Working Title	The effect of monthly, high-dose vitamin D supplementation on fractures: outcomes from the randomised, placebo-controlled D-Health Trial		
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Person conducting analysis	Mary Waterhouse	Email	Mary.Waterhouse@qimrberghofer.edu.au
Potential Authors	Mary Waterhouse, Catherine Baxter, Briony Duarte Romero, Donald McLeod, Bruce Armstrong, Peter Ebeling, Dallas English, Gunter Hartel, Michael Kimlin, Rachel O'Connell, Jolieke Van Der Pols, Alison Venn, Penelope Webb, David Whiteman, Rachel Neale		
Background and overview			
Background	Fractures are a major public health concern, with an estimated 178 million new fractures worldwide in 2019.[1] The majority of fractures occur in older people,[1] and risk factors for fractures in this population include female sex, advancing age, and osteoporosis.[1,2] Hip fractures in the elderly are especially serious due to high morbidity,[3] excess mortality,[4] and considerable financial burden; the average health and social costs incurred in the year following hip fracture are estimated to be approximately US$44,000.[5] Since the number of fractures is likely to increase as a consequence of population growth and ageing, identifying ways of reducing fracture risk is important. It is plausible that vitamin D might protect against fractures since vitamin D plays a central role in calcium homeostasis. Meta-analyses of observational studies have found that lower concentrations of serum 25-hydroxy vitamin D (25(OH)D) are associated with increased risk of total fracture,[6,7] and hip fracture.[6-9] However, these findings may be a result of reverse causality or uncontrolled confounding. Mendelian randomisation (MR) studies largely overcome these issues, although results regarding fractures are inconsistent. A recent MR study found increased concentrations of genetically predicted 25(OH)D to be associated with lower risk of leg and femur fractures,[10] while other MR studies found no relationship with total (i.e., at any site) fracture,[11] and nonvertebral fracture.[12] Umbrella reviews of systematic reviews and meta-analyses of randomised controlled trials (RCTs) have found no evidence that supplementation with vitamin D alone reduces fracture risk,[13,14] and may even cause harm.[13] This may be driven, in part, by RCTs of intermittent, high-dose vitamin D supplementation. A recent meta-analysis found increased risk of hip fracture when high doses of vitamin D were given annually, but not when given more frequently (e.g., once a week).[15] Moreover, the VITamin D and OmegA-3 Trial (VITAL), the largest RCT of high-dose vitamin D supplementation to date, the findings of which were published subsequent to the umbrella reviews, found little evidence to suggest that vitamin D supplementation had an effect on risk of total fractures (hazard ratio (HR) 0.98; 95% confidence interval (CI) 0.89 to 1.08), nonvertebral fractures (HR 0.97; 95% CI 0.87 to 1.07), or hip fractures (HR 1.01; 95% CI 0.70 to 1.47).[16] VITAL used a daily dosing regimen, and there are few large studies using a monthly dosing regimen. Thus, uncertainty persists regarding the effect of vitamin D, particularly of monthly dosing, on fractures. We will conduct an analysis of fractures among people enrolled in a population-based randomised, placebo-controlled vitamin D trial for the prevention of all-cause mortality[17] (the D-Health Trial). Our primary aim is to determine if supplementing older Australians with monthly doses of 60,000 international units		

	(IU) vitamin D_3 for a maximum of 5 years alters the risk of total fracture. We will also examine the effect of supplementation on risk of nonvertebral fractures, and fractures commonly associated with osteoporosis.

Aims	Our primary aim is to investigate whether randomisation to long-term supplementation with monthly doses of 60,000 IU of vitamin D3 alters the risk of total fracture.
	
	Our secondary aims are to investigate whether:
	• Randomisation to vitamin D alters the risk of:
	  o Nonvertebral fracture;
	  o Major osteoporotic fracture (hip, wrist, proximal humerus, spine);
	  o Hip fracture.
	• The effect of vitamin D supplementation on fractures (total, nonvertebral, major osteoporotic, and hip separately) is modified by:
	  o Age at baseline (< 70 years, ≥ 70 years);
	  o Sex (men, women);
	  o Body mass index (BMI) at baseline (< 25 kg/m^2, ≥ 25 kg/m^2); or
	  o Predicted baseline 25(OH)D concentration[18] (< 50 nmol/L, ≥ 50 nmol/L).

Instruments	We will ascertain outcomes using two sources: 1. Hospital admitted patient data from all 6 states of Australia (New South Wales, Queensland, Victoria, South Australia, Tasmania, and Western Australia); and 2. Medicare Benefits Schedule (MBS) database. Admissions to private hospitals are not included in hospital admissions data from South Australia and Tasmania, and we also do not have hospital admissions data from either the Australian Capital Territory (ACT) or the Northern Territory (NT). Almost all admissions to private hospitals are subsidised by the MBS. Hence, MBS data will enable us to ascertain the vast majority of fractures that were treated in private hospitals in South Australia, Tasmania, the ACT, and the NT; this data will also allow us to capture fractures that were not treated in hospital.
Outcomes and hypotheses	

Outcomes	• The primary outcome is first fracture at any site following randomisation.
	• The secondary outcomes are:
	  o first nonvertebral fracture following randomisation;
	  o first major osteoporotic fracture following randomisation; and
	  o first hip fracture following randomisation.
	
	For all outcomes, we will exclude fractures that are a consequence of bone cancer or surgical complications.

Follow-up	For each outcome, follow-up will begin at randomisation, and end at the earliest of: (i) the date the outcome first occurs; (ii) 31/12/2019;[1] (iii) 5 years and 1 month after randomisation; or (iv) the date last known to be alive. [1] All states provided hospital data up to and including 31/12/2019.
Ascertaining outcomes	Ascertaining new fractures using hospital data We will extract all admissions for which the principal diagnosis and/or any of the additional diagnosis fields contain an International Classification of Diseases 10th Revision (ICD-10) code from Table A1. We will discard admissions where the fracture(s) is a consequence of bone cancer or surgical complications (n=24; see

	Table A2 (Appendix A) for more details. We will also identify and exclude cases where it is reasonable to assume that the fracture code refers to a pre-existing fracture; see Appendix B for details. Ascertaining fractures using MBS data *Note: The primary reason we are using MBS data is to capture fractures that:* • *Were treated in a private hospital in South Australia, Tasmania, the ACT, or the NT; or* • *Did not require hospitalisation for treatment.* *MBS data will also allow us to better estimate the date a fracture occurred in some cases.* We will extract from the MBS database all records with a Medicare item number from Table A3 (Appendix A). We will discard a record if the service was provided <14 days subsequent to an earlier service for a fracture at the same site. Since hip fractures are sometimes treated using arthroplasty, we will perform a sensitivity analysis in which we also include MBS records with an item number pertaining to hip arthroplasty (without mention of treatment for fracture) (Table A4, Appendix A). To reduce the probability of false positives (e.g., including an arthroplasty performed for osteoarthritis and not fracture), we will, where possible, compare MBS records to hospital data; we will not include the MBS record if hospital records indicate that the participant did not have a hip fracture at the time the hip arthroplasty was performed (see Appendix B for details). Estimating the date a fracture occurred We will use the date of service from the MBS database to estimate the date the fracture occurred if the fracture was ascertained using MBS data only. If the fracture was ascertained using both hospital *and* MBS data, *and* the admission occurred in Victoria, then we will use the earliest of date of service and approximate date of admission[1]. In all other cases, we will use the date of admission to hospital. [1] Since hospital data from Victoria included only the year and month of admission, we are approximating the date of admission using the 15th day of the month.
Hypotheses	Compared to the placebo group, participants randomised to 60,000 IU/month of vitamin D_3 supplementation will have different rate of fracture (total, nonvertebral, major osteoporotic, and hip). For analyses of both the primary and secondary outcomes there will be interactions between randomisation group and: • Age at baseline (< 70 years, ≥ 70 years); • Sex (men, women); • BMI at baseline (< 25 kg/m^2, ≥ 25 kg/m^2); and • Predicted baseline 25(OH)D concentration (< 50 nmol/L, ≥ 50 nmol/L).
Detectable effect size	The D-Health Trial was designed to enable 80% power to detect a HR of 0.91 (α=0.05) for all-cause mortality over a follow-up period of up to 10 years.[19] The analysis of fractures will include 20,326 participants (n=10,172 in the placebo group; n=10,154 in the vitamin D group). Using data from VITAL[16] to estimate the probability of having no fractures over 5 years amongst placebo participants, we estimate that, for the analysis of total fracture, we will be able to detect a HR of 0.85 with 80% power (α=0.05) (Appendix C).

