≥ 180	14,107 (3.2)	1.20 (1.12-1.28)	1.11 (1.06-1.16)
DBP (mmHg), n (%)			
< 90	339,695 (76.2)	Ref	Ref
90 - < 100	80,494 (18.6)	1.07 (1.04-1.11)	1.04 (1.02-1.06)
≥ 100	25,412 (5.7)	1.19 (1.13-1.25)	1.07 (1.03-1.11)
C-reactive protein (mg/L), n (%)			
< 1	176,359(39.7)	Ref	Ref
≥ 1	268,004 (60.3)	0.94 (0.92-0.97)	0.98 (0.96-0.99)
FEV1 (L), mean (SD)	2.8 (0.8)	0.83 (0.82-0.85)	0.92 (0.91-0.93)
Hand grip strength (Kg), mean (SD)	32.8 (11.3)	0.94 (0.93-0.96)	1.00 (0.99-1.02)

Determinants	N (%) or Mean (SD)	Association with vitamin D deficiency (n=93,435)[a]	Association with vitamin D insufficiency (n=152,963)[b]
		OR (95%CI)	OR (95%CI)
GENERAL HEALTH			
No. of drugs, mean (SD)	2.5 (2.7)	0.93 (0.93-0.94)	0.95 (0.95-0.95)
No. of chronic diseases, mean (SD)	2.0 (1.9)	1.04 (1.04-1.05)	1.02 (1.02-1.03)
Disability (%)			
No	416,221 (94.2)	Ref	Ref
Yes	25,804 (5.8)	1.10 (1.05-1.16)	0.97 (0.93-1.00)
General self-reported health, n (%)			
Excellent	73,647 (16.6)	Ref	Ref
Good	257,579 (58.1)	1.17 (1.13-1.20)	1.09 (1.07-1.11)
Fair	92,924 (20.9)	1.48 (1.42-1.54)	1.21 (1.18-1.24)
Poor	19,512 (4.4)	1.77 (1.66-1.89)	1.29 (1.22-1.35)
VITAMIN D SPECIFIC FACTORS			
Latitude of study center (per 1°), mean	53 (1.4)	1.19 (1.18-1.19)	1.08 (1.07-1.09)
Month of attending the study center			
1	30,525 (6.9)	Ref	Ref
2-3	78,567 (17.6)	1.19 (1.14-1.24)	1.01 (0.97-1.05)
4	38,840 (8.7)	0.84 (0.80-0.88)	0.92 (0.88-0.96)
5	46,385 (10.4)	0.33 (0.31-0.34)	0.68 (0.65-0.70)
6	46,041 (10.3)	0.09 (0.08-0.09)	0.36 (0.35-0.38)
7	38,146 (8.6)	0.04 (0.04-0.04)	0.23 (0.22-0.24)
8	33,959 (7.6)	0.03 (0.03-0.03)	0.20 (0.19-0.21)
9	32,629 (7.3)	0.04 (0.04-0.04)	0.22 (0.21-0.23)
10	38,249 (8.6)	0.10 (0.09-0.10)	0.34 (0.33-0.36)
11	37,345 (8.4)	0.27 (0.25-0.28)	0.57 (0.55-0.59)
12	24,915 (5.6)	0.51 (0.48-0.53)	0.75 (0.72-0.79)
Regular vitamin D intake, n (%)[c]			
No	335,634 (75.3)	Ref	Ref
Multivitamins ± minerals	90,782 (20.4)	0.26 (0.25-0.27)	0.55 (0.54-0.56)
OTC vitamin D	15,985 (3.6)	0.16 (0.15-0.17)	0.44 (0.42-0.45)
Prescribed vitamin D	3,200 (0.7)	0.11 (0.09-0.13)	0.44 (0.40-0.48)
Time spent outdoors in summer (h/day), n (%)			
<1	18,621 (4.4)	Ref	Ref
1-2	130,297 (31.0)	0.61 (0.57-0.64)	0.76 (0.73-0.79)
3-4	138,780 (33.0)	0.40 (0.37-0.42)	0.60 (0.57-0.62)
5-6	84,329 (20.1)	0.28 (0.26-0.29)	0.49 (0.47-0.51)
≥ 7	48,351 (11.5)	0.21 (0.19-0.22)	0.41 (0.39-0.44)
Time spent outdoors in winter (h/day),			
<1	83,784 (19.9)	Ref	Ref
1-2	238,815 (56.8)	1.06 (1.03-1.10)	1.04 (1.02-1.07)
3-4	63,540 (15.1)	1.17 (1.12-1.24)	1.11 (1.08-1.15)
≥ 5	34,094 (8.1)	1.25 (1.17-1.33)	1.16 (1.11-1.21)

Determinants	N (%) or Mean (SD)	Association with vitamin D deficiency (n=93,435)[a]	Association with vitamin D insufficiency (n=152,963)[b]
		OR (95%CI)	OR (95%CI)
Skin colour, n (%)			
Very fair	34,037 (7.7)	Ref	Ref
Fair	299,648 (68.2)	0.77 (0.74-0.79)	0.89 (0.87-0.92)
Olive	89,942 (20.5)	0.81 (0.77-0.84)	0.91 (0.88-0.93)
Brown	12,432 (2.8)	5.39 (5.01-5.81)	1.88 (1.77-2.00)
Black	3,364 (0.8)	3.45 (3.01-3.95)	1.79 (1.59-2.01)
Ease of skin tanning, n (%)			
Very tanned	94,049 (21.7)	Ref	Ref
Moderately tanned	173,095 (39.9)	1.28 (1.24-1.32)	1.16 (1.14-1.19)
Mildly/occasionally tanned	91,931 (21.2)	2.01 (1.94-2.08)	1.55 (1.51-1.59)
Never tan, only burn	74,649 (17.2)	2.25 (2.17-2.34)	1.62 (1.58-1.66)
Sunscreen/UV protection use, n (%)			
Never/rarely	44,863 (10.1)	Ref	Ref
Sometimes	148,300 (33.3)	0.63 (0.60-0.65)	0.82 (0.80-0.84)
Most of times/always	249,086 (56.0)	0.49 (0.47-0.51)	0.72 (0.70-0.74)
Do not go out in sunshine	2,666 (0.6)	1.65 (1.44-1.91)	1.24 (1.10-1.40)
Solarium/sunlamp use (times per			
Never	399,686 (90.6)	Ref	Ref
< 1	21,594 (4.9)	0.84 (0.80-0.88)	0.91 (0.88-0.94)
1 - 6	10,725 (2.4)	0.19 (0.18-0.21)	0.45 (0.43-0.47)
7 - 12	4,627 (1.1)	0.06 (0.05-0.07)	0.22 (0.21-0.24)
> 12	4,390 (1.0)	0.02 (0.01-0.02)	0.11 (0.10-0.12)

Abbreviations: BMI: body mass index, COPD: chronic obstructive pulmonary disease, CHD: coronary heart disease, SBP: systolic blood pressure, DBP: diastolic blood pressure, eGRF: estimated Glomerular filtration rate, FEV1: Forced expiratory volume in 1-second, Ref: reference.

[a] Result of multivariate logistic regression models simultaneously including all variables shown in the table. Subjects with vitamin D insufficiency were excluded.

[b] Result of multivariate logistic regression models simultaneously including with all variables shown in the table. Subjects with vitamin D deficiency were excluded.

[c] Vitamin D status was not included in the survival analysis.

Appendix 2. Determinants of vitamin D and multivitamin supplements users in 445,601 UK Biobank participants

Determinants	N (%) or Mean (SD)	Association with vitamin D intake (n=19,185) [a]	Association with multivitamin intake (n=90,782) [b]
		OR (95%CI)	OR (95%CI)
SOCIO-DEMOGRAPHIC/ECONOMIC FACTORS			
Age (years), mean (SD)	56.5 (8.1)	1.03 (1.03-1.03)	1.00 (1.00-1.00)
Sex, n (%)			
Female	239,004 (53.6)	Ref	Ref
Male	206,597 (46.4)	0.65 (0.62-0.68)	0.86 (0.84-0.88)
Townsend deprivation index (points), mean (SD)	-1.3 (3.1)	1.06 (1.04-1.08)	0.99 (0.98-1.00)
No. of individuals in household, n (%)			
1	81,587 (18.4)	1.12 (1.07-1.16)	1.18 (1.16-1.20)
2	206,612 (46.7)	Ref	Ref
3-4	130,508 (29.5)	0.91 (0.87-0.95)	0.91 (0.89-0.93)
≥ 5	23,889 (5.4)	0.85 (0.78-0.92)	0.82 (0.78-0.85)
Annual household income (£), n (%)			
< 18,000	85,757 (22.4)	Ref	Ref
18,000 - <51,999	196,860 (51.5)	1.06 (1.02-1.10)	1.04 (1.02-1.06)
≥ 52,000	99,659 (26.1)	1.14 (1.06-1.23)	1.03 (0.99-1.07)
LIFESTYLE FACTORS			
Smoking, n (%)			
Never	244,534 (54.9)	Ref	Ref
Smoker	200,923 (45.1)	0.82 (0.77-0.88)	0.88 (0.85-0.90)
Alcohol intake, n (%)			
Abstainer	137,490 (30.9)	Ref	Ref
Drinkers	307,615 (69.1)	0.90 (0.87-0.93)	0.97 (0.95-0.98)
Venturesome personality, n (%)			
No	313,159 (73.0)	Ref	Ref
Yes	115,745 (27.0)	1.29 (1.25-1.34)	1.17 (1.15-1.19)
Total physical activity (hours/day), n (%)			
≤ 1 h	67,824 (18.8)	Ref	Ref
≤ 2 h	147,275 (40.7)	1.11 (1.06-1.17)	1.08 (1.05-1.12)
> 2h	146,501 (40.5)	1.32 (1.25-1.38)	1.24 (1.20-1.28)
Visiting friend/family, n (%)			
Almost daily	37,198 (8.4)	Ref	Ref
2-4 times/week	59,778 (13.5)	0.89 (0.83-0.95)	1.00 (0.97-1.04)
Once/week	158,310 (35.7)	0.79 (0.74-0.83)	0.94 (0.92-0.97)
Once every few months/rare	187,696 (42.4)	0.75 (0.71-0.79)	0.89 (0.86-0.91)
Oily fish intake, n (%)			
Never/ less than once a week	195,569 (44.1)	Ref	Ref
At least once a week	247,530 (55.9)	1.28 (1.24-1.32)	1.17 (1.15-1.19)
Processed meat intake, n (%)			
Never/ less than once a week	176,446 (39.7)	Ref	Ref
At least once a week	268,206 (60.3)	0.82 (0.80-0.85)	0.88 (0.87-0.90)

Determinants	N (%) or Mean (SD)	Association with vitamin D intake (n=19,185) [a]	Association with multivitamin intake (n=90,782) [b]
		OR (95%CI)	OR (95%CI)
Milk intake, n (%)			
No (never/rarely)	14,593 (3.3)	Ref	Ref
Yes	430,688 (96.7)	0.72 (0.67-0.78)	0.95 (0.91-0.99)
Spread type, n (%)			
Never/rarely	48,214 (10.8)	Ref	Ref
Butter	160,710 (36.1)	0.78 (0.74-0.81)	0.93 (0.91-0.96)
Margarine/others	235,904 (53.0)	0.82 (0.78-0.86)	1.00 (0.98-1.03)
Preferred bread type, n (%)			
White	113,460 (26.4)	Ref	Ref
Brown	53,986 (12.6)	1.28 (1.20-1.36)	1.18 (1.15-1.21)
Wholemeal/wholegrain	243,947 (56.7)	1.44 (1.38-1.51)	1.39 (1.36-1.41)
Other types	18,364 (4.3)	1.79 (1.66-1.92)	1.48 (1.42-1.54)
DISEASES & DISEASE SYMPTOMS			
Cancer, n (%)			
No	410,722 (92.4)	Ref	Ref
Yes	33,575 (7.6)	1.20 (1.14-1.26)	0.98 (0.95-1.01)
Hypertension, n (%)			
No	325,573 (73.1)	Ref	Ref
Untreated hypertension	33,256 (7.5)	1.09 (1.03-1.16)	1.00 (0.98-1.03)
Treated hypertension	86,683 (19.5)	0.55 (0.52-0.57)	0.64 (0.63-0.66)
Diabetes, n (%)			
No	423,235 (95.0)	Ref	Ref
Yes	22,268 (5.0)	0.53 (0.48-0.59)	0.60 (0.57-0.63)
Stroke, n (%)			
No	439,517 (98.7)	Ref	Ref
Yes	5,985 (1.3)	0.72 (0.63-0.83)	0.69 (0.64-0.75)
CHD, n (%)			
No	424,655 (95.3)	Ref	Ref
Yes	20,847 (4.7)	0.50 (0.45-0.55)	0.59 (0.56-0.62)
COPD, n (%)			
No	444,014 (99.7)	Ref	Ref
Yes	1,488 (0.3)	0.46 (0.35-0.60)	0.69 (0.60-0.80)
Asthma, n (%)			
No	393,827 (88.4)	Ref	Ref
Yes	51,675 (11.6)	0.71 (0.68-0.75)	0.85 (0.83-0.87)
Osteoporosis, n (%)			
No	434,538 (97.5)	Ref	Ref
Yes	10,964 (2.5)	2.99 (2.83-3.16)	0.69 (0.65-0.73)
Fracture in last 5 years, n (%)			
No	401,440 (90.5)	Ref	Ref
Yes	41,926 (9.5)	1.22 (1.16-1.28)	1.02 (1.00-1.05)
Arthritis, n (%)			

Determinants	N (%) or Mean (SD)	Association with vitamin D intake (n=19,185) [a]	Association with multivitamin intake (n=90,782) [b]
		OR (95%CI)	OR (95%CI)
No	399,020 (89.6)	Ref	Ref
Yes	46,482 (10.4)	0.86 (0.82-0.90)	0.91 (0.89-0.94)
Gout, n (%)			
No	438,319 (98.4)	Ref	Ref
Yes	7,183 (1.6)	0.74 (0.64-0.86)	0.73 (0.68-0.78)
Parkinson, n (%)			
No	444,732 (99.8)	Ref	Ref
Yes	770 (0.2)	0.55 (0.39-0.75)	0.59 (0.49-0.71)
Depressed mood in last 2 weeks, n (%)			
≤ half the days	404,547 (95.6)	Ref	Ref
> half the days	21,027 (4.9)	1.11 (1.05-1.17)	1.13 (1.10-1.16)
Tiredness/lethargy in last 2 weeks, n (%)			
≤ half the days	377,364 (87.4)	Ref	Ref
> half the days	54,417 (12.6)	1.13 (1.07-1.18)	1.09 (1.07-1.12)
Chronic fatigue syndrome, n (%)			
No	443,585 (99.6)	Ref	Ref
Yes	1,917 (0.4)	1.89 (1.59-2.25)	1.76 (1.59-1.96)
Hypothyroidism, n (%)			
No	424,040 (95.2)	Ref	Ref
Yes	21,462 (4.8)	0.76 (0.71-0.81)	0.83 (0.80-0.86)
Dementia, n (%)			
No	442,933 (99.4)	Ref	Ref
Yes	2,569 (0.56)	1.86 (1.62-2.14)	2.16 (1.98-2.35)
BIOMARKERS			
BMI (kg/m^2), n (%)			
Underweight, < 18.5	2,285 (0.5)	1.34 (1.14-1.57)	1.07 (0.97-1.19)
Low normal weight, 18.5 - <20	8,193 (1.9)	1.22 (1.11-1.34)	0.98 (0.92-1.03)
High normal weight, 20 - < 25	137,462 (31.0)	Ref	Ref
Overweight: 25 - < 30	188,152 (42.4)	0.93 (0.89-0.97)	1.02 (1.00-1.04)
Obesity class I: 30 - < 35	77,292 (17.4)	0.87 (0.81-0.93)	1.00 (0.96-1.03)
Obesity class II-III: ≥ 35	30,542 (6.9)	0.79 (0.71-0.88)	0.99 (0.94-1.04)
Waist circumference (cm), mean (SD)	90.3 (13.5)	0.89 (0.86-0.92)	0.96 (0.95-0.98)
eGFR, n (%)			
≥90	264,798 (59.5)	Ref	Ref
< 90	180,262 (40.5)	0.91 (0.88-0.94)	0.90 (0.88-0.91)
C-reactive protein (mg/L), n (%)			
< 1	176,359 (39.7)	Ref	Ref
≥1	268,004 (60.3)	0.92 (0.89-0.96)	0.98 (0.96-1.00)
GENERAL HEALTH AND DRUG USE			
Disability, n (%)			
No	416,221 (94.2)	Ref	Ref

