Version	Date	Changes made	Page number
V1.1	12/05/2022	Number of missing data for statin and cardiovascular drug use at baseline changed from 74 to 16.	5
Note: The analyses pre-specified in Version 1.1 of the statistical analysis plan were completed prior to writing Version 2.0 of the statistical analysis plan. We prepared code for the updated analyses using scrambled data.			
V2.0	10/01/2023	Using date last known to be alive in the calculation used to determine censoring date. V1.1 used date of death.	5
		Specifying that the manuscript will include participant flow diagram (to appear as Figure 1).	6
		Using Aalen-Johansen method to estimate cause-specific cumulative incidence. V1.1 specified the use of Kaplan-Meier methods.	6-7
		Using competing risks analysis to estimate cause-specific standardised cumulative incidence functions, treating death without prior cardiovascular event as a competing risk. In V1.1 we did not treat death as a competing risk.	6-7
		Not including a plot of standardised survival curves according to randomisation groups (was SFigure 1 in V1.1).	Not applicable

Working Title	Cardiovascular disease among participants of D-Health, a randomised trial of vitamin D supplementation		
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Background and overview			
Background	Coronary heart disease (CHD) and stroke are the leading causes of death globally.[1] The risk of CHD and stroke increases with age, and CHD is more prevalent in men than women across all age groups.[2] Cardiovascular diseases are a major burden on the population. In Australia they are the largest cause of years of life lost[3] and the single most expensive disease group in terms of health system cost.[2] CHD incidence will likely continue to increase as the average age increases in populations of developed countries, and as cause of death shifts towards non-communicable diseases in low- to middle-income countries.[4] Vitamin D is crucial for calcium homeostasis, and is best known for its role in musculoskeletal health. It has a number of biological effects which suggest it		

	may also have an influence on cardiovascular disease. The vitamin D receptor is expressed in cells throughout the vascular system; many of these also express 1α-hydroxylase, and are therefore able to convert 25 hydroxy vitamin D (25(OH)D) to calcitriol, the active form of vitamin D. Calcitriol has been shown to reduce inflammation, regulate the renin angiotensin aldosterone system, and inhibit proliferation of vascular smooth muscle.[5] Meta-analyses of observational studies suggest that low serum 25(OH)D concentration is associated with increased risk of various cardiovascular diseases.[6-9] However, these findings may be a result of reverse causality or uncontrolled confounding. In support of this, Mendelian randomisation studies, which largely overcome these biases, have not identified links between genetically predicted 25(OH)D concentration and cardiovascular disease.[10,11] A meta-analysis of randomised controlled trials (RCTs) concluded that vitamin D supplementation does not prevent cardiovascular events.[12] However, 45% of the 83,291 participants included were from the Women's Health Initiative Trial which, in addition to being restricted to women, used a low dose of vitamin D and had relatively poor compliance. In total, 74% of the participants in the meta-analysis were women. Further, most studies were restricted to population subgroups such as women who had experienced an osteoporotic fracture, or people with kidney disease or pre-existing cardiovascular disease.[12] There have been only two RCTs of high-dose vitamin D supplementation, the ViDA[13] and VITAL trials,[14] that were powered to evaluate total cardiovascular events; both found that vitamin D supplementation had no effect, but the power for specific cardiovascular events was limited.[15,16] Further RCT evidence is important to better understand the effect of vitamin D supplementation on specific cardiovascular events. The D-Health trial is the second largest RCT of high-dose vitamin D supplementation. We aim to determine whether supplementing Australians aged 60 years and over with monthly doses of 60,000 IU of vitamin D influences incidence of major cardiovascular events.
Aims	The <u>primary aim</u> of this analysis is to investigate whether randomisation to oral vitamin D supplementation with 60,000 IU per month reduces the incidence rate of first major cardiovascular events (composite grouping of myocardial infarction, stroke, and coronary revascularisation) in the study period. The <u>secondary aims</u> are to investigate the effect of vitamin D supplementation on: 1. Incidence of first major cardiovascular event within subgroups of: age (<70, ≥70 years); sex; body mass index (BMI) (<25, ≥25 kg/m^2); and predicted deseasonalised baseline serum 25(OH)D concentration (<50, ≥50 nmol/L); use of statins; use of cardiovascular drugs; 2. Each of: myocardial infarction, coronary revascularisation, stroke, ischaemic stroke and haemorrhagic stroke.
Outcomes and instrument	
Instrument	**Cardiovascular events** Cardiovascular events will be determined from hospital admissions, Medicare Benefits Schedule (MBS), and mortality data. Hospital admissions data are

	available from each state, although admissions to private hospitals are not included in data from Tasmania or South Australia; data weren't available from territories (i.e. ACT and NT). If a death occurred from myocardial infarction or stroke, with no prior hospitalisation for these conditions,[1] the date of death will be assumed to be the date of the first event. **Statin use at baseline** For participants who consented to linkage with the Pharmaceutical Benefits Scheme (PBS), we will use their PBS data to ascertain statin use at baseline. We will assume that if a person was supplied with any medication with Anatomical Therapeutic Chemical (ATC) code C10 during the 3 months following randomisation then they were using statins at baseline; otherwise they will be classified as not using statins at baseline. For people who did not consent to linkage with the PBS, statin use will be ascertained from self-reported use of medication at baseline for the treatment for hypercholesterolaemia. **Cardiovascular medication use at baseline** Ascertainment of use of medication (other than statins) for the management of cardiovascular disease will proceed as for statin use, with some minor differences. For this we will consider medications with ATC codes C01 – C09, and if a participant did not consent to PBS linkage, cardiovascular drug use will be ascertained from self-reported use of anti-hypertensive medication at baseline[2]. [1]We will only mortality data only when an ICD code was provided for underlying cause of death. [2] Participants were not asked about treatment for other cardiovascular conditions at baseline.
Outcomes	The <u>primary outcome</u> is first major cardiovascular event (composite of myocardial infarction, stroke, or coronary revascularisation) experienced after randomisation. Myocardial infarction (ICD-10 codes I21-I22) and stroke (ICD-10 codes I60-I64) will be identified using principal diagnosis ICD-10 codes from hospital admissions data and underlying cause of death ICD-10 codes from death registration data. Coronary revascularisation will be identified using the Australian Classification of Health Interventions (ACHI) codes from hospital admissions data. Coronary revascularisation will also be identified from MBS data if not identified from the hospital admissions data (admissions to private hospitals are not included in hospital admissions data from Tasmania and South Australia). *See Appendix 1 for more detail on ICD-10, ACHI codes and MBS item codes* *See Appendix 2 for concordance between coronary revascularisation from ACHI codes in hospital admission data and Medicare item numbers in the Medicare data.* The <u>secondary outcomes</u> include each of the following: • First myocardial infarction

	• First stroke (separately for ischaemic and haemorrhagic, as well as combined) • First coronary revascularisation
Documentation	
Analysis packages	SAS 9.4 R version 4.0.3 Stata 17.0
Dataset	**Original datasets:** L:\Lab_RachelN\DHealthDataAnalysis\SAS Files\hospitalisations\hospitalisations_20211124.sas7bdat R:\Lab_RachelN\Dhealth\original data\mbsreport20180329.sas7bdat R:\Lab_RachelN\Dhealth\original data\mbsreport20191231.sas7bdat R:\Lab_RachelN\Dhealth\original data\dhealthbase20210517.sas7bdat **Final datasets will be stored here:** L:\Lab_RachelN\DHealthDataAnalysis\Projects\CardiovascularDisease\Data\Data for analysis R:\Lab_RachelN\Dhealth\CardiovascularRDrive\Data\FinalData
Statistical code	Code used to prepare original datasets: L:\Lab_RachelN\DHealthDataAnalysis\SASCode\CoreDataManipulation\ProjectSetup\cardiovascularEvents\ cardiovascularEvents_createScrambledDatasets_20221221.sas Programs for analysis will be saved in these locations: L:\Lab_RachelN\DHealthDataAnalysis\Projects\CardiovascularDisease\Code\analysis R:\Lab_RachelN\Dhealth\original data\cardiovascular\code
Participants and data	
Participants and eligibility	All randomised participants from the D-Health Trial are eligible excluding the five participants who withdrew from the trial and requested deletion of their data (n=21,310). From this cohort, we will further exclude participants who: - Withdrew consent for linkage to health registers (n=2); - Had unreliable hospital data[a] (n=6); [a] n=6 participants had obviously incorrect hospital data; we have concluded that an error occurred with the probabilistic linkage.
Exposure variable(s)	Randomisation group
Covariates	<u>Adjustment variables:</u> Age: 60-64; 65-69; 70-74; 75+ Sex: F; M State: NSW; QLD; SA; TAS; VIC; WA <u>Variables considered as potential effect modifiers:</u> Sex (male vs female)

	Age at randomisation (<70 years vs ≥70 years) BMI at randomisation (<25 vs ≥25 kg/m^2) Predicted baseline 25(OH)D concentration (<50 vs ≥50 nmol/L) [17] Use of statins at baseline (yes vs no) Use of cardiovascular medication (other than statins) at baseline (yes vs no)
Data cleaning	Date of event Hospital data from the Australian state, Victoria, contains the month and year of admission only. For some admissions we could calculate the actual date of admission (e.g., if a person died in hospital, the date of admission could sometimes be calculated using the date of death (if exact date known) and the length of stay). In all other cases, we approximated the admission date using the 15th of the month. In cases where the date of admission is approximate, we will use the date of service from MBS data, where available.
Handling missing data	We will not impute any data. Intention-to-treat analyses Of the covariates used in the analysis of potential effect modifiers, there are missing data for BMI (n=119 (0.6%)), use of statins at baseline (n=16 (0.1%)), and use of cardiovascular medication (other than statins) at baseline (n=16 (0.1%)). Participants will be excluded from a stratified analysis if the value for the stratification variable is missing.
Maintaining blinding	Code will be written and debugged using a dataset in which the participant identification number has been removed and participants have been randomly assigned to two new groups of equal size so that there is no relationship between the new groups and the true treatment allocation. Development and testing of code will include producing all results, including tables and figures, as they will appear in the manuscript.
Analysis details	
Analysis	The analyses will follow the intention-to-treat principle. Events that occurred within 5 years and 1 month from date of randomisation will be determined from the instruments detailed above. Follow-up will be calculated separately for the primary outcome and each of the secondary outcomes. Follow-up will begin at date of randomisation and end at the date the outcome first occurred, death, or censoring, whichever came first. Date of censoring will be determined by date last known to be alive, the 31st December 2019, or a maximum follow-up period of five years and one month from randomisation (i.e., whichever is first). 1. We will show participant flow using a CONSORT flow diagram (Figure 1). 2. We will describe selected baseline characteristics according to randomisation group (Table 1). Note that the cohort is essentially the same as that used for the mortality analysis (i.e., it has eight fewer participants; two withdraw their data from the study, and six were not correctly linked to hospital admissions data) and the mortality manuscript presented detailed baseline characteristics.[18] Hence, Table

1 will include only variables used in subgroup analyses and those that may be relevant for cardiovascular disease. An extended table of baseline characteristics will be included as STable 1.

Primary outcome analysis

3. We will plot the cause-specific cumulative incidence of people experiencing at least one major cardiovascular event for each randomisation group, using Aalen-Johansen methods (Figure 2).
4. To assess the effect of vitamin D supplementation on hazard of first major cardiovascular event, we will fit two flexible parametric survival models (FPSMs).[19,20] Both models will include randomisation group and the randomisation stratification variables of age, sex, and state of residence at baseline.
    a. Model 1 will not include any time-varying coefficients; it will be used to estimate an "overall" hazard ratio (HR) and 95% confidence interval (CI). This will be almost equivalent to fitting a Cox proportional hazards model. We will model the baseline log cumulative hazard function using a restricted cubic spline with two internal knots (placed at the 33rd and 67th percentiles of the uncensored log survival times). We will present the number and percentage of people who experienced a major event within each randomisation group, and the overall HR (95% CI) (Table 2). We will also embed the overall HR (95% CI) in Figure 2.
    b. Model 2 will include an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times), thereby allowing the HR for randomisation group to vary with time. We will report the p-value from the likelihood ratio test comparing Models 1 and 2 (i.e. testing the effect of including the interaction between time and randomisation group). Using Model 2, we will plot the estimated HR (95% CI) as a function of time since randomisation (Figure 3a), and report values at 2 and 5 years post-randomisation (STable 2).
5. We will estimate the difference in cause-specific standardised cumulative incidence, treating death without prior major cardiovascular event as a competing risk (Figure 3b), reporting values at 2 and 5 years post-randomisation (STable 2). For this analysis we will use the user-written standsurv command in Stata with the competing risks models option. The analysis will use estimates from FPSMs that include randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation; we will model the baseline log cumulative hazard function and the interaction as described previously.

Interactions and subgroup analyses

We will investigate whether the effect of supplementation on major cardiovascular events is modified by the following baseline characteristics:

	• Age at baseline (< 70 years, ≥ 70 years); • Sex (men, women); • BMI at baseline (< 25 kg/m2, ≥ 25 kg/m2); • Predicted deseasonalised 25(OH)D concentration (< 50 nmol/L, ≥ 50 nmol/L); • Use of statins at baseline (yes vs no); and • Use of cardiovascular medication (other than statins) at baseline (yes vs no). For each baseline characteristics we will: Use Aalen-Johansen methods to plot cause-specific cumulative incidence of major cardiovascular events for each randomisation group within each stratum of the characteristic; age (SFigure 1), sex (SFigure 3), BMI (SFigure 5), predicted deseasonalised 25(OH)D concentration (SFigure 7), statin use (SFigure 9), and cardiovascular medication use (SFigure 11). For each level of the baseline characteristic, we will use FPSMs to estimate: a. An overall HR (95% CI); b. The HR (95% CI) as a function of time since randomisation; and c. The difference in cause-specific standardised cumulative incidence functions. In all FPSMs, we will model the baseline log cumulative hazard function using a restricted cubic spline with two internal knots (placed at the 33rd and 67th percentiles of the uncensored log survival times). All FPSMs will include randomisation group, the baseline charateristic of interest, an interaction between the baseline characteristic and randomisation group, age, sex, and state of residence at baseline. When the FPSM includes an interaction between randomisation group and time since randomisation (b and c), we will fit it as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). For part c, we will treat death without prior cardiovascular event as a competing risk, and we will use the user-written standsurv command in Stata with the competing risks models option. To assess the significance of an interaction term, we will use the likelihood ratio test (i.e., compare models with and without the interaction term of interest). We will report the overall HRs in a forest plot (Figure 4), and also embed them in the relevant supplementary figure of cause-specific cumulative incidence. We will plot the time-varying HR and difference in cause-specific standardised cumulative incidence functions [age (SFigure 2), sex (SFigure 4), BMI (SFigure 6), predicted deseasonalised 25(OH)D concentration (SFigure 8), statin use (SFigure 10), and cardiovascular medication use (SFigure 12)]. Secondary outcome analyses Analysis steps 3 – 5 will be repeated for each secondary outcome (Table 2, STable 2; SFigures 13-22). Sensitivity analyses We will evaluate individual-level concordance between self-reported statin use and claims for statins in the PBS data (STable 3a). We will also evaluate

	individual-level concordance between self-reported anti-hypertensive use and claims for drugs for treatment of the cardiovascular system in the PBS data (STable 3b). In a sensitivity analysis we will exclude people without PBS data from the subgroup analysis for statin use at baseline and cardiovascular drug use at baseline (comment in results only). Retention, compliance, and adverse events We will not tabulate retention, compliance and adverse events with study tablets as they have been described in the mortality paper. We will refer to these and cite the mortality paper.
Planned main tables	**Appendix 3** Table 1: Baseline characteristics according to randomisation group. Table 2: Effect of supplementation with vitamin D on incidence of major cardiovascular events.
Planned supplementary tables	**Appendix 4** STable 1: Extended list of baseline characteristics according to randomisation group. STable 2. Effect of supplementation with vitamin D on incidence of major cardiovascular events. Predicted difference in cause-specific standardised cumulative incidence and time-varying hazard ratio at 2 and 5 years post-randomisation, and predicted overall hazard ratio. STable 3a. Concordance between statin use from PBS data with self-reported treatment for hypercholesterolaemia at baseline. STable 3b. Concordance between cardiovascular medication (other than statins) use from PBS data with self-reported treatment for hypertension at baseline.
Planned main figures	**Appendix 5** Figure 1. Participant flow for analyses of major cardiovascular events (CONSORT flow diagram). Figure 2. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group and time since randomisation. Figure 3. Effect of vitamin D supplementation on incidence of major cardiovascular events. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions. Figure 4. Effect of vitamin D supplementation on incidence of major cardiovascular events for all participants and by selected baseline characteristics. (Forest plot)
Planned supplementary figures	**Appendix 6** SFigure 1. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by age at baseline.