Documentation	
Analysis packages	SAS Version 9.4, Stata 15.1, R Version 4.0.3
Datasets	The original dataset will be located here: L:\Lab_RachelN\DHealthDataAnalysis\Projects\Fractures\data\original data\ The final dataset including any constructed variables will be located here: L:\Lab_RachelN\DHealthDataAnalysis\Projects\Fractures\data\final data\ A copy of the final dataset will also be saved here: R:\Lab_RachelN\Dhealth\Datasets\Fractures\
Statistical code	The code that is used to prepare and analyse data will be stored in: L:\Lab_RachelN\DHealthDataAnalysis\Projects\Fractures\code\ Once finalised, a copy will be placed on R drive: R:\Lab_RachelN\Dhealth\StatisticalCode\Fractures\
Participants and data	
Participants	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 (n=6);[1] • Did not consent to MBS linkage (n=976). [1] n=6 participants had obviously incorrect hospital data; we have concluded that an error occurred with the probabilistic linkage.
Exposure variable	Randomisation group
Covariates	Covariates to be included in all models (randomisation stratification variables): • Age at randomisation: 60-64; 65-69; 70-74; ≥75 years • Sex: Male; Female • State of residence at baseline: NSW; QLD; SA; TAS; VIC; WA Baseline variables that will be used to derive interaction terms: • Age: <70 vs ≥70 years • Sex: Male vs Female • BMI: <25 vs ≥25 kg/m^2 • Predicted baseline 25(OH)D concentration: <50 vs ≥50 nmol/L
Data Cleaning	We are assuming that item numbers and dates of service in the MBS dataset are correct. We have done the following cleaning of hospital data. *Admission and discharge dates* Victoria supplied only the month and year for both admission and discharge. We were able to calculate the exact dates in some cases.[1] When it was not possible to calculate an exact date we let the date of admission be the 15th day of the month. *Combining records* We combined data from records when there were subsequent admissions that pertained to a continuation of treatment/care. For example, we combined consecutive records if the date of admission for one record was the same as the date of discharge for the other record. Since admission and discharge dates were approximated for Victorian records (see above), we manually reviewed records

	before deciding whether or not to combine records; this allowed us to take into account additional information such as admission source[2] and discharge status[3]. [1] For example, if a person died in hospital and we know their date of death, then the date of discharge for the admission in which they died is set to the date of death, and the date of admission is calculated using the date of death and length of stay. [2] Examples of admission source: admission from private residence; transfer from acute hospital/extended care/rehabilitation/geriatric centre; statistical admission. [3] Examples of discharge status: separation to private accommodation or home; separation and transfer to acute hospital/extended care; statistical separation.
Handling missing data	Outcomes: A fracture that was not treated, or that was treated but not captured in either the hospital or MBS datasets (e.g., treated outside hospital and the costs were covered by the Department of Veterans' Affairs) will not be ascertained. We are assuming that such 'missingness' is non-differential between the groups. <u>We will discuss this as a limitation of outcome ascertainment.</u> Covariates: The only covariate for which data are missing is BMI (n missing = 94). We will exclude participants missing BMI from the relevant subgroup analysis.
Maintaining blinding	Investigators will remain blinded to study group allocation until this statistical analysis is finalised and saved on the R:\ drive. • Analysis code will be written and debugged using data in which participants will be randomly reassigned to two new groups (of equal size), such that there is no relationship between the new groups and the true treatment allocation. • After the statistical analysis plan has been finalised, and all code written to produce the tables and figures contained herein, analyses will be re-run using the correct randomisation codes. Any analyses performed after unblinding will be declared as exploratory.
Proposed sequence of analysis	
	We will show participant flow using a CONSORT diagram (**Figure 1**). We will compare selected baseline characteristics of participants included and excluded from the analyses of fractures, reporting p-values from chi-squared tests (**STable 1**). We will present selected baseline characteristics of included participants according to randomisation group (**Table 1**). **Effect of randomisation to supplementation with vitamin D on fractures** These analyses will follow the intention-to-treat principle. When fitting flexible parametric survival models[20] (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. If the FPSM includes an interaction between randomisation group and time since randomisation, this will be fitted as a restricted cubic spline with one internal knot, placed at the median of uncensored log survival times. The choice of spline functions follows the recommendations made by Royston and Parmar.[20,21] FPSMs

will include randomisation group, and the randomisation stratification variables of age, sex, and state of residence at baseline.

- We will report the number (%) of people who experienced at least one fracture according to randomisation group.
- We will use Kaplan-Meier methods to plot the cumulative incidences of total fracture **(Figure 2**), nonvertebral fracture (**SFigure 6**), major osteoporotic fracture (**SFigure 8)**, and hip fracture (**SFigure 10**) for each randomisation group. For each outcome, we will embed the p-value from a log-rank test in the corresponding figure panel.
- For each outcome, we will fit two FPSMs. Model 1 will not include any time-varying coefficients; it will be used to estimate an "overall" HR and 95% confidence interval (CI); the HRs will be embedded in Figure 2. Model 2 will include an interaction between randomisation group and time since randomisation, thereby allowing the HR for randomisation group to vary with time.
- Using Model 2, we will plot the following as functions of time since randomisation: (a) the estimated HR; and (b) the difference in standardised survival curves. The plots will include 95% CIs. **Figure 3** will show plots for the primary outcome; **SFigures 7, 9, and 11** will show plots for the secondary outcomes. We will embed in the figure 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).
- For all outcomes, we will also report the estimated HR (95% CI), and difference in standardised survival (95% CI) at 2, and 5 years post-randomisation (**STable 2**).

Interactions and subgroup analyses

For all outcomes, we will investigate whether the effect of supplementation is modified by the following:

- Age at baseline (< 70 years, ≥ 70 years);
- Sex (men, women);
- BMI at baseline (< 25 kg/m^2, ≥ 25 kg/m^2); and
- Predicted deseasonalised baseline 25(OH)D concentration (< 50 nmol/L, ≥ 50 nmol/L).

For each outcome and each characteristic listed above we will:

- Use Kaplan-Meier methods to plot cumulative incidence of the outcome for each randomisation group within each stratum of the characteristic (**SFigures 1, 12, 14, 16**).
- Fit a FPSM that, in addition to the standard variables, includes the baseline characteristic of interest, and an interaction term between randomisation group and the baseline characteristic of interest. Using this model, we will report estimated HRs (95% CI) for each level of the baseline characteristic (**Figure 4, SFigures 13, 15, 17**); estimates will also be embedded in the relevant supplementary figure of cumulative incidence). We will report the p-value from the likelihood ratio test comparing models with and without the interaction term.

For the primary outcome only, we will investigate whether the effect of randomisation varies with time for a specific level of the baseline characteristic. We will fit two FPSMs to the data from participants within the subgroup of interest. The first FPSM will not include any time-varying coefficients. The second

	FPSM will include an interaction between randomisation group and time since randomisation. We will use the likelihood ratio test to compare the two models. We will also use the second model to plot the estimated HR as a function of time since randomisation for that level of the baseline characteristic (**SFigures 2-5**). **Sensitivity analyses** We will perform sensitivity analyses in which hip arthroplasty will also be used to ascertain hip fractures. We will repeat the analyses used to produce Figure 2, and SFigures 6, 8, and 10, and STable 2. Results of the sensitivity analyses will be presented in **SFigure 18** and **STable 3**. **Associations with risk factors for fracture** We will use FPSMs to estimate the association between selected risk factors for fracture and the primary and secondary outcomes. We will model the baseline log cumulative hazard function as described for the intention-to-treat analyses, and all models will include age at randomisation and sex. (**STable 4**). **Retention, compliance, intake of off-trial vitamin D supplementation, and adverse events** We have described these outcomes in the mortality paper and therefore we will not include them here.
Significance level	We will use a significance level of 0.05. We will not adjust for multiple testing.[22]
Summary of tables and figures	
Planned main tables (Appendix D)	**Table 1.** Baseline characteristics of participants included in the analysis of fractures according to randomisation group.
Planned main figures (Appendix E)	**Figure 1.** Participant flow for analyses of fractures (CONSORT flow diagram). **Figure 2.** Cumulative incidence of total fractures according to randomisation group and time since randomisation. **Figure 3.** Time-dependent effect of vitamin D supplementation on total fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation. **Figure 4.** Effect of vitamin D supplementation on total fractures for all participants and by selected baseline characteristics.
Planned supplementary tables (Appendix F)	**STable 1.** Baseline characteristics of D-Health participants according to whether or not they were included in the analysis of fractures. **STable 2.** Effect of supplementation with vitamin D on fractures. Predicted difference in standardised survival and time-varying hazard ratio at 2, and 5 years post-randomisation, and predicted overall hazard ratio. **STable 3.** Sensitivity analysis: Effect of supplementation with vitamin D on fractures. Predicted difference in standardised survival and time-varying hazard ratio at 2, and 5 years post-randomisation, and predicted overall hazard ratio. **STable 4.** Associations between selected baseline characteristics and fractures.
Planned supplementary figures	**SFigure 1.** Cumulative incidence of total fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation,