Determinants	N (%) or Mean (SD)	Association with vitamin D intake (n=19,185) [a]	Association with multivitamin intake (n=90,782) [b]
		OR (95%CI)	OR (95%CI)
Yes	25,804 (5.8)	0.77 (0.71-0.82)	0.74 (0.71-0.77)
General self-reported health, n (%)			
Excellent	73,647 (16.6)	Ref	Ref
Good	257,579 (58.1)	0.93 (0.89,0.97)	1.06 (1.04,1.09)
Fair	92,924 (20.9)	0.86 (0.81,0.91)	0.98 (0.95,1.01)
Poor	19,512 (4.4)	0.81 (0.74,0.89)	0.75 (0.72,0.79)
No. of drugs, n (%)	2.5 (2.7)	1.31 (1.30-1.32)	1.22 (1.22-1.23)
Low-dose aspirin use, n (%)			
No	382,411 (85.8)	Ref	Ref
Yes	63,091 (14.2)	0.95 (0.90-0.999)	1.02 (0.99-1.05)
Lipid-lowering drugs use, n (%)			
No	365,910 (82.1)	Ref	Ref
Yes	79,599 (17.9)	0.61 (0.58-0.65)	0.70 (0.68-0.71)
Anti-depressants use, n (%)			
No	416,140 (93.4)	Ref	Ref
Yes	29,362 (6.6)	0.66 (0.62-0.71)	0.76 (0.74-0.79)
VITAMIN D SPECIFIC FACTORS			
Latitude of study center (per 1°), mean (SD)	53 (1.4)	0.87 (0.86-0.88)	0.94 (0.93-0.94)
Month of attending in the center			
1	30,525 (6.9)	Ref	Ref
2-3	78,567 (17.6)	1.01 (0.94-1.08)	1.02 (0.98-1.05)
4	38,840 (8.7)	0.94 (0.87-1.02)	0.97 (0.93-1.01)
5-8	164,531 (36.9)	0.92 (0.86-0.98)	0.95 (0.92-0.98)
9	32,629 (7.3)	0.84 (0.78-0.91)	0.95 (0.91-0.99)
10-11	75,594 (17.0)	0.89 (0.83-0.95)	0.97 (0.94-1.01)
12	24,915 (5.6)	0.94 (0.86-1.02)	1.02 (0.98-1.06)
Time spent oudoors in summer (h/day), n (%)			
<1h	18,621 (4.4)	Ref	Ref
1-2h	130,297 (31.0)	0.91 (0.85-0.98)	0.99 (0.94-1.03)
3-4h	138,780 (33.0)	0.79 (0.74-0.85)	0.92 (0.88-0.96)
≥ 5h	132,680 (31.6)	0.75 (0.69-0.80)	0.87 (0.84-0.91)
Skin colour, n (%)			
Very fair	34,037 (7.7)	Ref	Ref
Fair	299,648 (68.2)	0.88 (0.83-0.92)	0.96 (0.93-0.99)
Olive	89,942 (20.5)	0.93 (0.87-0.99)	1.00 (0.97-1.03)
Brown	12,432 (2.8)	1.77 (1.61-1.94)	1.49 (1.42-1.57)
Black	3,364 (0.8)	1.64 (1.40-1.92)	1.59 (1.46-1.73)
Ease of skin tanning, n (%)			
Tanned (mild, moderate, or very tanned)	359,075(82.8)	Ref	Ref
Never tan, only burn	74,649 (17.2)	0.94 (0.90-0.99)	0.93 (0.91-0.95)
Sunscreen/UV protection, n (%)			
Never/less frequent	195,829 (44.0)	Ref	Ref

Determinants	N (%) or Mean (SD)	Association with vitamin D intake (n=19,185) [a]	Association with multivitamin intake (n=90,782) [b]
		OR (95%CI)	OR (95%CI)
Most of times/always	249,086 (56.0)	1.09 (1.06-1.13)	1.18 (1.16-1.20)
Use of solarium/sunlamp, n (%)			
Never	399,686 (95.3)	Ref	Ref
≤ 6x per year	10,725 (2.6)	1.14 (1.04-1.26)	1.36 (1.30-1.42)
≤ 12x per year	4,627 (1.1)	1.26 (1.09-1.47)	1.47 (1.37-1.57)
> 12x per year	4,390 (1.0)	1.45 (1.25-1.68)	1.57 (1.47-1.68)

Abbreviations: BMI: body mass index, COPD: chronic obstructive pulmonary disease, CHD: coronary heart disease, eGRF: estimated Glomerular filtration rate, Ref: reference.

[a] Result of multivariate logistic regression models simultaneously including all variables shown in the table. Multivitamin users were excluded.

[b] Result of multivariate logistic regression models simultaneously including all variables shown in the table. Vitamin D supplement users were excluded.

Appendix 3. Associations of an additional category of potentially insufficient 25-hydroxyvitamin D levels of 50-<60 nmol/L with all-cause and cause-specific mortality in 445,601 UK Biobank participants

Mortality	Serum 25(OH)D concentration			
	<30 nmol/L (n=93,435)	**30-<50 nmol/L (n=152,963)**	**50-<60 nmol/L (n= 71,939)**	**>60 nmol/L (n= 12,7264)**
	HR(95%CI)[a]	**HR(95%CI) [a]**	**HR(95%CI) [a]**	**HR (95%CI) [a]**
All-cause mortality (N_{deaths}=29,107)	1.30 (1.25; 1.35)	1.11 (1.07; 1.14)	1.02 (0.99; 1.06)	Ref
CVD specific mortality (N_{deaths}=5,943)	1.41 (1.30; 1.54)	1.20 (1.11; 1.29)	1.10 (1.01; 1.20)	Ref
Cancer mortality (N_{deaths}=15,184)	1.14 (1.08,1.21)	1.03 (0.99,1.07)	0.98 (0.93,1.03)	Ref
Respiratory disease specific mortality (N_{deaths}=2,084)	1.70 (1.47; 1.96)	1.37 (1.21; 1.56)	1.14 (0.97; 1.33)	Ref

Abbreviations: CI: confidence interval, CVD: cardiovascular disease, HR: hazard ratio, Ref: reference

[a] Cox proportional hazard ratio regression models were adjusted for variables of main model 5 (see legend of Table 5)

Appendix 4. Complete list of baseline characteristics of the study population (N=411,436)

Variables	N (%) / Median (IQR)
SOCIO-DEMOGRAPHIC/ -ECONOMIC FACTORS	
Age (years), median (IQR)	57 (50; 63)
Sex, n (%)	
Female	217,594 (52.9)
Male	193,842 (47.1)
Education (years), median (IQR)	3 (1; 5)
Townsend deprivation index (points), median (IQR)	-2.2 (-3.7; 0.5)
No. of individuals in household, n (%)	
1	74,344 (18.2)
2	188,169 (46.0)
3-4	123,250 (30.1)
≥ 5	22,946 (5.6)
Annual household income (£), n (%)	
< 18,000	77,604 (21.9)
18,000 - < 30,999	88,803 (25.1)
31,000- < 51,999	93,369 (26.4)
52,000 - < 100,000	74,160 (21.0)
≥ 100,000	19,749 (5.6)
LIFE-STYLE FACTORS	
Smoking, n (%)	
Never	227,132 (55.2)
Occasionally	58,239 (14.2)
Regularly	125,929 (30.6)
Alcohol consumption (g ethanol/d), n (%)	
Abstainer	126,161 (30.7)
Women 0 - < 20 / men 0 - < 40	165,309 (40.2)
Women 20 - < 40 / men 40 - < 60	69,839 (17.0)
Women ≥ 40 / men ≥ 60	49,663 (12.1)
Venturesome personality, n (%)	
No	288,696 (72.9)
Yes	107,250 (27.1)
Total physical activity (hours/day), n (%)	
≤ 1	62,507 (18.7)
≤ 2	135,895 (40.6)
> 2	135,939 (40.7)
Frequency of visiting friends/family, n (%)	
Almost daily	34,741 (8.5)
2-4 times/week	55,808 (13.6)
Once/week	146,941 (35.9)
Once every few months/rare	171,506 (42.0)
Oily fish consumption, n (%)	
Never/ less than once a week	182,019 (44.5)
At least once a week	227,069 (55.5)

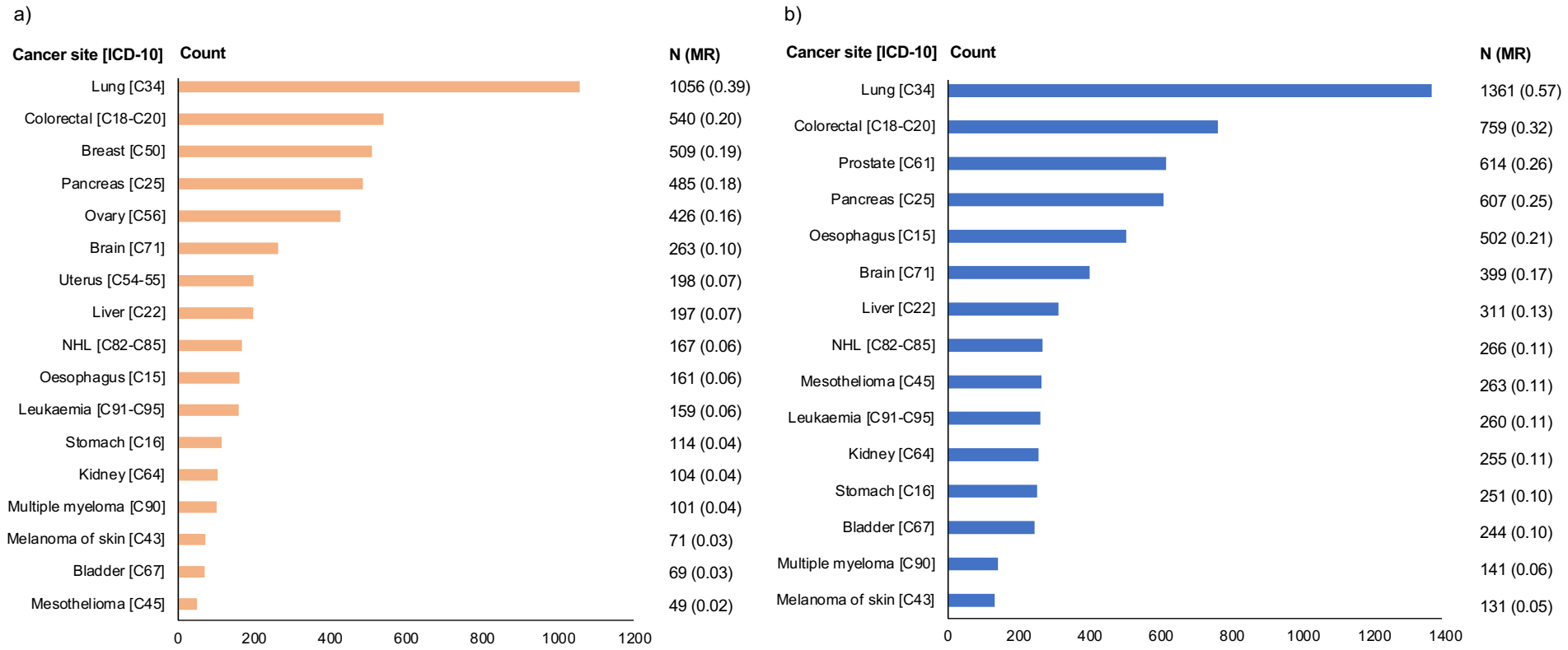
Variables	N (%) / Median (IQR)
Cereal consumption (bowls/week), n (%)	
Never	70,404 (17.2)
< 7	183,973 (44.9)
≥ 7	155,659 (38)
Processed meat intake, n (%)	
Never/ less than once a week	162,054 (39.5)
At least once a week	248,495 (60.5)
Milk consumption, n (%)	
Never/rarely	13,417 (3.3)
Occasionally/regularly	397,721 (96.7)
Spread consumption, n (%)	
Never/rarely	44,527 (10.8)
Butter	147,986 (36)
Margarine/others	218,191 (53.1)
Preferred bread type, n (%)	
White	105,112 (26.5)
Wholemeal/wholegrain/brown	291,816 (73.5)
DISEASES & DISEASE SYMPTOMS	
Diabetes, n (%)	
No	391,026 (95.1)
Yes	20,316 (4.9)
Stroke, n (%)	
No	405,969 (98.7)
Yes	5,372 (1.3)
CHD, n (%)	
No	392,371 (95.4)
Yes	18,970 (4.6)
COPD, n (%)	
No	410,030 (99.7)
Yes	1,311 (0.3)
Hypertension, n (%)	
No	302,146 (73.5)
Untreated hypertension	30,829 (7.5)
Treated hypertension	78,376 (19.1)
Asthma, n (%)	
No	363,668 (88.4)
Yes	47,673 (11.6)
Osteoporosis, n (%)	
No	402,170 (97.8)
Yes	9,171 (2.2)
Fracture in last 5 years, n (%)	
No	371,014 (90.6)
Yes	38,330 (9.4)
Arthritis, n (%)	
No	369,107 (89.7)

Variables	N (%) / Median (IQR)
Yes	42,234 (10.3)
Gout, n (%)	
No	404,756 (98.4)
Yes	6,585 (1.6)
Parkinson, n (%)	
No	410,492 (99.8)
Yes	849 (0.2)
Depressed mood in last 2 weeks, n (%)	
≤ half the days	373,518 (95.1)
> half the days	19,413 (4.9)
Tiredness/lethargy in last 2 weeks, n (%)	
≤ half the days	348,915 (87.5)
> half the days	49,758 (12.5)
Chronic fatigue syndrome, n (%)	
No	409,562 (99.6)
Yes	1,779 (0.4)
Hypothyroidism, n (%)	
No	391,931 (95.3)
Yes	19,410 (4.7)
Dementia, n (%)	
No	408,906 (99.4)
Yes	2,435 (0.6)
BIOMARKERS	
BMI (kg/m^2), n (%)	
Underweight, < 18.5	2,061 (0.5)
Low normal weight, 18.5 - <20	7,484 (1.8)
High normal weight, 20 - < 25	126,839 (30.9)
Overweight: 25 - < 30	174,086 (42.5)
Obesity class I: 30 - < 35	71315 (17.4)
Obesity class II: 35 - < 40	20,275 (4.9)
Obesity class III: ≥ 40	7,828 (1.9)
Waist circumference (cm), median (IQR)	90 (80; 99)
eGFR (ml/min/1,73 m^2), n (%)	
≥ 90	246,968 (60.1)
< 90	163,969 (39.9)
HbA_{1c}, (%), n (%)	
< 6	359,339 (92.1)
6 - < 6.5	15,816 (4.1)
6.5 - < 7	5,626 (1.4)
7 - < 8	5,457 (1.4)
≥ 8	4,032 (1.0)
HDL cholesterol (mg/dl), n (%)	
< 40	47,851 (12.7)
≥ 40	328,263 (87.3)
SBP (mmHg), n (%)	

Variables	N (%) / Median (IQR)
< 140	219,860 (53.5)
140 - < 160	129,198 (31.4)
160 - < 180	49,148 (12.0)
≥ 180	12,802 (3.1)
DBP (mmHg), n (%)	
< 90	313,048 (76.2)
90 - < 100	74,370 (18.1)
≥ 100	23,601 (5.7)
C-reactive protein (mg/L), n (%)	
< 1	165,684 (40.3)
≥ 1	245,752 (59.7)
FEV1 (L), median (IQR)	2.8 (2.3; 3.4)
Hand grip strength (Kg), median (IQR)	32 (24; 41)
GENERAL HEALTH	
Disability (%)	
No	385,963 (94.6)
Yes	22,187 (5.4)
General self-reported health, n (%)	
Excellent	69,968 (17.1)
Good	239,116 (58.4)
Fair	83,774 (20.4)
Poor	16,877 (4.1)
No of chronic diseases, median (IQR)	1 (0; 3)
No of drugs, median (IQR)	2 (0; 4)
Low-dose aspirin use, n (%)	
No	353,707 (86.0)
Yes	57,634 (14.0)
Lipid-lowering drugs use, n (%)	
No	338,995 (82.4)
Yes	72,353 (17.6)
Anti-depressants use, n (%)	
No	384,913 (93.6)
Yes	26,428 (6.4)
VITAMIN D SPECIFIC FACTORS	
Latitude of study center (per 1°), median (IQR)	53.0 (51.5; 53.8)
Calendar month of blood draw	
1	28,250 (6.9)
2	32,428 (7.9)
3	40,141 (9.8)
4	35,877 (8.7)
5	42,858 (10.4)
6	42,454 (10.3)
7	35,117 (8.5)
8	31,368 (7.6)

Variables	N (%) / Median (IQR)
9	30,150 (7.3)
10	35,290 (8.6)
11	34,451 (8.4)
12	23,052 (5.6)
Time spent outdoors in summer (h/day), n (%)	
<1	17,223 (4.4)
1-2	121,146 (31.2)
3-4	127,784 (32.9)
5-6	77,219 (19.9)
≥ 7	44,868 (11.6)
Time spent outdoors in winter (h/day), n (%)	
<1	77,649 (20.0)
1-2	220,277 (56.8)
3-4	58,360 (15.0)
≥ 5	31,797 (8.2)
Skin color, n (%)	
Very fair	30,695 (7.6)
Fair	276,191 (68.1)
Olive	75,962 (18.7)
Brown	7,722 (1.9)
Black	11,897 (2.9)
Unknown	3,210 (0.8)
Ease of skin tanning, n (%)	
Very tanned	87,237 (21.8)
Moderately tanned	160,414 (40.1)
Mildly/occasionally tanned	84,746 (21.2)
Never tan, only burn	67,955 (17.0)
Sun screen/UV protection use, n (%)	
Never/rarely	42,193 (10.3)
Sometimes	138,433 (33.7)
Most of times	145,293 (35.4)
Always	82,465 (20.1)
Do not go out in sunshine	2,390 (0.6)
Solarium/sunlamp use (times per year), n (%)	
Never	368,235 (90.4)
< 1	20,067 (4.9)
1 - 6	10,218 (2.5)
7 - 12	4,399 (1.1)
> 12	4,201 (1.0)

Abbreviations: BMI: body mass index; CHD: coronary heart disease; COPD: chronic obstructive pulmonary disease; DBP: diastolic blood pressure; eGRF: estimated Glomerular filtration rate; FEV1: Forced expiratory volume in 1-second; IQR: interquartile range; SBP: systolic blood pressure.