	SFigure 2. Effect of vitamin D supplementation on incidence of major cardiovascular events according to age at randomisation. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions. SFigure 3. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by sex. SFigure 4. Effect of vitamin D supplementation on incidence of major cardiovascular events according to sex. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions. SFigure 5. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by body mass index at baseline. SFigure 6. Effect of vitamin D supplementation on incidence of major cardiovascular events according to body mass index at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions. SFigure 7. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by predicted deseasonalised serum 25(OH)D concentration at baseline. SFigure 8. Effect of vitamin D supplementation on incidence of major cardiovascular events according to predicted deseasonalised serum 25(OH)D concentration at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions. SFigure 9. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by statin use at baseline. SFigure 10. Effect of vitamin D supplementation on incidence of major cardiovascular events according to statin use at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions. SFigure 11. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by cardiovascular medication use (other than statins) at baseline. SFigure 12. Effect of vitamin D supplementation on incidence of major cardiovascular events according to cardiovascular medication use (other than statins) at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

	SFigure 13. Cause-specific cumulative incidence of myocardial infarction according to randomisation group and time since randomisation. SFigure 14. Effect of vitamin D supplementation on incidence of myocardial infarction. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions. SFigure 15. Cause-specific cumulative incidence of coronary revascularisation according to randomisation group and time since randomisation. SFigure 16. Effect of vitamin D supplementation on incidence of coronary revascularisation. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions. SFigure 17. Cause-specific cumulative incidence of stroke according to randomisation group and time since randomisation. SFigure 18. Effect of vitamin D supplementation on incidence of stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions. SFigure 19. Cause-specific cumulative incidence of haemorrhagic stroke according to randomisation group and time since randomisation. SFigure 20. Effect of vitamin D supplementation on incidence of haemorrhagic stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions. SFigure 21. Cause-specific cumulative incidence of ischaemic stroke according to randomisation group and time since randomisation. SFigure 22. Effect of vitamin D supplementation on incidence of ischaemic stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

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Appendix 1: Codes used to identify major cardiovascular events.

Major cardiovascular event	Codes
ICD-10-AM 9th edition (1 July 2015)	
Myocardial infarction	I21, I22
Stroke	Haemorrhagic: I60, I61, I62 Ischaemic: I63 Not specified as either haemorrhagic or ischaemic: I64
Australian Classification of Health Interventions (Block code)	
Stent (coronary)	3830600, 3830601, 3830602, 3830603, 3830604, 3830605 (671)
Balloon (coronary)	3830000, 3830300, 3830001, 3830301 (370)
Artherectomy (coronary)	3830900, 3831200, 3831201, 3831500, 3831800, 3831801 (669)
Thromboectomy (coronary)	9021800, 9021801, 9021802, 9021803 (669)
Endarterectomy (open)	3850500 (669)
Coronary Artery Bypass Graft	3849700, 3849701, 3849702, 3849703, 3849704, 3849705, 3849706, 3849707, 3850000, 3850001, 3850301, 3850002, 3850300, 3850302, 3850003, 3850303, 3850004, 3850304, 3850005, 3850305, 9020100, 9020101, 9020102, 9020103 (672 – 679)
Medicare Benefits Schedule	
Stent (coronary)	38306
Balloon (coronary)	38300, 38303, 38309, 38312, 38315, 38318
Artherectomy (coronary)	38309, 38312, 38315, 38318
Endarterectomy (open)	38505
Coronary Artery Bypass Graft	38497, 38498, 38500, 38501, 38503, 38504

Appendix 2: Concordance between coronary revascularisation from ACHI codes in the hospital admissions data with Medicare data.

NOTE: These numbers have been obtained using a preliminary dataset.

State	A. Total hospital coronary revascularisation	Total matched with Medicare record within 21 days	Hospital only	B. MBS only	Total coronary revascularisation (A plus B)
Total	851	449 (47.1)	397 (41.7)	102 (10.7)	953
QLD	200	113 (55.9)	86 (42.6)	2 (1.0)	202
NSW	184	92 (45.1)	91 (44.6)	20 (9.8)	204
VIC	204	128 (61.0)	76 (36.2)	6 (2.9)	210
TAS	68	37 (41.6)	28 (31.5)	21 (23.6)	89
SA	48	10 (10.0)	38 (38.0)	52 (52.0)	100
WA	147	69 (46.6)	78 (52.7)	1 (0.7)	148

THE FOLLOWING APPENDICES CONTAIN SAMPLE TABLES AND FIGURES BASED ON "FAKE" DATA

To generate the "fake" data, we removed the true randomisation and participant identification codes from the original dataset, and then randomly assigned participants to two groups of equal size. There is no relationship between the new groups and the true treatment allocation.

Appendix 3. Planned main tables

Table 1: Baseline characteristics according to randomisation group.

Characteristic	N (%) Vitamin D (N = 10,651)	Placebo (N = 10,651)
Age (years)		
60-64	2611 (24.5)	2640 (24.8)
65-69	2883 (27.1)	2951 (27.7)
70-74	2933 (27.5)	2859 (26.8)
≥ 75	2224 (20.9)	2201 (20.7)
Sex		
Men	5741 (53.9)	5784 (54.3)
Women	4910 (46.1)	4867 (45.7)
Body mass index (kg/m²)		
< 25	3191 (30.1)	3223 (30.4)
≥ 25	7399 (69.9)	7370 (69.6)
Missing	*61*	*58*
Predicted 25(OH)D concentration (nmol/L)		
< 50	2626 (24.7)	2573 (24.2)
≥ 50	8025 (75.3)	8078 (75.8)
Statin use at baseline[a]		
No	6849 (64.4)	6987 (65.6)
Yes	3790 (35.6)	3660 (34.4)
Missing	*12*	*4*
Cardiovascular medication use at baseline[b]		
No	5676 (53.4)	5734 (53.9)
Yes	4963 (46.6)	4913 (46.1)
Missing	*12*	*4*
Self-reported history of hypertension		
No	6170 (58.2)	6199 (58.4)
Yes	4439 (41.8)	4412 (41.6)
Missing	*42*	*40*
Self-reported history of hypercholesterolaemia		
No	7140 (67.3)	7216 (68.0)
Yes	3465 (32.7)	3392 (32.0)
Missing	*46*	*43*
Self-reported history of other cardiovascular disease[c]		
No	8232 (77.8)	8221 (77.6)
Yes	2355 (22.2)	2368 (22.4)
Missing	*64*	*62*

[a] Anatomical Therapeutic Chemical code C10 in PBS data within 3 months of randomisation, or self-reported treatment for hypercholesterolaemia prior to randomisation.
[b] Anatomical Therapeutic Chemical codes C01 – C09 in PBS data within 3 months of randomisation, or self-reported treatment for hypertension prior to randomisation.
[c] We assumed that a participant had a history of cardiovascular disease if they reported having experienced and / or been diagnosed with any of the following prior to randomisation: heart attack; stroke; transient ischaemic attack; angioplasty; pacemaker insertion; insertion of a coronary stent: coronary artery bypass graft; thrombosis; angina; or arrhythmia.

Table 2: The effect of vitamin D supplementation on incidence of major cardiovascular events.

Outcome	N (%)[a] Vitamin D (N = 10,651)	Placebo (N = 10,651)	HR (95% CI)
Major event[b]	665 (6.2)	671 (6.3)	0.99 (0.89 to 1.10)
Myocardial infaction	211 (2.0)	221 (2.1)	0.95 (0.79 to 1.15)
Coronary revascularisation[c]	418 (3.9)	457 (4.3)	0.91 (0.80 to 1.04)
Stroke[d]	183 (1.7)	162 (1.5)	1.13 (0.91 to 1.39)
Haemorrhagic stroke	47 (0.4)	34 (0.3)	1.38 (0.89 to 2.14)
Ischaemic stroke	118 (1.1)	111 (1.0)	1.06 (0.82 to 1.37)

[a] The number (%) of people with at least one event.

[b] Composite endpoint including myocardial infarction, stroke and coronary revascularisation. The number of people who experienced at least one major event is less than the total of the numbers presented for myocardial infarction, stroke and coronary revascularisation because participants could experience more than one type of event.

[c] Composite endpoint including percutaneous coronary intervention (insertion of stent or balloon, artherectomy, thromboectomy and endarterectomy) or coronary-artery bypass grafting.

[d] Stroke includes diagnosis code I64 (unspecified) and therefore exceeds the total number of ischaemic and haemorrhagic strokes.

[e] Estimated using flexible parametric survival models that included age, sex, and state of residence at baseline. The baseline log cumulative hazard function was modelled using a restricted cubic spline with two internal knots (placed at the 33rd and 67th percentiles of the uncensored log survival times).

Abbreviation: CI, confidence interval

Appendix 4. Selected planned supplementary tables

STable 1. Extended list of baseline characteristics according to randomisation group.

Characteristic	N (%) Vitamin D (N = 10,651)	Placebo (N = 10,651)
Ancestry		
British/European	9715 (93.1)	9729 (92.7)
Australian/New Zealander	357 (3.4)	368 (3.5)
Asian	123 (1.2)	118 (1.1)
Indigenous	65 (0.6)	86 (0.8)
Mixed/other	171 (1.6)	194 (1.8)
Missing	*220*	*156*
Highest qualification obtained		
None	1094 (10.4)	1050 (10.0)
School or intermediate certificate	1753 (16.7)	1801 (17.1)
Higher school or leaving certificate	1392 (13.3)	1571 (14.9)
Apprenticeship or certificate	3508 (33.4)	3520 (33.4)
University degree or higher	2757 (26.2)	2593 (24.6)
Missing	*147*	*116*
Alcohol consumption (drinks/week)		
< 1	2564 (25.1)	2482 (24.2)
1 to 7	4518 (44.2)	4586 (44.7)
> 7 to 14	1876 (18.4)	1876 (18.3)
> 14	1261 (12.3)	1314 (12.8)
Missing	*432*	*393*
Smoking history		
Never	5749 (54.5)	5840 (55.3)
Ex-smoker	4375 (41.5)	4258 (40.3)
Current	429 (4.1)	466 (4.4)
Missing	*98*	*87*
Self-rated overall health		
Excellent or very good	5803 (55.4)	5840 (55.8)
Good	3794 (36.2)	3721 (35.5)
Fair or poor	885 (8.4)	914 (8.7)
Missing	*169*	*176*
Statin and/or cardiovascular medication use at baseline[a]		
No	4595 (43.2)	4644 (43.6)
Yes	6044 (56.8)	6003 (56.4)
Missing	*12*	*4*
Self-reported history of diabetes		
No	9731 (91.8)	9722 (91.7)
Yes	873 (8.2)	885 (8.3)
Missing	*47*	*44*

Characteristic	N (%) Vitamin D (N = 10,651)	Placebo (N = 10,651)
Self-reported history of stroke (including transient ischaemic attack)		
No	10019 (94.7)	10014 (94.6)
Yes	564 (5.3)	574 (5.4)
Missing	*68*	*63*
Self-reported history of coronary revascularisation		
No	9826 (92.7)	9866 (93.0)
Yes	775 (7.3)	741 (7.0)
Missing	*50*	*44*
Self-reported history of myocardial infarction		
No	10016 (94.6)	10039 (94.8)
Yes	567 (5.4)	549 (5.2)
Missing	*68*	*63*

[a] Anatomical Therapeutic Chemical codes C01 – C10 in PBS data within 3 months of randomisation, or self-reported treatment for hypercholesterolaemia and/or hypertension prior to randomisation.

STable 2. Effect of supplementation with vitamin D on incidence of major cardiovascular events. Predicted difference in cause-specific standardised cumulative incidence and time-varying hazard ratio at 2 and 5 years post-randomisation, and predicted overall hazard ratio.[a]

Years since randomisation	CIF Difference (95% CI)	Hazard Ratio (95% CI)
Major event		
2	-0.0003 (-0.0041 to 0.0035)	0.98 (0.87 to 1.10)
5	-0.0009 (-0.0073 to 0.0054)	0.99 (0.83 to 1.18)
Overall HR	..	0.99 (0.89 to 1.10)
Myocardial infarction		
2	0.0001 (-0.0021 to 0.0022)	0.95 (0.77 to 1.16)
5	-0.0010 (-0.0048 to 0.0027)	0.89 (0.66 to 1.20)
Overall HR	..	0.95 (0.79 to 1.15)
Coronary revascularisation		
2	-0.0016 (-0.0048 to 0.0015)	0.91 (0.78 to 1.05)
5	-0.0038 (-0.0091 to 0.0014)	0.91 (0.73 to 1.14)
Overall HR	..	0.91 (0.80 to 1.04)
Stroke		
2	0.0004 (-0.0013 to 0.0022)	1.10 (0.87 to 1.41)
5	0.0019 (-0.0015 to 0.0052)	1.18 (0.82 to 1.68)
Overall HR	..	1.13 (0.91 to 1.39)
Haemorrhagic stroke		
2	-0.0001 (-0.0009 to 0.0007)	1.25 (0.70 to 2.21)
5	0.0012 (-0.0005 to 0.0028)	2.00 (0.87 to 4.57)
Overall HR	..	1.38 (0.89 to 2.14)
Ischaemic stroke		
2	0.0005 (-0.0008 to 0.0018)	1.08 (0.80 to 1.47)
5	0.0006 (-0.0021 to 0.0033)	0.97 (0.63 to 1.49)
Overall HR	..	1.06 (0.82 to 1.37)

[a] Estimates (comparing vitamin D to placebo) are from flexible parametric survival models that include randomisation group, age, sex, and state of residence at baseline. Time-varying estimates (i.e., estimates at 2 and 5 years post randomisation) were predicted using a model that also included an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). Cause-specific standardised cumulative incidence was estimated treating death (without prior cardiovascular event of interest) as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort.

Abbreviations: CI, confidence interval; CIF, cumulative incidence function; HR, hazard ratio

Table 3a. Concordance between statin use from PBS data with and self-reported treatment for hypercholesterolaemia at baseline.