(Appendix G)	stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration. **SFigure 2.** Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to baseline age (<70 years, ≥70 years). **SFigure 3.** Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to sex (men, women). **SFigure 4.** Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to baseline body mass index (<25 kg/m^2, ≥25 kg/m^2). **SFigure 5.** Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to predicted deseasonalised baseline 25(OH)D concentration (<50 nmol/L, ≥50 nmol/L). **SFigure 6.** Cumulative incidence of nonvertebral fractures according to randomisation group and time since randomisation. **SFigure 7.** Time-dependent effect of vitamin D supplementation on nonvertebral fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation. **SFigure 8.** Cumulative incidence of major osteoporotic fractures according to randomisation group and time since randomisation. **SFigure 9.** Time-dependent effect of vitamin D supplementation on major osteoporotic fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation. **SFigure 10.** Cumulative incidence of hip fractures according to randomisation group and time since randomisation. **SFigure 11.** Time-dependent effect of vitamin D supplementation on hip fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation. **SFigure 12.** Cumulative incidence of nonvertebral fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration. **SFigure 13.** Effect of vitamin D supplementation on nonvertebral fractures for all participants and by selected baseline characteristics. **SFigure 14.** Cumulative incidence of major osteoporotic fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration. **SFigure 15.** Effect of vitamin D supplementation on major osteoporotic fractures for all participants and by selected baseline characteristics. **SFigure 16.** Cumulative incidence of hip fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration. **SFigure 17.** Effect of vitamin D supplementation on hip fractures for all participants and by selected baseline characteristics.

	SFigure 18. Sensitivity analysis: Cumulative incidence of fractures according to randomisation group and time since randomisation. Panel A – total fracture; panel B – nonvertebral fracture; panel C – major osteoporotic fracture; panel D – hip fracture.

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Appendix A – Ascertaining fractures

Table A1. International Classification of Diseases 10th Revision (ICD-10) codes used to ascertain fractures in the hospital admitted patient dataset.

ICD-10 Code	Description
USED IN ASCERTAINMENT OF NONVERTEBRAL AND TOTAL FRACTURES	
Hip[a]	
S72.0	Fracture of neck of femur
S72.1	Pertrochanteric fracture
S72.2	Subtrochanteric fracture
Wrist[a]	
S52.5	Fracture of lower end of radius
S52.6	Fracture of lower end of both ulna and radius
S62.0	Fracture of navicular [scaphoid] bone of hand
S62.1	Fracture of other carpal bone(s)
S62.8	Fracture of other and unspecified parts of wrist and hand
Proximal humerus[a]	
S42.2	Fracture of upper end of humerus
Skull, and facial bones	
S02.0	Fracture of vault of skull
S02.1	Fracture of base of skull
S02.2	Fracture of nasal bones
S02.3	Fracture of orbital floor
S02.4	Fracture of malar and maxillary bones
S02.6	Fracture of mandible
S02.7	Multiple fractures involving skull and facial bones
S02.8	Fractures of other skull and facial bones
S02.9	Fracture of skull and facial bones, part unspecified
Rib(s), and sternum	
S22.2[b]	Fracture of sternum
S22.3[b]	Fracture of rib
S22.4[b]	Multiple fractures of ribs
S22.5[b]	Flail chest
S22.8	Fracture of other parts of bony thorax
S22.9	Fracture of bony thorax, part unspecified
Pelvis	
S32.1	Fracture of sacrum
S32.2	Fracture of coccyx
S32.3	Fracture of ilium
S32.4	Fracture of acetabulum
S32.5	Fracture of pubis
S32.7[c]	Multiple fractures of lumbar spine and pelvis
S32.8 [c]	Fracture of other and unspecified parts of lumbar spine and pelvis
Shoulder and upper arm (excluding proximal humerus)	
S42.0	Fracture of clavicle
S42.1	Fracture of scapula
S42.3	Fracture of shaft of humerus
S42.4	Fracture of lower end of humerus
S42.7	Multiple fractures of clavicle, scapula and humerus
S42.8	Fracture of other parts of shoulder and upper arm
S42.9	Fracture of shoulder girdle, part unspecified

ICD-10 Code	Description
Forearm (excluding distal radius)	
S52.0	Fracture of upper end of ulna
S52.1	Fracture of upper end of radius
S52.2	Fracture of shaft of ulna
S52.3	Fracture of shaft of radius
S52.4	Fracture of shafts of both ulna and radius
S52.7	Multiple fractures of forearm
S52.8	Fracture of other parts of forearm
S52.9	Fracture of forearm, part unspecified
Hand, and fingers	
S62.2	Fracture of first metacarpal bone
S62.3	Fracture of other metacarpal bone
S62.4	Multiple fractures of metacarpal bones
S62.5	Fracture of thumb
S62.6	Fracture of other finger
S62.7	Multiple fractures of fingers
Femur (excluding hip)	
S72.3	Fracture of shaft of femur
S72.4	Fracture of lower end of femur
S72.7	Multiple fractures of femur
S72.8	Fractures of other parts of femur
S72.9	Fracture of femur, part unspecified
Lower leg (including ankle)	
S82.0	Fracture of patella
S82.1	Fracture of upper end of tibia
S82.2	Fracture of shaft of tibia
S82.3	Fracture of lower end of tibia
S82.4	Fracture of fibula alone
S82.5	Fracture of medial malleolus
S82.6	Fracture of lateral malleolus
S82.7	Multiple fractures of lower leg
S82.8	Fractures of other parts of lower leg
S82.9	Fracture of lower leg, part unspecified
Foot, and toes	
S92.0	Fracture of calcaneus
S92.1	Fracture of talus
S92.2	Fracture of other tarsal bone(s)
S92.3	Fracture of metatarsal bone
S92.4	Fracture of great toe
S92.5	Fracture of other toe
S92.7	Multiple fractures of foot
S92.9	Fracture of foot, unspecified
Fractures involving multiple body regions	
T02.0[c]	Fractures involving head with neck
T02.1[c]	Fractures involving thorax with lower back and pelvis
T02.2	Fractures involving multiple regions of one upper limb
T02.3	Fractures involving multiple regions of one lower limb
T02.4	Fractures involving multiple regions of both upper limbs
T02.5	Fractures involving multiple regions of both lower limbs
T02.6	Fractures involving multiple regions of upper limb(s) with lower limb(s)

ICD-10 Code	Description
T02.7[c]	Fractures involving thorax with lower back and pelvis with limb(s)
Site incompletely specified	
T10	Fracture of upper limb, level unspecified
T12	Fracture of lower limb, level unspecified
USED IN ASCERTAINMENT OF VERTEBRAL AND TOTAL FRACTURES	
Spine[a]	
M48.4	Fatigue fracture of vertebra
M48.5	Collapsed vertebra, not elsewhere classified
M49.5	Collapsed vertebra in diseases classified elsewhere
S12.0	Fracture of first cervical vertebra
S12.1	Fracture of second cervical vertebra
S12.2	Fracture of other specified cervical vertebra
S12.7	Multiple fractures of cervical spine
S12.8	Fracture of other parts of neck
S12.9	Fracture of neck, part unspecified
S22.0	Fracture of thoracic vertebra
S22.1	Multiple fractures of thoracic spine
S32.0	Fracture of lumbar vertebra
S32.7[c]	Multiple fractures of lumbar spine and pelvis
S32.8[c]	Fracture of other and unspecified parts of lumbar spine and pelvis
T02.0[c]	Fractures involving head with neck
T02.1[c]	Fractures involving thorax with lower back and pelvis
T02.7[c]	Fractures involving thorax with lower back and pelvis with limb(s)
T08	Fracture of spine, level unspecified
USED IN ASCERTAINMENT OF TOTAL FRACTURES ONLY	
Site completely unspecified	
M80	Osteoporosis with pathological fracture
M80.0	Postmenopausal osteoporosis with pathological fracture
M80.1	Postoophorectomy osteoporosis with pathological fracture
M80.2	Osteoporosis of disuse with pathological fracture
M80.3	Postsurgical malabsorption osteoporosis with pathological fracture
M80.4	Drug-induced osteoporosis with pathological fracture
M80.5	Idiopathic osteoporosis with pathological fracture
M80.8	Other osteoporosis with pathological fracture
M80.9	Unspecified osteoporosis with pathological fracture
M84.3	Stress fracture, not elsewhere classified
M84.4	Pathological fracture, not elsewhere classified
M96.6[c]	Fracture of bone following insertion of orthopaedic implant, joint prosthesis, or bone plate
T02.8	Fractures involving other combinations of body regions
T02.9	Multiple fractures, unspecified
T14.2	Fracture of unspecified body region
X59.0	Exposure to unspecified factor causing fracture

[a] Used to ascertain the composite outcome of any fracture of hip, wrist, proximal humerus, and/or spine.

