Working Title	**Effect of vitamin D supplementation on hypertension and hypercholesterolemia in older Australian adults**		
Date of plan	17 March 2023		
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Background and objective

Background

Hypertension and hypercholesterolemia are the leading clinical risk factors for cardiovascular diseases.[1,2] In 2017-18, 2.6 million and 1.5 million Australians (~11% and 6% of population) reported having hypertension and hypercholesterolemia, respectively, with the prevalence being similar for males and females.[3,4] The prevalence of these conditions increases with age; 45% of Australians aged ≥75 years reported having hypertension[3] and 21% aged ≥65 years reported hypercholesterolemia.[4] Hypertension and hypercholesterolemia can be managed by pharmacologic treatment as well as by lifestyle modification.[5-9] However, side effects due to medications[10] and lack of adherence to a healthy lifestyle are common.[11]

Vitamin D prevents rickets and osteomalacia, and evidence is emerging to suggest that it may reduce the risk of high blood pressure or high blood cholesterol. With respect to hypertension, it suppresses release of renin from the kidneys, thus playing an important role in the renin–angiotensin–aldosterone system, and improves endothelial/vascular function.[12] There are a number of mechanisms by which it may influence serum cholesterol, such as inhibiting the activation of sterol regulatory element-binding protein.[13]

The results of epidemiological studies regarding the link between vitamin D and hypertension are inconclusive. A meta-analysis of 11 cohort studies (8,397 people with incident hypertension ascertained from self-reported questionnaires) suggested an inverse association between serum 25(OH)D concentration and hypertension; each 25 nmol/L increment in 25(OH)D concentration was associated with a 7% decrease in risk of incident hypertension (heterogeneity 62%).[14] A Mendelian randomisation study also found an inverse association between serum 25(OH)D concentration and diastolic blood pressure (DBP), systolic blood pressure (SBP), and risk of hypertension (defined as SBP ≥ 140 mm, DBP ≥ 90 mm, or current use of antihypertensive medications); each 10% increase in genetically instrumented 25(OH)D concentration was associated with changes of -0.29 mm Hg in DPB, -0.37 mm HG in SBP and an 8.1% reduced odds of hypertension (n=142,255).[15] In contrast, a meta-analysis (N=3810) of 27 randomised controlled trials (RCTs) found no evidence that supplementing adults with vitamin D reduces SBP or DBP.[14] However, it is important to note that blood pressure measurements are highly variable, so an elevated measurement in a research setting is not necessarily indicative of hypertension. Two RCTs, not included in the meta-analysis, investigated the effect of vitamin D on hypertension (as diagnosed by a medical professional). They did not find a statistically significant effect of vitamin D supplementation on the incidence of hypertension, although the number of events in one study was small (N=74) and in the other the dose of vitamin D used was low.[16,17]

	The effect of vitamin D supplementation on serum lipids is also unclear. Observational studies have shown that higher circulating 25(OH)D levels are associated with reduced total cholesterol (TC), low-density lipoprotein (LDL) cholesterol levels, and triglycerides, but not associated with high-density lipoprotein (HDL) cholesterol.[18,19] However, Mendelian randomisation analysis suggested a causal positive association between serum 25(OH)D concentration and HDL cholesterol only.[20] A meta-analysis of 41 RCTs (3,434 participants; 1,699 people randomised to receive vitamin D supplementation) also reported similar effects of vitamin D supplementation on TC, LDL cholesterol, and triglycerides.[21] However, 24 trials were conducted specifically in people with diabetes or who were overweight or obese, the sample size was small in all trials (n<230), and the heterogeneity was high. Considering the limited evidence from large-scale RCTs, we aim to use data from the D-Health Trial, a large, population-based RCT for the prevention of all-cause mortality, to examine whether supplementing older Australians with monthly doses of 60,000 international unit (IU) of vitamin D_3 for 5 years alters the incidence of hypertension and hypercholesterolemia, using prescription of medication as a surrogate for diagnosis.
Specific objectives	1. To assess whether randomisation to monthly supplementation with 60,000 IU vitamin D_3 or placebo has an effect on the - incidence of treatment for hypertension (co-primary outcome) - incidence of treatment for hypercholesterolemia (co-primary outcome) 2. For each co-primary outcome, to investigate the effect of randomisation to supplementary vitamin D or placebo within subgroups of: age (<70, ≥70 years); sex; body mass index (BMI) (<25, 25 to <30, ≥30 kg/m^2); predicted deseasonalised baseline serum 25(OH)D concentration (<50, ≥50 nmol/L); prevalent use of lipid-modifying agents (no, yes) (analysis of incident hypertension only); and prevalent use of hypertension medication (no, yes) (analysis of incident hypercholesterolaemia only).
Outcomes and hypotheses	
Instrument	We will use linked Pharmaceutical Benefits Scheme (PBS) records to determine whether/when participants started using medication to treat hypertension and/or hypercholesterolemia. PBS records provide information related to prescribed medication, including date of dispensing, drug name and item number, and anatomic therapeutic classification (ATC) codes. The details of ATC classes used in this analysis are listed in **Table S1** (in Appendix C). Briefly, we will use the following ATC codes: <u>For hypertension</u> *Main analysis*[a] **C08** Calcium channel blockers **C09A and C09B** Angiotensin-converting-enzyme (ACE) inhibitors **C09C and C09D** Angiotensin II receptor blockers (ARBs) **C03A** Thiazide diuretics *In a sensitivity analysis we will ADDITIONALLY include:* **C09X** Other agents acting on the renin-angiotensin system

	C03B, C03C, C03D, C03E and C03X Diuretics **C02** Antihypertensives[b] **C07** Beta-blocking Agents <u>For hypercholesterolemia</u> **C10** Lipid-modifying agents These outcome measures were developed in collaboration with a general practitioner. [a] This broadly follows the Heart Foundation of Australia 2016 guideline for the treatment hypertension, which says "thiazide diuretics, calcium channel blockers, ACE inhibitors or ARBs are suitable first-line drugs for the treatment of hypertension, either as monotherapy or in some combinations".[22] [b] We are using C02 medications in sensitivity analyses only as many have other indications and they are rarely used as single agents for hypertension.
Outcomes	The co-primary outcomes for this analysis are starting a medication treatment for: - hypertension (i.e., supplied with a drug that comes under ATC classes C08, C09A, C09B, C09C, C09D, and C03A); and - hypercholesterolemia (i.e., supplied with a drug that comes under ATC class C10) Follow-up time will begin six months after randomisation, and end at the earliest of: (i) first supply of an abovementioned medication; (ii) date last known to be alive; or (iii) 5 years and 1 month after randomisation.
Hypotheses	<u>Specific Hypotheses</u> - The hazard rate of incident hypertension medication* use and the hazard rate of incident lipid-modifying agent use will be different between the vitamin D and placebo groups. - Vitamin D supplementation will interact with age, sex, BMI, and predicted baseline 25(OH)D concentration to alter the incidence of each co-primary outcome. * the classes of medications used to treat hypertension could also be used for a range of other indications. The term 'hypertension medication' is used here and onwards for easier understanding/navigation of readers.
Data details	
Analysis package	SAS 9.4, STATA version 15 and R version 4.1.1
Dataset	The SAS dataset used to generate the published results will be stored in L:\Lab_RachelN\DHealthDataAnalysis\Projects\Hypertension\Data R:\Lab_RachelN\DHealthDataAnalysis\Projects\Hypertension\Data
Participants	To be eligible for either analysis, a participant must have consented to PBS linkage and have date last known to be alive >6 months from randomisation. People supplied with a hypertension medication within 6 months of randomisation (prevalent user) will