Self-reported treatment for hypercholesterolaemia	PBS claim for statins at baseline n (row %)			Did not consent to linkage with PBS
	No	Yes	Total	
No	11789 (90.2)	1288 (9.8)	13077	1279
Yes	715 (11.3)	5625 (88.7)	6340	517
Missing	53 (72.6)	20 (27.4)	73	16
Total, n	12557	6933		1812

[a] Anatomical Therapeutic Chemical code C10 in PBS data within 3 months of randomisation, or self-reported treatment for hypercholesterolaemia prior to randomisation.

STable 3b. Concordance between cardiovascular medication use (other than statins) from PBS data with and self-reported treatment for hypertension at baseline.

Self-reported treatment for hypertension	PBS claim for cardiovascular drugs at baseline n (row %)			Did not consent to linkage with PBS
	No	Yes	Total	
No	9563 (84.9)	1702 (15.1)	11265	1104
Yes	705 (8.6)	7454 (91.4)	8159	692
Missing	38 (57.6)	28 (42.4)	66	16
Total, n	10306	9184		1812

[a] Anatomical Therapeutic Chemical codes C01 – C09 in PBS data within 3 months of randomisation, or self-reported treatment for hypertension prior to hypertension.

Appendix 5. Planned main figures

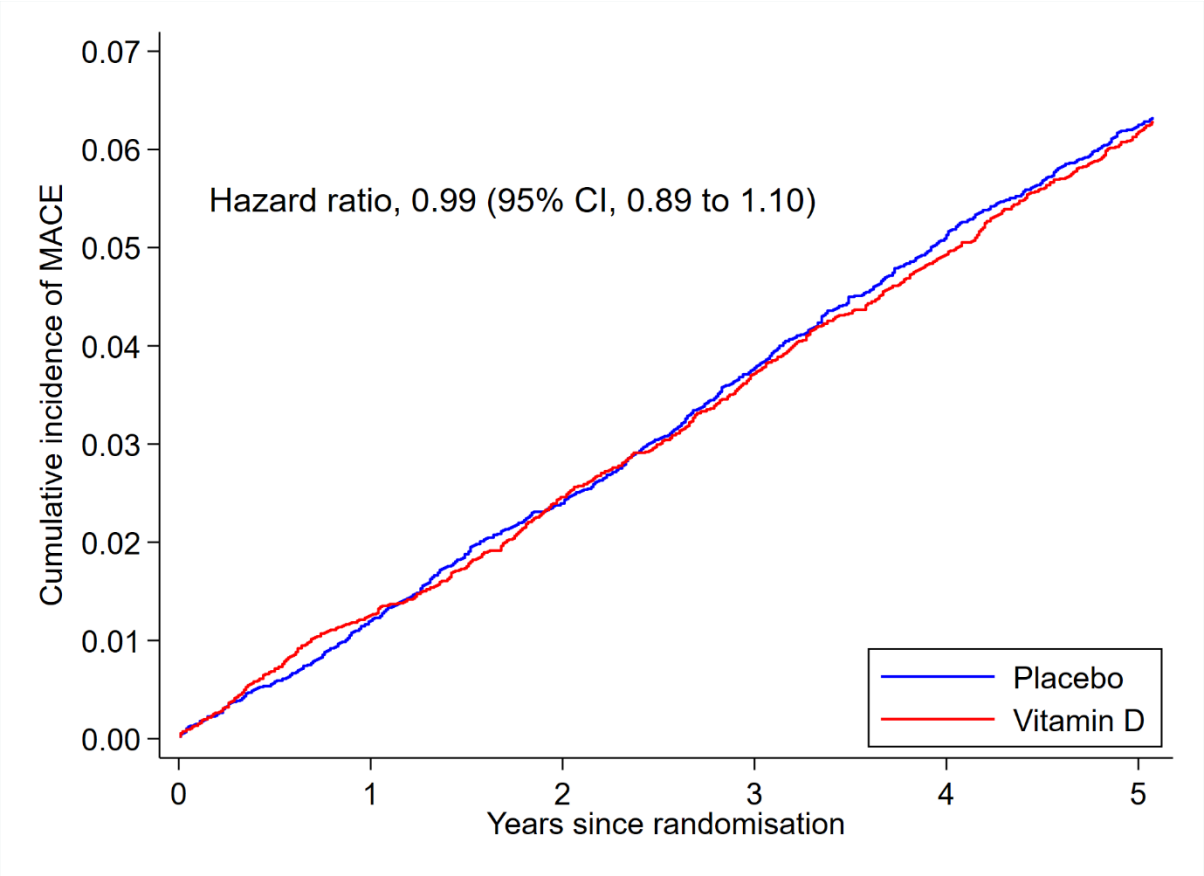


Figure 2. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.

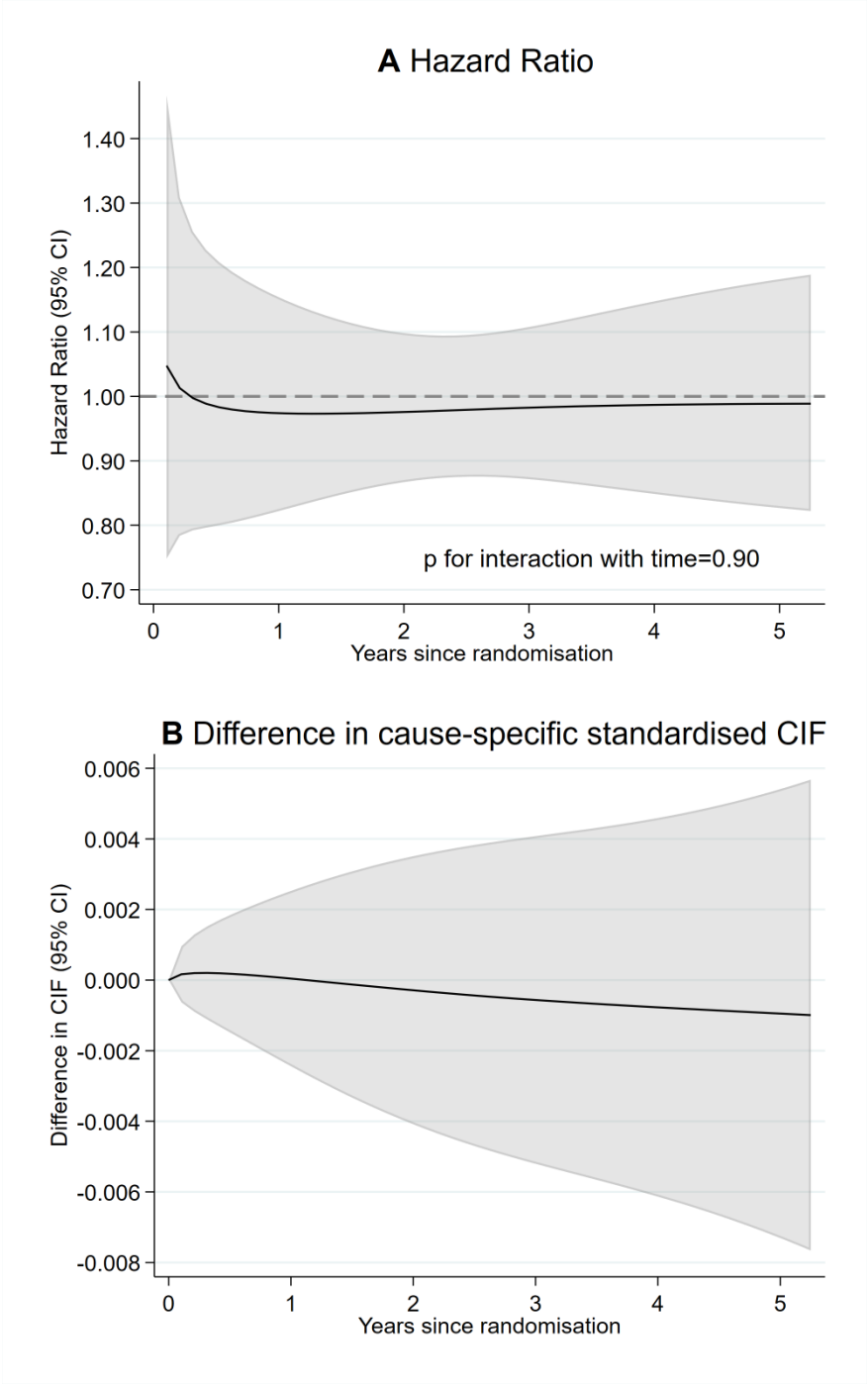


Figure 3. Effect of vitamin D supplementation on incidence of major cardiovascular events. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.

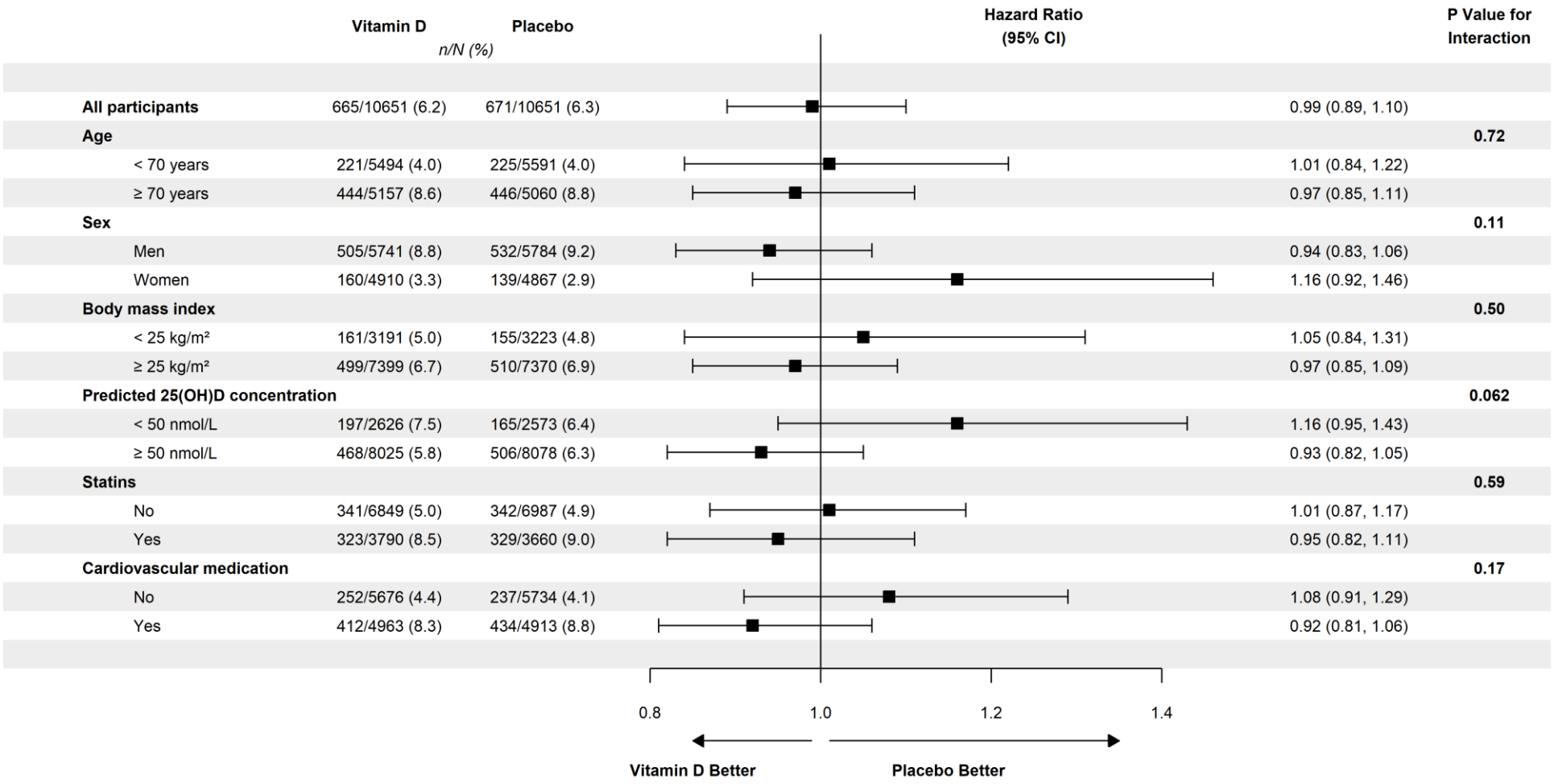
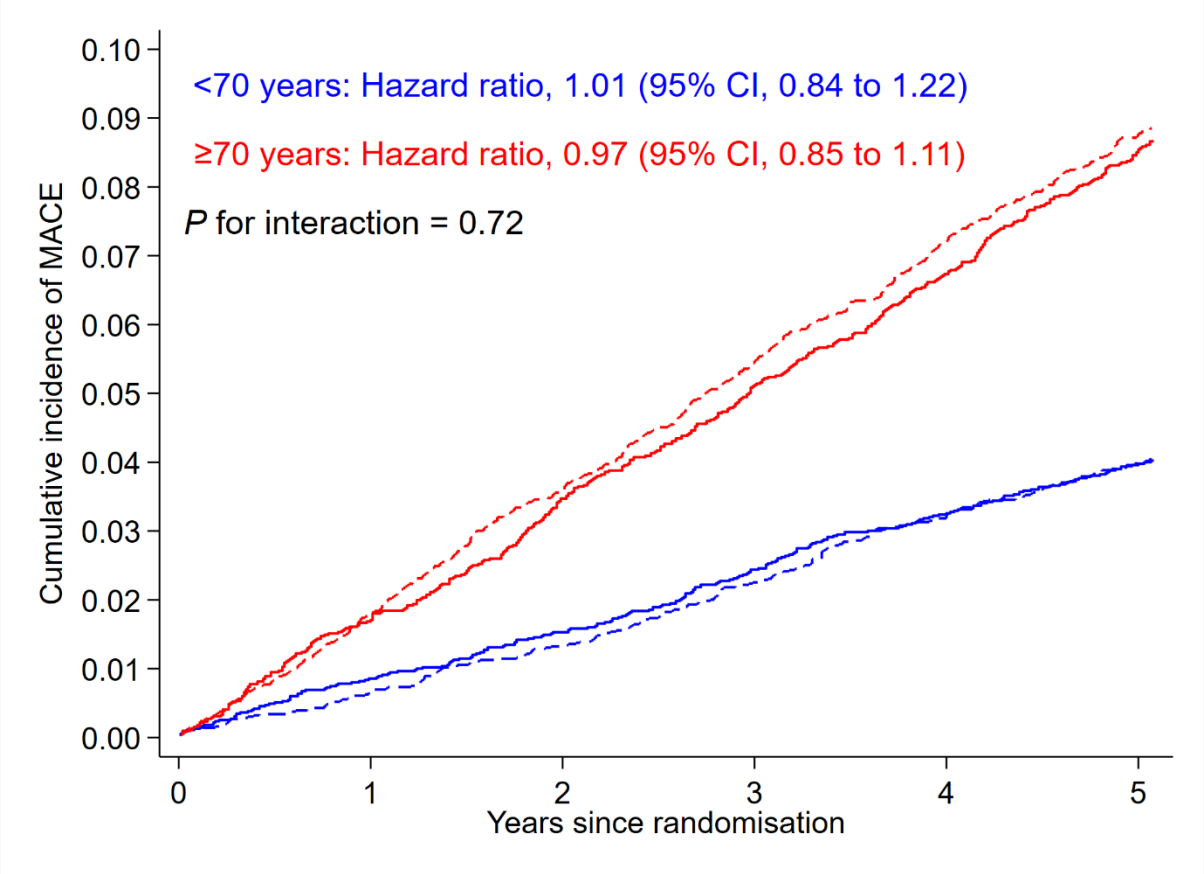