[b] The fracture will not be included if the associated admission contains: (a) I46.0 (Cardiac arrest with successful resuscitation) or I46.9 (Cardiac arrest, unspecified) in a diagnosis field (n=12 fracture codes from 7 participants).

[c] Used in ascertainment of both nonvertebral and vertebral fractures

[d] Excluded if due to surgical complications (see Table A2)

Table A2. Criteria for identifying admissions with a fracture(s) due to bone cancer or surgical complications.

Cause of fracture	Criteria for identifying admission	N admissions identified
Bone cancer	ICD-10 code C79.5 (Secondary malignant neoplasm of bone and bone marrow) and/or M90.7 (Fracture of bone in neoplastic disease) appear in any of the diagnosis fields.	12
Surgical complications	The diagnosis fields contain the ICD-10 code M96.6 (Fracture of bone following insertion of orthopaedic implant, joint prosthesis, or bone plate) and at least one of the following ICD-10 codes: • Y83.1 (Surgical operation with implant of artificial internal device as the cause of abnormal reaction of the patient, or of later complication, without mention of misadventure at the time of the procedure); and/or • Y65.8 (Other specified misadventures during surgical and medical care)	12

Abbreviation: ICD-10, International Classification of Diseases 10th Revision

Table A3. Medicare Item Numbers used to ascertain fractures in the Medicare Benefits Schedule database.

Item number	Item description
USED IN ASCERTAINMENT OF NONVERTEBRAL AND TOTAL FRACTURES	
Hip[a]	
47519	Femur, treatment of trochanteric or subcapital fracture of, by internal fixation
47522	Femur, treatment of subcapital fracture of, by hemi-arthroplasty
49336	Hip, treatment of a fracture of the femur where revision total hip replacement is required as part of the treatment of the fracture (not including intra-operative fracture)
57721	Femur, internal fixation of neck or intertrochanteric (pertrochanteric) fracture
Wrist[a]	
47348	Carpus (excluding scaphoid), treatment of fracture of
47351	Carpus (excluding scaphoid), treatment of fracture of, by open reduction
47354	Carpal scaphoid, treatment of fracture of
47357	Carpal scaphoid, treatment of fracture of, by open reduction
47360[b]	Radius or ulna, distal end of, treatment of fracture of, by cast immobilisation
47361[b]	Radius or ulna, or radius and ulna, distal end of, treatment of fracture of, by cast immobilisation
47362[b]	Radius or ulna, or radius and ulna, distal end of, treatment of fracture of, by closed reduction, requiring general or major regional anaesthesia, but excluding local infiltration
47364[b]	Radius or ulna, distal end of, not involving joint surface, treatment of fracture of, by open reduction with fixation
47366[b]	Radius or ulna, distal end of, treatment of fracture of, by open reduction
47367	Radius, distal end of, treatment of fracture of, by closed reduction with percutaneous fixation

Item number	Item description
47369	Radius, distal end of, treatment of Colles', Smith's or Barton's fracture of, by cast immobilisation
47370	Radius, distal end of, treatment of intra articular fracture of, by open reduction with fixation
47372	Radius, distal end of, treatment of Colles', Smith's or Barton's fracture, by closed reduction
47375	Radius, distal end of, treatment of Colles', Smith's or Barton's fracture of, by open reduction
Proximal humerus[a]	
47411	Humerus, treatment of fracture of tuberosity of
47414	Humerus, treatment of fracture of tuberosity of, by open reduction
47417	Humerus, treatment of fracture of tuberosity of, and associated dislocation of shoulder, by closed reduction
47420	Humerus, treatment of fracture of tuberosity of, and associated dislocation of shoulder, by open reduction
47423	Humerus, proximal, treatment of fracture of
47426	Humerus, proximal, treatment of fracture of, by closed reduction, undertaken in the operating theatre of a hospital
47429	Humerus, proximal, treatment of fracture of, by open reduction
47432	Humerus, proximal, treatment of intra-articular fracture of, by open reduction
47435	Humerus, proximal, treatment of fracture of, and associated dislocation of shoulder, by closed reduction
47438	Humerus, proximal, treatment of fracture of, and associated dislocation of shoulder, by open reduction
47441	Humerus, proximal, treatment of intra-articular fracture of, and associated dislocation of shoulder, by open reduction
Skull, and facial bones	
39606	Fractured skull, depressed or comminuted, operation for
39609	Fractured skull, compound, without dural penetration, operation for
39612	Fractured skull, compound, depressed or complicated, with dural penetration and brain laceration, operation for
39615	Fractured skull with rhinorrhoea or otorrhoea, repair of by cranioplasty or endoscopic approach
45975	Maxilla, unilateral or bilateral, treatment of fracture of, not requiring splinting
45978	Mandible, treatment of fracture of, not requiring splinting
45981	Zygomatic bone, treatment of fracture of, not requiring surgical reduction
45984	Maxilla, treatment of a complicated fracture of, involving viscera, blood vessels or nerves requiring open reduction not involving plate(s)
45987	Mandible, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction not involving plate(s)
45990	Maxilla, treatment of a complicated fracture of, involving viscera, blood vessels or nerves requiring open reduction involving the use of plate(s)
45993	Mandible, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction involving the use of plate(s)
45996	Mandible, treatment of a closed fracture of, involving a joint surface
47735	Nasal bones, treatment of fracture of - each attendance
47738	Nasal bones, treatment of fracture of, by reduction

Item number	Item description
47741	Nasal bones, treatment of fracture of, by open reduction involving osteotomies
47753	Maxilla, treatment of fracture of, requiring splinting, wiring of teeth, circumosseous fixation or external fixation
47756	Mandible, treatment of fracture of, requiring splinting, wiring of teeth, circumosseous fixation or external fixation
47762	Zygomatic bone, treatment of fracture of, requiring surgical reduction by a temporal, intra-oral or other approach
47765	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation at 1 site
47768	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation or both at 2 sites
47771	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation or both at 3 sites
47774	Maxilla, treatment of fracture of, requiring open operation
47777	Mandible, treatment of fracture of, requiring open reduction
47780	Maxilla, treatment of fracture of, requiring open reduction and internal fixation not involving plate(s)
47783	Mandible, treatment of fracture of, requiring open reduction and internal fixation not involving plate(s)
47786	Maxilla, treatment of fracture of, requiring open reduction and internal fixation involving plate(s)
47789	Mandible, treatment of fracture of, requiring open reduction and internal fixation involving plate(s)
53400	Maxilla, unilateral or bilateral, treatment of fracture of, not requiring splinting
53403	Mandible, treatment of fracture of, not requiring splinting
53406	Maxilla, treatment of fracture of, requiring splinting, wiring of teeth, circumosseous fixation or external fixation
53409	Mandible, treatment of fracture of, requiring splinting, wiring of teeth, circumosseous fixation or external fixation
53410	Zygomatic bone, treatment of fracture of, not requiring surgical reduction
53411	Zygomatic bone, treatment of fracture of, requiring surgical reduction by a temporal, intra-oral or other approach
53412	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation at 1 site
53413	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation or both at 2 sites
53414	Zygomatic bone, treatment of fracture of, requiring surgical reduction and involving internal or external fixation or both at 3 sites
53415	Maxilla, treatment of fracture of, requiring open reduction
53416	Mandible, treatment of fracture of, requiring open reduction
53418	Maxilla, treatment of fracture of, requiring open reduction and internal fixation not involving plate(s)
53419	Mandible, treatment of fracture of, requiring open reduction and internal fixation not involving plate(s)
53422	Maxilla, treatment of fracture of, requiring open reduction and internal fixation involving plate(s)
53423	Mandible, treatment of fracture of, requiring open reduction and internal fixation involving plate(s)