	be excluded from the analysis of hypertension. Similarly, those supplied with a lipid-modifying agent within 6 months of randomisation (prevalent user) will be excluded from the analysis of hypercholesterolemia.
Codebook	L:\Lab_RachelN\DHealthDataAnalysis\Projects\Hypertension\Codebook
Exposure variable(s)	Randomisation group
Covariates	<u>Adjustment variables:</u> ▪ Age at randomisation: 60-64; 65-69; 70-74; 75+ ▪ Sex: F; M ▪ State of residence at randomisation: NSW; QLD; SA; TAS; VIC; WA <u>Variables considered to be potential effect modifiers:</u> ▪ Sex (men, women) ▪ Age at randomisation (<70 years, ≥ 70 years) ▪ BMI at randomisation (<25, 25 to <30, ≥30 kg/m^2) ▪ Predicted baseline 25(OH)D concentration (<50, ≥ 50 nmol/L) ▪ Prevalent use of lipid-modifying agents (no, yes)[1] ▪ Prevalent use of hypertension medication (no, yes)[2] [1] For analyses of incident hypertension only [2] For analyses of incident hypercholesterolaemia only
Handling missing data	<u>Missing outcome data</u> We will assume there is no missing outcome data since we will exclude participants who did not consent to PBS linkage. <u>Missing covariate data</u> Participants with missing BMI data (<0.5%) will be excluded from analyses stratified by BMI.
Maintaining blinding	Analysts will be blinded to study group allocation during initial analysis. Code will be written and tested using a dataset in which the randomisation allocation and the participants' identification code have been removed. Development and testing of code will include producing all results, including tables and figures, as they will appear in the manuscript. Once all the investigators have approved the analysis plan, the analyst will be given 'unblinded' data for the completion of all pre-specified analyses. Any analyses that we perform that are not pre-specified will be declared as exploratory.
Proposed sequence of Statistical Analysis	
File management	The code used to generate the results will be stored in L:\Lab_RachelN\DHealthDataAnalysis\Projects\Hypertension\Code R:\Lab_RachelN\DHealthDataAnalysis\Projects\Hypertension\Code
Analysis	- Flow of the participants included in the analyses of the co-primary outcomes will be presented using a CONSORT flow diagram **(Figure 1)**.

	- Distributions of baseline characteristics will be compared between participants included and excluded from the analytic datasets. We will report p-values from chi-squared tests **(Table S2)**. - We will present the baseline characteristics of the participants included in the analyses according to randomisation group (**Table 1**). Since 49% and 43% of D-Health participants are excluded from the analyses of hypertension and hypercholesterolaemia, respectively, we will use chi-squared tests to assess whether characteristics vary between the randomisation groups. **Associations with risk factors** - We will present descriptive statistics for hypertension medication and lipid-modifying agent use within subgroups of selected baseline characteristics. The associations between potential risk factors ascertained at baseline and outcome variables [(i) incident hypertension medication use; (ii) incident lipid-modifying agent use] will be estimated using flexible parametric survival models (FPSMs). All estimates will be adjusted for randomisation group, age and sex (**Table S3**). We will assume proportional hazards for all covariates included in the models. **Effect of supplementation on use of hypertension medication** - We will use Aalen-Johansen methods to plot the cause-specific cumulative probability of hypertension medication use for each randomisation group, treating death without prior hypertension medication use as a competing risk (**Figure 2A**). - For our analysis of the effect of vitamin D supplementation on incidence of hypertension medication use, we will fit two FPSMs.[23,24] Both models will include randomisation group and the randomisation stratification variables of age, sex, and state of residence at baseline. 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). a. To estimate an overall hazard ratio (HR), we will use an FPSM that assumes proportional hazards (Model 1). The overall HR and 95% CI will be embedded in **Figure 2A** and reported in **Table S4**. b. To allow the HR to vary with time, we will use a second FPSM (Model 2) that includes an interaction between randomisation group and time since the start of follow-up (fitted as a restricted cubic spline with one internal knot placed at the median of uncensored log survival times). Using Model 2, we will report the HR (95% CI) at 2 and 4 years since the start of follow-up (**Table S4**) and plot the estimated HR (95% CI) as a function of time since randomisation (**Figure S1A**). We will also report the p-value from a likelihood ratio test (embedded in **Figure S1A)** comparing Models 1 and 2 (i.e. testing the effect of including the interaction between time and randomisation group). - We will estimate the difference in cause-specific standardized cumulative incidence, treating death without prior medication treatment of hypertension as a competing risk (**Figure S1B**), reporting values at 2 and 4 years of follow up (**Table S4**). For this analysis, we will use estimates from FPSMs and the user-written *standsurv* command in Stata with the competing risks models option. The baseline log cumulative hazard function and the interaction between randomisation group and time will be modelled as described above. All FPSMs will include

	randomisation group, and the randomisation stratification variables of age, sex, and state of residence at baseline. **Effect of supplementation on use of lipid-modifying agents** - We will follow the same analytic approach as for use of hypertension medication. The cause-specific cumulative probability of use of lipid-modifying agents for each randomisation group will be presented as **Figure 2B**. - Results from FPSM models that include an interaction between randomisation group and time since start of follow-up will be presented in **Figure S2A** and **Figure S2B**. - The estimated HR (95% CI) and difference in cause-specific standardised cumulative incidence (95% CI) at 2 and 4 years of follow-up will be presented in **Table S4.** **Subgroup analyses** For each outcome, we will use FPSMs to examine whether the effect of supplementation is modified by the following baseline characteristics: o Age (< 70 years, ≥ 70 years); o Sex (men, women); o BMI (<25, 25 to <30, ≥30 kg/m^2); o Predicted deseasonalised 25(OH)D concentration (< 50 nmol/L, ≥ 50 nmol/L); o Prevalent use of lipid-modifying agents (no, yes) (analysis of incident hypertension only); and o Prevalent use of hypertension medication (no, yes) (analysis of incident hypercholesterolaemia only). The baseline hazard will be modelled as described previously. The FPSM will include randomisation group, age, sex, and state of residence at baseline, the baseline characteristic of interest, and an interaction between the baseline characteristic and randomisation group. We will assume proportional hazards for all covariates. We will use a likelihood ratio test to compare models with and without the interaction term. Results will be presented as forest plots (**Figure 3** and **Figure 4**). **Sensitivity analysis that accounts for all possible classes of hypertension medication** - We will repeat the main analyses of incident hypertension medication use considering all possible classes of hypertension medication including C02, C03, C07, C08, and C09 (vs C08, C09A, C09B, C09C, C09D, and C03A in the main analysis). We will reproduce figure 2A to form **Figure S3**.
Significance level	We will use a significance level of 0.05. We will not adjust for multiple testing. [25,26]
Planned main tables (Appendix A)	**Table 1.** Baseline characteristics of the participants included in analyses according to randomisation group

Planned main figures (Appendix B)	**Figure 1.** Flow of the participants included in the analyses of incident hypertension medication use and incident lipid-modifying agent use (CONSORT flow diagram) **Figure 2.** Cause-specific probability of (A) hypertension medication; and (B) lipid-modifying agent use according to follow-up time and randomisation group **Figure 3.** Effect of vitamin D supplementation on incident hypertension medication use overall and within participant subgroups **Figure 4.** Effect of vitamin D supplementation on incident lipid-modifying agent use overall and within participant subgroups
Planned supplementary tables (Appendix C)	**Table S1.** Anatomical Therapeutic Chemical code for hypertension medication and lipid-modifying agents **Table S2.** Baseline characteristics of participants included versus excluded from the final analyses **Table S3.** Associations between selected baseline characteristics and incidence of hypertension and hypercholesterolemia medication **Table S4.** Effect of vitamin D supplementation on incident hypertension medication and lipid-modifying agent use. Predicted difference in cause-specific standardised cumulative incidence and time-varying hazard ratio at 2 and 4 years of follow-up, and predicted overall hazard ratio
Planned supplementary figures (Appendix D)	**Figure S1.** Effect of vitamin D supplementation on incident use of hypertension medication. Panel A shows the time-varying hazard ratio and panel B shows the difference in the cause-specific standardised cumulative incidence functions **Figure S2.** Effect of vitamin D supplementation on incident use of lipid-modifying agents. Panel A shows the time-varying hazard ratio and panel B shows the difference in the cause-specific standardised cumulative incidence functions **Figure S3.** Cause-specific cumulative probability of hypertension medication use according to follow-up time in the vitamin D and placebo groups, a sensitivity analysis accounting for all possible hypertension medications (including ATC classes C02, C03, C07, C08, C09)

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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 A. Main Tables

Table 1. Baseline characteristics of the participants included in the analyses according to randomisation group ***[Note: based on dummy data]***