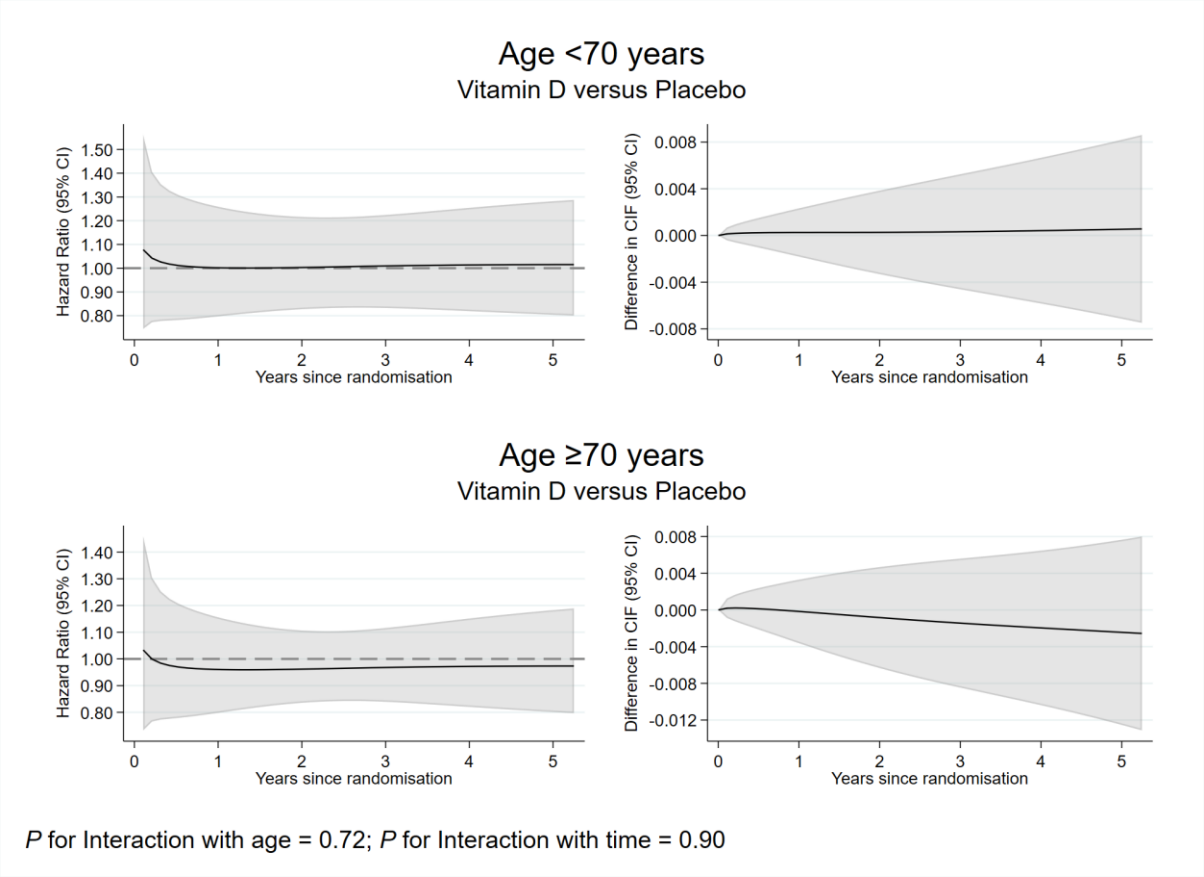
Figure 4. Effect of vitamin D supplementation on incidence of major cardiovascular events for all participants and by selected baseline characteristics.

Appendix 6. Selected planned supplementary figures



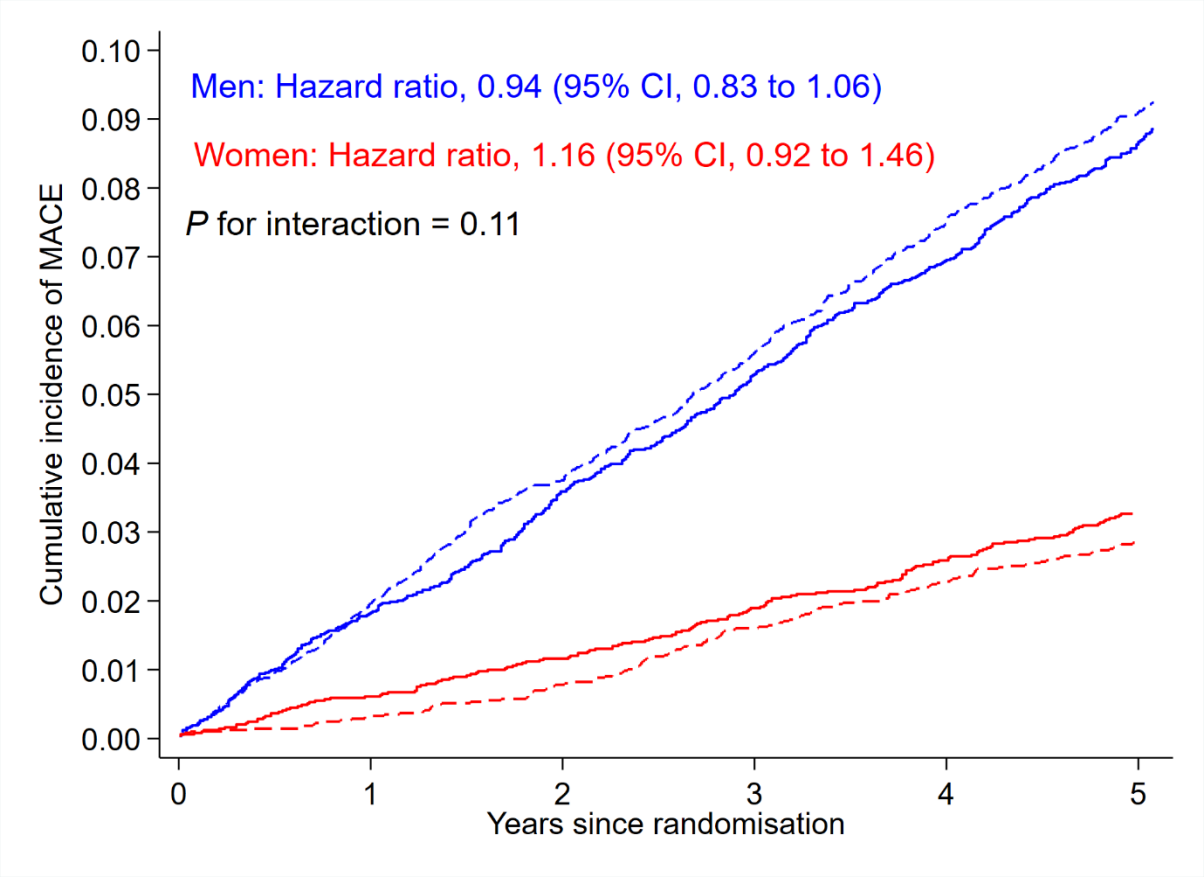
SFigure 1. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by age at baseline.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, age, sex, state of residence, and an interaction between randomisation group and age. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



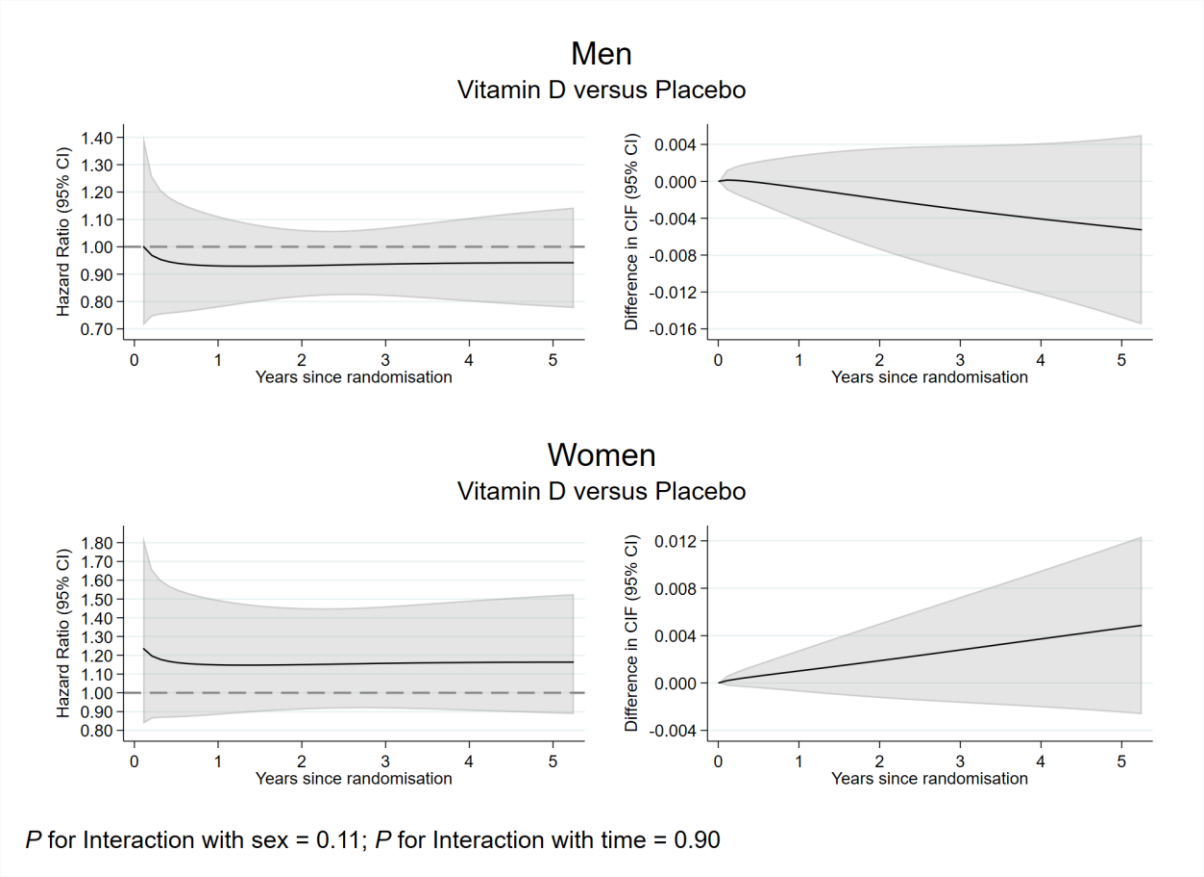
SFigure 2. Effect of vitamin D supplementation on incidence of major cardiovascular events according to age at randomisation. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, state of residence, an interaction between randomisation group and age, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



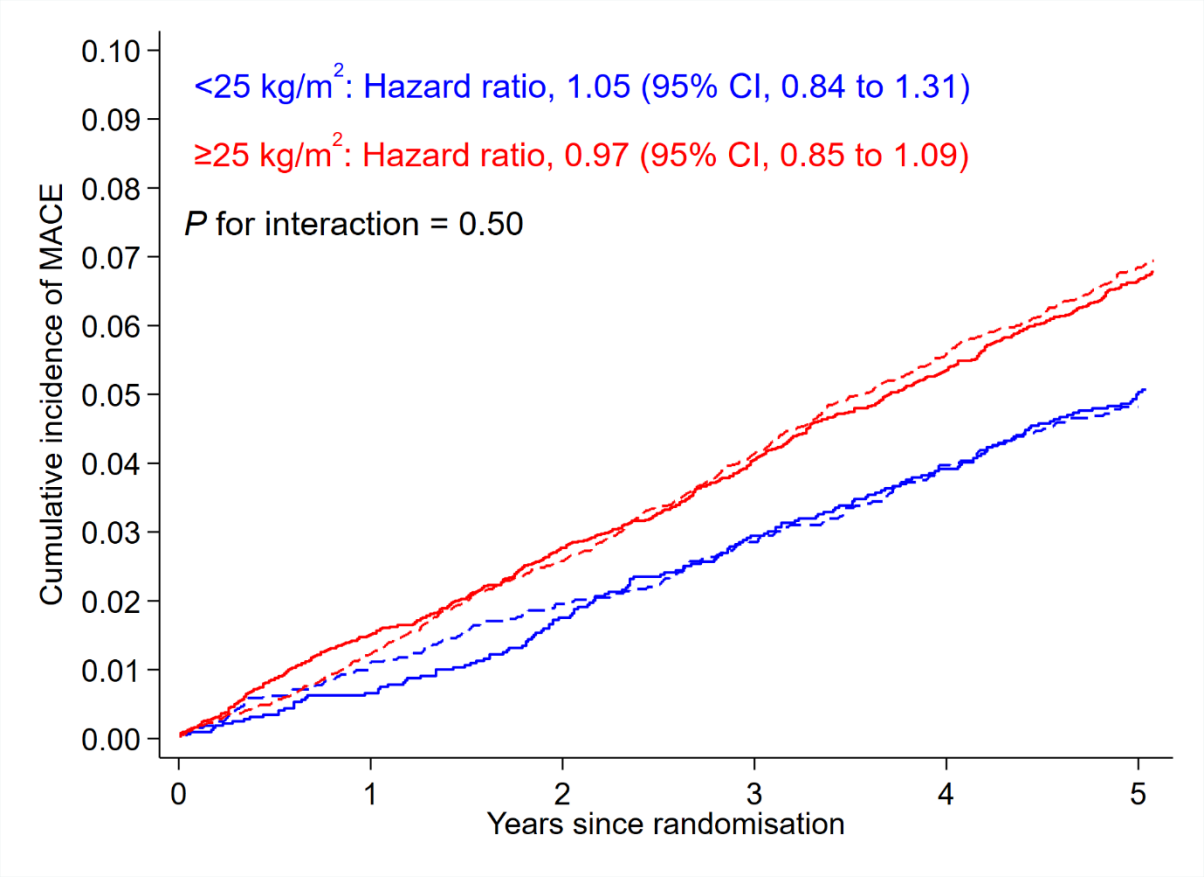
SFigure 3. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by sex.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, age, sex, state of residence, and an interaction between randomisation group and sex. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