Item number	Item description
53424	Maxilla, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction not involving plate(s)
53425	Mandible, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction not involving plate(s)
53427	Maxilla, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction involving the use of plate(s)
53429	Mandible, treatment of a complicated fracture of, involving viscera, blood vessels or nerves, requiring open reduction involving the use of plate(s)
53439	Mandible, treatment of a closed fracture of, involving a joint surface
53453[c]	Orbital cavity, reconstruction of a wall or floor with or without foreign implant
53455[c]	Orbital cavity, bone or cartilage graft to orbital wall or floor including reduction of prolapsed or entrapped orbital contents
53458	Nasal bones, treatment of fracture of
53459	Nasal bones, treatment of fracture of, by reduction
53460	Nasal bones, treatment of fractures of, by open reduction involving osteotomies
Rib(s), and sternum	
47466	Sternum, treatment of fracture of
47467	Sternum, treatment of fracture of, by open reduction
47471	Ribs (1 or more), treatment of fracture of - each attendance
Pelvis	
47474	Pelvic ring, treatment of fracture of, not involving disruption of pelvic ring or acetabulum
47477	Pelvic ring, treatment of fracture of, with disruption of pelvic ring or acetabulum
47480	Pelvic ring, treatment of fracture of, requiring traction
47483	Pelvic ring, treatment of fracture of, requiring control by external fixation
47486	Pelvic ring, treatment of fracture of, by open reduction and involving internal fixation of anterior segment, including diastasis of pubic symphysis
47489	Pelvic ring, treatment of fracture of, by open reduction and involving internal fixation of posterior segment (including sacro-iliac joint), with or without fixation of anterior segment
47492	Acetabulum, treatment of fracture of, and associated dislocation of hip
47495	Acetabulum, treatment of fracture of, and associated dislocation of hip, requiring traction
47498	Acetabulum, treatment of fracture of, and associated dislocation of hip, requiring internal fixation, with or without traction
47501	Acetabulum, treatment of single column fracture of, by open reduction and internal fixation, including any osteotomy, osteectomy or capsulotomy required for exposure and subsequent repair
47504	Acetabulum, treatment of t-shape fracture of, by open reduction and internal fixation, including any osteotomy, osteectomy or capsulotomy required for exposure and subsequent repair
47507	Acetabulum, treatment of transverse fracture of, by open reduction and internal fixation, including any osteotomy, osteectomy or capsulotomy required for exposure and subsequent repair
47510	Acetabulum, treatment of double column fracture of, by open reduction and internal fixation, including any osteotomy, osteectomy or capsulotomy required for exposure and subsequent repair

Item number	Item description
47511	Treatment of combined column t-type, transverse, anterior column or posterior hemitransverse fractures of acetabulum, by open reduction, with internal fixation, performed through single or dual approach
47513[c]	Sacro-iliac joint disruption, treatment of, requiring internal fixation, being a service associated with a service to which items 47501 to 47510 apply
Shoulder, and upper arm (excluding proximal humerus)	
47444	Humerus, shaft of, treatment of fracture of
47447	Humerus, shaft of, treatment of fracture of, by closed reduction, undertaken in the operating theatre of a hospital
47450	Humerus, shaft of, treatment of fracture of, by internal or external fixation
47451	Humerus, shaft of, treatment of fracture of, by intramedullary fixation
47453	Humerus, distal, (supracondylar or condylar), treatment of fracture of
47456	Humerus, distal (supracondylar or condylar), treatment of fracture of, by closed reduction, undertaken in the operating theatre of a hospital
47459	Humerus, distal (supracondylar or condylar), treatment of fracture of, by open reduction, undertaken in the operating theatre of a hospital
47462	Clavicle, treatment of fracture of
47465	Clavicle, treatment of fracture of, by open reduction
47468	Scapula, neck or glenoid region of, treatment of fracture of, by open reduction
Forearm (excluding distal radius)	
47373	Ulna, distal end of, treatment of intra articular fracture of, by open reduction with fixation
47378	Radius or ulna, shaft of, treatment of fracture of, by cast immobilisation
47381	Radius or ulna, shaft of, treatment of fracture of, by closed reduction undertaken in the operating theatre of a hospital
47384	Radius or ulna, shaft of, treatment of fracture of, by open reduction
47385	Radius or ulna, shaft of, treatment of fracture of, in conjunction with dislocation of distal radio ulnar joint or proximal radio-humeral joint (Galeazzi or Monteggia injury), by closed reduction undertaken in the operating theatre of a hospital
47386	Radius or ulna, shaft of, treatment of fracture of, in conjunction with dislocation of distal radio ulnar joint or proximal radio-humeral joint (Galeazzi or Monteggia injury), by open reduction or internal fixation
47387	Radius and ulna, shafts of, treatment of fracture of, by cast immobilisation
47390	Radius and ulna, shafts of, treatment of fracture of, by closed reduction undertaken in the operating theatre of a hospital
47393	Radius and ulna, shafts of, treatment of fracture of, by open reduction
47396	Olecranon, treatment of fracture of
47399	Olecranon, treatment of fracture of, by open reduction
47402	Olecranon, treatment of fracture of, involving excision of olecranon fragment and reimplantation of tendon
47405	Radius, treatment of fracture of head or neck of, closed reduction of
47408	Radius, treatment of fracture of head or neck of, open reduction of, including internal fixation and excision where performed
Hand, and fingers	
46442	Mallet finger with intra articular fracture involving more than one third of base of terminal phalanx - open reduction
47300	Distal phalanx of finger or thumb, treatment of fracture of, by closed reduction, including percutaneous fixation where used

Item number	Item description
47301	Phalanx, middle or proximal, treatment of fracture of, by closed reduction, requiring anaesthesia,
47303	Distal phalanx of finger or thumb, treatment of intra-articular fracture of, by closed reduction
47304	Metacarpal, treatment of fracture of, by closed reduction, requiring anaesthesia
47307	Phalanx or metacarpal, treatment of fracture of, by closed reduction with percutaneous k wire fixation
47310	Phalanx or metacarpal, treatment of fracture of, by open reduction with fixation
47313	Phalanx or metacarpal, treatment of intra articular fracture of, by closed reduction with percutaneous k wire fixation
47316	Phalanx or metacarpal, treatment of intra articular fracture of, by open reduction with fixation
47319	Middle phalanx, proximal end, treatment of intra articular fracture of, by open reduction with fixation
47324	Proximal phalanx of finger or thumb, treatment of fracture of, by closed reduction
47336	Metacarpal, treatment of fracture of, by closed reduction
47345	Metacarpal, treatment of intra-articular fracture of, by open reduction
Femur (excluding hip)	
47516	Femur, treatment of fracture of, by closed reduction or traction
47525	Femur, treatment of fracture of, for slipped capital femoral epiphysis
47528	Femur, treatment of fracture of, by internal fixation or external fixation
47531	Femur, treatment of fracture of shaft, by intramedullary fixation and cross fixation
47534	Femur, condylar region of, treatment of intra-articular (t-shaped condylar) fracture of, requiring internal fixation, with or without internal fixation of 1 or more osteochondral fragments
47537	Femur, condylar region of, treatment of fracture of, requiring internal fixation of 1 or more osteochondral fragments
Lower leg (including ankle)	
47543	Tibia, plateau of, treatment of medial or lateral fracture of
47546	Tibia, plateau of, treatment of medial or lateral fracture of, by closed reduction
47549	Tibia, plateau of, treatment of medial or lateral fracture of, by open reduction
47552	Tibia, plateau of, treatment of both medial and lateral fractures of
47555	Tibia, plateau of, treatment of both medial and lateral fractures of, by closed reduction
47558	Tibia, plateau of, treatment of both medial and lateral fractures of, by open reduction
47561	Tibia, shaft of, treatment of fracture of, by cast immobilisation
47564	Tibia, shaft of, treatment of fracture of, by closed reduction, with or without treatment of fibular fracture
47565	Tibia, shaft of, treatment of fracture of, by internal fixation or external fixation
47566	Tibia, shaft of, treatment of fracture of, by intramedullary fixation and cross fixation

Item number	Item description
47567	Tibia, shaft of, treatment of intra-articular fracture of, by closed reduction, with or without treatment of fibular fracture
47568	Closed reduction of proximal tibia, distal tibia or shaft of tibia, with or without treatment of fibular fracture
47570	Tibia, shaft of, treatment of fracture of, by open reduction, with or without treatment of fibular fracture
47573	Tibia, shaft of, treatment of intra-articular fracture of, by open reduction, with or without treatment of fibula fracture
47576	Fibula, treatment of fracture of
47579	Patella, treatment of fracture of
47582	Patella, treatment of fracture of, by excision of patella or pole with reattachment of tendon
47585	Patella, treatment of fracture of, by internal fixation
47588	Knee joint, treatment of fracture of, by internal fixation of intra-articular fractures of femoral condylar or tibial articular surfaces and requiring repair or reconstruction of 1 or more ligaments
47591	Knee joint, treatment of fracture of, by internal fixation of intra-articular fractures of femoral condylar and tibial articular surfaces and requiring repair or reconstruction of 1 or more ligaments
47594	Ankle joint, treatment of fracture of
47597	Ankle joint, treatment of fracture of, by closed reduction
47600	Ankle joint, treatment of fracture of, by internal fixation of 1 of malleolus, fibula or diastasis
47603	Ankle joint, treatment of fracture of, by internal fixation of more than 1 of malleolus, fibula or diastasis
Foot, and toes	
47606	Calcaneum or talus, treatment of fracture of, with or without dislocation
47609	Calcaneum or talus, treatment of fracture of, by closed reduction, with or without dislocation
47612	Calcaneum or talus, treatment of intra-articular fracture of, by closed reduction, with or without dislocation
47615	Calcaneum or talus, treatment of fracture of, by open reduction, with or without dislocation
47618	Calcaneum or talus, treatment of intra-articular fracture of, by open reduction, with or without dislocation
47621	Tarso-metatarsal, treatment of intra-articular fracture of, by closed reduction, with or without dislocation
47624	Tarso-metatarsal, treatment of fracture of, by open reduction, with or without dislocation
47627	Tarsus (excluding calcaneum or talus), treatment of fracture of
47630	Tarsus (excluding calcaneum or talus), treatment of fracture of, by open reduction, with or without dislocation
47633	Metatarsal, 1 of, treatment of fracture of
47636	Metatarsal, 1 of, treatment of fracture of, by closed reduction
47637	Treatment of fractures of metatarsal, by closed reduction-one or more metatarsals of one foot
47639	Metatarsal, 1 of, treatment of fracture of, by open reduction
47642	Metatarsals, 2 of, treatment of fracture of
47645	Metatarsals, 2 of, treatment of fracture of, by closed reduction
47648	Metatarsals, 2 of, treatment of fracture of, by open reduction