Appendix 5. Cancer site-specific mortality rates in female (a) and male (b) participants of the UK Biobank (N=411,436)

Abbreviations: ICD-10: the 10th revision of the International Statistical Classification of Diseases, MR: mortality rate per 1000 person-year, N: absolute number of cases, NHL: non-Hodgkin lymphoma.

Appendix 6. Associations of vitamin D deficiency and insufficiency with total cancer mortality and 18 types of cancer-specific mortality with increasing adjustment from model 1 to 5 (N=411,436)

Vitamin D status	**Vitamin D deficiency N=86, 638**	**Vitamin D insufficiency N=141,429**	**Vitamin D sufficiency N=183,369**
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
All cancers [C00-C97]	3028 (2.82)	4395 (2.49)	5524 (2.41)
N (MR)			
Model 1 [a]	1.52 (1.45, 1.60)	1.15 (1.11, 1.20)	Ref.
Model 2 [b]	1.44 (1.37, 1.51)	1.13 (1.09, 1.18)	Ref.
Model 3 [c]	1.25 (1.18, 1.31)	1.08 (1.03, 1.12)	Ref.
Model 4 [d]	1.19 (1.13, 1.25)	1.05 (1.00, 1.09)	Ref.
Model 5 [e]	1.15 (1.09, 1.22)	1.04 (0.99, 1.08)	Ref.
Oesophagus [C15]	149 (0.14)	234 (0.13)	280 (0.12)
N (MR)			
Model 1 [a]	1.44 (1.16,1.80)	1.19 (0.99,1.42)	Ref.
Model 2 [b]	1.39 (1.11,1.73)	1.18 (0.98,1.41)	Ref.
Model 3 [c]	1.12 (0.89,1.42)	1.09 (0.91,1.31)	Ref.
Model 4 [d]	1.01 (0.80,1.28)	1.03 (0.86,1.24)	Ref.
Model 5 [e]	0.98 (0.77,1.23)	1.02 (0.85,1.23)	Ref.
Stomach [C16]	106 (0.10)	113 (0.06)	146 (0.06)
N (MR)			
Model 1 [a]	1.77 (1.33,2.36)	1.06 (0.82,1.37)	Ref.
Model 2 [b]	1.69 (1.27,2.23)	1.04 (0.81,1.34)	Ref.
Model 3 [c]	1.55 (1.15,2.08)	1.00 (0.77,1.29)	Ref.
Model 4 [d]	1.44 (1.06,1.94)	0.96 (0.74,1.24)	Ref.
Model 5 [e]	1.42 (1.05,1.92)	0.94 (0.73,1.22)	Ref.
Colorectal [C18-C20]	296 (0.28)	459 (0.26)	544 (0.24)
N (MR)			
Model 1 [a]	1.44 (1.23,1.68)	1.21 (1.06,1.38)	Ref.
Model 2 [b]	1.47 (1.26,1.72)	1.22 (1.07,1.39)	Ref.
Model 3 [c]	1.34 (1.13,1.58)	1.17 (1.03,1.34)	Ref.
Model 4 [d]	1.26 (1.07,1.49)	1.13 (0.99,1.29)	Ref.
Model 5 [e]	1.27 (1.07,1.50)	1.14 (1.00,1.30)	Ref.
Liver [C22]	136 (0.13)	161 (0.09)	211 (0.09)
N (MR)			
Model 1 [a]	1.74 (1.37,2.22)	1.11 (0.90,1.37)	Ref.
Model 2 [b]	1.79 (1.40,2.28)	1.12 (0.91,1.39)	Ref.
Model 3 [c]	1.48 (1.15,1.91)	1.05 (0.85,1.31)	Ref.
Model 4 [d]	1.27 (0.98,1.64)	0.96 (0.78,1.20)	Ref.
Model 5 [e]	1.17 (0.90,1.52)	0.95 (0.76,1.18)	Ref.
Pancreas [C25]	230 (0.21)	391 (0.22)	471 (0.21)
N (MR)			
Model 1 [a]	1.33 (1.12,1.58)	1.21 (1.05,1.39)	Ref.
Model 2 [b]	1.35 (1.13,1.61)	1.21 (1.06,1.39)	Ref.
Model 3 [c]	1.27 (1.06,1.53)	1.20 (1.04,1.38)	Ref.
Model 4 [d]	1.18 (0.98,1.42)	1.14 (0.99,1.32)	Ref.
Model 5 [e]	1.13 (0.93,1.36)	1.13 (0.98,1.30)	Ref.
Lung [C34]	667 (0.62)	856 (0.49)	894 (0.39)
N (MR)			
Model 1 [a]	2.16 (1.93,2.42)	1.42 (1.29,1.57)	Ref.
Model 2 [b]	1.90 (1.70,2.13)	1.37 (1.24,1.51)	Ref.

Vitamin D status	**Vitamin D deficiency N=86, 638**	**Vitamin D insufficiency N=141,429**	**Vitamin D sufficiency N=183,369**
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Model 3 [c]	1.34 (1.19,1.51)	1.23 (1.11,1.35)	Ref.
Model 4 [d]	1.32 (1.18,1.49)	1.22 (1.10,1.34)	Ref.
Model 5 [e]	1.24 (1.10,1.40)	1.19 (1.08,1.32)	Ref.
Melanoma of skin [C43]	38 (0.04)	58 (0.03)	106 (0.05)
N (MR)			
Model 1 [a]	0.85 (0.57,1.25)	0.73 (0.53,1.02)	Ref.
Model 2 [b]	0.91 (0.61,1.37)	0.75 (0.54,1.05)	Ref.
Model 3 [c]	0.86 (0.56,1.32)	0.73 (0.52,1.02)	Ref.
Model 4 [d]	0.86 (0.56,1.33)	0.74 (0.53,1.04)	Ref.
Model 5 [e]	0.89 (0.58,1.38)	0.76 (0.54,1.06)	Ref.
Mesothelioma [C45]	47 (0.04)	106 (0.06)	159 (0.07)
N (MR)			
Model 1 [a]	0.82 (0.58,1.16)	0.97 (0.75,1.25)	Ref.
Model 2 [b]	0.90 (0.63,1.29)	1.02 (0.79,1.32)	Ref.
Model 3 [c]	0.95 (0.66,1.38)	1.06 (0.82,1.38)	Ref.
Model 4 [d]	1.00 (0.69,1.45)	1.09 (0.84,1.41)	Ref.
Model 5 [e]	0.99 (0.68,1.44)	1.08 (0.83,1.41)	Ref.
Breast [C50]	119 (0.21)	169 (0.18)	221 (0.18)
N (MR)			
Model 1 [a]	1.33 (1.04,1.70)	1.06 (0.87,1.30)	Ref.
Model 2 [b]	1.33 (1.04,1.69)	1.06 (0.86,1.30)	Ref.
Model 3 [c]	1.22 (0.95,1.57)	1.02 (0.83,1.26)	Ref.
Model 4 [d]	1.12 (0.86,1.45)	0.97 (0.79,1.19)	Ref.
Model 5 [e]	1.13 (0.87,1.46)	0.97 (0.78,1.20)	Ref.
Uterus [C54-55]	50 (0.09)	83 (0.09)	65 (0.05)
N (MR)			
Model 1 [a]	1.67 (1.13,2.47)	1.64 (1.19,2.27)	Ref.
Model 2 [b]	1.64 (1.11,2.45)	1.62 (1.16,2.25)	Ref.
Model 3 [c]	1.47 (0.98,2.22)	1.51 (1.08,2.12)	Ref.
Model 4 [d]	1.16 (0.77,1.76)	1.33 (0.95,1.86)	Ref.
Model 5 [e]	1.14 (0.75,1.75)	1.29 (0.92,1.82)	Ref.
Ovary [C56]	92 (0.16)	146 (0.16)	188 (0.15)
N (MR)			
Model 1 [a]	1.22 (0.93,1.60)	1.06 (0.85,1.33)	Ref.
Model 2 [b]	1.23 (0.94,1.60)	1.06 (0.85,1.33)	Ref.
Model 3 [c]	1.07 (0.81,1.42)	1.00 (0.80,1.25)	Ref.
Model 4 [d]	1.04 (0.78,1.38)	0.98 (0.78,1.23)	Ref.
Model 5 [e]	1.05 (0.79,1.40)	0.99 (0.79,1.25)	Ref.
Prostate [C61]	127 (0.25)	209 (0.25)	278 (0.26)
N (MR)			
Model 1 [a]	1.31 (1.05,1.65)	1.12 (0.93,1.34)	Ref.
Model 2 [b]	1.43 (1.13,1.81)	1.16 (0.96,1.39)	Ref.
Model 3 [c]	1.46 (1.14,1.88)	1.18 (0.98,1.43)	Ref.
Model 4 [d]	1.41 (1.10,1.80)	1.15 (0.95,1.39)	Ref.
Model 5 [e]	1.36 (1.06,1.75)	1.14 (0.94,1.38)	Ref.
Kidney [C64]	68 (0.06)	125 (0.07)	166 (0.07)
N (MR)			
Model 1 [a]	1.02 (0.75,1.38)	1.04 (0.81,1.32)	Ref.
Model 2 [b]	1.02 (0.74,1.38)	1.04 (0.82,1.32)	Ref.

Vitamin D status	**Vitamin D deficiency N=86, 638**	**Vitamin D insufficiency N=141,429**	**Vitamin D sufficiency N=183,369**
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Model 3 [c]	0.89 (0.65,1.24)	0.98 (0.77,1.25)	Ref.
Model 4 [d]	0.81 (0.59,1.13)	0.92 (0.72,1.18)	Ref.
Model 5 [e]	0.79 (0.57,1.10)	0.92 (0.72,1.18)	Ref.
Bladder [C67]	78 (0.07)	101 (0.06)	134 (0.06)
N (MR)			
Model 1 [a]	1.72 (1.26,2.35)	1.13 (0.87,1.48)	Ref.
Model 2 [b]	1.70 (1.24,2.32)	1.13 (0.87,1.48)	Ref.
Model 3 [c]	1.40 (1.01,1.95)	1.05 (0.80,1.38)	Ref.
Model 4 [d]	1.31 (0.94,1.83)	1.01 (0.77,1.32)	Ref.
Model 5 [e]	1.31 (0.94,1.84)	1.02 (0.77,1.34)	Ref.
Brain [C71]	126 (0.12)	226 (0.13)	310 (0.14)
N (MR)			
Model 1 [a]	0.94 (0.75,1.17)	0.98 (0.82,1.16)	Ref.
Model 2 [b]	0.96 (0.76,1.21)	0.98 (0.82,1.18)	Ref.
Model 3 [c]	0.94 (0.74,1.19)	0.97 (0.81,1.16)	Ref.
Model 4 [d]	0.97 (0.76,1.23)	0.99 (0.82,1.18)	Ref.
Model 5 [e]	0.95 (0.75,1.21)	0.97 (0.81,1.17)	Ref.
Non-Hodgkin lymphoma [C82-C85]	82 (0.08)	141 (0.08)	210 (0.09)
N (MR)			
Model 1 [a]	1.03 (0.78,1.35)	0.97 (0.78,1.20)	Ref.
Model 2 [b]	1.07 (0.81,1.42)	0.98 (0.79,1.22)	Ref.
Model 3 [c]	0.96 (0.71,1.28)	0.94 (0.75,1.18)	Ref.
Model 4 [d]	0.96 (0.71,1.29)	0.94 (0.75,1.17)	Ref.
Model 5 [e]	1.02 (0.76,1.38)	0.98 (0.78,1.22)	Ref.
Multiple myeloma [C90]	59 (0.06)	64 (0.04)	119 (0.05)
N (MR)			
Model 1 [a]	1.45 (1.04,2.01)	0.80 (0.59,1.09)	Ref.
Model 2 [b]	1.48 (1.04,2.09)	0.80 (0.59,1.10)	Ref.
Model 3 [c]	1.28 (0.89,1.84)	0.75 (0.55,1.03)	Ref.
Model 4 [d]	1.20 (0.83,1.74)	0.72 (0.53,1.00)	Ref.
Model 5 [e]	1.24 (0.85,1.81)	0.74 (0.54,1.02)	Ref.
Leukaemia [C91-C95]	78 (0.07)	138 (0.08)	203 (0.09)
N (MR)			
Model 1 [a]	1.01 (0.76,1.33)	0.96 (0.76,1.20)	Ref.
Model 2 [b]	1.05 (0.79,1.40)	0.97 (0.78,1.22)	Ref.
Model 3 [c]	1.00 (0.74,1.34)	0.95 (0.76,1.20)	Ref.
Model 4 [d]	0.95 (0.70,1.29)	0.93 (0.74,1.16)	Ref.
Model 5 [e]	0.93 (0.69,1.26)	0.92 (0.73,1.15)	Ref.

Abbreviations: CI: confidence interval, HR: hazard ratio, MR: mortality rate per 1000 person-year, Ref.: reference

[a] Model 1: Age, sex, skin colour, latitude of study center and the calendar month of blood draw.

[b] Model 2: Model 1 variables plus socio-economic factors (education, Townsend deprivation index, no of individuals in household, and household income).

[c] Model 3: Model 2 variables plus life-style factors (smoking, alcohol consumption, physical activity, frequency of visiting friends/family and consumption of oily fish, cereal, processed meat, milk, bread and spread), and vitamin D specific factors (time spend outdoors in summer and winter, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use).

[d] Model 4: Model 3 variables plus weight variables (body mass index and waist circumference).

[e] Model 5: Model 4 variables plus diseases and disease symptoms (diabetes, stroke, coronary heart disease, chronic obstructive pulmonary disease, osteoporosis, arthritis, gout, Parkinson, depressed mood, and tiredness/lethargy), biomarkers (estimated glomerular filtration rate, HbA_{1c}, HDL cholesterol, systolic blood pressure, diastolic blood pressure, C-reactive protein, forced expiratory volume in 1-second, and hand grip strength), and general health status (no. of drugs, no. of chronic diseases, disability, and general self-rated health).