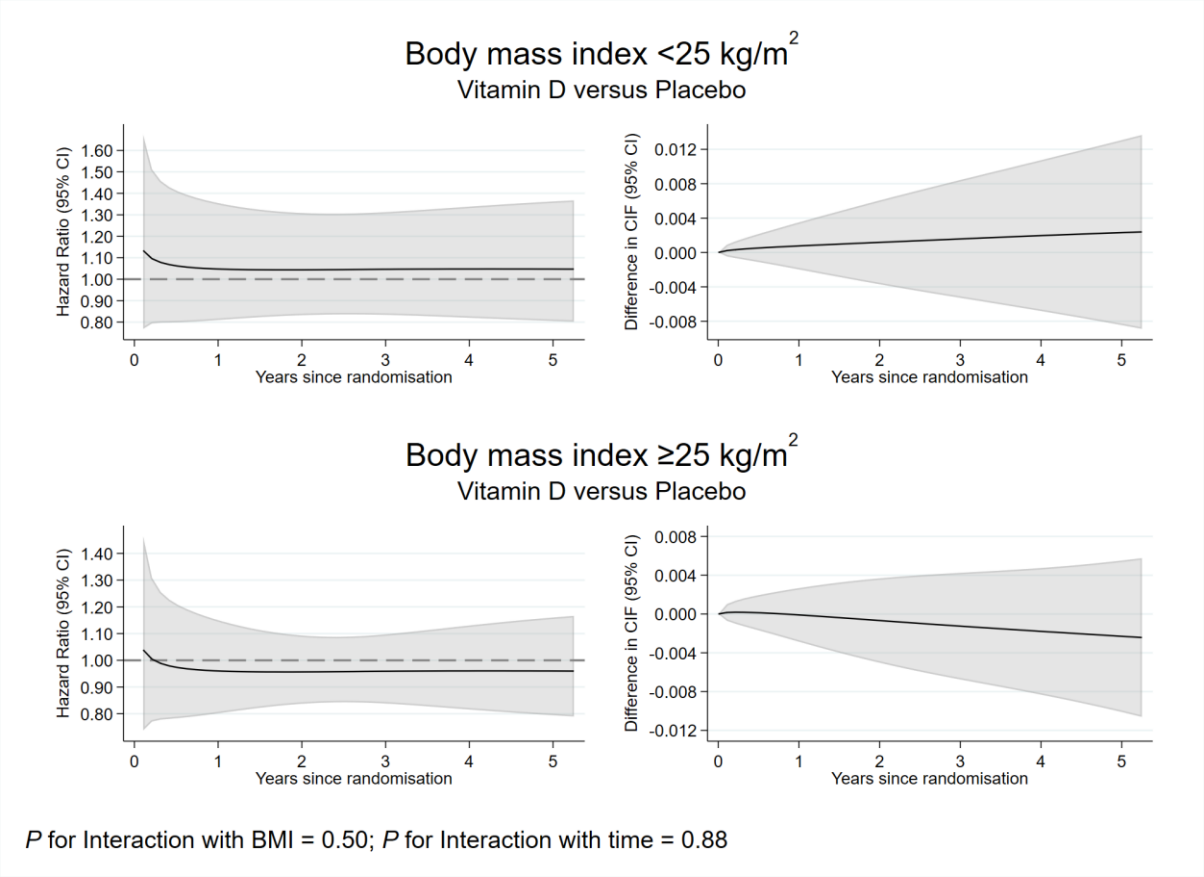
SFigure 4. Effect of vitamin D supplementation on incidence of major cardiovascular events according to sex. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, state of residence, an interaction between randomisation group and sex, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



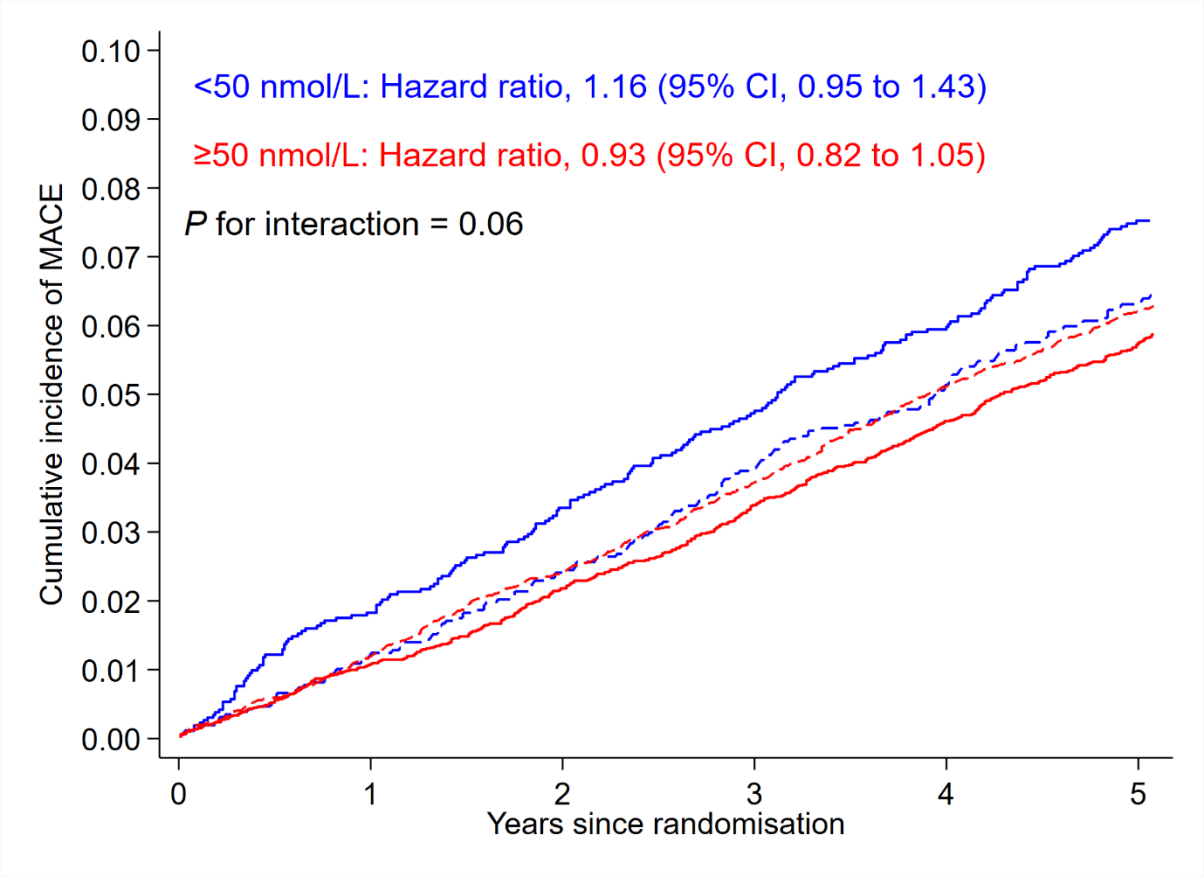
SFigure 5. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by body mass index at baseline.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, BMI, age, sex, state of residence, and an interaction between randomisation group and BMI. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: BMI, body mass index; CI, confidence interval; MACE, major cardiovascular event.



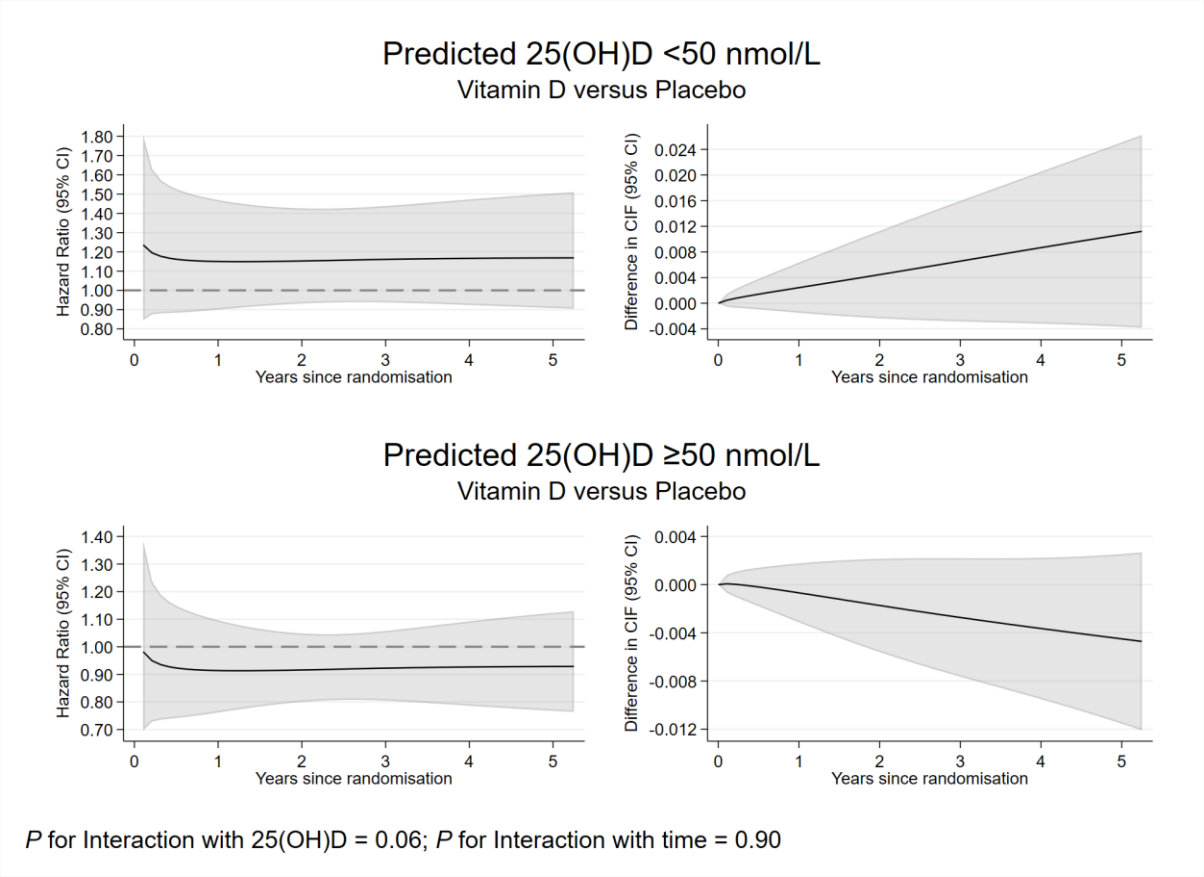
SFigure 6. Effect of vitamin D supplementation on incidence of major cardiovascular events according to body mass index at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, BMI, age, sex, state of residence, an interaction between randomisation group and BMI, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: BMI, body mass index; CI, confidence interval; CIF, cumulative incidence function.



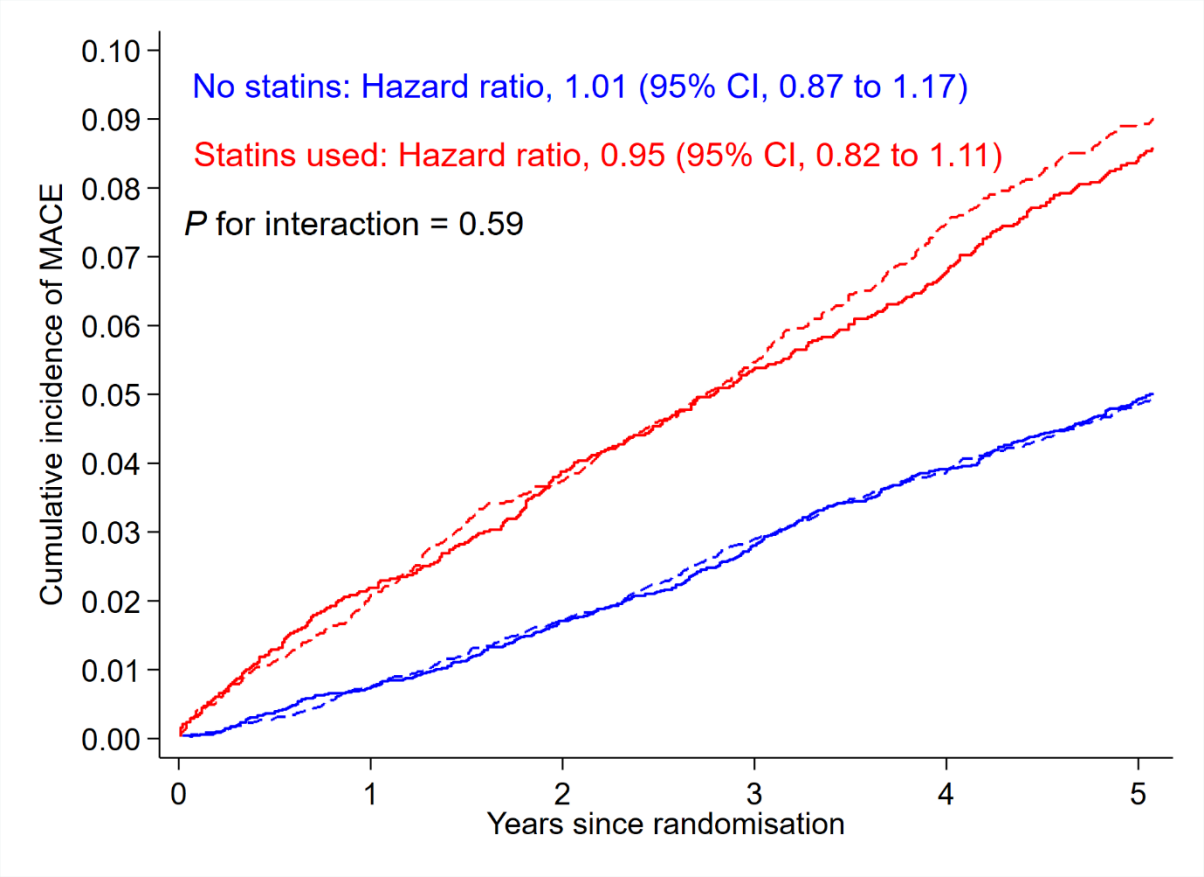
SFigure 7. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by predicted deseasonalised baseline 25(OH)D concentration.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, predicted 25(OH)D concentration, age, sex, state of residence, and an interaction between randomisation group and predicted 25(OH)D concentration. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



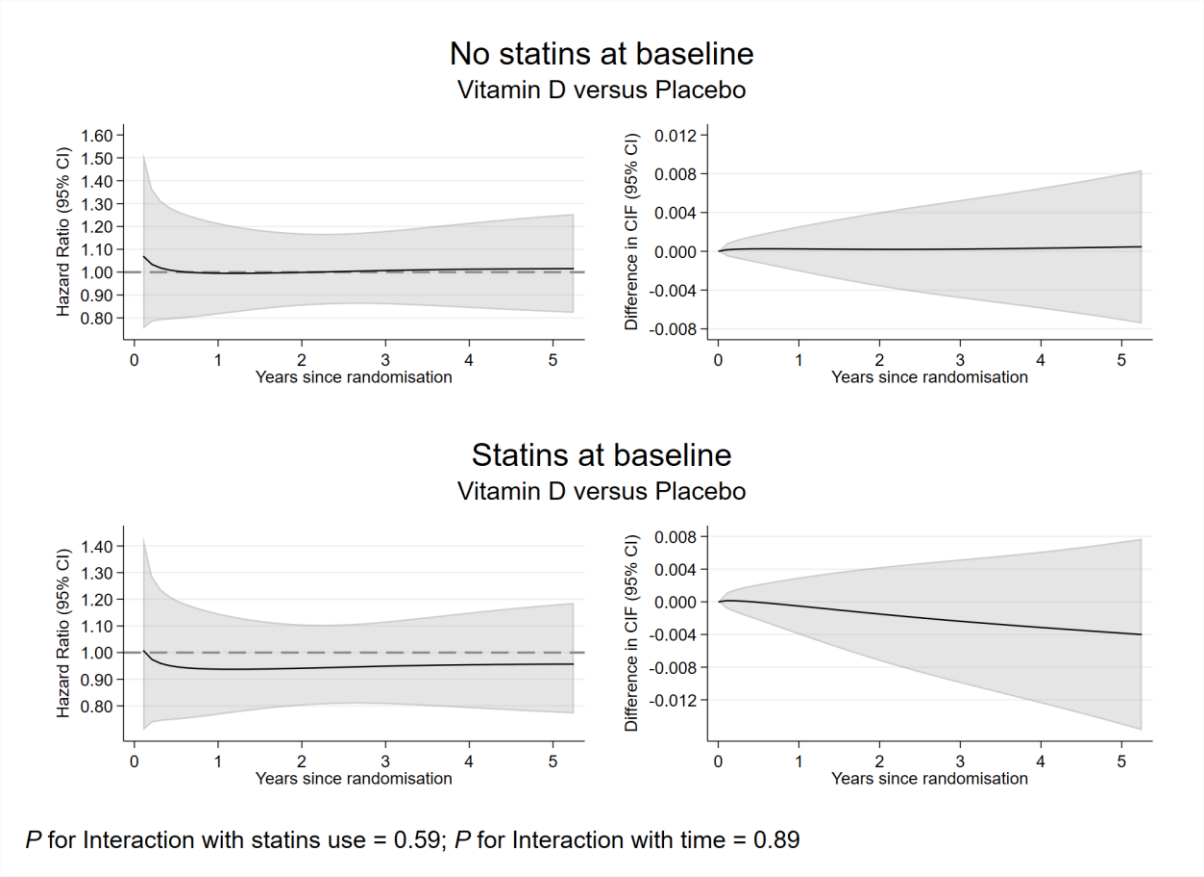
SFigure 8. Effect of vitamin D supplementation on incidence of major cardiovascular events according to predicted deseasonlised baseline 25(OH)D concentration. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, predicted 25(OH)D concentration, age, sex, state of residence, an interaction between randomisation group and predicted 25(OH)D concentration, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