Item number	Item description
47651	Metatarsals, 3 or more of, treatment of fracture of
47654	Metatarsals, 3 or more of, treatment of fracture of, by closed reduction
47657	Metatarsals, 3 or more of, treatment of fracture of, by open reduction
47663	Phalanx of great toe, treatment of fracture of, by closed reduction
47666	Phalanx of great toe, treatment of fracture of, by open reduction
47672	Phalanx of toe (other than great toe), 1 of, treatment of fracture of, by open reduction
47678	Phalanx of toe (other than great toe), more than 1 of, treatment of fracture of, by open reduction
Site unspecified or incompletely specified	
47540[c]	Hip spica or shoulder spica, application of, as an independent procedure
47595	Treatment of fracture of ankle joint, hindfoot, midfoot, metatarsals or toes, by non-surgical management-one leg
USED IN ASCERTAINMENT OF VERTEBRAL AND TOTAL FRACTURES	
Spine[a]	
47696[d]	Spine, reduction of fracture or dislocation of, without cord involvement, undertaken in the operating theatre of a hospital
51110[d]	Spine, treatment of fracture, dislocation or fracture dislocation, with immobilisation by calipers or halo, not including application of skull tongs or calipers as part of operative positioning
Site completely unspecified	
47726[c]	Bone graft, harvesting of, via separate incision, in conjunction with another service - autogenous - small quantity
47729[c]	Bone graft, harvesting of, via separate incision, in conjunction with another service - autogenous - large quantity
47732[c]	Vascularised pedicle bone graft, harvesting of, in conjunction with another service

[a] Used to ascertain the composite outcome of any fracture of hip, wrist, proximal humerus, and/or spine.
[b] We will assume that there has been a fracture of the distal radius
[c] Although the item descriptions do not specifically mention fractures, these codes were described in sections of the Medicare Benefits Schedule Book that pertain to treatment of fractures.
[d] We will assume that all records with these item numbers pertained to a fracture.

Table A4. Medicare Item Numbers for hip arthroplasty to be used in a sensitivity analysis to ascertain hip fractures in the Medicare Benefits Schedule database

Item number	Item description
49315	Hip, arthroplasty of, unipolar or bipolar
49318	Hip, total replacement arthroplasty of, including minor bone grafting
49319	Hip, total replacement arthroplasty of, including associated minor grafting, if performed - bilateral
49321	Hip, total replacement arthroplasty of, including major bone grafting, including obtaining of graft

Appendix B - Identifying records to exclude when ascertaining fractures

When ascertaining outcomes using hospital data, we will assume that a fracture code does not pertain to a new fracture if the associated admission:

1. Has at least one diagnosis code (Table B1) and/or procedure code (Table B2) indicative of follow-up care/treatment; or
2. Occurs within one year of discharge from the 'index admission' for that particular fracture and, if the admission is not in the same month or subsequent month to the index admission, then either the:
    a. Length of stay is 1 day; or
    b. ICD-10 code in the principal diagnosis does not begin with 'S' (injuries).

To qualify as the 'index admission', the record must be the earliest admission (not satisfying condition 1 above) to list the fracture code of interest in any of the diagnosis fields.

In sensitivity analyses, we will also use Medicare Item Numbers for hip arthroplasty (without mention of treatment for fracture) to ascertain hip fractures from Medicare Benefits Schedule (MBS) data. We will not include the MBS record if we know that the procedure was performed for something other than a hip fracture (i.e., there exists a hospital admission at the time the MBS service was provided, hip arthroplasty was performed during the admission (see Table B3 for relevant procedure codes), and none of the diagnosis fields include an ICD-10 code for hip fracture (S72.0, S72.1, S72.2)).

Table B1. International Classification of Diseases 10th Revision (ICD-10) codes used to identify fracture codes that do not pertain to a new fracture.

Code	Description
M84.0	Malunion of fracture
M84.1	Nonunion of fracture [pseudarthrosis]
M84.2	Delayed union of fracture
Z09.4	Follow-up examination after treatment of fracture
Z47.0	Follow-up care involving removal of fracture plate and other internal fixation device
Z47.8[a]	Other specified orthopaedic follow-up care
Z47.9[a]	Orthopaedic follow-up care, unspecified
Z48.8[a]	Other specified surgical follow-up care

[a] Must appear in principal diagnosis field

Table B2. Australian Classification of Health Interventions (ACHI) codes used to identify fractures codes[a] that do not pertain to new fractures.

ACHI Code	Description
Fractures at any site (applies to all ICD-10 codes in Table A1)	
47927-00	Removal of pin, screw or wire, not elsewhere classified
47930-00	Removal of plate, rod or nail, not elsewhere classified
47948-00[b]	Removal of external fixation device
50309-00	Adjustment of ring fixator or similar device
Fractures of the maxilla or mandible (ICD-10 Code: S02.4, S02.6)	
45823-00	Removal of arch bars from maxilla or mandible
52102-00	Removal of pin, screw or wire from maxilla, mandible or zygoma
Fractures of the sternum (ICD-10 Code: S22.2)	
38460-00	Removal of sternal wire
38466-00	Reoperation on sternum involving reopening of mediastinum
90596-00	Rewiring of sternum
Fractures of the shoulder (ICD-10 Codes: S42.0, S42.1, S42.2, S42.7, S42.8, S42.9)	
48921-00	Revision of total arthroplasty of shoulder
48924-00	Revision of total arthroplasty of shoulder with bone graft to scapula or humerus
48927-00	Removal of shoulder prosthesis
48942-00	Arthrodesis of shoulder with removal of prosthesis
Fractures of the elbow (ICD-10 Codes: S42.4, S52.0, S52.1)	
49116-00	Revision arthroplasty of elbow
49117-00	Revision arthroplasty of elbow with bone graft
Fractures of the wrist (ICD-10 Codes: S52.5, S52.6, S62.0, S62.1)	
49210-00	Revision arthroplasty of wrist
49211-00	Revision arthroplasty of wrist with bone graft
Fractures of the femur (ICD-10 Codes beginning with S72)	
47927-01	Removal of pin, screw or wire from femur
47930-01	Removal of plate, rod or nail from femur
49324-00	Revision of total arthroplasty of hip
49327-00	Revision of total arthroplasty of hip with bone graft to acetabulum
49330-00	Revision of total arthroplasty of hip with bone graft to femur
49333-00	Revision of total arthroplasty of hip with bone graft to acetabulum and femur
49339-00	Revision of total arthroplasty of hip with anatomic specific allograft to acetabulum
49342-00	Revision of total arthroplasty of hip with anatomic specific allograft to femur
49345-00	Revision of total arthroplasty of hip with anatomic specific allograft to acetabulum and femur
Fractures of the knee (ICD-10 Codes: S72.4, S82.0, S82.1)	
49346-00	Revision of partial arthroplasty of hip
49512-00	Arthrodesis of knee with removal of prosthesis
49515-00	Removal of knee prosthesis
49527-00	Revision of total arthroplasty of knee
49530-00	Revision of total arthroplasty of knee with bone graft to femur
49530-01	Revision of total arthroplasty of knee with bone graft to tibia
49533-00	Revision of total arthroplasty of knee with bone graft to femur and tibia
49545-00	Revision arthrodesis of knee
49548-00	Revision of patellofemoral stabilisation of knee
49551-00	Revision of reconstructive surgery of knee
49554-00	Revision of total arthroplasty of knee with anatomic specific allograft
Fractures of the ankle (ICD-10 Codes: S82.3, S82.4, S82.5, S82.6, S92.1)	

ACHI Code	Description
49716-00	Revision arthroplasty of ankle
49717-00	Revision arthroplasty of ankle with bone graft
Fractures of the heel (ICD-10 Codes: S92.0)	
49724-00	Secondary (delayed) repair of achilles' tendon
Fractures of the spine (ICD-10 Codes: M48.4, M48.5, M49.5, codes beginning with S12, S22.0, S32.0, S32.7, T08)	
50616-00	Revision of spinal procedure with adjustment of spinal fixation
50616-01	Revision of spinal procedure with removal of spinal fixation
50616-02	Revision of spinal procedure with bone graft
50620-00	Other revision of spinal procedure

[a] Descriptions of the ICD-10 codes for fractures are shown in Table A1.