Appendix 7. Associations of vitamin D deficiency and insufficiency with 5-year, 10-year, and 15-year total cancer mortality and cancer cause-specific mortality (N=411,436)

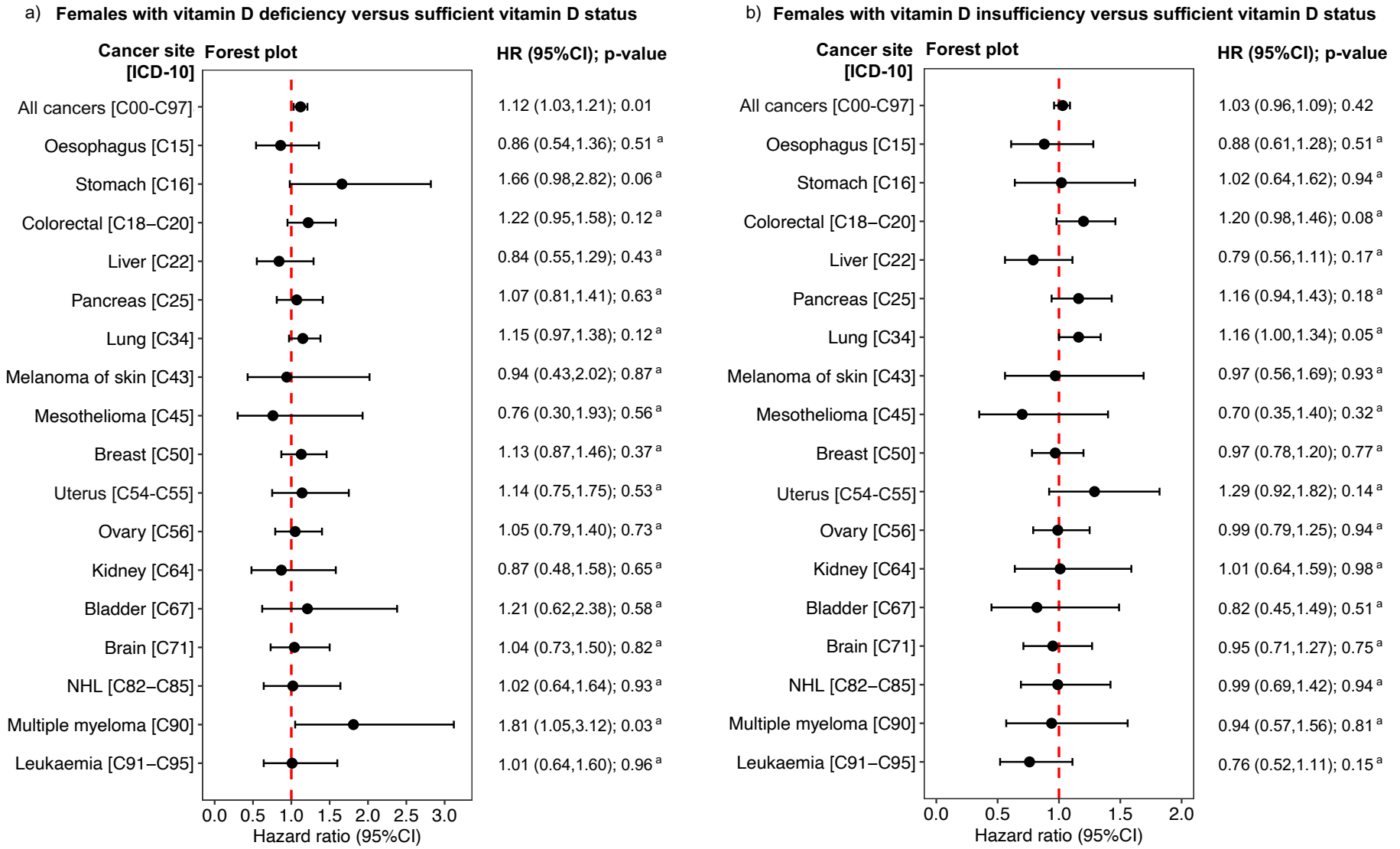
	Vitamin D deficiency [a]					
Cancer	**5-year follow up**		**10-year follow up**		**15-year follow up [b]**	
Mortality	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)
All cancers	718 (1.67)	**1.14 (1.02, 1.27)**	2069 (2.44)	**1.14 (1.07, 1.22)**	3028 (2.82)	**1.15 (1.09, 1.22)**
Stomach	26 (0.06)	1.31 (0.72, 2.39)	68 (0.08)	1.27 (0.88, 1.83)	106 (0.10)	**1.42 (1.05,1.92)**
Colorectal	80 (0.19)	**1.50 (1.06, 2.12)**	204 (0.24)	**1.30 (1.06, 1.59)**	296 (0.28)	**1.27 (1.07,1.50)**
Lung	180 (0.42)	1.21 (0.97, 1.53)	492 (0.58)	**1.25 (1.08, 1.44)**	667 (0.62)	**1.24 (1.10,1.40)**
Prostate (in males)	17 (0.08)	1.16 (0.58, 2.32)	80 (0.20)	**1.43 (1.04, 1.97)**	127 (0.25)	**1.36 (1.06,1.75)**
	Vitamin D insufficiency [a]					
Cancer	**5-year follow up**		**10-year follow up**		**15-year follow up [b]**	
Mortality	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)
All cancers	958 (1.36)	0.98 (0.89, 1.07)	3003 (2.16)	1.04 (0.99, 1.09)	4395 (2.49)	1.04 (0.99, 1.08)
Stomach	31 (0.04)	0.94 (0.57, 1.55)	89 (0.06)	1.01 (0.75, 1.36)	113 (0.06)	0.94 (0.73,1.22)
Colorectal	95 (0.14)	1.11 (0.83, 1.49)	297 (0.21)	1.09 (0.92, 1.28)	459 (0.26)	1.14 (1.00,1.30)
Lung	224 (0.32)	1.11 (0.92, 1.34)	601 (0.43)	**1.15 (1.02, 1.29)**	856 (0.49)	**1.19 (1.08,1.32)**
Prostate (in males)	28 (0.08)	1.12 (0.66, 1.90)	134 (0.21)	1.21 (0.95, 1.54)	209 (0.25)	1.14 (0.94,1.38)

Abbreviations: CI: confidence interval, HR: hazard ratio, MR: mortality rate per 1000 person-year.

[a]: Vitamin D sufficiency as reference group.

[b]: Complete follow-up time.

All analyses included all factors in Model 5 as covariates (see legend of Appendix 6).

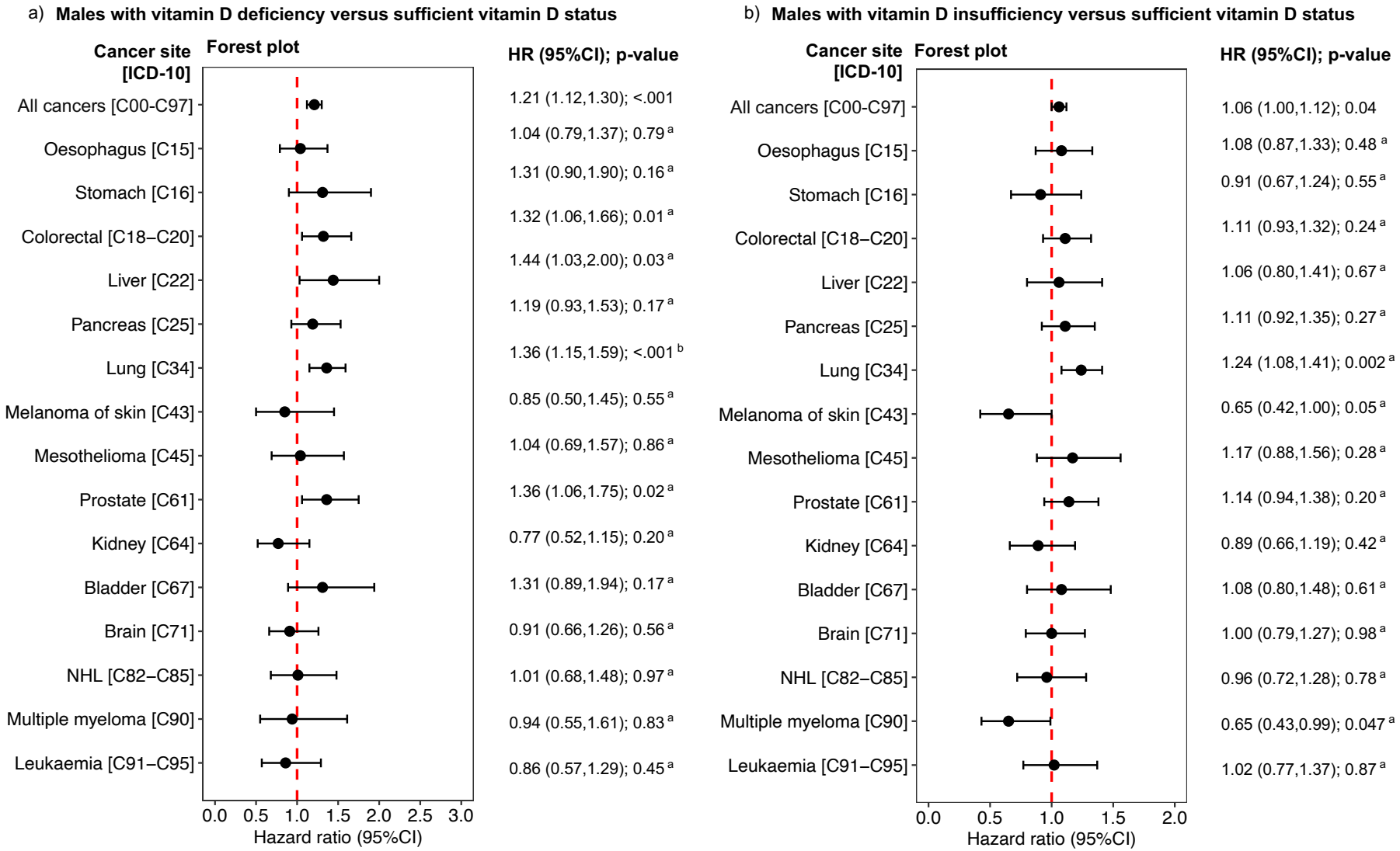


Appendix 8. Associations of vitamin D deficiency (a) and insufficiency (b) with total cancer and 17 types of cancer-specific mortality in females (N=217,594)

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma.

Models adjusted for all covariates in model 5 (see legend of Appendix 6)

[a]: Not statistically significant with false discovery rate of 5% considering the n=34 statistical tests of cancer site-specific mortality made for the analysis.



Appendix 9. Associations of vitamin D deficiency (a) and insufficiency (b) with total cancer and 15 types of cancer-specific mortality in males (N=193,842)

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma.

Models adjusted for all covariates in model 5 (see legend of Appendix 6)

[a]: Not statistically significant with false discovery rate of 5% considering the n=30 statistical tests of cancer site-specific mortality made for the analysis.

[b]: Also statistically significant with false discovery rate of 5% considering the n=30 statistical tests of cancer site-specific mortality made for the analysis.

Appendix 10. Associations of vitamin D supplement use and multivitamin use with total cancer mortality and 18 types of cancer-specific mortality with increasing adjustment from model 1 to 5 (N=411,436)

Vitamin D status	**Non-user N=310,731**	**Multivitamin user N=83,719**	**Vitamin D user N=16,986**
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
All cancers [C00-C97]	10,058 (2.60)	2407 (2.30)	482 (2.29)
N (MR)			
Model 1 [a]	Ref.	0.94 (0.90, 0.98)	0.83 (0.76, 0.91)
Model 2 [b]	Ref.	0.94 (0.90, 0.98)	0.82 (0.75, 0.90)
Model 3 [c]	Ref.	0.98 (0.94, 1.02)	0.86 (0.79, 0.94)
Model 4 [d]	Ref.	0.98 (0.94, 1.03)	0.87 (0.80, 0.96)
Model 5 [e]	Ref.	0.98 (0.93, 1.02)	0.85 (0.78, 0.93)
Oesophagus [C15]	521 (0.13)	122 (0.12)	20 (0.09)
N (MR)			
Model 1 [a]	Ref.	0.99 (0.81,1.21)	0.80 (0.51,1.26)
Model 2 [b]	Ref.	0.99 (0.81,1.20)	0.79 (0.50,1.23)
Model 3 [c]	Ref.	1.04 (0.85,1.27)	0.84 (0.53,1.31)
Model 4 [d]	Ref.	1.05 (0.86,1.28)	0.85 (0.54,1.33)
Model 5 [e]	Ref.	1.03 (0.84,1.26)	0.80 (0.51,1.27)
Stomach [C16]	295 (0.08)	59 (0.06)	11 (0.05)
N (MR)			
Model 1 [a]	Ref.	0.83 (0.62,1.09)	0.74 (0.40,1.35)
Model 2 [b]	Ref.	0.83 (0.63,1.10)	0.73 (0.40,1.33)
Model 3 [c]	Ref.	0.86 (0.65,1.15)	0.77 (0.42,1.41)
Model 4 [d]	Ref.	0.87 (0.66,1.16)	0.78 (0.43,1.43)
Model 5 [e]	Ref.	0.87 (0.66,1.16)	0.82 (0.45,1.52)
Colorectal [C18-C20]	1012 (0.26)	238 (0.23)	49 (0.23)
N (MR)			
Model 1 [a]	Ref.	0.92 (0.80,1.06)	0.86 (0.65,1.15)
Model 2 [b]	Ref.	0.92 (0.80,1.06)	0.85 (0.64,1.14)
Model 3 [c]	Ref.	0.95 (0.82,1.09)	0.88 (0.66,1.17)
Model 4 [d]	Ref.	0.95 (0.82,1.10)	0.90 (0.67,1.20)
Model 5 [e]	Ref.	0.95 (0.82,1.10)	0.86 (0.64,1.16)
Liver [C22]	409 (0.11)	84 (0.08)	15 (0.07)
N (MR)			
Model 1 [a]	Ref.	0.81 (0.64,1.03)	0.65 (0.39,1.09)
Model 2 [b]	Ref.	0.81 (0.64,1.02)	0.64 (0.38,1.08)
Model 3 [c]	Ref.	0.85 (0.67,1.08)	0.68 (0.41,1.14)
Model 4 [d]	Ref.	0.87 (0.68,1.10)	0.71 (0.42,1.19)
Model 5 [e]	Ref.	0.86 (0.68,1.09)	0.66 (0.39,1.11)
Pancreas [C25]	838 (0.22)	210 (0.20)	44 (0.21)
N (MR)			
Model 1 [a]	Ref.	0.97 (0.84,1.13)	0.88 (0.65,1.19)
Model 2 [b]	Ref.	0.97 (0.83,1.13)	0.87 (0.64,1.18)
Model 3 [c]	Ref.	0.98 (0.84,1.14)	0.88 (0.65,1.19)
Model 4 [d]	Ref.	0.99 (0.85,1.15)	0.91 (0.67,1.23)
Model 5 [e]	Ref.	0.98 (0.84,1.14)	0.91 (0.67,1.24)
Lung [C34]	1935 (0.50)	404 (0.39)	78 (0.37)
N (MR)			
Model 1 [a]	Ref.	0.82 (0.74,0.92)	0.69 (0.55,0.87)
Model 2 [b]	Ref.	0.83 (0.75,0.92)	0.68 (0.54,0.85)

Vitamin D status	**Non-user N=310,731**	**Multivitamin user N=83,719**	**Vitamin D user N=16,986**
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Model 3 [c]	Ref.	0.93 (0.83,1.04)	0.78 (0.62,0.98)
Model 4 [d]	Ref.	0.93 (0.83,1.04)	0.78 (0.62,0.98)
Model 5 [e]	Ref.	0.91 (0.82,1.02)	0.75 (0.60,0.95)
Melanoma of skin [C43] *N (MR)*	167 (0.04)	28 (0.03)	7 (0.03)
Model 1 [a]	Ref.	0.67 (0.45,1.00)	0.81 (0.38,1.74)
Model 2 [b]	Ref.	0.67 (0.45,1.00)	0.81 (0.38,1.74)
Model 3 [c]	Ref.	0.66 (0.44,0.98)	0.80 (0.37,1.72)
Model 4 [d]	Ref.	0.66 (0.44,0.98)	0.80 (0.37,1.72)
Model 5 [e]	Ref.	0.64 (0.43,0.97)	0.76 (0.35,1.65)
Mesothelioma [C45] *N (MR)*	249 (0.06)	56 (0.05)	7 (0.03)
Model 1 [a]	Ref.	1.01 (0.75,1.35)	0.62 (0.29,1.32)
Model 2 [b]	Ref.	1.02 (0.76,1.36)	0.63 (0.30,1.33)
Model 3 [c]	Ref.	1.03 (0.77,1.39)	0.65 (0.30,1.37)
Model 4 [d]	Ref.	1.03 (0.77,1.38)	0.64 (0.30,1.37)
Model 5 [e]	Ref.	1.01 (0.75,1.36)	0.63 (0.30,1.35)
Breast [C50] *N (MR)*	370 (0.19)	114 (0.18)	25 (0.17)
Model 1 [a]	Ref.	0.95 (0.77,1.18)	0.81 (0.54,1.22)
Model 2 [b]	Ref.	0.96 (0.78,1.18)	0.81 (0.54,1.22)
Model 3 [c]	Ref.	0.97 (0.78,1.20)	0.81 (0.54,1.22)
Model 4 [d]	Ref.	0.98 (0.79,1.21)	0.84 (0.56,1.26)
Model 5 [e]	Ref.	0.99 (0.80,1.23)	0.80 (0.53,1.21)
Uterus [C54-55] *N (MR)*	148 (0.08)	36 (0.06)	14 (0.09)
Model 1 [a]	Ref.	0.75 (0.52,1.08)	1.03 (0.59,1.79)
Model 2 [b]	Ref.	0.75 (0.52,1.08)	1.03 (0.59,1.79)
Model 3 [c]	Ref.	0.75 (0.52,1.08)	1.00 (0.58,1.74)
Model 4 [d]	Ref.	0.77 (0.53,1.11)	1.10 (0.63,1.92)
Model 5 [e]	Ref.	0.83 (0.57,1.20)	1.33 (0.76,2.35)
Ovary [C56] *N (MR)*	305 (0.16)	93 (0.15)	28 (0.19)
Model 1 [a]	Ref.	0.97 (0.77,1.22)	1.03 (0.70,1.53)
Model 2 [b]	Ref.	0.96 (0.76,1.21)	1.03 (0.70,1.51)
Model 3 [c]	Ref.	0.97 (0.77,1.23)	1.03 (0.70,1.52)
Model 4 [d]	Ref.	0.98 (0.77,1.24)	1.05 (0.71,1.55)
Model 5 [e]	Ref.	0.97 (0.77,1.23)	1.03 (0.69,1.53)
Prostate [C61] *N (MR)*	481 (0.25)	115 (0.27)	18 (0.29)
Model 1 [a]	Ref.	1.12 (0.91,1.37)	1.00 (0.62,1.60)
Model 2 [b]	Ref.	1.11 (0.91,1.36)	0.99 (0.62,1.59)
Model 3 [c]	Ref.	1.13 (0.92,1.38)	1.02 (0.63,1.63)
Model 4 [d]	Ref.	1.13 (0.92,1.39)	1.02 (0.64,1.64)
Model 5 [e]	Ref.	1.14 (0.93,1.40)	1.03 (0.64,1.66)
Kidney [C64] *N (MR)*	284 (0.07)	65 (0.06)	10 (0.05)
Model 1 [a]	Ref.	0.95 (0.73,1.25)	0.70 (0.37,1.32)
Model 2 [b]	Ref.	0.95 (0.72,1.24)	0.69 (0.37,1.30)
Model 3 [c]	Ref.	0.99 (0.75,1.30)	0.73 (0.39,1.38)