Characteristic	Outcome: Hypertension medication use[1] N (%) Vitamin D (N = 5520)	Placebo (N = 5442)	P-value[3]	Outcome: Lipid-modifying agent use[2] N (%) Vitamin D (N = 6101)	Placebo (N = 6025)	P-value[3]
Age (years)						
60-64	1654 (30.0)	1605 (29.5)	0.24	1809 (29.7)	1759 (29.2)	0.12
65-69	1560 (28.3)	1634 (30.0)		1693 (27.7)	1764 (29.3)	
70-74	1389 (25.2)	1326 (24.4)		1500 (24.6)	1497 (24.8)	
≥ 75	917 (16.6)	877 (16.1)		1099 (18.0)	1005 (16.7)	
Sex						
Men	2867 (51.9)	2800 (51.5)	0.61	3109 (51.0)	3081 (51.1)	0.84
Women	2653 (48.1)	2642 (48.5)		2992 (49.0)	2944 (48.9)	
Body mass index (kg/m²)						
< 25	2047 (37.3)	2000 (36.9)	0.78	2116 (34.8)	2053 (34.2)	0.46
25 to < 30	2327 (42.3)	2329 (43.0)		2533 (41.7)	2569 (42.8)	
≥ 30	1121 (20.4)	1087 (20.1)		1425 (23.5)	1377 (23.0)	
Missing	*25*	*26*		*27*	*26*	
Predicted 25(OH)D concentration (nmol/L)						
< 50	1280 (23.2)	1227 (22.5)	0.42	1453 (23.8)	1387 (23.0)	0.30
≥ 50	4240 (76.8)	4215 (77.5)		4648 (76.2)	4638 (77.0)	
State of residence						
Queensland	1135 (20.6)	1101 (20.2)	0.70	1210 (19.8)	1159 (19.2)	0.27
New South Wales	1120 (20.3)	1079 (19.8)		1202 (19.7)	1212 (20.1)	
Victoria	931 (16.9)	894 (16.4)		1091 (17.9)	1004 (16.7)	
Tasmania	650 (11.8)	642 (11.8)		748 (12.3)	748 (12.4)	
South Australia	784 (14.2)	832 (15.3)		872 (14.3)	933 (15.5)	
Western Australia	900 (16.3)	894 (16.4)		978 (16.0)	969 (16.1)	

Characteristic	Outcome: Hypertension medication use[1] N (%)			Outcome: Lipid-modifying agent use[2] N (%)		
	Vitamin D (N = 5520)	Placebo (N = 5442)	P-value[3]	Vitamin D (N = 6101)	Placebo (N = 6025)	P-value[3]
Highest qualification obtained						
None	443 (8.1)	473 (8.8)	0.81	490 (8.1)	536 (9.0)	0.27
School or intermediate certificate	870 (15.9)	856 (15.9)		962 (15.9)	996 (16.7)	
Higher school or leaving certificate	768 (14.1)	750 (13.9)		848 (14.0)	818 (13.7)	
Apprenticeship or certificate	1814 (33.2)	1767 (32.8)		2009 (33.2)	1954 (32.8)	
University degree or higher	1566 (28.7)	1547 (28.7)		1739 (28.8)	1660 (27.8)	
Missing	*59*	*49*		*53*	*61*	
Smoking history						
Never	3123 (57.0)	3073 (56.9)	0.63	3447 (56.9)	3417 (57.2)	0.82
Ex-smoker	2123 (38.7)	2078 (38.5)		2349 (38.8)	2312 (38.7)	
Current	233 (4.3)	250 (4.6)		264 (4.4)	247 (4.1)	
Missing	*41*	*41*		*41*	*49*	
Alcohol consumption (drinks/week)						
< 1	1243 (23.3)	1233 (23.5)	0.82	1364 (23.2)	1406 (24.2)	0.24
1 to 7	2496 (46.9)	2441 (46.6)		2751 (46.8)	2626 (45.3)	
> 7 to 14	976 (18.3)	990 (18.9)		1102 (18.7)	1073 (18.5)	
> 14	610 (11.5)	579 (11.0)		664 (11.3)	697 (12.0)	
Missing	*195*	*199*		*220*	*223*	
Living alone						
No	4422 (80.5)	4369 (80.7)	0.87	4870 (80.2)	4804 (80.2)	0.99
Yes	1068 (19.5)	1047 (19.3)		1202 (19.8)	1185 (19.8)	
Missing	*30*	*26*		*29*	*36*	

Characteristic	Outcome: Hypertension medication use[1] N (%) Vitamin D (N = 5520)	Placebo (N = 5442)	P-value[3]	Outcome: Lipid-modifying agent use[2] N (%) Vitamin D (N = 6101)	Placebo (N = 6025)	P-value[3]
Self-rated overall health						
Excellent or very good	3456 (63.6)	3404 (63.6)	0.99	3709 (61.8)	3652 (61.5)	0.62
Good	1653 (30.4)	1634 (30.5)		1892 (31.5)	1909 (32.1)	
Fair or poor	325 (6.0)	318 (5.9)		404 (6.7)	379 (6.4)	
Missing	*86*	*86*		*96*	*85*	
Self-rated quality of life						
Excellent or very good	3898 (72.3)	3829 (71.7)	0.37	4227 (70.8)	4144 (70.1)	0.62
Good	1258 (23.3)	1249 (23.4)		1454 (24.4)	1486 (25.1)	
Fair or poor	237 (4.4)	265 (5.0)		286 (4.8)	284 (4.8)	
Missing	*127*	*99*		*134*	*111*	
Prevalent hypertension medication user[4]						
No	5520 (100.0)	5442 (100.0)		4260 (69.8)	4160 (69.0)	0.35
Yes				1841 (30.2)	1865 (31.0)	
Prevalent lipid-modifying agent user[5]						
No	4260 (77.2)	4160 (76.4)	0.36	6101 (100.0)	6025 (100.0)	
Yes	1260 (22.8)	1282 (23.6)				

[1] Participants who had given consent for PBS linkage, were known to be alive 6 months after randomisation, and who had not had any hypertension medication prescribed within 6 months of being randomised are included in the final analysis

[2] Participants who had given consent for PBS linkage, were known to be alive 6 months after randomisation, and who had not had any lipid-modifying agents prescribed within 6 months of being randomised are included in the final analysis

[3] P-value from chi-squared test

[4] Defined as supplied hypertension medication within 6 months after being randomised

[5] Defined as supplied lipid-modifying agent within 6 months after being randomised

Abbreviation: PBS – Pharmaceutical Benefits Scheme

Appendix B. Main Figures

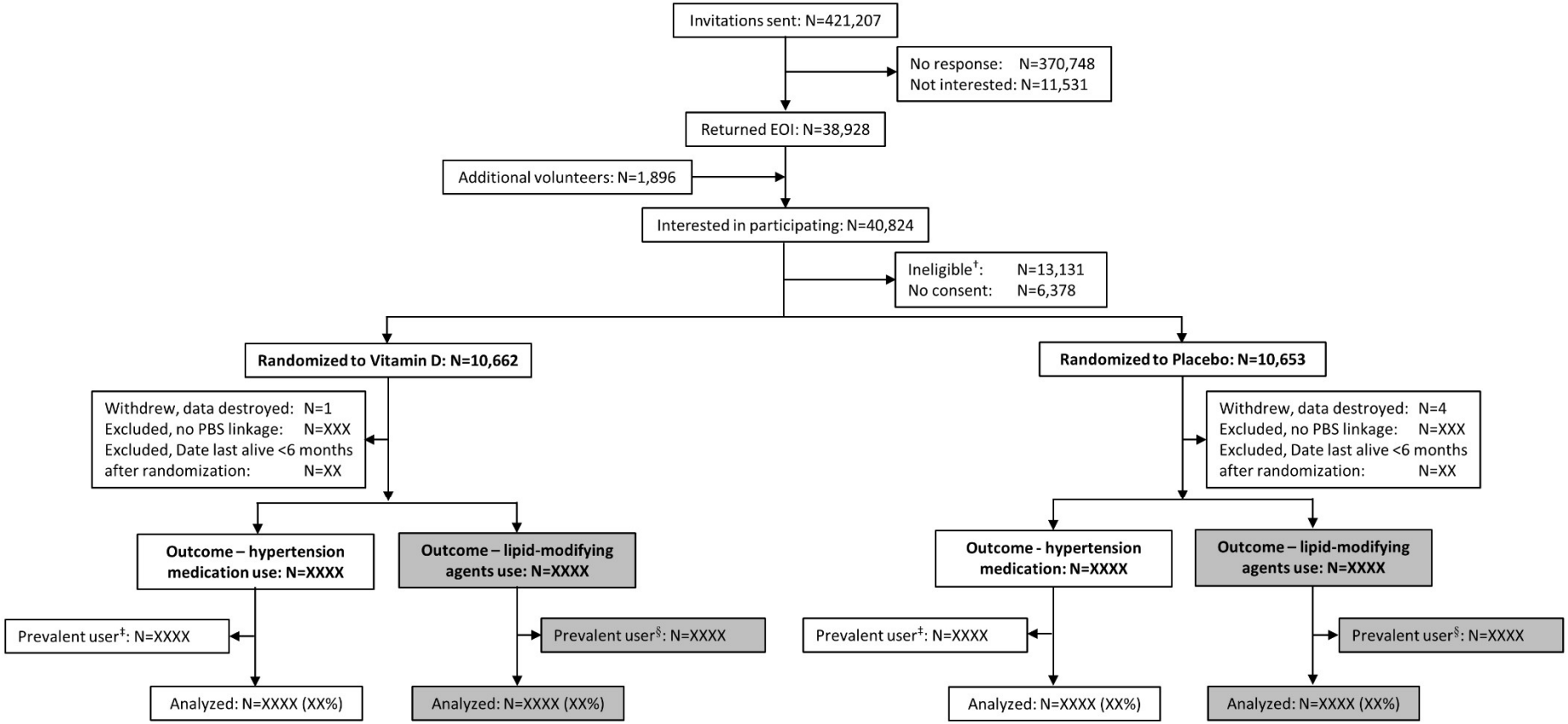

Figure 1. Flow of the participants included in the analyses of incident hypertension medication use and incident lipid-modifying agent use (CONSORT flow diagram)