[b] Assume that fracture is old only if procedure with ACHI code 50130-00 (Application of external fixation device not elsewhere classified) was not performed during the admission.

Table B3. Australian Classification of Health Interventions (ACHI) codes for hip arthroplasty.

ACHI Code	Description
47522-00	Hemiarthroplasty of femur
49312-00	Excision arthroplasty of hip
49315-00	Partial arthroplasty of hip
49318-00	Total arthroplasty of hip, unilateral
49319-00	Total arthroplasty of hip, bilateral

Appendix C – Detectable effect size

The analysis of fractures will include 20,326 participants (n=10,172 in the placebo group; n=10,154 in the vitamin D group). We are interested in estimating the difference that we could detect with 80% power, assuming the use of a two-sided test with significance level set at α=0.05.

Table C1 shows results from the Vitamin D and Omega-3 Trial (VITAL) analysis of fractures. Since VITAL found little difference in risk of fractures between the vitamin D and placebo group, the numbers shown in Table C1 are combined across both groups.

Table C1. Number of VITAL participants experiencing at least one fracture during follow-up, according to age group.

Age group	No. of participants	No. participants with ≥1 fracture	Estimated IR per 1000 person-years[1]
< 66.7 years	12,859	567	8.3
≥ 66.7 years	13,012	984	14.3

[1] For simplicity, when estimating the incidence rates (IRs), we have assumed that all participants had a follow-up of 5.3 years (the median follow-up).

We want to estimate how many D-Health placebo participants will experience at least one fracture during 5 years of follow-up. To do this, we will use the data from Table C1, and make the following assumptions:

1. The incidence rates estimated for VITAL participants aged <66.7 years and ≥66.7 years are valid approximations for the rates amongst D-Health placebo participants aged 60-64 years and ≥65 years, respectively; and
2. All D-Health participants had a follow-up of 5 years.

The results of our calculations are shown in Table C2.

Table C2. Estimated number of D-Health placebo participants[1] who will experience at least one fracture during follow-up, according to age group and overall.

Age group	No. of participants[1]	Estimated no. participants with ≥1 fracture
60-64 years	2519	105
≥65 years	7653	546
Total	10,172	651

[1] Restricted to D-Health placebo participants who are eligible for inclusion in the fractures analysis.

Hence, we estimate that the probability of having no fractures over 5 years of follow-up amongst placebo participants included in the analysis of fractures is (10,172 – 651)/10172 = 0.936.

Given our sample sizes and a "survival" probability of 0.936 in the placebo group, a two sided log-rank test with power of 0.8 and significance level of 0.05 could detect a hazard ratio of 0.85.

APPENDICES D-F 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 D – PLANNED MAIN TABLES

Table 1. Baseline characteristics of participants included in the analysis of fractures according to randomisation group.

Characteristic	N (%) Group B (N = 10,168)	Group A (N = 10,158)
Age (years)		
60-64	2502 (24.6)	2518 (24.8)
65-69	2779 (27.3)	2789 (27.5)
70-74	2761 (27.2)	2758 (27.2)
≥ 75	2126 (20.9)	2093 (20.6)
Sex		
Men	5565 (54.7)	5466 (53.8)
Women	4603 (45.3)	4692 (46.2)
Body mass index (kg/m²)		
< 25	3021 (29.9)	3128 (30.9)
25 to < 30	4396 (43.4)	4226 (41.8)
≥ 30	2703 (26.7)	2758 (27.3)
Missing	*48*	*46*
Predicted 25(OH)D concentration (nmol/L)		
< 50	2483 (24.4)	2449 (24.1)
≥ 50	7685 (75.6)	7709 (75.9)
Ancestry		
British/European	9290 (92.8)	9298 (93.2)
Australian/New Zealander	355 (3.5)	337 (3.4)
Asian	118 (1.2)	104 (1.0)
Indigenous	63 (0.6)	80 (0.8)
Mixed/other	180 (1.8)	158 (1.6)
Missing	*162*	*181*
Highest qualification obtained		
None	1010 (10.0)	1009 (10.1)
School or intermediate certificate	1670 (16.6)	1710 (17.0)
Higher school or leaving certificate	1416 (14.1)	1405 (14.0)
Apprenticeship or certificate	3376 (33.6)	3343 (33.3)
University degree or higher	2589 (25.7)	2572 (25.6)
Missing	*107*	*119*
Alcohol consumption (drinks/week)		
< 1	2468 (25.2)	2339 (24.0)
1 to 7	4357 (44.4)	4340 (44.4)
> 7 to 14	1750 (17.8)	1837 (18.8)
> 14	1231 (12.6)	1248 (12.8)
Missing	*362*	*394*

Characteristic	N (%) Group B (N = 10,168)	Group A (N = 10,158)
Smoking history		
Never	5533 (54.8)	5526 (54.9)
Ex-smoker	4128 (40.9)	4122 (41.0)
Current	438 (4.3)	416 (4.1)
Missing	*69*	*94*
Time outdoors (hours/week)		
Low (< 8)	3294 (33.2)	3255 (32.8)
Moderate (8 to < 18)	3269 (32.9)	3330 (33.6)
High (≥ 18)	3360 (33.9)	3336 (33.6)
Missing	*245*	*237*
Self-rated overall health		
Excellent or very good	5557 (55.5)	5623 (56.2)
Good	3583 (35.8)	3554 (35.5)
Fair or poor	873 (8.7)	823 (8.2)
Missing	*155*	*158*
Self-rated quality of life		
Excellent or very good	6653 (67.0)	6746 (67.9)
Good	2684 (27.0)	2647 (26.6)
Fair or poor	592 (6.0)	546 (5.5)
Missing	*239*	*219*
History of osteoporosis[a]		
No	9379 (96.9)	9336 (96.7)
Yes	300 (3.1)	321 (3.3)
Missing	*489*	*501*

[a] Derived using Pharmaceutical Benefits Scheme (PBS) data. We assumed that a participant had osteoporosis at baseline if they were prescribed a medication for osteoporosis (i.e., PBS items with Anatomical Therapeutic Chemical code of: M05BA; M05BB; M05BX03; M05BX04; G03XC01; H05AA02; H05AA04; M05BX06) within twelve months of randomisation.