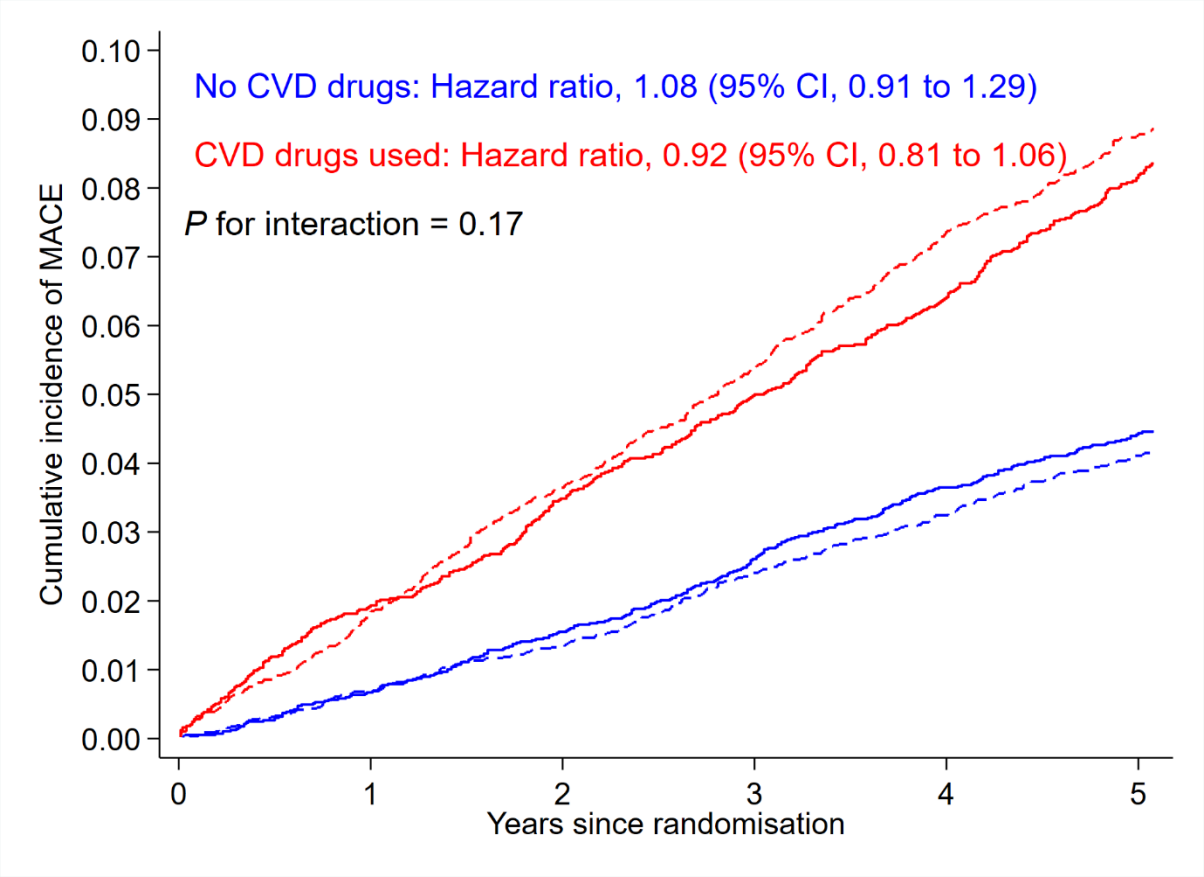
SFigure 9. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by use of statins at baseline.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, statin use, age, sex, state of residence, and an interaction between randomisation group and statin use. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



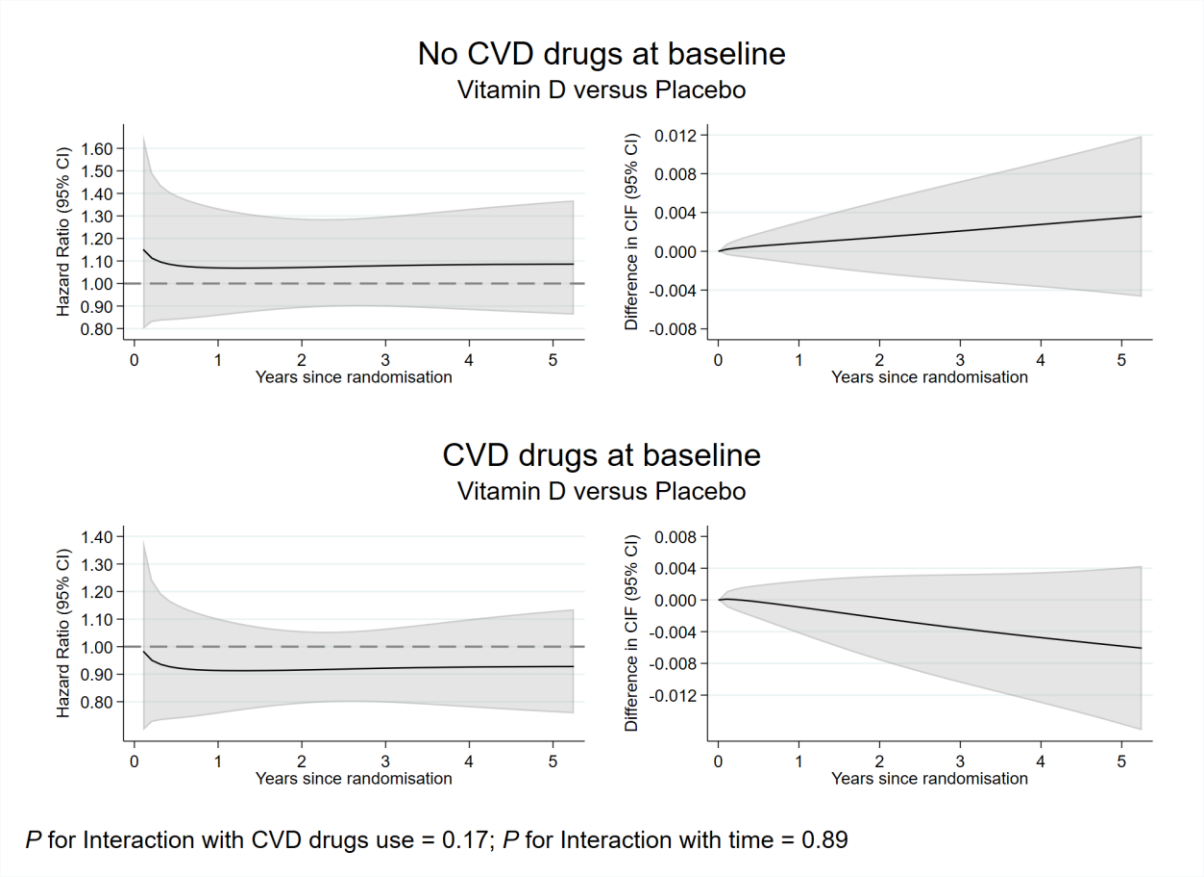
SFigure 10. Effect of vitamin D supplementation on incidence of major cardiovascular events according to statin use at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, statin use, age, sex, state of residence, an interaction between randomisation group and statin use, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



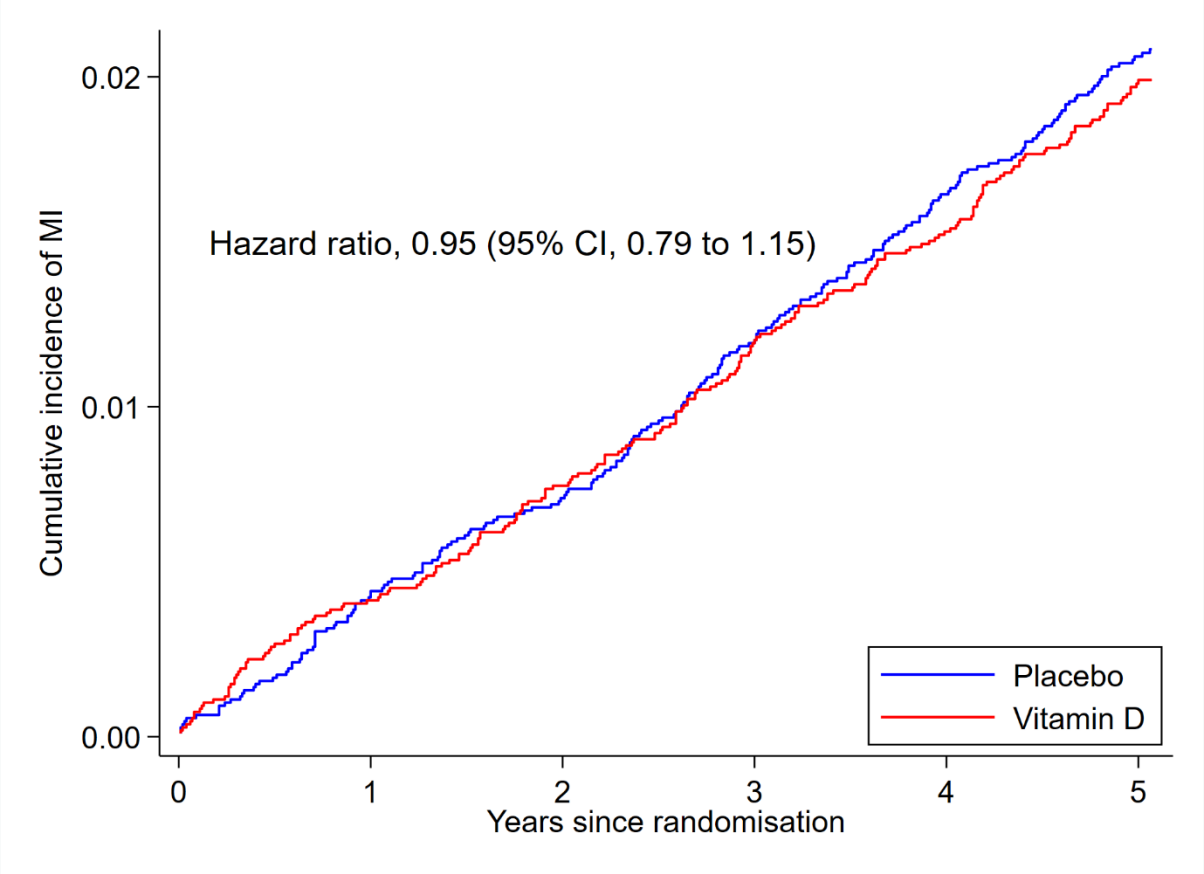
SFigure 11. Cause-specific cumulative incidence of major cardiovascular events according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by cardiovascular medication use (other than statins) at baseline.

Curves estimated using Aalen-Johansen methods, treating death without prior major cardiovascular event as a competing risk. The hazard ratios (vitamin D versus placebo) were estimated using a flexible parametric survival model that included randomisation group, statin use, age, sex, state of residence, and an interaction between randomisation group and statin use. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



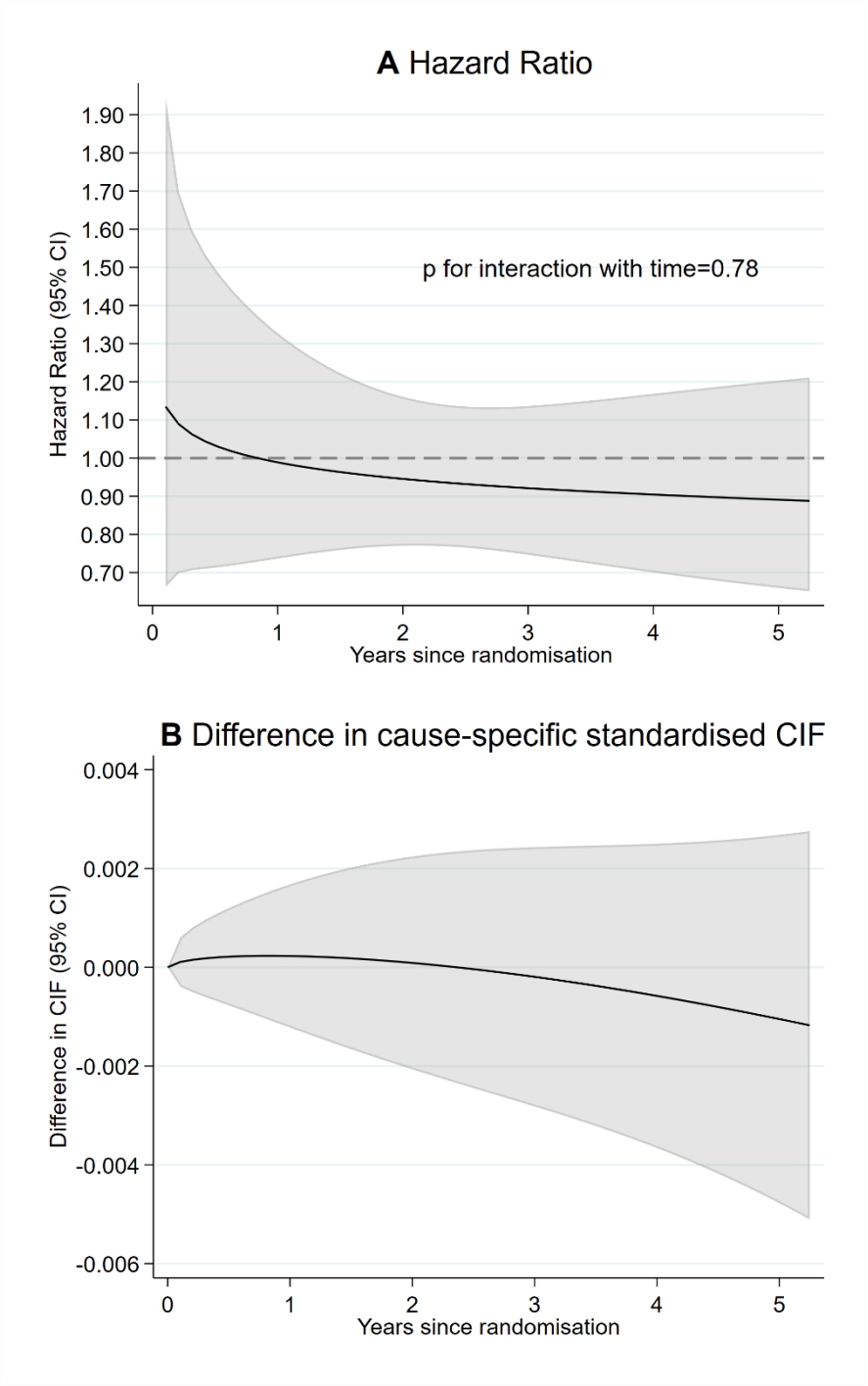
SFigure 12. Effect of vitamin D supplementation on incidence of major cardiovascular events according to cardiovascular medication use (other than statins) at baseline. Plots on the left hand side show the time-varying hazard ratio. Plots on the right hand side show the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, cardiovascular medication use, age, sex, state of residence, an interaction between randomisation group and cardiovascular medication use, and an interaction between randomisation group and time since randomisation. P values for interactions are from likelihood ratio tests that compared models with and without the interaction term of interest. Cause-specific standardised cumulative incidence was estimated treating death without prior major cardiovascular event as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function; CVD, cardiovascular disease.