† Those who self-reported a previous or current diagnosis of hypercalcemia, hyperparathyroidism, kidney stones, osteomalacia or sarcoidosis, or who were taking >500 international units supplemental vitamin D per day were ineligible for randomisation

‡ Defined as supplied any hypertension medication within 6 months after being randomised

§ Defined as supplied any lipid-modifying agent within 6 months after being randomised

Abbreviations: EOI – Expression of interest; PBS – Pharmaceutical Benefits Scheme

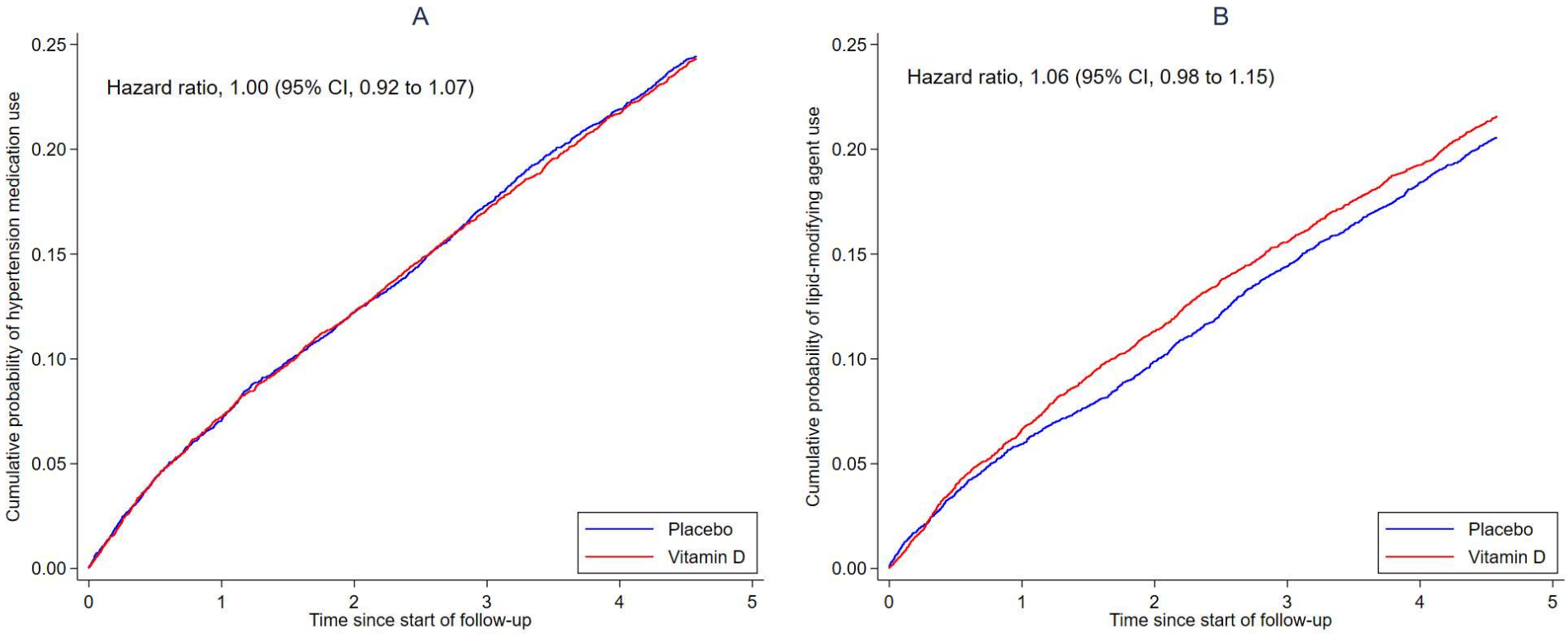

Figure 2. Cause-specific cumulative probability of: (A) hypertension medication; and (B) lipid-modifying agent use according to follow-up time and randomisation group. *[**Note:** based on dummy data]*

Curves estimated using Aalen-Johansen methods, treating death without prior medication use 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. Time 0 is at 6 months after randomisation, when follow-up began. People supplied with the medications within 6 months of randomisation were excluded, as were participants whose last known date alive was within 6 months of randomisation.

Abbreviation: CI – confidence interval

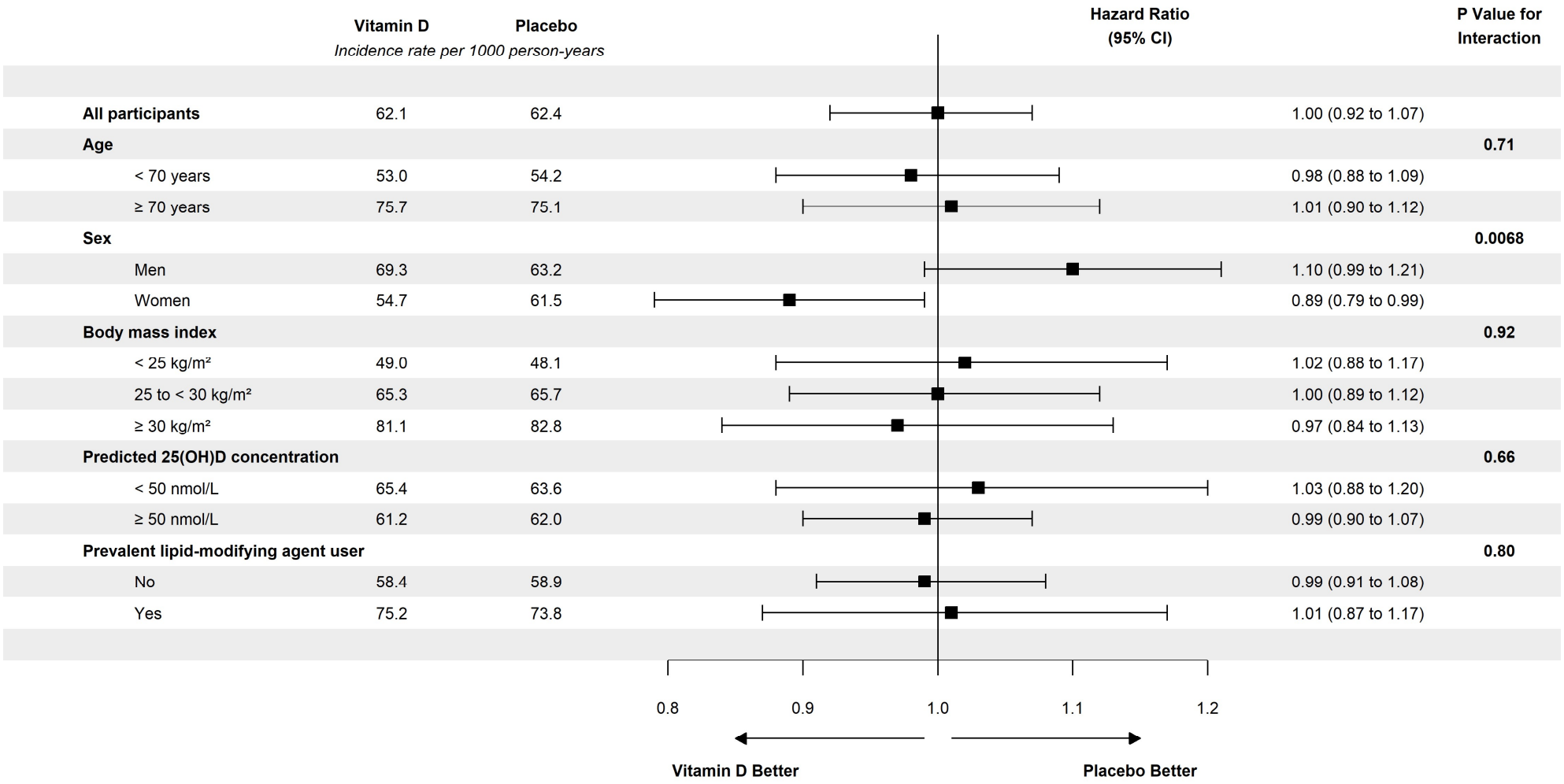

Figure 3: Effect of vitamin D supplementation on incident hypertension medication use overall and within participant subgroups *[**Note:** based on dummy data]*