Vitamin D status	Non-user N=310,731	Multivitamin user N=83,719	Vitamin D user N=16,986
Cancer mortality	**HR (95%CI)**	**HR (95%CI)**	**HR (95%CI)**
Model 4 [d]	Ref.	1.00 (0.76,1.31)	0.76 (0.40,1.44)
Model 5 [e]	Ref.	1.02 (0.77,1.34)	0.77 (0.40,1.46)
Bladder [C67] *N (MR)*	244 (0.06)	60 (0.06)	9 (0.04)
Model 1 [a]	Ref.	1.05 (0.79,1.39)	0.76 (0.39,1.48)
Model 2 [b]	Ref.	1.05 (0.79,1.40)	0.75 (0.38,1.46)
Model 3 [c]	Ref.	1.10 (0.83,1.47)	0.78 (0.40,1.52)
Model 4 [d]	Ref.	1.11 (0.83,1.48)	0.79 (0.40,1.54)
Model 5 [e]	Ref.	1.06 (0.79,1.42)	0.72 (0.37,1.42)
Brain [C71] *N (MR)*	506 (0.13)	139 (0.13)	17 (0.08)
Model 1 [a]	Ref.	1.09 (0.90,1.31)	0.63 (0.39,1.03)
Model 2 [b]	Ref.	1.08 (0.89,1.30)	0.63 (0.39,1.02)
Model 3 [c]	Ref.	1.08 (0.90,1.31)	0.63 (0.39,1.02)
Model 4 [d]	Ref.	1.08 (0.89,1.31)	0.63 (0.39,1.02)
Model 5 [e]	Ref.	1.09 (0.90,1.32)	0.66 (0.40,1.08)
Non-Hodgkin lymphoma [C82-C85] *N (MR)*	321 (0.08)	95 (0.09)	17 (0.08)
Model 1 [a]	Ref.	1.19 (0.94,1.49)	0.94 (0.57,1.53)
Model 2 [b]	Ref.	1.19 (0.95,1.50)	0.94 (0.58,1.54)
Model 3 [c]	Ref.	1.22 (0.97,1.54)	0.96 (0.59,1.57)
Model 4 [d]	Ref.	1.22 (0.97,1.54)	0.96 (0.59,1.57)
Model 5 [e]	Ref.	1.20 (0.95,1.52)	0.88 (0.53,1.45)
Multiple myeloma [C90] *N (MR)*	182 (0.05)	49 (0.05)	11 (0.05)
Model 1 [a]	Ref.	1.05 (0.77,1.44)	1.00 (0.54,1.85)
Model 2 [b]	Ref.	1.05 (0.76,1.44)	1.00 (0.54,1.84)
Model 3 [c]	Ref.	1.04 (0.76,1.43)	0.98 (0.53,1.81)
Model 4 [d]	Ref.	1.05 (0.76,1.44)	1.00 (0.54,1.85)
Model 5 [e]	Ref.	1.02 (0.74,1.41)	0.90 (0.48,1.69)
Leukaemia [C91-C95] *N (MR)*	319 (0.08)	85 (0.08)	15 (0.07)
Model 1 [a]	Ref.	1.07 (0.84,1.36)	0.83 (0.50,1.40)
Model 2 [b]	Ref.	1.06 (0.84,1.35)	0.83 (0.49,1.40)
Model 3 [c]	Ref.	1.07 (0.84,1.37)	0.83 (0.49,1.40)
Model 4 [d]	Ref.	1.08 (0.85,1.37)	0.85 (0.51,1.44)
Model 5 [e]	Ref.	1.06 (0.83,1.35)	0.84 (0.49,1.42)

Abbreviations: CI: confidence interval, HR: hazard ratio, MR: mortality rate per 1000 person-year, Ref.: reference

[a] Model 1: Age, sex, skin colour, latitude of study center and the calendar month of blood draw.

[b] Model 2: Model 1 variables plus socio-economic factors (Townsend deprivation index, no of individuals in household, and household income).

[c] Model 3: Model 2 variables plus life-style factors (smoking, alcohol consumption, physical activity, venturesome personality, frequency of visiting friends/family) and vitamin D specific factors (consumption of oily fish, processed meat, milk, bread, spread, time spend outdoors in summer, ease of skin tanning, use of sun screen/UV protection, and solarium/sunlamp use).

[d] Model 4: Model 3 variables plus weight variables (body mass index and waist circumference).

[e] Model 5: Model 4 variables plus diseases & disease symptoms (cancer, hypertension, stroke, coronary heart disease, chronic obstructive pulmonary disease, asthma, osteoporosis, fractured in last 5 years, arthritis, gout, diabetes, hypothyroidism, chronic fatigue syndrome, tiredness/lethargy in last 2 weeks, dementia, Parkinson, and depressed mood), biomarkers (estimated glomerular filtration rate, C-reactive protein), general health status (disability, general self-rated health and no. of drugs), and medication intake (low dose aspirin, lipid-lowering drugs, and anti-depression drugs).

Appendix 11. Associations of vitamin D supplement use and multivitamin use with 5-year, 10-year, and 15-year total cancer mortality and lung cancer mortality (N=411,436)

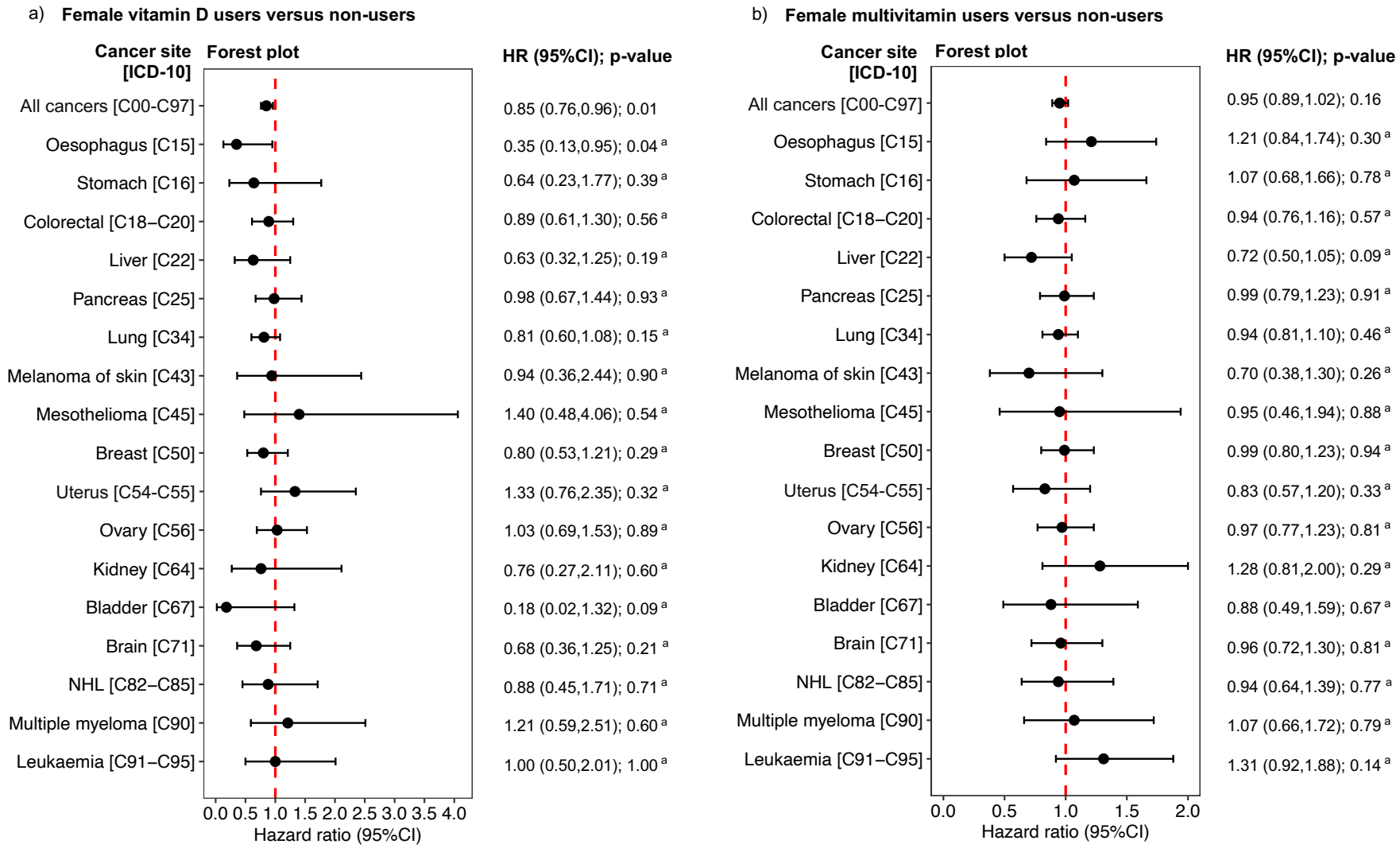
	Vitamin D supplement use [a]					
Cancer	**5-year follow up**		**10-year follow up**		**15-year follow up [b]**	
Mortality	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)
All cancers	101 (1.20)	**0.78 (0.64, 0.96)**	319 (1.91)	**0.83 (0.74, 0.93)**	482 (2.29)	**0.85 (0.78, 0.93)**
Lung	20 (0.24)	0.74 (0.47, 1.16)	56 (0.34)	**0.75 (0.57, 0.99)**	78 (0.37)	**0.75 (0.60, 0.95)**
	Multivitamin use [a]					
Cancer	**5-year follow up**		**10-year follow up**		**15-year follow up [b]**	
Mortality	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)	N (MR)	HR (95%CI)
All cancers	542 (1.30)	0.98 (0.89, 1.08)	1658 (2.01)	0.99 (0.94, 1.05)	2407 (2.30)	0.98 (0.93, 1.02)
Lung	106 (0.25)	0.90 (0.73, 1.12)	281 (0.34)	0.87 (0.77, 1.00)	404 (0.39)	0.91 (0.82, 1.02)

Abbreviations: CI: confidence interval, HR: hazard ratio, MR: mortality rate per 1000 person-year.

[a]: Non-user as reference group.

[b]: Complete follow-up time.

All analyses included all factors in Model 5 as covariates (see legend of Appendix 10).

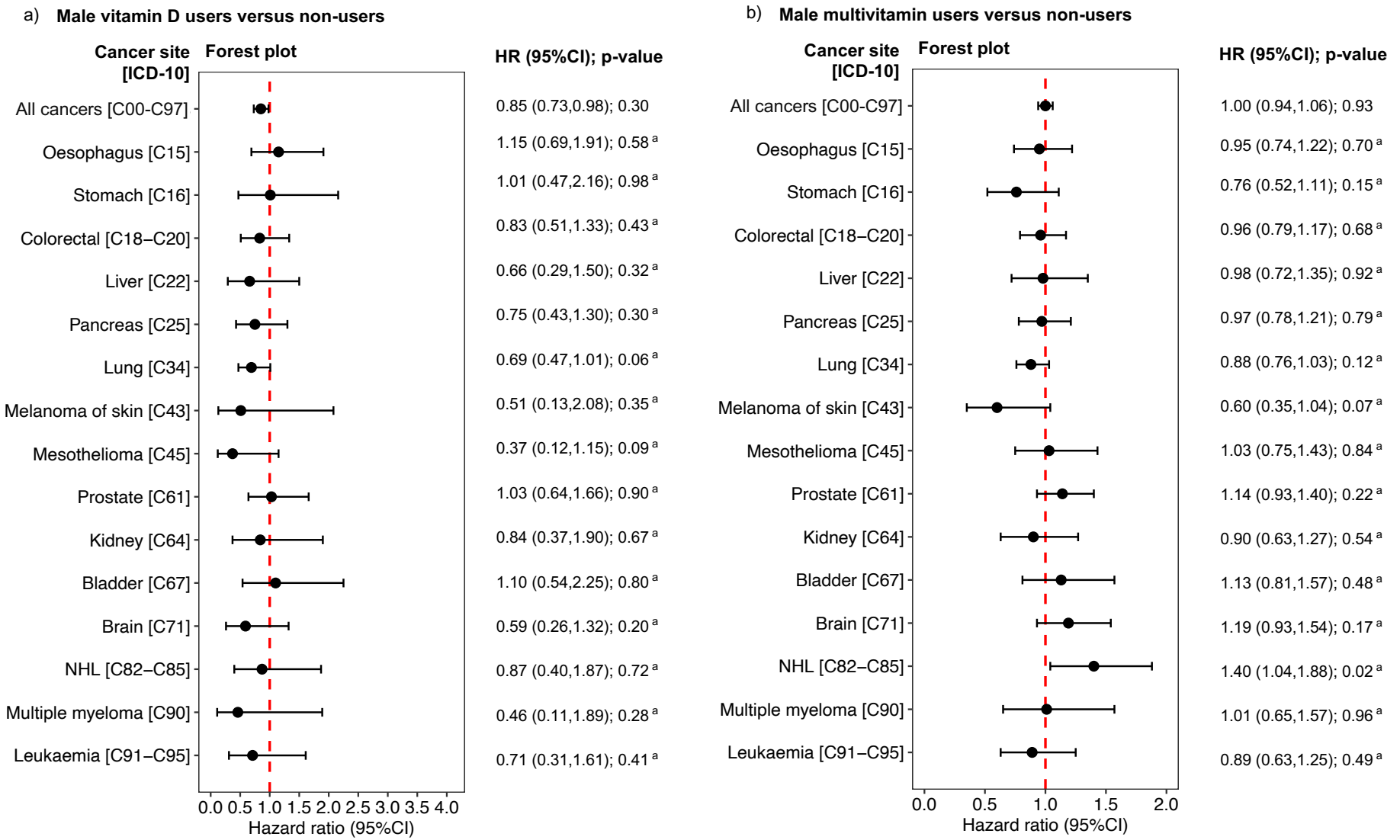


Appendix 12. Associations of vitamin D supplement use (a) and multivitamin use (b) with total cancer and 17 types of cancer-specific mortality in females (N=217,594)

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma.

Note: The reference group is non-users of both vitamin D and multivitamin preparations. Models adjusted for all covariates in model 5 (see legend of Appendix 10)

[a]: Not statistically significant with false discovery rate of 5% considering the n=34 statistical tests of cancer site-specific mortality made for the analysis.



Appendix 13. Associations of vitamin D supplement use (a) and multivitamin use (b) with total cancer and 15 types of cancer-specific mortality in males (N=193,842)

Abbreviations: CI: confidence interval, HR: hazard ratio, ICD-10: the 10th revision of the International Statistical Classification of Diseases, NHL: non-Hodgkin lymphoma.

Note: The reference group is non-users of both vitamin D and multivitamin preparations. Models adjusted for all covariates in model 5 (see legend of Appendix 10)

[a]: Not statistically significant with false discovery rate of 5% considering the n=30 statistical tests of cancer site-specific mortality made for the analysis.