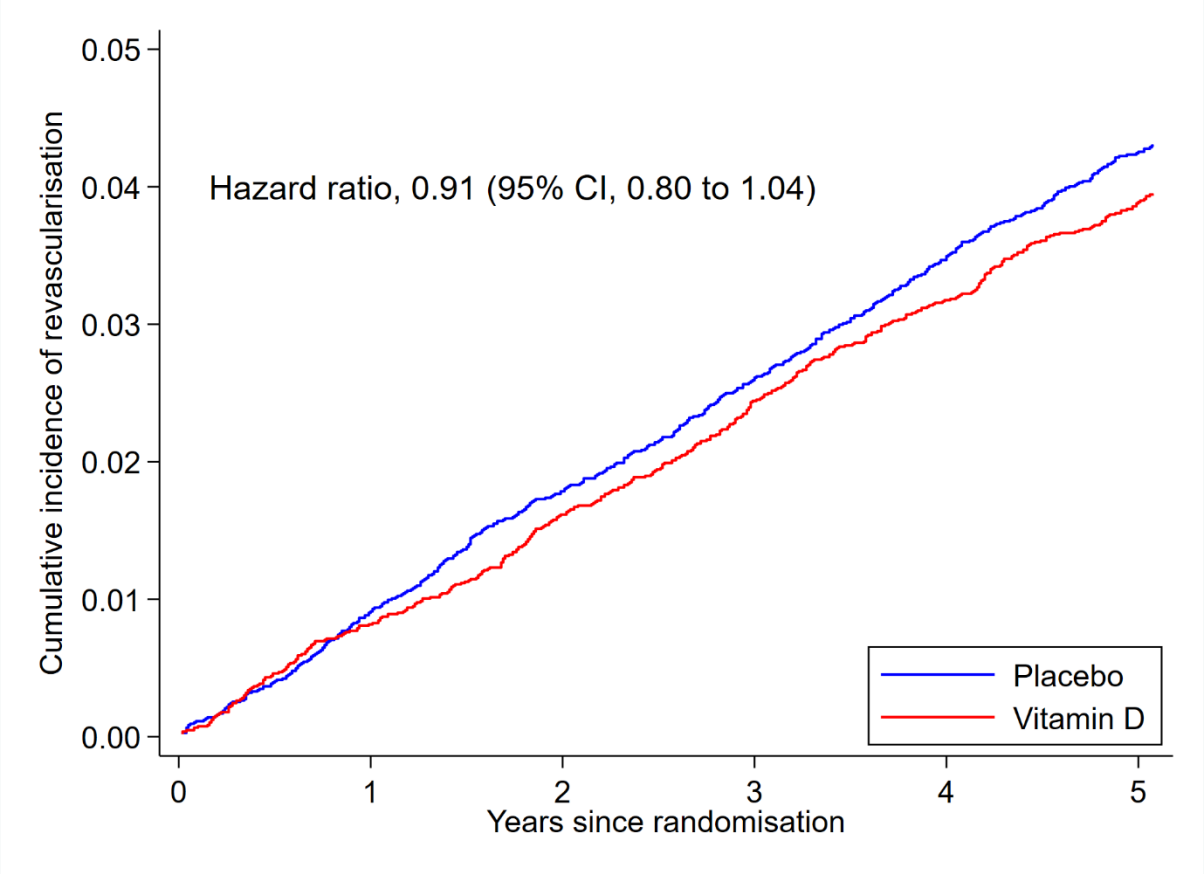
SFigure 13. Cause-specific cumulative incidence of myocardial infarction according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior myocardial infarction as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event; MI, myocardial infarction.



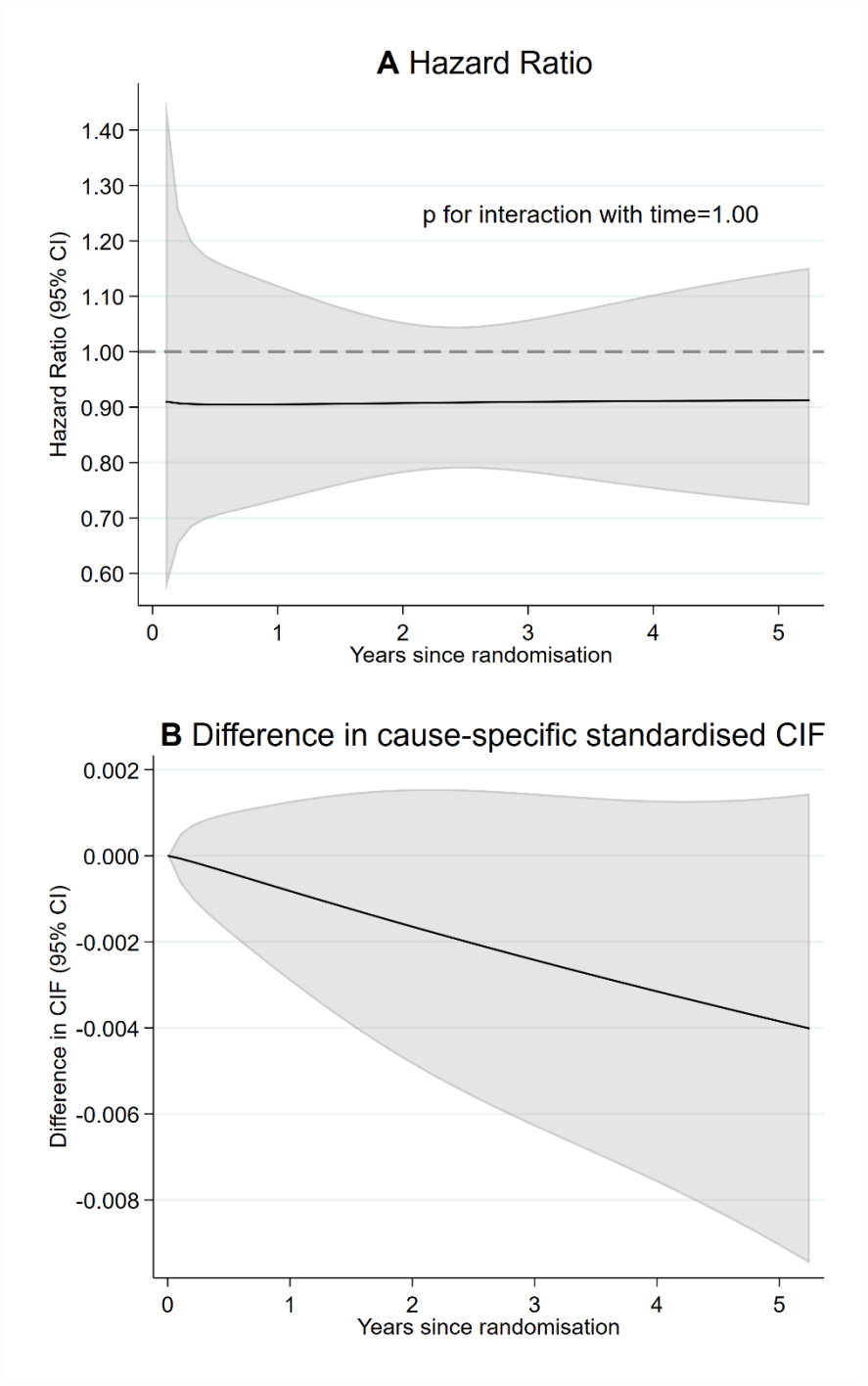
SFigure 14. Effect of vitamin D supplementation on incidence of myocardial infarction. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior myocardial infarction as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



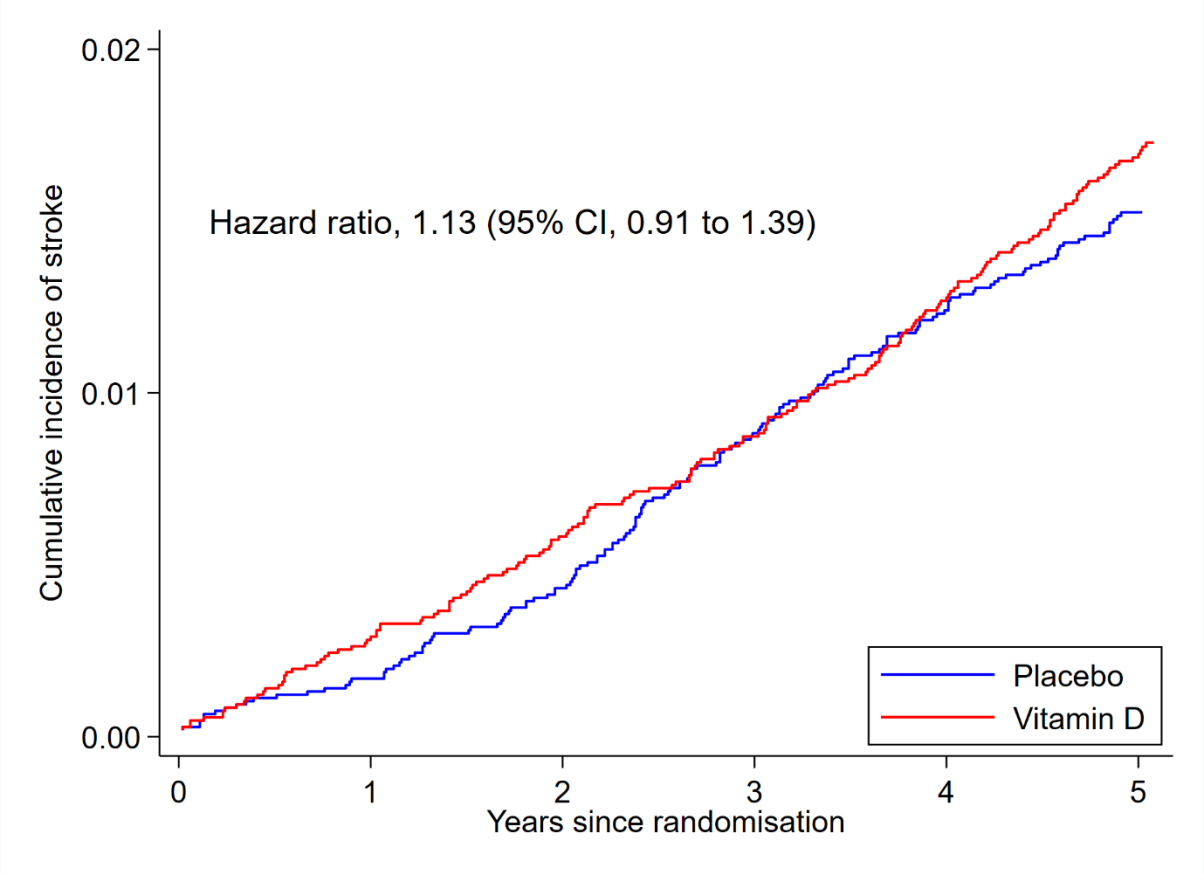
SFigure 15. Cause-specific cumulative incidence of coronary revascularisation according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior coronary revascularisation as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



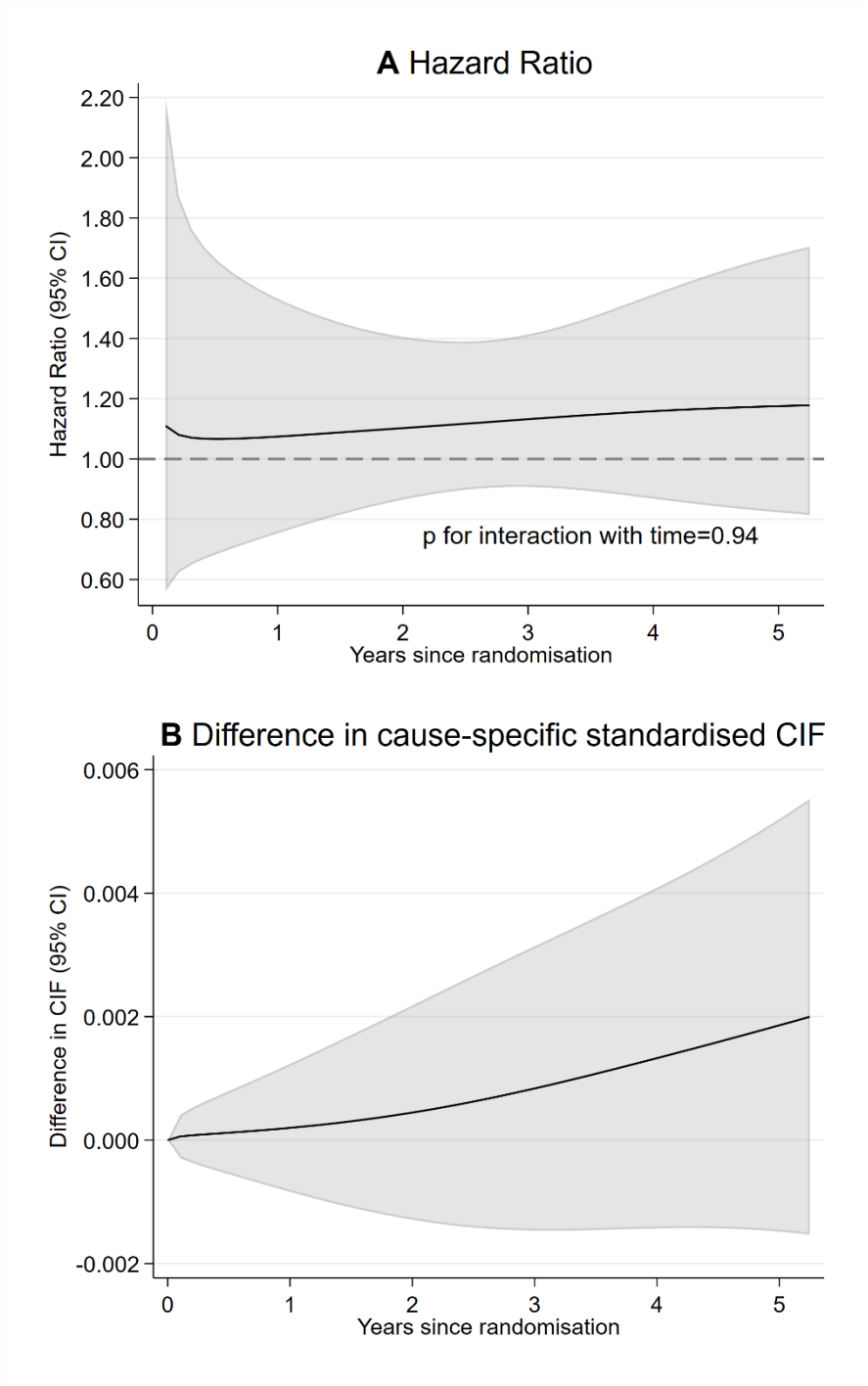
SFigure 16. Effect of vitamin D supplementation on incidence of coronary revascularisation. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior coronary revascularisation as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