Hazard ratios were calculated using flexible parametric survival models. All models included randomisation group, age, sex, and state of residence at baseline. Models producing estimates by levels of age, sex, BMI, and predicted 25(OH)D concentration included the characteristic of interest and an interaction between randomisation group and the characteristic of interest. Proportional hazards was assumed for all covariates. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI – confidence interval

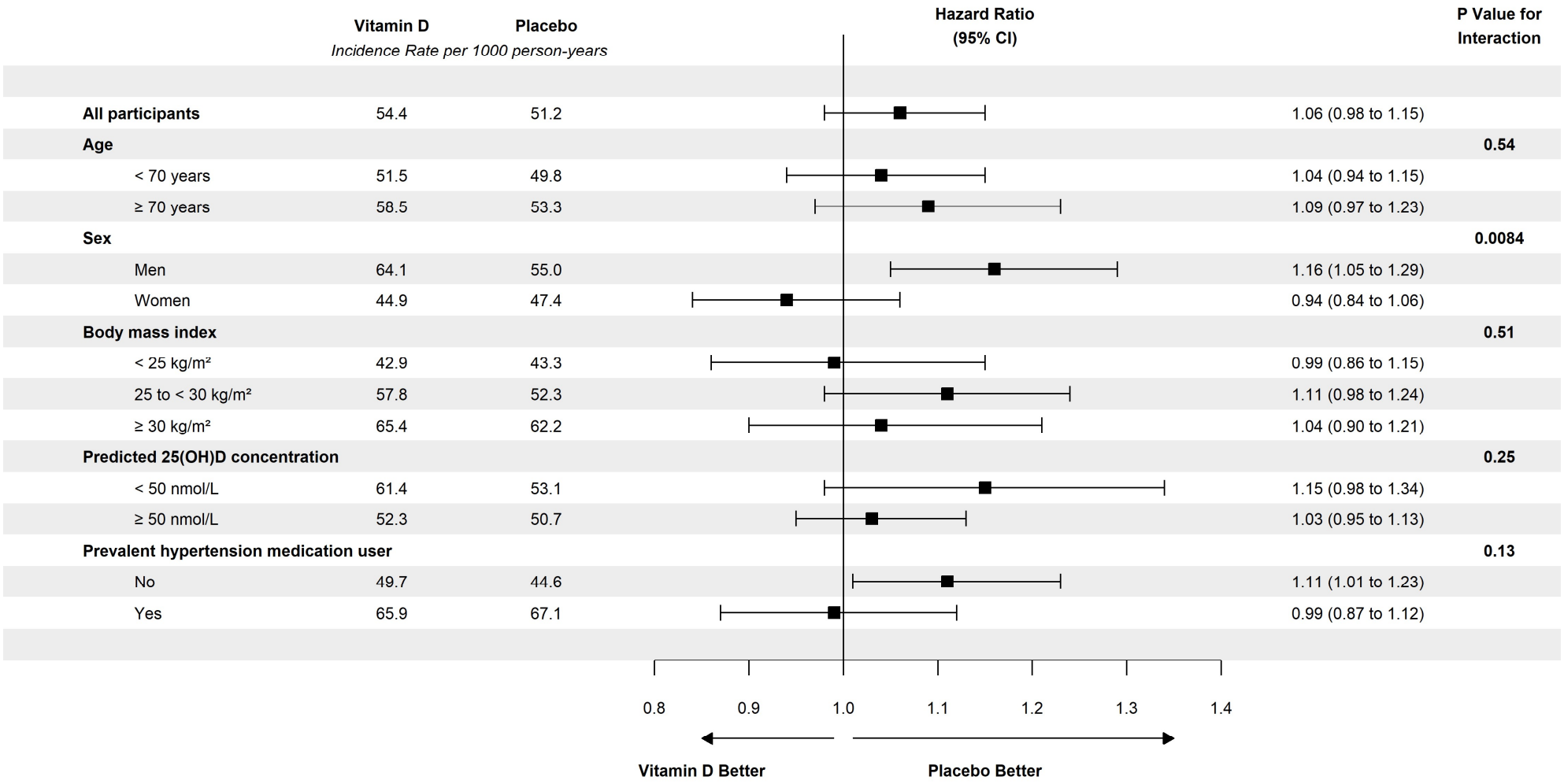

Figure 4: Effect of vitamin D supplementation on incident lipid-modifying agent use overall and within participant subgroups *[**Note:** based on dummy data]*

Hazard ratios were calculated using flexible parametric survival models. All models included randomisation group, age, sex, and state of residence at baseline. Models producing estimates by levels of age, sex, BMI, and predicted 25(OH)D concentration included the characteristic of interest and an interaction between randomisation group and the characteristic of interest. Proportional hazards was assumed for all covariates. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI – confidence interval

Appendix C. Supplementary Tables

Table S1. Anatomical Therapeutic Chemical codes for hypertension medication and lipid-modifying agents

Anatomical Therapeutic Chemical code[1]	
C CARDIOVASCULAR SYSTEM	
C02 ANTIHYPERTENSIVES[2]	C02A ANTIADRENERGIC AGENTS, CENTRALLY ACTING C02B ANTIADRENERGIC AGENTS, GANGLION-BLOCKING C02C ANTIADRENERGIC AGENTS, PERIPHERALLY ACTING C02D ARTERIOLAR SMOOTH MUSCLE, AGENTS ACTING ON C02K OTHER ANTIHYPERTENSIVES C02L ANTIHYPERTENSIVES AND DIURETICS IN COMBINATION C02N COMBINATIONS OF ANTIHYPERTENSIVES IN ATC-GR. C02
C03 DIURETICS	C03A LOW-CEILING DIURETICS, THIAZIDES C03B LOW-CEILING DIURETICS, EXCL. THIAZIDES[2] C03C HIGH-CEILING DIURETICS[2] C03D ALDOSTERONE ANTAGONISTS AND OTHER POTASSIUM-SPARING AGENTS[2] C03E DIURETICS AND POTASSIUM-SPARING AGENTS IN COMBINATION[2] C03X OTHER DIURETICS[2]
C07 BETA BLOCKING AGENTS[2]	C07A BETA BLOCKING AGENTS C07B BETA BLOCKING AGENTS AND THIAZIDES C07C BETA BLOCKING AGENTS AND OTHER DIURETICS C07D BETA BLOCKING AGENTS, THIAZIDES AND OTHER DIURETICS C07E BETA BLOCKING AGENTS AND VASODILATORS C07F BETA BLOCKING AGENTS, OTHER COMBINATIONS
C08 CALCIUM CHANNEL BLOCKERS	C08C SELECTIVE CALCIUM CHANNEL BLOCKERS WITH MAINLY VASCULAR EFFECTS C08D SELECTIVE CALCIUM CHANNEL BLOCKERS WITH DIRECT CARDIAC EFFECTS C08E NON-SELECTIVE CALCIUM CHANNEL BLOCKERS C08G CALCIUM CHANNEL BLOCKERS AND DIURETICS
C09 AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	C09A ACE INHIBITORS, PLAIN C09B ACE INHIBITORS, COMBINATIONS C09C ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), PLAIN C09D ANGIOTENSIN II RECEPTOR BLOCKERS (ARBs), COMBINATIONS C09X OTHER AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM[2]
C10 LIPID-MODIFYING AGENTS	C10A LIPID-MODIFYING AGENTS, PLAIN C10B LIPID-MODIFYING AGENTS, COMBINATIONS

[1] Source: https://www.whocc.no/atc_ddd_index/?code=C02&showdescription=no; [2] used in the sensitivity analyses only

Table S2. Baseline characteristics of participants included versus excluded from the final analyses *[**Note:** based on dummy data]*