Appendix 14. Complete list of baseline characteristics of the study population (N=397,737)

Variables	Study population
	N (%) / Median (IQR)
SOCIO-DEMOGRAPHIC/-ECONOMIC FACTORS	
Age (years), median (IQR)	58 (50, 63)
Sex, n (%)	
Female	210,982 (53.1)
Male	186,755 (47.0)
Education (years), median (IQR)	3 (1, 5)
Townsend deprivation index (points), median (IQR)	-2.2 (-3.7, 0.5)
No. of individuals in household, n (%)	
1	72,736 (18.4)
2	184,281 (46.7)
3-4	116,217 (29.5)
≥ 5	21,312(5.4)
Annual household income (£), n (%)	
< 18,000	76,625 (22.5)
18,000 - < 30,999	86,043 (25.3)
31,000- < 51,999	89,022 (26.2)
52,000 - < 100,000	69,973 (20.6)
≥ 100,000	18,668 (5.5)
LIFE-STYLE FACTORS	
Smoking, n (%)	
Never	217,643 (54.8)
Occasionally	56,401 (14.2)
Regularly	123,091 (31.0)
Alcohol consumption (g ethanol/d), n (%)	
Abstainer	122,438 (30.9)
Women 0 - < 20 / men 0 - < 40	159,230 (40.1)
Women 20 - < 40 / men 40 - < 60	67,419 (17.0)
Women ≥ 40 / men ≥ 60	47,679 (12.0)
Total physical activity (hours/day), n (%)	
≤ 1	60,491 (18.8)
≤ 2	130,989 (40.7)
> 2	130,419 (40.5)
Frequency of visiting friends/family, n (%)	
Almost daily	33,213 (8.4)
2-4 times/week	53,314 (13.5)
Once/week	140,953 (35.7)
Once every few months/rare	167373 (42.4)
Oily fish consumption, n (%)	
Never/ less than once a week	174,21 (44.1)
At least once a week	220,731 (55.9)
Cereal consumption (bowls/week), n (%)	
Never	67,68 (17.1)
< 7	176,728 (44.7)

Variables	Study population
	N (%) / Median (IQR)
≥ 7	151,373 (38.3)
Processed meat intake, n (%)	
Never/ less than once a week	156,518 (39.5)
At least once a week	239,834 (60.5)
Milk consumption, n (%)	
Never/rarely	12,96 (3.3)
Occasionally/regularly	383,977 (96.7)
Spread consumption, n (%)	
Never/rarely	42,863 (10.8)
Butter	143,089 (36.1)
Margarine/others	210,525 (53.1)
Preferred bread type, n (%)	
White	101,670 (26.5)
Wholemeal/wholegrain/brown	281,481 (73.5)
DISEASES & DISEASE SYMPTOMS	
Diabetes, n (%)	
No	377,677 (95.0)
Yes	19,953 (5.0)
Cancer, n (%)	
No	366,221 (92.5)
Yes	29,71 (7.5)
Stroke, n (%)	
No	392,258 (98.7)
Yes	5,372 (1.4)
CHD, n (%)	
No	378,891 (95.3)
Yes	18,739 (4.7)
COPD, n (%)	
No	396,296 (99.7)
Yes	1,334 (0.3)
History of pulmonary embolism, n (%)	
No	394,403 (99.2)
Yes	3,227 (0.8)
Inflammatory bowel disease, n (%)	
No	397,488 (> 99.9)
Yes	142 (< 0.01)
Periodontitis, n (%)	
No	338,837 (85.3)
Yes	58,496 (14.7)
Arthritis, n (%)	
No	356,086 (89.6)
Yes	41,544 (10.5)
Osteoporosis, n (%)	
No	396,296 (99.7)
Yes	1,334 (0.3)

Variables	Study population
	N (%) / Median (IQR)
Gout, n (%)	
No	391,196 (98.4)
Yes	6,434 (1.6)
Parkinson, n (%)	
No	396,810 (99.8)
Yes	820 (0.2)
Depressed mood in last 2 weeks, n (%)	
≤ half the days	360,268 (95.1)
> half the days	18,754 (5.0)
Tiredness/lethargy in last 2 weeks, n (%)	
≤ half the days	360,268 (95.1)
> half the days	18,754 (5.0)
BIOMARKERS	
BMI (kg/m^2), n (%)	
Underweight, < 18.5	2,029 (0.5)
Low normal weight, 18.5 - <20	7,195 (1.8)
High normal weight, 20 - < 25	122,032 (30.8)
Overweight/obesity class I: 25 - < 35	237,590 (60.0)
Obesity class II: 35 - < 40	19,710 (5.0)
Obesity class III: ≥ 40	7,640 (1.9)
Waist circumference (cm), median (IQR)	89 (80, 98)
eGFR (ml/min/1,73 m^2), n (%)	
≥ 90	236,348 (59.5)
< 90	161,126 (40.5)
HbA_{1c}, (%), n (%)	
< 6	346,935 (91.9)
6 - < 6.5	15,723 (4.2)
6.5 - < 7	5,549 (1.5)
7 - < 8	5,412 (1.4)
≥ 8	3,915 (1)
HDL cholesterol (mg/dl), n (%)	
< 40	50,361 (12.7)
≥ 40	347,088 (87.3)
SBP (mmHg), n (%)	
< 140	210,366 (53.0)
140 - < 160	125,839 (31.7)
160 - < 180	48,493 (12.2)
≥ 180	12,584 (3.2)
DBP (mmHg), n (%)	
< 90	302,37 (76.1)
90 - < 100	72,118 (18.2)
≥ 100	22,805 (5.7)
FEV1 (L), median (IQR)	2.8 (2.3, 3.3)
Hand grip strength (Kg), median (IQR)	31 (24, 41)

Variables	Study population
	N (%) / Median (IQR)
GENERAL HEALTH	
No of drugs, median (IQR)	2 (0, 4)
No of chronic diseases, median (IQR)	2 (1, 3)
Disability (%)	
No	370,723 (94.1)
Yes	23,102 (5.9)
General self-reported health, n (%)	
Excellent	65,495 (16.6)
Good	229,374 (58.0)
Fair	83,086 (21.0)
Poor	17,458 (4.4)
VITAMIN D SPECIFIC FACTORS	
Latitude of study center (per 1°), median (IQR)	53.0 (51.5, 53.8)
Month of attending the study center	
1	27,084 (6.8)
2	31,850 (8.0)
3	40,027 (10.1)
4	35,422 (8.9)
5	42,495 (10.7)
6	41,636 (10.5)
7	34,489 (8.7)
8	28,381 (7.1)
9	27,375 (6.9)
10	33,727 (8.5)
11	32,964 (8.3)
12	22,287 (5.6)
25(OH)D, nmol/L, median (IQR)	46.8 (32.3, 62.4)
Vitamin D status, n (%)	
Vitamin D deficiency	83,929 (21.1)
Vitamin D insufficiency	136,692 (34.4)
Vitamin D sufficiency	177,116 (44.5)
Time spent outdoors in summer (h/day), n (%)	
<1	16,573 (4.4)
1-2	115,708 (30.9)
3-4	123,575 (33.0)
5-6	75,304 (20.1)
≥ 7	43,404 (11.6)
Time spent outdoors in winter (h/day), n (%)	
<1	74,601 (19.9)
1-2	212,54 (56.8)
3-4	56,614 (15.1)
≥ 5	30,649 (8.2)
Skin color, n (%)	
Very fair	30,256 (7.7)
Fair	267,131 (68.2)
Olive	72,673 (18.6)

Variables	Study population
	N (%) / Median (IQR)
Brown	7,403 (1.9)
Black	11,100 (2.8)
Unknown	3,032 (0.8)
Ease of skin tanning, n (%)	
Very tanned	84,012 (21.7)
Moderately tanned	154,199 (39.9)
Mildly/occasionally tanned	81,754 (21.2)
Never tan, only burn	66,484 (17.2)
Sun screen/UV protection use, n (%)	
Never/rarely	40,309 (10.2)
Sometimes	132,512 (33.4)
Most of times	139,854 (35.3)
Always	81,439 (20.5)
Do not go out in sunshine	2,384 (0.6)
Solarium/sunlamp use (times per year), n (%)	
Never	356,176 (90.7)
< 1	19,253 (4.9)
1 - 6	9,534 (2.4)
7 - 12	4,099 (1.0)
> 12	3,872 (1.0)
BIOMARKERS OF SYSTEMIC INFLAMMATORY RESPONSE	
CRP-based biomarkers	
CRP (mg/L)	1.3 (0.7, 2.8)
mGPS	
0	381,157 (95.8)
1	16,496 (4.2)
2	84 (0.0)
HS_mGPS	
0	307,861 (77.4)
1	89,728 (22.6)
2	148 (0.0)
Blood cell-based biomarkers	
NLR	2.1 (1.7, 2.8)
PLR	132.3 (105.4, 166.5)
LMR	4.2 (3.2, 5.3)
SII	529.0 (392.2, 716.8)
PNI	54.7 (52.2, 57.4)
NPS	
0	382,192 (96.1)
1	14,811 (3.7)
2	734 (0.2)

Abbreviations: 25(OH)D: 25-hydroxyvitamin D, BMI: body mass index, CHD: coronary heart disease, COPD: chronic obstructive pulmonary disease, CRP: C-reactive protein, DBP: diastolic blood pressure, eGRF: estimated Glomerular filtration rate, FEV1: Forced expiratory volume in 1-second, HS_mGPS: High-sensitive mGPS, IQR: interquartile range, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, NLR:

neutrophil-to-lymphocyte ratio, NPS: neutrophil-platelet score, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, SBP: systolic blood pressure, SII: systemic immune-inflammation index.

Appendix 15. Associations of dichotomized biomarkers of systemic inflammatory response with all-cause and cause-specific mortality, by age group (N=397,737)

	Biomarkers of systemic inflammatory response, HR (95%CI) [a]								
Mortality	**CRP**	**mGPS**	**HS_mGPS**	**NLR**	**PLR**	**LMR**	**SII**	**PNI**	**NPS**
Age, 37-64 years									
All-cause (N_{deaths}= 17,249)	1.73 (1.67,1.79)	1.74 (1.69,1.80)	1.80 (1.72,1.87)	1.52 (1.48,1.57)	2.02 (1.91,2.13)	1.74 (1.65,1.84)	1.82 (1.74,1.89)	1.44 (1.40,1.49)	1.98 (1.87,2.09)
CVD (N_{deaths}= 3,402)	1.81 (1.68,1.95)	1.80 (1.67,1.94)	1.97 (1.80,2.14)	1.79 (1.67,1.92)	2.20 (1.95,2.49)	1.74 (1.52,1.98)	1.87 (1.71,2.06)	1.65 (1.54,1.77)	1.87 (1.65,2.11)
Cancer (N_{deaths}= 9,185)	1.65 (1.57,1.73)	1.65 (1.57,1.72)	1.57 (1.48,1.67)	1.35 (1.29,1.41)	1.66 (1.53,1.81)	1.63 (1.51,1.77)	1.57 (1.48,1.67)	1.31 (1.25,1.37)	1.79 (1.65,1.94)
Respiratory (N_{deaths}= 1,062)	2.95 (2.59,3.36)	2.99 (2.62,3.41)	2.50 (2.16,2.89)	2.15 (1.91,2.43)	4.33 (3.67,5.10)	2.37 (1.95,2.89)	2.33 (2.00,2.73)	2.28 (2.02,2.57)	3.39 (2.82,4.07)
Age, 65-73 years									
All-cause (N_{deaths}= 12,299)	1.44 (1.38,1.49)	1.44 (1.39,1.50)	1.44 (1.38,1.51)	1.42 (1.37,1.47)	1.91 (1.79,2.05)	1.44 (1.34,1.54)	1.38 (1.31,1.44)	1.42 (1.37,1.47)	1.82 (1.70,1.94)
CVD (N_{deaths}= 2,689)	1.44 (1.33,1.56)	1.49 (1.38,1.62)	1.61 (1.47,1.77)	1.59 (1.47,1.72)	2.19 (1.90,2.51)	1.26 (1.07,1.48)	1.38 (1.25,1.52)	1.53 (1.41,1.65)	1.71 (1.49,1.96)
Cancer (N_{deaths}= 5,710)	1.43 (1.35,1.51)	1.43 (1.35,1.52)	1.33 (1.24,1.42)	1.24 (1.17,1.31)	1.52 (1.36,1.71)	1.43 (1.30,1.59)	1.33 (1.24,1.43)	1.29 (1.22,1.37)	1.73 (1.57,1.90)
Respiratory (N_{deaths}= 1,024)	2.41 (2.12,2.73)	2.37 (2.08,2.69)	1.83 (1.58,2.11)	1.80 (1.59,2.04)	3.67 (3.05,4.42)	1.94 (1.57,2.39)	1.59 (1.37,1.85)	1.99 (1.76,2.26)	3.27 (2.74,3.91)
Interaction p-value[b]									
All-cause	**<0.01**	**<0.01**	**<0.01**	0.10	**<0.01**	**<0.01**	0.20	**<0.01**	**<0.01**
CVD	**<0.01**	0.13	**<0.01**	0.70	0.07	0.32	0.63	0.09	0.57
Cancer	**<0.01**	0.14	**0.02**	0.11	0.09	0.11	0.27	**<0.01**	**0.04**
Respiratory	**<0.01**	**0.04**	**<0.01**	**0.04**	0.44	**0.047**	0.06	**<0.01**	**0.01**

Abbreviations: CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; HR: hazard ratio; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

[a]: The models are adjusted for sex, body mass index, waist circumference, and vitamin D status. [b]: Statistically significant interactions with age ($p<0.05$) were printed in bold.

Appendix 16. Associations of dichotomized biomarkers of systemic inflammatory response with all-cause and cause-specific mortality, by sex (N=397,737)

	Biomarkers of systemic inflammatory response, HR (95%CI) [a]								
	CRP	**mGPS**	**HS_mGPS**	**NLR**	**PLR**	**LMR**	**SII**	**PNI**	**NPS**
Mortality	> 2.75 mg/L	≥ 1	≥ 1	> 2.78	> 237	< 2.56	> 717	< 50	≥ 1
Females									
All-cause (N_{deaths}=11,648)	1.42 (1.36,1.47)	1.78 (1.66,1.89)	1.42 (1.36,1.48)	1.49 (1.43,1.55)	1.67 (1.57,1.79)	1.76 (1.65,1.87)	1.42 (1.36,1.47)	1.52 (1.44,1.59)	1.89 (1.77,2.03)
CVD (N_{deaths}=1,783)	1.34 (1.21,1.49)	1.58 (1.35,1.86)	1.35 (1.22,1.50)	1.71 (1.55,1.90)	1.50 (1.26,1.80)	1.97 (1.70,2.29)	1.57 (1.43,1.74)	1.50 (1.32,1.71)	2.04 (1.73,2.41)
Cancer (N_{deaths}=6,657)	1.39 (1.32,1.47)	1.59 (1.45,1.74)	1.40 (1.32,1.48)	1.31 (1.24,1.38)	1.61 (1.47,1.76)	1.56 (1.43,1.70)	1.26 (1.20,1.33)	1.40 (1.31,1.50)	1.55 (1.40,1.71)
Respiratory (N_{deaths}=730)	2.60 (2.21,3.05)	3.59 (2.93,4.40)	2.50 (2.13,2.94)	2.16 (1.85,2.51)	2.27 (1.80,2.86)	2.45 (1.99,3.03)	2.18 (1.89,2.53)	1.81 (1.50,2.18)	3.99 (3.26,4.89)
Males									
All-cause (N_{deaths}=17,900)	1.66 (1.61,1.71)	1.98 (1.88,2.09)	1.67 (1.62,1.73)	1.44 (1.39,1.48)	1.55 (1.47,1.65)	1.46 (1.41,1.51)	1.46 (1.42,1.51)	1.49 (1.43,1.55)	2.14 (2.02,2.26)
CVD (N_{deaths}=4,308)	1.72 (1.62,1.84)	1.91 (1.72,2.14)	1.75 (1.64,1.87)	1.64 (1.54,1.74)	1.50 (1.33,1.69)	1.62 (1.51,1.73)	1.61 (1.51,1.71)	1.51 (1.39,1.63)	2.35 (2.11,2.62)
Cancer (N_{deaths}=8,238)	1.62 (1.54,1.70)	1.88 (1.73,2.04)	1.62 (1.54,1.70)	1.27 (1.22,1.33)	1.50 (1.38,1.64)	1.30 (1.24,1.37)	1.36 (1.30,1.42)	1.35 (1.27,1.43)	1.77 (1.62,1.94)
Respiratory (N_{deaths}=1,356)	2.56 (2.29,2.86)	3.05 (2.58,3.59)	2.60 (2.32,2.90)	1.82 (1.64,2.03)	2.03 (1.69,2.44)	1.86 (1.65,2.09)	2.10 (1.89,2.34)	1.72 (1.50,1.97)	4.14 (3.55,4.84)
Interaction p-value									
All-cause	**<0.01**	**<0.01**	**<0.01**	0.38	0.18	**<0.01**	0.10	0.87	**<0.01**
CVD	**<0.01**	**0.03**	**<0.01**	0.41	0.96	**<0.01**	0.69	0.89	0.12
Cancer	**<0.01**	**<0.01**	**<0.01**	0.84	0.36	**<0.01**	**0.02**	0.94	**0.03**
Respiratory	0.46	0.12	0.87	0.11	0.79	**0.04**	0.75	0.77	0.74

Abbreviations: CI: confidence interval; CRP: C-reactive protein; CVD: cardiovascular disease; HR: hazard ratio; HS_mGPS: High-sensitive mGPS; LMR: lymphocyte-to-monocyte ratio; mGPS: modified Glasgow prognostic score; NLR: neutrophil-to-lymphocyte ratio; NPS: neutrophil-platelet score; PLR: platelet-to-lymphocyte ratio; PNI: prognostic nutritional index; SII: systemic immune-inflammation index.

[a]: The models are adjusted for age, body mass index, waist circumference, and vitamin D status. [b]: Statistically significant interactions with sex ($p<0.05$) were printed in bold.