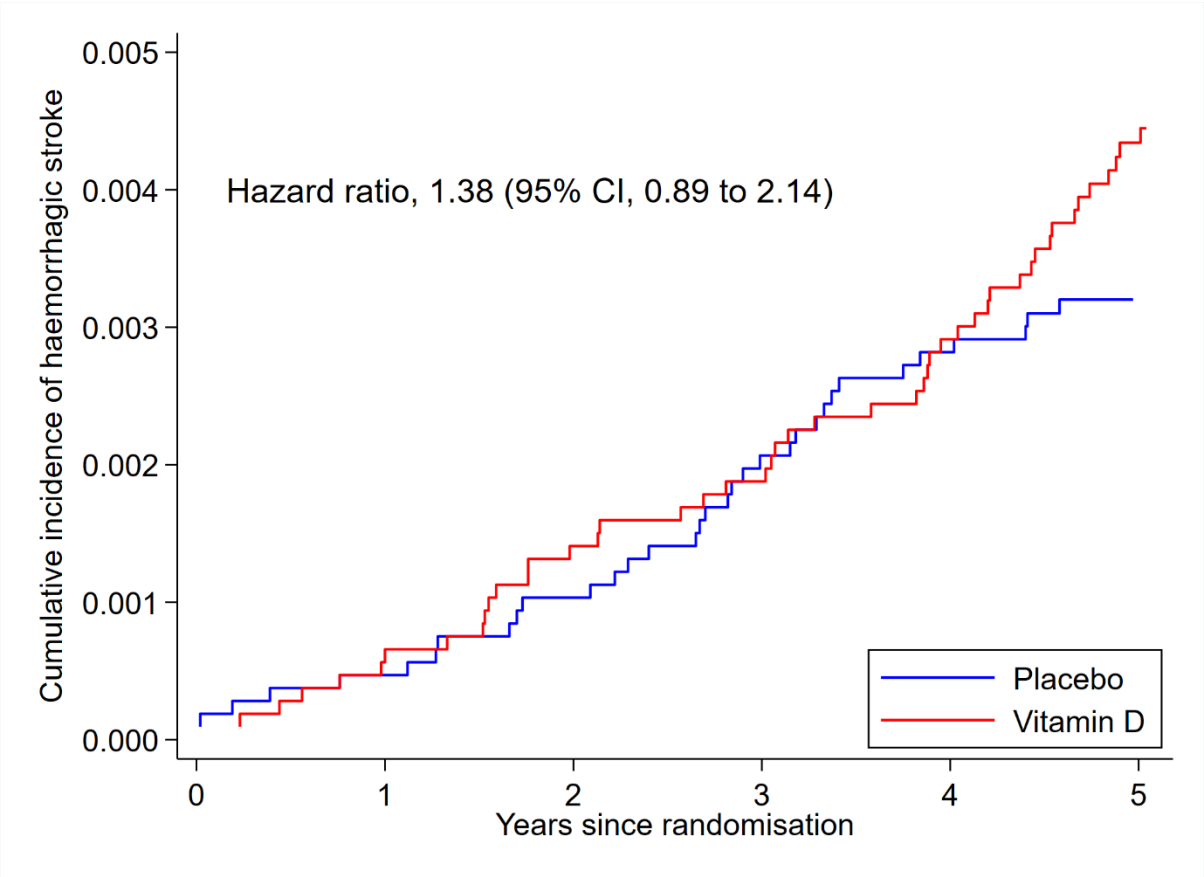
SFigure 17. Cause-specific cumulative incidence of stroke according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior stroke as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



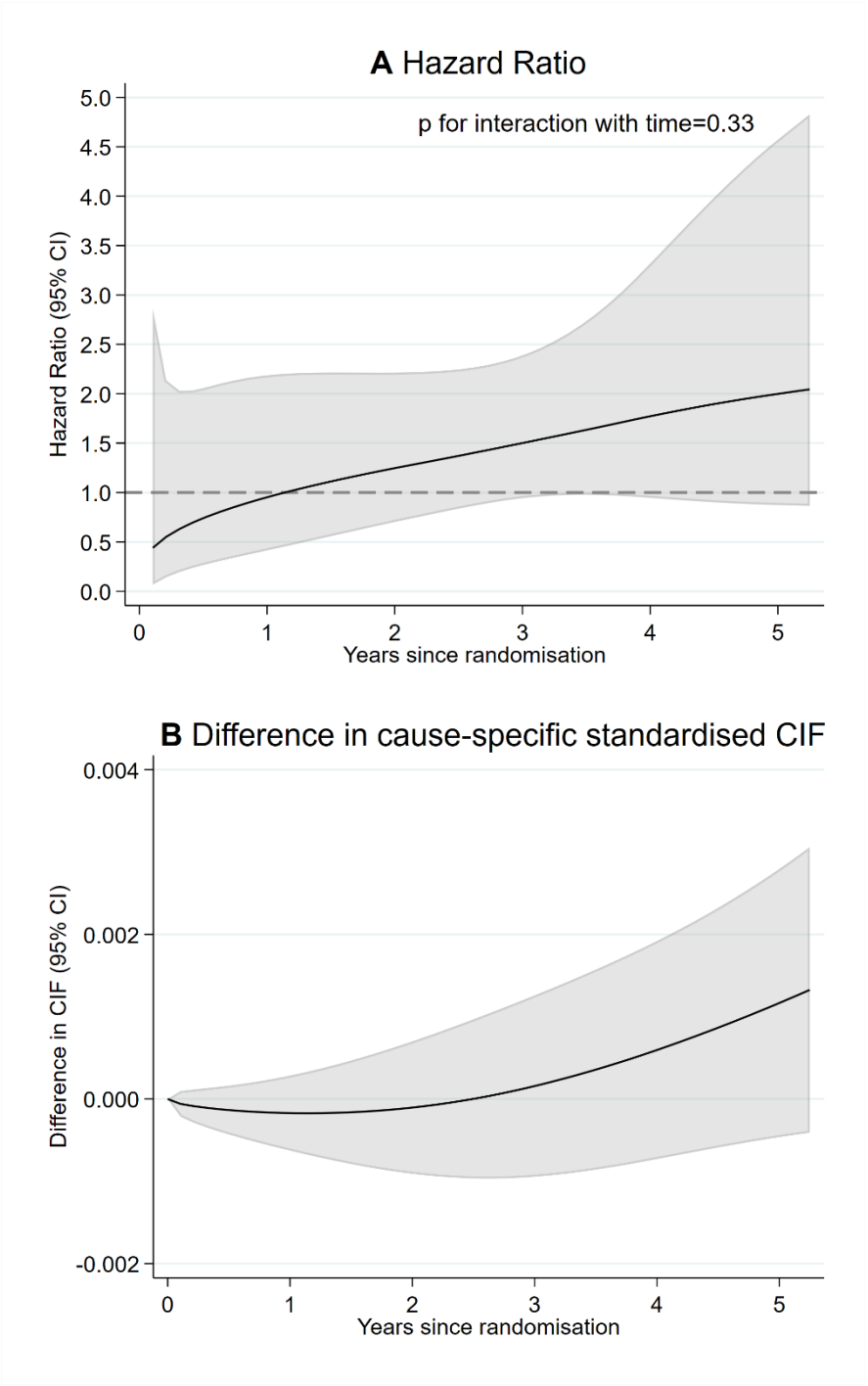
SFigure 18. Effect of vitamin D supplementation on incidence of stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior stroke as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



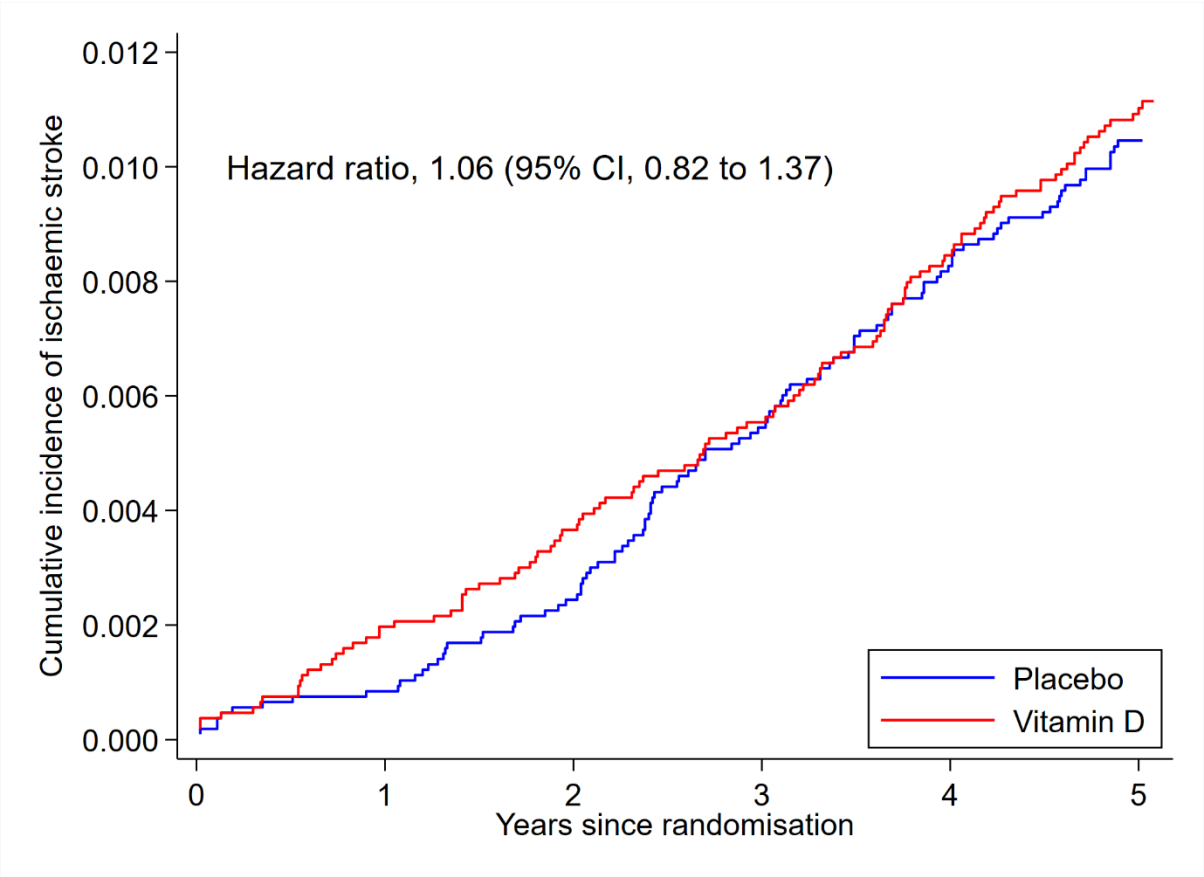
SFigure 19. Cause-specific cumulative incidence of haemorrhagic stroke according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior haemorrhagic stroke as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



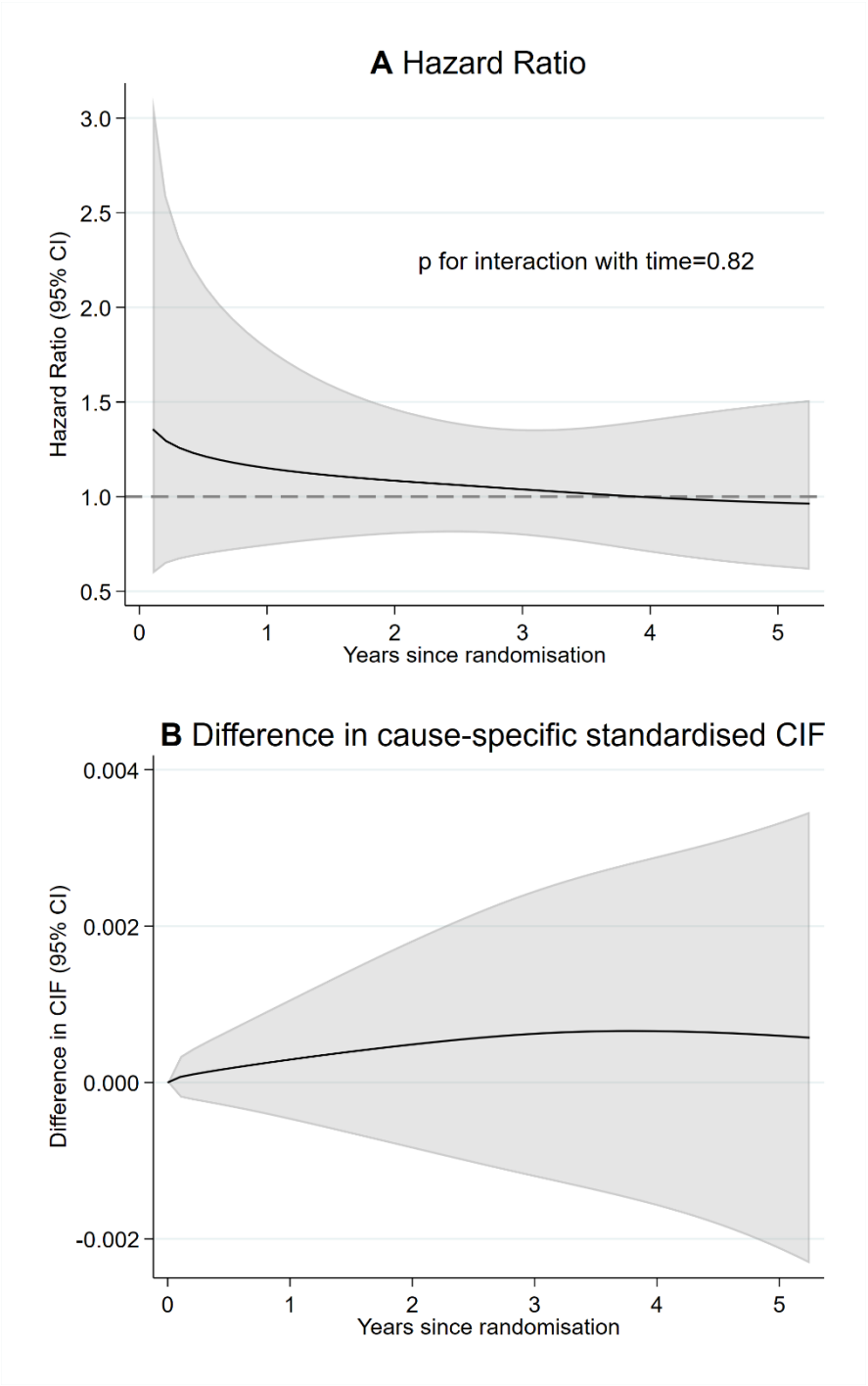
SFigure 20. Effect of vitamin D supplementation on incidence of haemorrhagic stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior haemorrhagic stroke as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.



SFigure 21. Cause-specific cumulative incidence of ischaemic stroke according to randomisation group and time since randomisation.

Curves estimated using Aalen-Johansen methods, treating death without prior ischaemic stroke as a competing risk. The hazard ratio (vitamin D versus placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. Abbreviation: CI, confidence interval; MACE, major cardiovascular event.



SFigure 22. Effect of vitamin D supplementation on incidence of ischaemic stroke. Panel A shows the time-varying hazard ratio and panel B shows the difference in cause-specific standardised cumulative incidence functions.

Estimates (comparing vitamin D and placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline, and an interaction between randomisation group and time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). The p-value for the interaction with time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific standardised cumulative incidence was estimated treating death without prior ischaemic stroke as a competing risk, and probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. Abbreviations: CI, confidence interval; CIF, cumulative incidence function.