	Consent to PBS linkage			Incident hypertension medication use[1]			Incident lipid-modifying agent use[2]		
Characteristic	**Yes N (%)**	**No N (%)**	**P-value[3]**	**Included N (%)**	**Excluded N (%)**	**P-value[3]**	**Included N (%)**	**Excluded N (%)**	**P-value[3]**
Randomisation Group									
Placebo	9803 (50.3)	852 (47.0)	0.01	5442 (49.6)	4361 (51.1)	0.04	6025 (49.7)	3778 (51.3)	0.03
Vitamin D	9694 (49.7)	961 (53.0)		5520 (50.4)	4174 (48.9)		6101 (50.3)	3593 (48.7)	
Age (years)									
60-64	4786 (24.5)	466 (25.7)	0.22	3259 (29.7)	1527 (17.9)	<0.01	3568 (29.4)	1218 (16.5)	<0.01
65-69	5367 (27.5)	467 (25.8)		3194 (29.1)	2173 (25.5)		3457 (28.5)	1910 (25.9)	
70-74	5314 (27.3)	482 (26.6)		2715 (24.8)	2599 (30.5)		2997 (24.7)	2317 (31.4)	
≥ 75	4030 (20.7)	398 (22.0)		1794 (16.4)	2236 (26.2)		2104 (17.4)	1926 (26.1)	
Sex									
Men	10663 (54.7)	867 (47.8)	<0.01	5667 (51.7)	4996 (58.5)	<0.01	6190 (51.0)	4473 (60.7)	<0.01
Women	8834 (45.3)	946 (52.2)		5295 (48.3)	3539 (41.5)		5936 (49.0)	2898 (39.3)	
Body mass index (kg/m²)									
< 25	5854 (30.2)	563 (31.6)	0.34	4047 (37.1)	1807 (21.3)	<0.01	4169 (34.5)	1685 (23.0)	<0.01
25 to < 30	8297 (42.7)	732 (41.1)		4656 (42.7)	3641 (42.8)		5102 (42.3)	3195 (43.5)	
≥ 30	5261 (27.1)	484 (27.2)		2208 (20.2)	3053 (35.9)		2802 (23.2)	2459 (33.5)	
Missing	*85*	*34*		*51*	*34*		*53*	*32*	
Predicted 25(OH)D concentration (nmol/L)									
< 50	4718 (24.2)	482 (26.6)	0.02	2507 (22.9)	2211 (25.9)	<0.01	2840 (23.4)	1878 (25.5)	<0.01
≥ 50	14779 (75.8)	1331 (73.4)		8455 (77.1)	6324 (74.1)		9286 (76.6)	5493 (74.5)	
State of residence									
Queensland	3893 (20.0)	313 (17.3)	0.03	2236 (20.4)	1657 (19.4)	0.02	2369 (19.5)	1524 (20.7)	<0.01
New South Wales	3989 (20.5)	353 (19.5)		2199 (20.1)	1790 (21.0)		2414 (19.9)	1575 (21.4)	
Victoria	3370 (17.3)	332 (18.3)		1825 (16.6)	1545 (18.1)		2095 (17.3)	1275 (17.3)	
Tasmania	2282 (11.7)	230 (12.7)		1292 (11.8)	990 (11.6)		1496 (12.3)	786 (10.7)	
South Australia	2855 (14.6)	266 (14.7)		1616 (14.7)	1239 (14.5)		1805 (14.9)	1050 (14.2)	
Western Australia	3108 (15.9)	319 (17.6)		1794 (16.4)	1314 (15.4)		1947 (16.1)	1161 (15.8)	

Characteristic	Consent to PBS linkage			Incident hypertension medication use[1]			Incident lipid-modifying agent use[2]		
	Yes N (%)	No N (%)	P-value[3]	Included N (%)	Excluded N (%)	P-value[3]	Included N (%)	Excluded N (%)	P-value[3]
Highest qualification obtained									
None	1907 (9.9)	237 (13.4)	<0.01	916 (8.4)	991 (11.8)	<0.01	1026 (8.5)	881 (12.1)	<0.01
School or intermediate cert.	3230 (16.7)	325 (18.4)		1726 (15.9)	1504 (17.8)		1958 (16.3)	1272 (17.5)	
Higher school or leaving cert.	2700 (14.0)	265 (15.0)		1518 (14.0)	1182 (14.0)		1666 (13.9)	1034 (14.2)	
Apprenticeship or cert.	6437 (33.4)	595 (33.7)		3581 (33.0)	2856 (33.9)		3963 (33.0)	2474 (34.0)	
University degree or higher	5010 (26.0)	341 (19.3)		3113 (28.7)	1897 (22.5)		3399 (28.3)	1611 (22.2)	
Missing	*213*	*50*		*108*	*105*		*114*	*99*	
Smoking history									
Never	10568 (54.6)	1024 (57.4)	0.04	6196 (56.9)	4372 (51.7)	<0.01	6864 (57.0)	3704 (50.7)	<0.01
Ex-smoker	7957 (41.1)	680 (38.1)		4201 (38.6)	3756 (44.4)		4661 (38.7)	3296 (45.1)	
Current	815 (4.2)	81 (4.5)		483 (4.4)	332 (3.9)		511 (4.2)	304 (4.2)	
Missing	*157*	*28*		*82*	*75*		*90*	*67*	
Alcohol consumption (drinks/week)									
< 1	4606 (24.5)	441 (25.7)	0.03	2476 (23.4)	2130 (26.0)	<0.01	2770 (23.7)	1836 (25.9)	<0.01
1 to 7	8310 (44.3)	794 (46.3)		4937 (46.7)	3373 (41.1)		5377 (46.0)	2933 (41.4)	
> 7 to 14	3457 (18.4)	297 (17.3)		1966 (18.6)	1491 (18.2)		2175 (18.6)	1282 (18.1)	
> 14	2398 (12.8)	182 (10.6)		1189 (11.3)	1209 (14.7)		1361 (11.6)	1037 (14.6)	
Missing	*726*	*99*		*394*	*332*		*443*	*283*	
Living alone									
No	15563 (80.2)	1397 (77.8)	0.01	8791 (80.6)	6772 (79.8)	0.14	9674 (80.2)	5889 (80.3)	0.91
Yes	3834 (19.8)	399 (22.2)		2115 (19.4)	1719 (20.2)		2387 (19.8)	1447 (19.7)	
Missing	*100*	*17*		*56*	*44*		*65*	*35*	
Self-rated overall health									
Excellent or very good	10719 (55.8)	928 (52.4)	0.02	6860 (63.6)	3859 (45.9)	<0.01	7361 (61.6)	3358 (46.3)	<0.01
Good	6838 (35.6)	680 (38.4)		3287 (30.5)	3551 (42.2)		3801 (31.8)	3037 (41.9)	
Fair or poor	1638 (8.5)	162 (9.2)		643 (6.0)	995 (11.8)		783 (6.6)	855 (11.8)	
Missing	*302*	*43*		*172*	*130*		*181*	*121*	

Characteristic	Consent to PBS linkage			Incident hypertension medication use[1]			Incident lipid-modifying agent use[2]		
	Yes N (%)	No N (%)	P-value[3]	Included N (%)	Excluded N (%)	P-value[3]	Included N (%)	Excluded N (%)	P-value[3]
Self-rated quality of life									
Excellent or very good	12903 (67.7)	1057 (60.7)	<0.01	7727 (72.0)	5176 (62.1)	<0.01	8371 (70.5)	4532 (63.0)	<0.01
Good	5075 (26.6)	556 (31.9)		2507 (23.4)	2568 (30.8)		2940 (24.7)	2135 (29.7)	
Fair or poor	1095 (5.7)	129 (7.4)		502 (4.7)	593 (7.1)		570 (4.8)	525 (7.3)	
Missing	*424*	*71*		*226*	*198*		*245*	*179*	
Prevalent hypertension medication user[4]									
No	..	..	..	10962 (100.0)	18 (0.2)	<0.01	8420 (69.4)	2560 (34.7)	<0.01
Yes	..	..		0 (0.0)	8517 (99.8)		3706 (30.6)	4811 (65.3)	
Prevalent lipid-modifying agent user[5]									
No	..	..	..	8420 (76.8)	3726 (43.7)	<0.01	12126 (100.0)	20 (0.3)	<0.01
Yes	..	..		2542 (23.2)	4809 (56.3)		0 (0.0)	7351 (99.7)	