Appendix 17. Associations of vitamin D deficiency in comparison to sufficient vitamin D status with biomarkers of systemic inflammatory response in logistic regression models, stratifying by age (N=261,045)

		Vitamin D deficiency, N=83,929		
Biomarkers of systemic inflammatory response		**Age, 37-64 years** N= 71,494	**Age, 65-73 years** N= 12,435	
N_{total}		**OR (95%CI) [b], FDR**	**OR (95%CI) [b], FDR**	**Interaction, FDR [c]**
CRP based	**CRP**	1.02 (1.00, 1.05), 0.148	0.98 (0.93, 1.03), 0.528	0.008
	mGPS	0.99 (0.94, 1.05), 0.882	0.97 (0.87, 1.07), 0.584	0.009
	HS_mGPS	1.03 (1.00, 1.06), 0.068	1.00 (0.95, 1.06), 0.882	0.125
Blood cell	**NPS**	1.12 (1.05, 1.18), <.001	1.16 (1.04, 1.30), 0.021	0.205
	NLR	1.10 (1.07, 1.13), <.001	1.10 (1.05, 1.16), <.001	0.180
	PLR	1.09 (1.04, 1.15), 0.002	1.10 (0.99, 1.22), 0.133	0.237
	LMR	1.05 (1.01, 1.09), 0.036	1.00 (0.93, 1.07), 0.996	0.483
	SII	1.16 (1.13, 1.19), <.001	1.16 (1.10, 1.23), <.001	0.676
	PNI	1.09 (1.04, 1.13), <.001	1.03 (0.96, 1.11), 0.483	0.017

Abbreviations: CRP: C-reactive protein, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, NLR: neutrophil-to-lymphocyte ratio, NPS: neutrophil-platelet score, OR: odds ratio, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, SII: systemic immune-inflammation index.

[a] N=136,692 participants with vitamin D sufficiency (reference group) not shown.

[b] The model is adjusted for covariates in Model 4 (see legend of Table 10)

[c] Age was considered as continuous variable when calculating interaction terms.

Appendix 18. Associations of vitamin D deficiency in comparison to sufficient vitamin D status with biomarkers of systemic inflammatory response in logistic regression models, stratifying by sex (N=261,045)

Biomarkers of systemic inflammatory response		Vitamin D deficiency, N=83,929 [a]		
		Females N=44,195	Males N=39,734	
N_{total}		OR (95%CI) [b], FDR	OR (95%CI) [b], FDR	Interaction, FDR
CRP based	**CRP**	0.97 (0.94, 1.01), 0.175	1.03 (0.99, 1.07), 0.148	0.216
	mGPS	0.95 (0.89, 1.01), 0.152	1.00 (0.92, 1.08), 0.987	0.036
	HS_mGPS	0.98 (0.95, 1.01), 0.318	1.05 (1.01, 1.09), 0.039	0.308
Blood cell	**NPS**	1.10 (1.03, 1.17), 0.015	1.13 (1.04, 1.22), 0.010	0.469
	NLR	1.12 (1.08, 1.16), <.001	1.08 (1.04, 1.11), <.001	<.001
	PLR	1.14 (1.07, 1.21), <.001	1.03 (0.96, 1.11), 0.483	<.001
	LMR	1.11 (1.04, 1.17), 0.003	1.01 (0.97, 1.05), 0.744	<.001
	SII	1.19 (1.15, 1.23), <.001	1.11 (1.07, 1.15), <.001	<.001
	PNI	1.08 (1.03, 1.13), 0.004	1.07 (1.01, 1.12), 0.035	<.001

Abbreviations: CRP: C-reactive protein, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, NLR: neutrophil-to-lymphocyte ratio, NPS: neutrophil-platelet score, OR: odds ratio, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, SII: systemic immune-inflammation index.

[a] N=136,692 participants with vitamin D sufficiency (reference group) not shown.

[b] The model is adjusted for covariates in Model 4 (see legend of Table 10).

Appendix 19. Estimates of mediation of biomarkers of systemic inflammatory response in the association between vitamin D deficiency (versus sufficient vitamin D status) with all-cause mortality and cause-specific mortality

Mortality outcomes	Mediator	Natural direct effect [a]	Natural indirect effect [b]	Total effect [c]	Proportion mediated [d]
		HR (95%CI) [e]	HR [e]	HR (95%CI) [e]	%
All-cause	**CRP**	1.35 (1.30,1.39)	1.00	1.35 (1.30,1.40)	0.3
	mGPS	1.34 (1.30,1.39)	1.00	1.34 (1.30,1.39)	-0.3
	HS_mGPS	1.34 (1.30,1.39)	1.00	1.35 (1.30,1.39)	0.5
	NPS	1.35 (1.30,1.39)	1.00	1.35 (1.30,1.40)	0.9
	NLR	1.34 (1.29,1.38)	1.01	1.34 (1.30,1.39)	2.6
	PLR	1.34 (1.30,1.39)	1.00	1.35 (1.31,1.40)	1.5
	LMR	1.34 (1.29,1.38)	1.00	1.34 (1.29,1.39)	1.1
	SII	1.34 (1.29,1.38)	1.01	1.35 (1.30,1.40)	3.7
	PNI	1.34 (1.30,1.39)	1.00	1.35 (1.30,1.39)	1.6
CVD	**CRP**	1.20 (1.14,1.26)	1.00	1.20 (1.14,1.26)	0.4
	mGPS	1.39 (1.29,1.50)	1.00	1.39 (1.29,1.50)	-0.2
	HS_mGPS	1.39 (1.29,1.50)	1.00	1.39 (1.29,1.50)	0.6
	NPS	1.40 (1.30,1.51)	1.00	1.41 (1.31,1.52)	0.9
	NLR	1.39 (1.29,1.50)	1.01	1.40 (1.30,1.51)	3.0
	PLR	1.40 (1.30,1.51)	1.00	1.41 (1.31,1.52)	1.1
	LMR	1.40 (1.30,1.51)	1.00	1.40 (1.30,1.51)	1.0
	SII	1.39 (1.29,1.50)	1.01	1.41 (1.31,1.52)	4.3
	PNI	1.40 (1.30,1.51)	1.00	1.41 (1.30,1.51)	1.2
Cancer	**CRP**	1.20 (1.14,1.26)	1.00	1.20 (1.14,1.26)	0.4
	mGPS	1.20 (1.14,1.25)	1.00	1.19 (1.14,1.25)	-0.3
	HS_mGPS	1.20 (1.14,1.26)	1.00	1.20 (1.14,1.26)	0.7
	NPS	1.19 (1.14,1.25)	1.00	1.19 (1.14,1.25)	1.0
	NLR	1.19 (1.13,1.25)	1.00	1.20 (1.14,1.25)	2.3
	PLR	1.19 (1.14,1.25)	1.00	1.20 (1.14,1.26)	2.5
	LMR	1.19 (1.13,1.25)	1.00	1.19 (1.13,1.25)	1.3
	SII	1.19 (1.13,1.25)	1.01	1.20 (1.14,1.26)	3.9
	PNI	1.19 (1.13,1.25)	1.00	1.19 (1.14,1.25)	1.9
Respiratory diseases	**CRP**	1.67 (1.47,1.90)	1.00	1.68 (1.47,1.91)	0.4
	mGPS	1.67 (1.47,1.90)	1.00	1.67 (1.47,1.90)	-0.3
	HS_mGPS	1.67 (1.47,1.90)	1.00	1.68 (1.47,1.91)	0.7
	NPS	1.70 (1.49,1.93)	1.00	1.70 (1.50,1.93)	1.0
	NLR	1.62 (1.42,1.84)	1.01	1.64 (1.44,1.86)	3.2
	PLR	1.65 (1.46,1.87)	1.01	1.66 (1.47,1.88)	1.6
	LMR	1.63 (1.43,1.85)	1.00	1.63 (1.44,1.85)	1.2
	SII	1.61 (1.41,1.82)	1.02	1.65 (1.45,1.87)	6.1

Mortality outcomes	Mediator	Natural direct effect [a]	Natural indirect effect [b]	Total effect [c]	Proportion mediated [d]
		HR (95%CI) [e]	**HR [e]**	**HR (95%CI) [e]**	**%**
	PNI	1.64 (1.45,1.86)	1.01	1.65 (1.46,1.88)	1.5

Abbreviations: CI: confidence interval, CRP: C-reactive protein, CVD: cardiovascular disease, HR: hazard ratio, HS_mGPS: High-sensitive mGPS, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, NA: not applicable, NLR: neutrophil-to-lymphocyte ratio, NPS: neutrophil-platelet score, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, SII: systemic immune-inflammation index.

[a]: The natural direct effect estimates the part of the total effect that does not operate through the mediator.

[b]: The natural indirect effect estimates the effect of an exposure on an outcome through its effect on the level of the mediator.

[c]: The total effect for a time-to-event model is the product of the natural indirect effect and the natural direct effect.

[d]: Proportion mediated = (natural direct effect * (natural indirect effect − 1)) / (natural direct effect * natural indirect effect − 1).

[e]: All models were adjusted for the covariates of Model 4 (see legend of Table 10). The first imputed dataset (imputation=1) was used in the analyses.

Appendix 20. Estimates of mediation of biomarkers of systemic inflammatory response in the association between vitamin D insufficiency (versus sufficient vitamin D status) with all-cause mortality and cause-specific mortality

Mortality outcome	Mediator	Natural direct effect [a]	Natural indirect effect [b]	Total effect [c]	Proportion mediated [d]
		HR (95%CI) [e]	HR (95%CI) [e]	HR (95%CI) [e]	%
All-cause	**CRP**	1.10 (1.07,1.13)	1.00	1.10 (1.07,1.13)	-1.6
	mGPS	1.10 (1.07,1.13)	1.00	1.10 (1.07,1.13)	-2.0
	HS_mGPS	1.10 (1.07,1.13)	1.00	1.10 (1.07,1.13)	-1.6
	NPS	1.09 (1.06,1.13)	1.00	1.09 (1.06,1.12)	-0.2
	NLR	1.09 (1.06,1.12)	1.00	1.09 (1.06,1.12)	0.8
	PLR	1.09 (1.06,1.13)	1.00	1.09 (1.06,1.13)	-0.1
	LMR	1.10 (1.07,1.13)	1.00	1.10 (1.07,1.13)	-0.3
	SII	1.09 (1.06,1.12)	1.00	1.09 (1.06,1.12)	2.7
	PNI	1.10 (1.07,1.13)	1.00	1.10 (1.06,1.13)	-0.4
CVD	**CRP**	1.13 (1.06,1.21)	1.00	1.13 (1.06,1.21)	-1.1
	mGPS	1.13 (1.06,1.20)	1.00	1.13 (1.06,1.20)	-1.3
	HS_mGPS	1.13 (1.06,1.21)	1.00	1.13 (1.06,1.20)	-1.2
	NPS	1.12 (1.05,1.19)	1.00	1.12 (1.05,1.19)	-0.2
	NLR	1.12 (1.05,1.19)	1.00	1.12 (1.05,1.19)	0.9
	PLR	1.12 (1.05,1.20)	1.00	1.12 (1.05,1.19)	-0.1
	LMR	1.13 (1.06,1.20)	1.00	1.13 (1.06,1.20)	-0.3
	SII	1.12 (1.05,1.19)	1.00	1.12 (1.05,1.19)	3.0
	PNI	1.12 (1.05,1.19)	1.00	1.12 (1.05,1.19)	-0.4
Cancer	**CRP**	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	-3.1
	mGPS	1.05 (1.01,1.10)	1.00	1.05 (1.01,1.09)	-3.3
	HS_mGPS	1.05 (1.01,1.10)	1.00	1.05 (1.01,1.09)	-3.0
	NPS	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	-0.2
	NLR	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	1.1
	PLR	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	-0.2
	LMR	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	-0.3
	SII	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	3.6
	PNI	1.05 (1.01,1.09)	1.00	1.05 (1.01,1.09)	-0.6
Respiratory diseases	**CRP**	1.25 (1.12,1.40)	1.00	1.25 (1.12,1.39)	-2.0
	mGPS	1.28 (1.14,1.42)	1.00	1.27 (1.14,1.42)	-2.0
	HS_mGPS	1.26 (1.13,1.41)	1.00	1.26 (1.13,1.41)	-1.7
	NPS	1.26 (1.13,1.41)	1.00	1.26 (1.13,1.40)	-0.2
	NLR	1.27 (1.14,1.41)	1.00	1.27 (1.14,1.42)	0.5
	PLR	1.29 (1.15,1.44)	1.00	1.29 (1.15,1.44)	-0.2
	LMR	1.26 (1.13,1.41)	1.00	1.26 (1.13,1.41)	-0.1
	SII	1.26 (1.13,1.40)	1.01	1.26 (1.13,1.41)	2.5

Mortality outcome	Mediator	Natural direct effect [a]	Natural indirect effect [b]	Total effect [c]	Proportion mediated [d]
		HR (95%CI) [e]	HR (95%CI) [e]	HR (95%CI) [e]	%
	PNI	1.27 (1.14,1.42)	1.00	1.27 (1.14,1.42)	-0.2

Abbreviations: CI: confidence interval, CRP: C-reactive protein, CVD: cardiovascular disease, HR: hazard ratio, HS_mGPS: High-sensitive mGPS, LMR: lymphocyte-to-monocyte ratio, mGPS: modified Glasgow prognostic score, NA: not applicable, NLR: neutrophil-to-lymphocyte ratio, NPS: neutrophil-platelet score, PLR: platelet-to-lymphocyte ratio, PNI: prognostic nutritional index, SII: systemic immune-inflammation index.

[a]: The natural direct effect estimates the part of the total effect that does not operate through the mediator.

[b]: The natural indirect effect estimates the effect of an exposure on an outcome through its effect on the level of the mediator.

[c]: The total effect for a time-to-event model is the product of the natural indirect effect and the natural direct effect.

[d]: Proportion mediated = (natural direct effect * (natural indirect effect − 1)) / (natural direct effect * natural indirect effect − 1).

[e]: All models were adjusted for the covariates of Model 4 (see legend of Table 10). The first imputed dataset (imputation=1) was used in the analyses.

Appendix 21. Distribution of full list of baseline characteristics of the study population in the cross-sectional and longitudinal analyses – for low back pain study

Variables	Cross-sectional analysis N(%)[b]/Median (IQR)	Longitudinal analysis [a] N(%)[b] /Median (IQR)
N_{total}	135,934	130,843
SOCIO-DEMOGRAPHIC/-ECONOMIC FACTORS		
Age (years), median (IQR)	58 (50; 63)	58 (50; 63)
Sex, n (%)		
Female	73,427 (54.0)	70,690 (54.0)
Male	62,507 (46.0)	60,153 (46.0)
Education (years), median (IQR)	12 (10; 17)	12 (10; 17)
Annual household income (£), n (%)		
< 18,000	25,666 (18.9)	24,310 (18.6)
18,000 - < 51,999	61,611 (45.3)	59,470 (45.5)
52,000 - < 100,000	24,065 (17.7)	23,431 (17.9)
≥ 100,000	6269 (4.6)	6141 (4.7)
LIFESTYLE FACTORS		
Smoking, n (%)		
Never	76,907 (56.6)	74,471 (56.9)
Ever	58,990 (43.4)	56,337 (43.1)
Venturesome personality, n (%)		
No	96,988 (71.4)	93,542 (71.5)
Yes	34,087 (25.1)	32,644 (25.0)
Total physical activity (hours/day), n (%)		
≤ 1	20,158 (14.8)	19,212 (14.7)
≤ 2	45,388 (33.4)	43,979 (33.6)
> 2	45,390 (33.4)	43,839 (33.5)
DISEASES & DISEASE SYMPTOMS		
Diabetes, n (%)		
No	129,609 (95.4)	124,850 (95.4)
Yes	6286 (4.6)	5957 (4.6)
Stroke, n (%)		
No	134,198 (98.7)	129,207 (98.8)
Yes	1696 (1.3)	1599 (1.2)
Coronary heart disease, n (%)		
No	130,097 (95.7)	125,377 (95.8)
Yes	5797 (4.3)	5429 (4.2)
Hypertension, n (%)		
No	100,883 (74.2)	97,450 (74.5)
Yes	35,014 (25.7)	33,359 (25.5)
History of depression, n (%)		
No	121,281 (89.2)	116,965 (89.4)
Yes	14,614 (10.8)	13,842 (10.6)
Frequency of depressed mood in last 2 weeks, n (%)		
≤ half the days	124,873 (91.9)	120,528 (92.1)