[1] Among participants with PBS linkage, those who were supplied hypertension medication within 6 months of being randomised, or whose last known date alive was within 6 months of randomisation are excluded from the final analysis

[2] Among participants with PBS linkage, those who were supplied lipid-modifying agents within 6 months of being randomised, or whose last known date alive was within 6 months of randomisation are excluded from the final analysis

[3] p-value from chi-squared test

[4] Defined as supplied any hypertension medication within 6 months after being randomised

[5] Defined as supplied any lipid-modifying agent within 6 months after being randomised

Abbreviation: cert., certificate; PBS, Pharmaceutical Benefits Scheme

Table S3. Associations between selected baseline characteristics and incident hypertension and hypercholesterolemia outcomes

	Incident use of hypertension medication			Incident use of lipid-modifying agents		
Characteristic	**N/person-years**	**IR per 1000 person-years**	**HR (95% CI)**	**N/person-years**	**IR per 1000 person-years**	**HR (95% CI)**
All participants	2671/42913	62.2	..	2554/48346	52.8	..
Age (years)						
60-64	638/13318	47.9	ref.	666/14599	45.6	ref.
65-69	752/12612	59.6	1.24 (1.12, 1.38)	769/13738	56.0	1.22 (1.10, 1.36)
70-74	746/10413	71.6	1.48 (1.33, 1.64)	640/11884	53.9	1.15 (1.03, 1.29)
≥ 75	535/6570	81.4	1.66 (1.48, 1.87)	479/8125	59.0	1.24 (1.10, 1.39)
Sex						
Men	1451/21911	66.2	ref.	1442/24236	59.5	ref.
Women	1220/21002	58.1	0.93 (0.86, 1.00)	1112/24110	46.1	0.78 (0.73, 0.85)
Body mass index (kg/m²)						
< 25	796/16401	48.5	ref.	735/17046	43.1	ref.
25 to < 30	1187/18131	65.5	1.34 (1.22, 1.46)	1116/20282	55.0	1.24 (1.13, 1.36)
≥ 30	672/8201	81.9	1.71 (1.54, 1.90)	690/10818	63.8	1.49 (1.34, 1.65)
Predicted 25(OH)D concentration (nmol/L)						
< 50	626/9707	64.5	1.07 (0.98, 1.17)	637/11108	57.3	1.14 (1.04, 1.25)
≥ 50	2045/33207	61.6	ref.	1917/37238	51.5	ref.
Self-rated overall health						
Excellent or very good	1471/27527	53.4	ref.	1354/30025	45.1	ref.
Good	931/12455	74.7	1.38 (1.27, 1.50)	925/14790	62.5	1.36 (1.25, 1.48)
Fair or poor	214/2279	93.9	1.74 (1.50, 2.00)	233/2831	82.3	1.78 (1.55, 2.05)
Self-rated quality of life						
Excellent or very good	1767/30692	57.6	ref.	1653/33814	48.9	ref.
Good	686/9556	71.8	1.22 (1.12, 1.34)	691/11492	60.1	1.21 (1.11, 1.33)
Fair or poor	155/1824	85.0	1.44 (1.22, 1.69)	149/2111	70.6	1.43 (1.21, 1.69)
Smoking history						
Never	1411/24589	57.4	ref.	1320/27820	47.4	ref.
Ex-smoker	1128/16136	69.9	1.19 (1.10, 1.29)	1082/18249	59.3	1.21 (1.11, 1.31)
Current	116/1856	62.5	1.14 (0.94, 1.38)	126/1941	64.9	1.36 (1.13, 1.63)

[1] Hazard ratios were estimated using flexible parametric survival models with adjustment for randomisation group, and age and sex at baseline. Proportional hazards assumed for all covariates. Abbreviations: CI – confidence interval; IR, incidence rate

Table S4. Effect of vitamin D supplementation on incident hypertension medication and lipid-modifying agent use. Predicted difference in cause-specific standardised cumulative incidence and time-varying hazard ratio at 2 and 4 years of follow-up, and predicted overall hazard ratio

Years of follow-up	% Difference in Cumulative Incidence (95% CI)	Hazard Ratio (95% CI)
Hypertension medication		
2	0.03 (-1.09 to 1.15)	1.00 (0.92 to 1.09)
4	-0.10 (-1.55 to 1.36)	0.98 (0.88 to 1.10)
Overall Hazard Ratio	..	1.00 (0.92 to 1.07)
Lipid-modifying agent		
2	1.27 (0.27 to 2.28)	1.07 (0.99 to 1.16)
4	1.18 (-0.14 to 2.50)	0.96 (0.85 to 1.08)
Overall Hazard Ratio	..	1.06 (0.98 to 1.15)

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 4 year of follow-up) were predicted using a model that also included an interaction between randomisation group and follow-up time, 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 use of medication 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. The difference in cumulative incidence is expressed as a percentage.

Abbreviation: CI – confidence interval; CIF, cumulative incidence function

Appendix D. Supplementary Figures

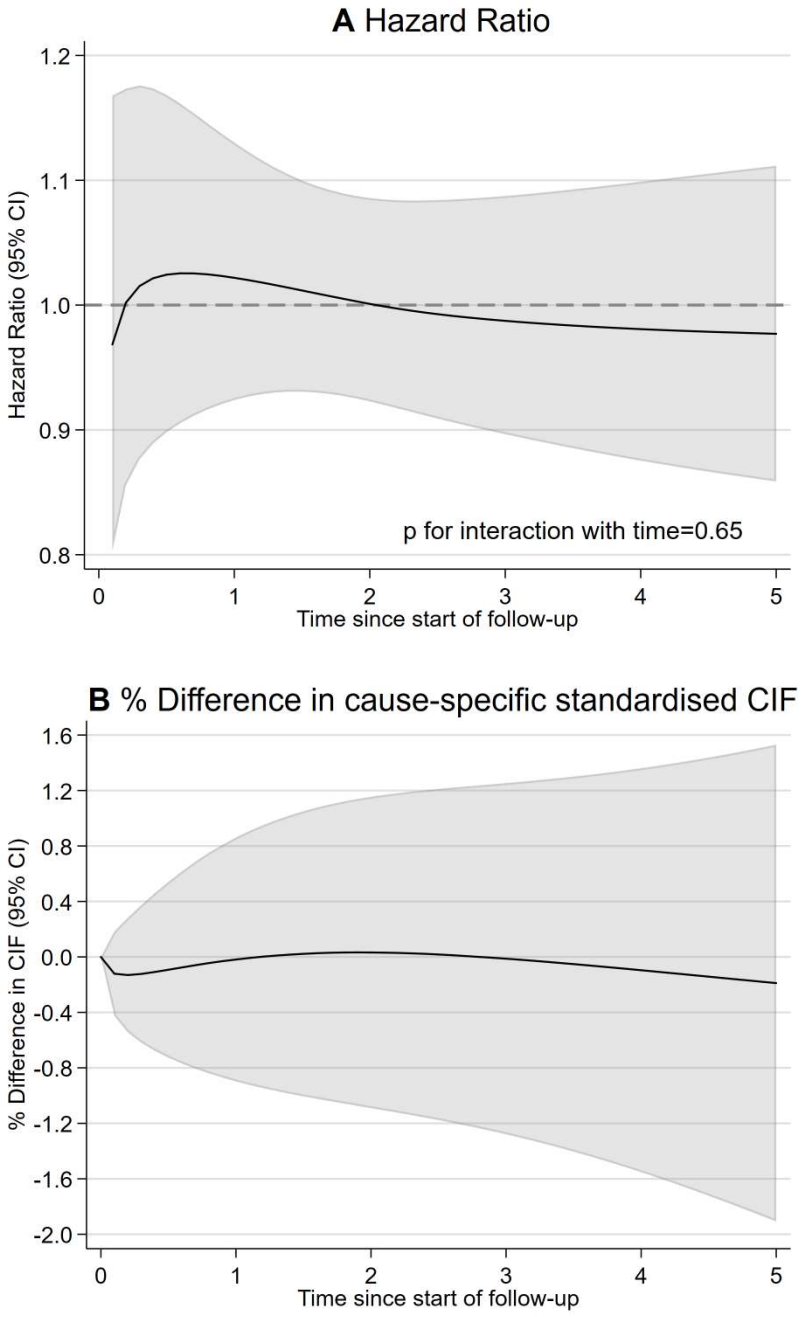

Figure S1. Effect of vitamin D supplementation on incident use of hypertension medication. Panel A shows the time-varying hazard ratio and panel B shows the difference in the cause-specific standardised cumulative incidence functions [***Note**: based on dummy data]*

Estimates (vitamin D versus placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The model included an interaction between randomisation group and follow-up time, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log incidence times). The interaction between randomisation group and follow-up time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific cumulative incidence probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort, and death without prior use of hypertension medication was treated as a competing risk.