Variables	Cross-sectional analysis N(%)[b]/Median (IQR)	Longitudinal analysis [a] N(%)[b] /Median (IQR)
> half the days	5448 (4.0)	5004 (3.8)
Tiredness/lethargy in last 2 weeks, n (%)		
≤ half the days	117,967 (86.8)	114,150 (87.2)
> half the days	13,967 (10.3)	12,860 (9.8)
History of musculoskeletal disease, n (%)		
No	63,150 (46.5)	62,319 (47.6)
Yes	72,784 (53.5)	68,524 (52.4)
History of injury to abdomen, lower back, lumbar spine and pelvis, n (%)		
No	133,260 (98.0)	128,459 (98.2)
Yes	2674 (2.0)	2384 (1.8)
Cancer, n (%)		
No	125,650 (92.4)	120,951 (92.4)
Yes	9922 (7.3)	9548 (7.3)
BIOMARKERS		
Body mass index (kg/m^2), n (%)		
Underweight, < 18.5	709 (0.5)	685 (0.5)
Normal weight, 18.5 - <25	45,916 (33.8)	44,666 (34.1)
Overweight: 25 - < 30	57,440 (42.3)	55,317 (42.3)
Obesity class: ≥ 30	31,368 (23.1)	29,703 (22.7)
Systolic blood pressure (mmHg), n (%)		
< 140	70,852 (52.1)	68,045 (52.0)
140 - < 160	43,070 (31.7)	41,497 (31.7)
160 - < 180	17,257 (12.7)	16,698 (12.8)
≥ 180	4590 (3.4)	4448 (3.4)
Forced expiratory volume in 1-second (L), median (IQR)	2.8 (2.3; 3.3)	2.8 (2.3; 3.3)
Hand grip strength (Kg), median (IQR)	31 (24; 41)	31 (24; 41)
GENERAL HEALTH		
Disability (%)		
No	128,905 (94.8)	124,728 (95.3)
Yes	6002 (4.4)	5165 (4.0)
General self-reported health, n (%)		
Excellent	25,577 (18.8)	25,248 (19.3)
Good	80,962 (59.6)	78,609 (60.1)
Fair	24,415 (18.0)	22,642 (17.3)
Poor	4472 (3.3)	3867 (3.0)
No of chronic diseases, median (IQR)	1 (0; 3)	1 (0; 3)
No of drugs, median (IQR)	2 (0; 3)	2 (0; 3)
Low-dose aspirin use, n (%)		
No	117,001 (86.1)	112,774 (86.2)
Yes	18,893 (13.9)	18,032 (13.8)
Lipid-lowering drugs use, n (%)		
No	112,724 (82.9)	108,794 (83.2)

Variables	Cross-sectional analysis N(%)[b]/Median (IQR)	Longitudinal analysis [a] N(%)[b] /Median (IQR)
Yes	23,172 (17.1)	22,014 (16.8)
Anti-depressants use, n (%)		
No	128,132 (94.3)	123,729 (94.6)
Yes	7762 (5.7)	7077 (5.4)
VITAMIN D SPECIFIC FACTORS		
Latitude of study center (per 1°), median (IQR)	53.4 (52.5; 54.6)	53.4 (52.5; 54.6)
Calendar month of attending the study center		
1	10,791 (7.9)	10,358 (7.9)
2-3	24,925 (18.3)	23,917 (18.3)
4	12,267 (9.0)	11,725 (9.0)
5	13,516 (9.9)	12,936 (9.9)
6	12,499 (9.2)	12,074 (9.2)
7	10,338 (7.6)	9977 (7.6)
8	10,705 (7.9)	10,362 (7.9)
9	9600 (7.1)	9294 (7.1)
10	11,331 (8.3)	10,959 (8.4)
11	12,396 (9.1)	11,951 (9.1)
12	7566 (5.6)	7290 (5.6)
Time spent outdoors in summer (h/day), n (%)		
<1	5506 (4.1)	5281 (4.0)
1-2	40,223 (29.6)	39,019 (29.8)
3-4	42,876 (31.5)	41,249 (31.5)
5-6	25,682 (18.9)	24,675 (18.9)
≥ 7	14,310 (10.5)	13,621 (10.4)
Skin color, n (%)		
Light (fair - olive)	127800 (94.0)	123,111 (94.1)
Brown	2428 (1.8)	2319 (1.8)
Black	3167 (2.3)	3006 (2.3)
Ease of skin tanning, n (%)		
Very tanned	27,287 (20.1)	26,106 (20.0)
Moderately tanned	53,107 (39.1)	51,233 (39.2)
Mildly/occasionally tanned	28,599 (21.0)	27,589 (21.1)
Never tan, only burn	23,537 (17.3)	22,653 (17.3)
Solarium/sunlamp use (times per year), n (%)		
Never	121,854 (89.6)	117,433 (89.8)
< 1	6652 (4.9)	6385 (4.9)
1 - 6	3316 (2.4)	3143 (2.4)
7 - 12	1450 (1.1)	1374 (11)
> 12	1386 (1.0)	1308 (1.0)

Abbreviations: IQR: interquartile range.

[a] Population with low back pain before/at baseline not included.

[b] Denominators in proportion calculations contain missing values.

Appendix 22. Cross-sectional association of covariates with low back pain at baseline (N=135,934)

Variable	OR (95%CI)
SOCIO-DEMOGRAPHIC/	
Age (years), median (IQR)	0.98 (0.98, 0.99)
Sex, n (%)	
Female	Ref
Male	0.75 (0.68, 0.83)
Education (years), median (IQR)	0.96 (0.95, 0.97)
Annual household income (£), n (%)	
< 18,000	Ref
18,000 - < 51,999	0.93 (0.86, 1.00)
52,000 - < 100,000	0.85 (0.76, 0.96)
≥ 100,000	0.78 (0.63, 0.96)
LIFESTYLE FACTORS	
Smoking, n (%)	
Never	Ref
Ever	1.34 (1.22, 1.47)
Venturesome personality, n (%)	
No	Ref
Yes	1.12 (1.05, 1.20)
Total physical activity (hours/day), n (%)	
≤ 1	Ref
≤ 2	0.88 (0.81, 0.96)
> 2	0.96 (0.87, 1.06)
DISEASES & DISEASE SYMPTOMS	
Diabetes, n (%)	
No	Ref
Yes	0.80 (0.75, 0.85)
Stroke, n (%)	
No	Ref
Yes	0.64 (0.51, 0.81)
Coronary heart disease, n (%)	
No	Ref
Yes	0.81 (0.71, 0.93)
Hypertension, n (%)	
No	Ref
Yes	0.80 (0.74, 0.87)
History of depression, n (%)	
No	Ref
Yes	0.81 (0.74, 0.89)
Frequency of depressed mood in last 2 weeks, n (%)	
≤ half the days	Ref
> half the days	1.16 (1.03, 1.31)
Tiredness/lethargy in last 2 weeks, n (%)	
≤ half the days	Ref

Variable	OR (95%CI)
> half the days	1.23 (1.13, 1.34)
History of musculoskeletal disease, n (%)	
No	Ref
Yes	3.79 (3.51, 4.09)
History of injury to abdomen, lower back, lumbar spine and pelvis, n (%)	
No	Ref
Yes	2.24 (1.96, 2.56)
Cancer, n (%)	
No	Ref
Yes	0.75 (0.67, 0.84)
BIOMARKERS	
Body mass index (kg/m^2), n (%)	
Underweight, < 18.5	0.95 (0.62, 1.46)
Normal weight, 18.5 - < 25	Ref
Overweight: 25 - < 30	1.13 (1.05, 1.22)
Obesity class: ≥ 30	1.13 (1.04, 1.23)
Systolic blood pressure (mmHg), n (%)	
< 140	Ref
140 - < 160	0.89 (0.83, 0.96)
160 - < 180	0.80 (0.72, 0.88)
≥ 180	0.81 (0.68, 0.97)
Forced expiratory volume in 1-second (L), median (IQR)	1.07 (1.02, 1.13)
Hand grip strength (Kg), median (IQR)	1.20 (1.14, 1.25)
GENERAL HEALTH	
Disability (%)	
No	Ref
Yes	1.76 (1.59, 1.95)
General self-reported health, n (%)	
Excellent	Ref
Good	1.85 (1.65, 2.09)
Fair	3.36 (2.96, 3.82)
Poor	3.53 (2.98, 4.19)
No of chronic diseases, median (IQR)	1.11 (1.09, 1.13)
No of drugs, median (IQR)	1.10 (1.09, 1.12)
Low-dose aspirin use, n (%)	
No	Ref
Yes	0.88 (0.80, 0.97)
Lipid-lowering drugs use, n (%)	
No	Ref
Yes	0.86 (0.78, 0.94)
Anti-depressants use, n (%)	
No	Ref
Yes	1.17 (1.06, 1.30)
VITAMIN D SPECIFIC FACTORS	
Latitude of study center (per 1°), median	0.88 (0.86, 0.90)

Variable	OR (95%CI)
Calendar month of attending the study center	
1	Ref
2-3	0.98 (0.87, 1.10)
4	1.09 (0.95, 1.24)
5	1.02 (0.90, 1.17)
6	0.82 (0.71, 0.94)
7	0.82 (0.71, 0.95)
8	0.77 (0.67, 0.90)
9	0.79 (0.68, 0.92)
10	0.82 (0.71, 0.95)
11	0.93 (0.81, 1.07)
12	0.94 (0.80, 1.10)
Time spent outdoors in summer (h/day), n (%)	
<1	Ref
1-2	0.95 (0.82, 1.11)
3-4	1.13 (0.96, 1.32)
5-6	1.13 (0.96, 1.32)
≥ 7	1.30 (1.10, 1.54)
Skin color, n (%)	
Light (fair - olive)	Ref
Brown	1.23 (1.03, 1.47)
Black	1.15 (0.80, 1.66)
Ease of skin tanning, n (%)	
Very tanned	Ref
Moderately tanned	0.94 (0.87, 1.01)
Mildly/occasionally tanned	0.93 (0.85, 1.02)
Never tan, only burn	0.91 (0.83, 1.00)
Solarium/sunlamp use (times per year), n (%)	
Never	Ref
< 1	1.10 (0.97, 1.26)
1 - 6	1.35 (1.14, 1.59)
7 - 12	1.37 (1.07, 1.75)
> 12	1.39 (1.09, 1.77)

Abbreviations: CI: confidence interval, OR: odds ratio, Ref: reference.

Appendix 23. Subgroup analyses on the associations of vitamin D deficiency and insufficiency with low back pain, cross-sectionally and longitudinally

Study population	Cross-sectional analyses						Longitudinal analyses					
	Vitamin D status						Vitamin D status					
	Deficiency		Insufficiency		Sufficiency		Deficiency		Insufficiency		Sufficiency	
	N_{case} (%)	OR (95%CI)	N_{case} (%)	OR (95%CI)	N_{case} (%)	OR (95%CI)	N_{case}(%)	HR (95%CI)	N_{case} (%)	HR (95%CI)	N_{case} (%)	HR (95%CI)
By age												
<65 years	1039 (4.1)	0.94 (0.86, 1.03)	1452 (3.8)	0.98 (0.90, 1.05)	1722 (3.7)	Ref	755 (3.1)	0.87 (0.79, 0.97) **	1255 (3.4)	1.00 (0.92, 1.08)	1481 (3.3)	Ref
≥65 years	164 (3.9)	1.00 (0.81, 1.23)	289 (3.4)	0.95 (0.81, 1.12)	425 (3.4)	Ref	119 (2.96)	0.85 (0.68, 1.07)	278 (3.39)	0.99 (0.85, 1.17)	400 (3.32)	Ref
By sex												
Females	657 (4.1)	0.97 (0.87, 1.09)	925 (3.67)	0.97 (0.88, 1.07)	1155 (3.57)	Ref	487 (3.20)	0.93 (0.82, 1.05)	841 (3.46)	1.05 (0.96, 1.16)	1007 (3.23)	Ref
Males	546 (4.0)	0.93 (0.81, 1.05)	816 (3.75)	0.97 (0.88, 1.08)	992 (3.65)	Ref	387 (2.98)	0.82 (0.71, 0.94)	692 (3.31)	0.94 (0.85, 1.05)	874 (3.33)	Ref
By history of depression												
Yes	179 (5.6)	0.76 (0.61,0.96) *	270 (5.43)	0.91 (0.75, 1.09)	324 (5.04)	Ref	108 (3.55)	0.85 (0.65, 1.11)	166 (3.53)	0.90 (0.73, 1.11)	233 (3.82)	Ref
No	1024 (3.9)	0.98 (0.90, 1.08)	1471 (3.50)	0.98 (0.91, 1.06)	1823 (3.43)	Ref	766 (3.0)	0.88 (0.79, 0.97) *	1367 (3.4)	1.01 (0.94, 1.09)	1648 (3.2)	Ref
By history of musculoskeletal disease												
Yes	994 (6.9)	0.97 (0.88, 1.07)	1455 (5.87)	0.99 (0.91, 1.06)	1811 (5.39)	Ref	532 (3.98)	0.90 (0.80, 1.01)	971 (4.16)	1.01 (0.92, 1.10)	1242 (3.90)	Ref
No	209 (1.4)	0.84 (0.69, 1.03)	286 (1.29)	0.90 (0.76, 1.07)	336 (1.30)	Ref	342 (2.30)	0.82 (0.70, 0.95) *	562 (2.57)	0.98 (0.87, 1.10)	639 (2.50)	Ref

Abbreviations: CI: confidence interval, HR: hazard ratio, OR: odds ratio, Ref: reference.

* p<0.05, ** p<0.001

[a]: Subgroup analyses adjusted for all covariates listed in Table 14, except for the one used for categorizing subgroups.

Appendix 24. Subgroup analyses on the associations of vitamin D supplement and multivitamin use with low back pain, cross-sectionally and longitudinally

Study population	Cross-sectional analyses						Longitudinal analyses					
	Vitamin supplement use						Vitamin supplement use					
	Non-users		Multivitamin		Vitamin D		Non-users		Multivitamin		Vitamin D	
	$N_{case\ (\%)}$	OR[a] (95%CI)	N_{case} (%)	OR[a] (95%CI)	N_{case} (%)	OR (95%CI)	$N_{case\ (\%)}$	HR[a] (95%CI)	N_{case} (%)	HR[a] (95%CI)	N_{case} (%)	HR[a] (95%CI)
By age												
<65 years	3173 (3.8)	Ref	848 (3.8)	0.96 (0.88, 1.04)	192 (4.6)	0.96 (0.82, 1.13)	2658 (3.3)	Ref	706 (3.3)	0.99 (0.91, 1.08)	127 (3.2)	0.95 (0.79, 1.14)
≥65 years	651 (3.4)	Ref	167 (3.59)	1.06 (0.88, 1.27)	60 (4.78)	1.20 (0.90, 1.60)	611 (3.3)	Ref	147 (3.3)	0.99 (0.82, 1.19)	39 (3.3)	0.95 (0.68, 1.32)
By sex												
Females	1969 (3.7)	Ref	597 (3.66)	0.93 (0.84, 1.03)	171 (4.48)	0.96 (0.81, 1.14)	1704 (3.32)	Ref	515 (3.27)	0.96 (0.87, 1.06)	116 (3.18)	0.92 (0.76, 1.11)
Males	1855 (3.7)	Ref	418 (3.99)	1.04 (0.93, 1.17)	81 (5.06)	1.11 (0.87, 1.41)	1565 (3.22)	Ref	338 (3.36)	1.04 (0.92, 1.17)	50 (3.29)	1.01 (0.76, 1.34)
By history of depression												
Yes	575 (5.4)	Ref	159 (4.88)	0.94 (0.78, 1.14)	39 (5.70)	0.84 (0.58, 1.20)	367 (3.63)	Ref	109 (3.52)	0.97 (0.78, 1.21)	31 (4.81)	1.25 (0.86, 1.83)
No	3249 (3.5)	Ref	856 (3.63)	0.99 (0.91, 1.07)	213 (4.50)	1.05 (0.90, 1.22)	2902 (3.2)	Ref	744 (3.3)	0.99 (0.91, 1.08)	135 (3.0)	0.89 (0.75, 1.07)
By history of musculoskeletal disease												
Yes	3173 (5.8)	Ref	863 (5.94)	1.01 (0.93, 1.10)	224 (6.80)	1.05 (0.90, 1.22)	2090 (4.03)	Ref	537 (3.93)	0.96 (0.88, 1.06)	118 (3.84)	0.96 (0.79, 1.15)
No	651 (1.3)	Ref	152 (1.24)	0.84 (0.70, 1.00)	28 (1.32)	0.82 (0.56, 1.22)	1179 (2.45)	Ref	316 (2.60)	1.04 (0.92, 1.19)	48 (2.29)	0.93 (0.69, 1.25)

Abbreviations: CI: confidence interval, HR: hazard ratio, OR: odds ratio, Ref: reference.

[a] Subgroup analyses adjusted for all covariates listed in Table 14, except for the one used for categorizing subgroups.

Curriculum Vitae

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Eidesstattliche Versicherung

1. Bei der eingereichten Dissertation zu dem Thema

   „ The associations of serum 25-hydroxyvitamin D levels and vitamin D supplement use with inflammation, mortality, and low back pain"

   handelt es sich um meine eigenständig erbrachte Leistung.

2. Ich habe nur die angegebenen Quellen und Hilfsmittel benutzt und mich keiner unzulässigen Hilfe Dritter bedient. Insbesondere habe ich wörtlich oder sinngemäß aus anderen Werken übernommene Inhalte als solche kenntlich gemacht.

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4. Die Richtigkeit der vorstehenden Erklärungen bestätige ich.

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