Abbreviations: CI, confidence interval; CIF, cumulative incidence function

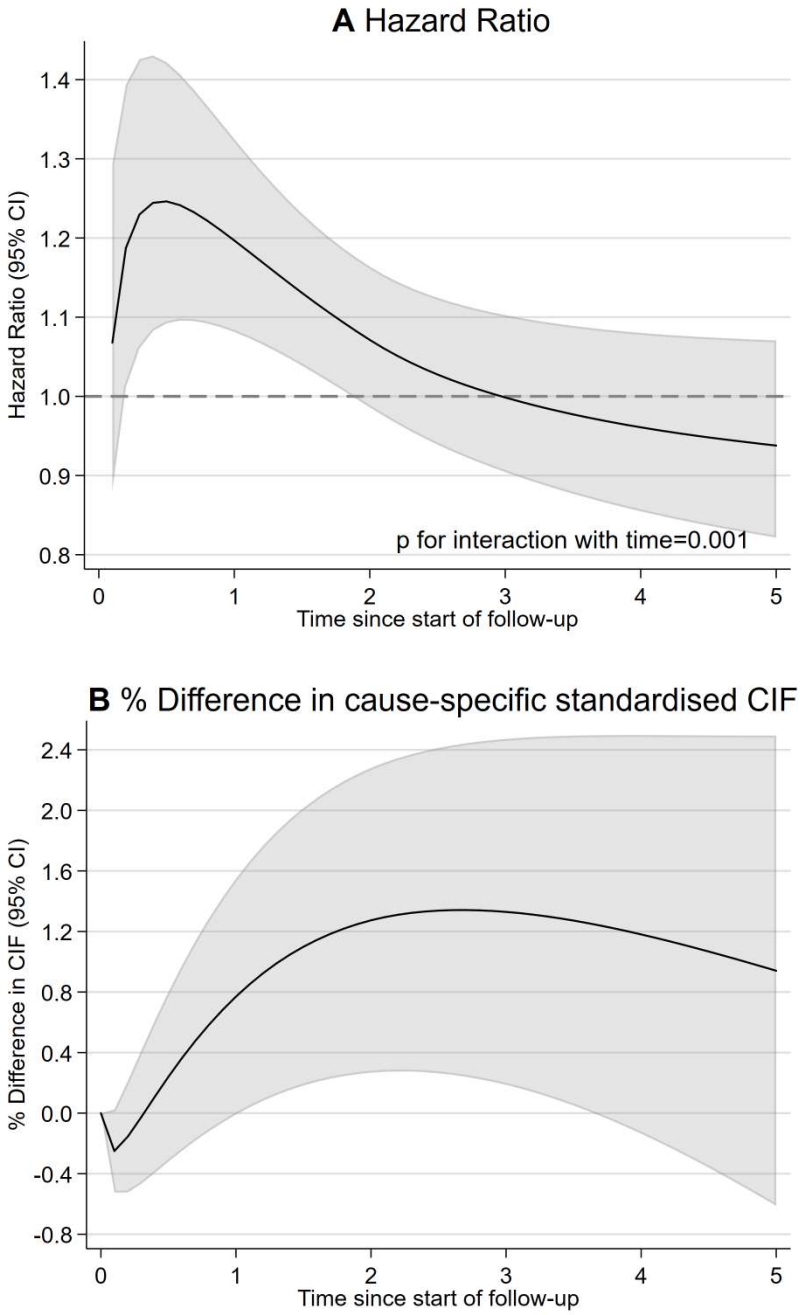

Figure S2. Effect of vitamin D supplementation on incident use of lipid-modifying agents. Panel A shows the time-varying hazard ratio and panel B shows the difference in the cause-specific standardised cumulative incidence functions *[**Note:** based on dummy data]*

Estimates (vitamin D versus placebo) are from a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The model included an interaction between randomisation group and follow-up time, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log incidence times). The interaction between randomisation group and follow-up time was assessed using a likelihood ratio test that compared models with and without the interaction term. Cause-specific cumulative incidence probabilities were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort, and death without prior use of lipid-modifying agents was treated as a competing risk.

Abbreviations: CI, confidence interval; CIF, cumulative incidence function

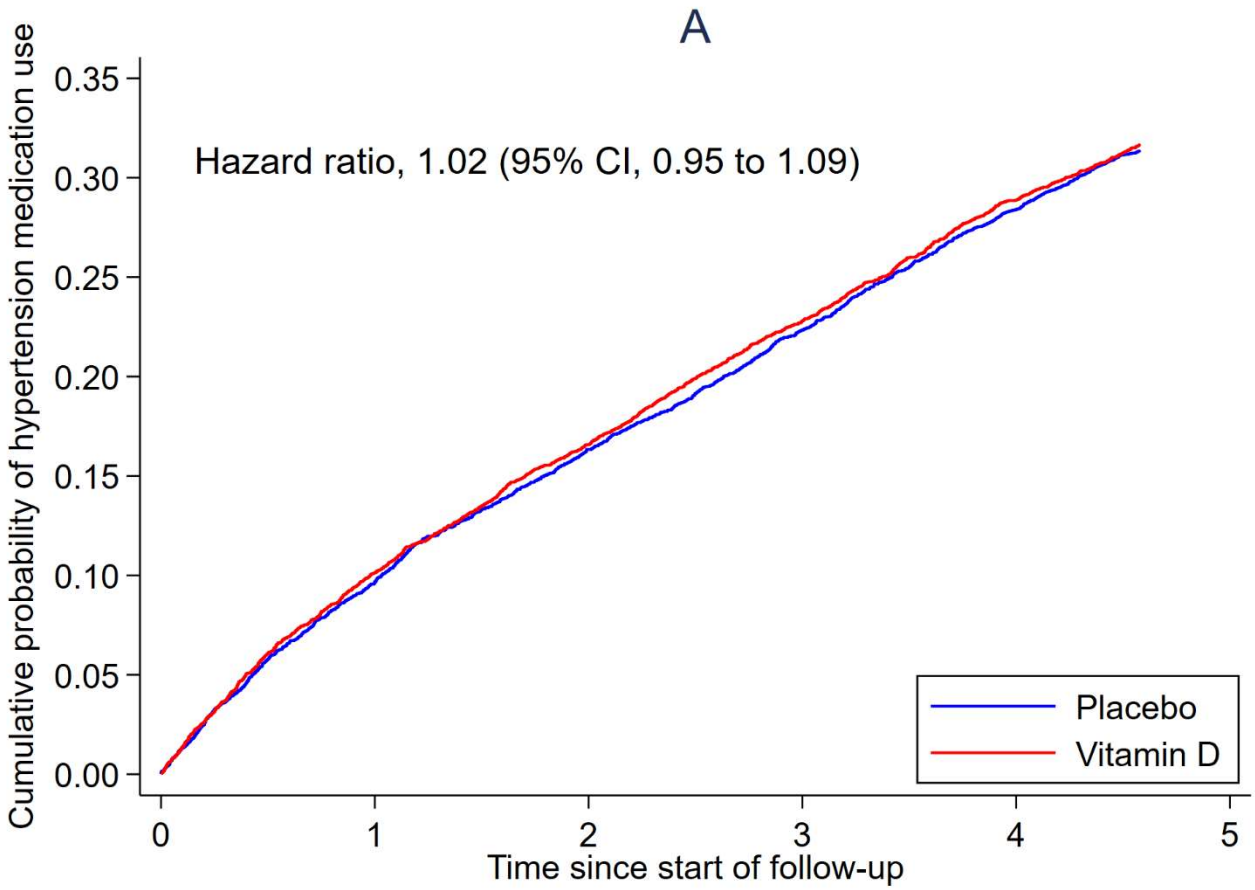

Figure S3. Cause-specific cumulative probability of hypertension medication use according to follow-up time in the vitamin D and placebo groups, a sensitivity analysis accounting for all possible hypertension medications (including ATC classes C02, C03, C07, C08, C09) *[**Note**: based on dummy data]*

Curves estimated using Aalen-Johansen methods, treating death without prior medication use 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. Time 0 is at 6 months after randomisation, when follow-up began.

Abbreviation: CI – confidence interval, ATC – Anatomical Therapeutic Chemical code