Appendix E – PLANNED MAIN FIGURES

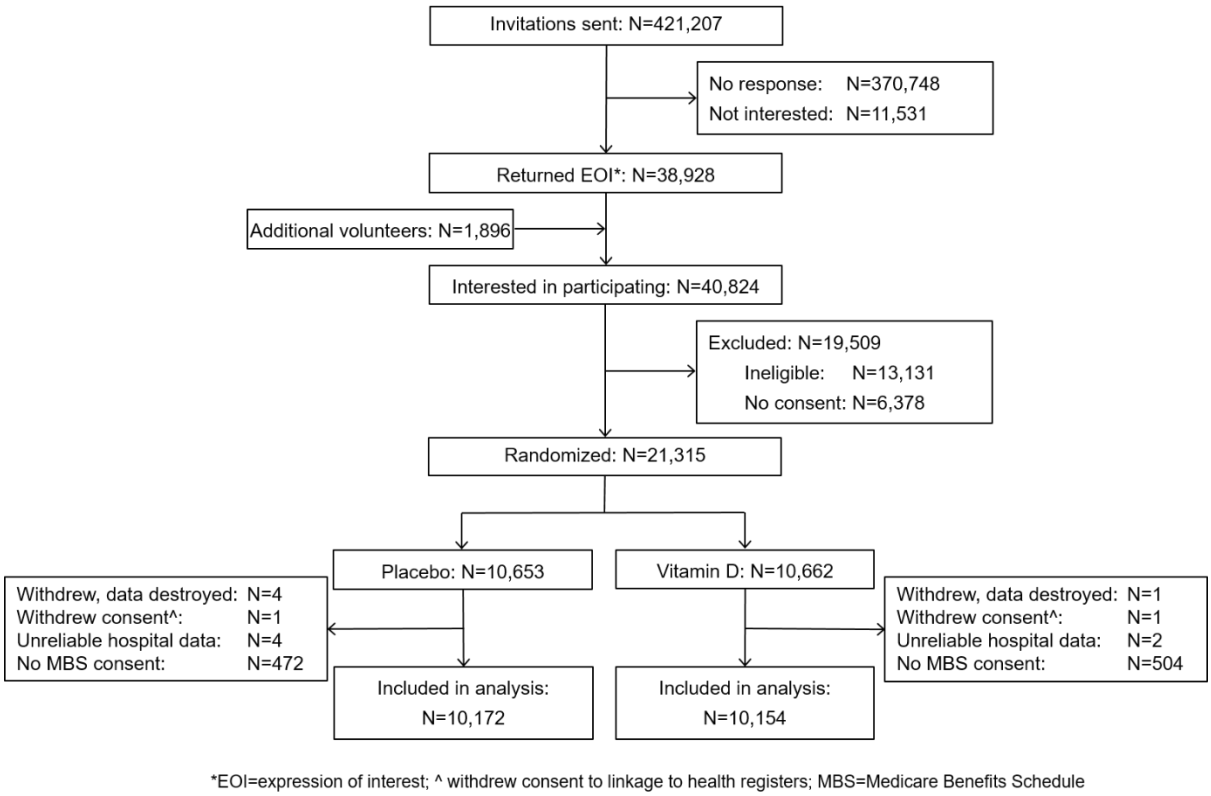


Figure 1. Participant flow for analyses of fractures (CONSORT flow diagram).

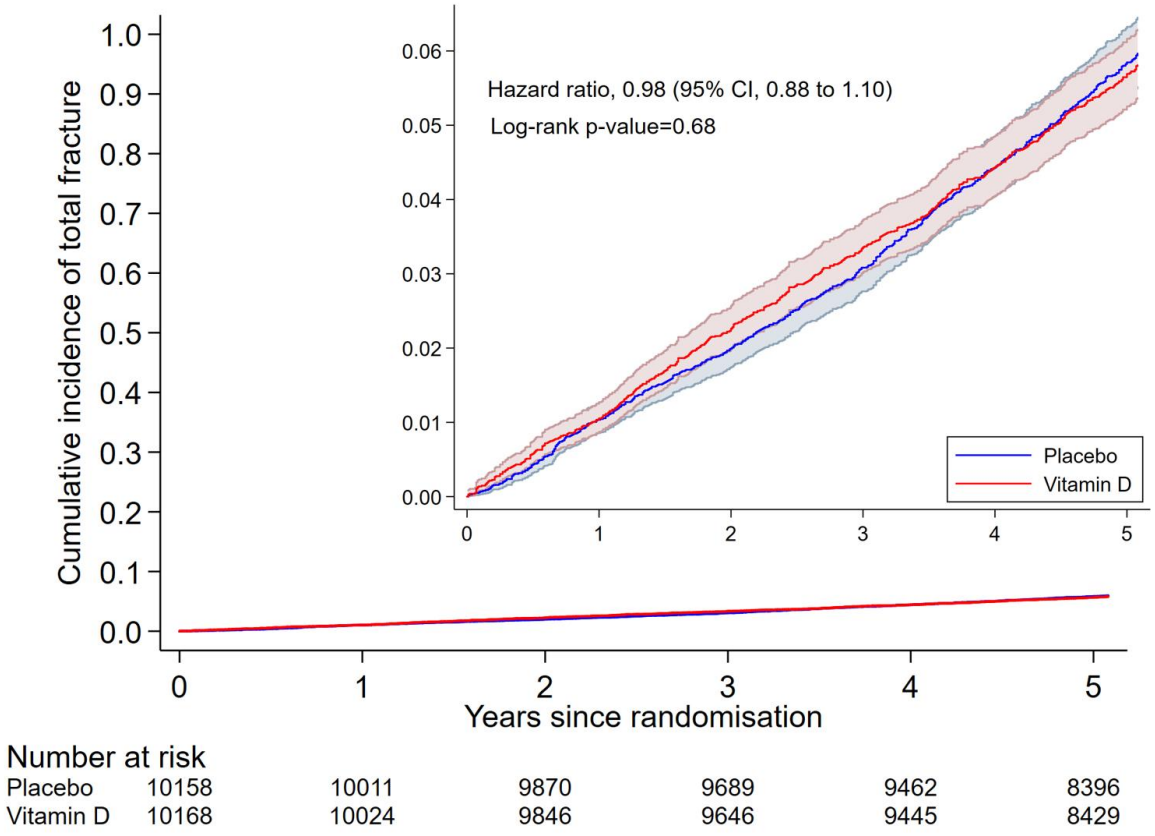


Figure 2. Cumulative incidence of total fractures according to randomisation group and time since randomisation.

Curves estimated using Kaplan-Meier methods and hazard ratio (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The inset shows the same data on an enlarged y axis.
Abbreviation: CI, confidence interval

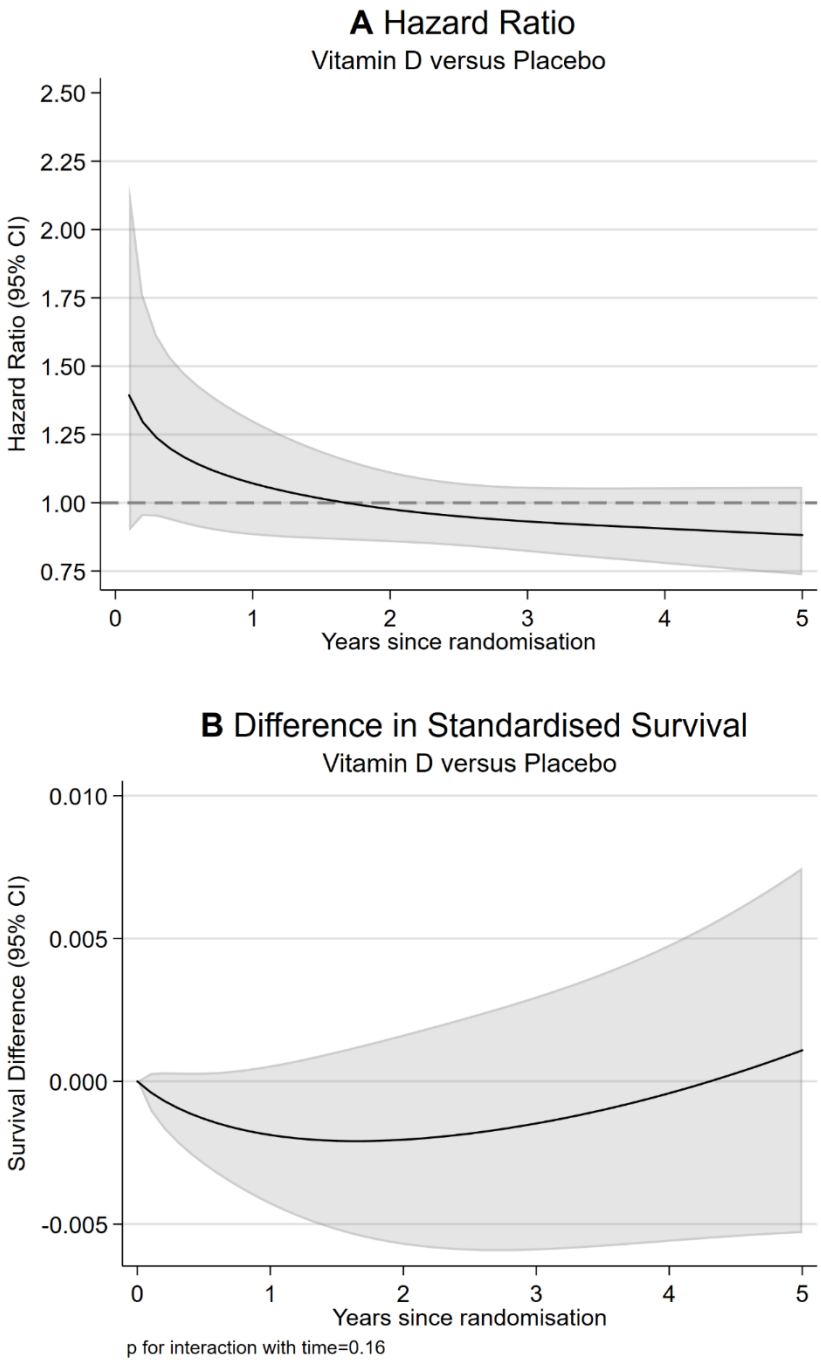


Figure 3. Time-dependent effect of vitamin D supplementation on total fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation.

The outcome is first fracture following randomisation. 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 time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. The interaction between randomisation group and time since randomisation was assessed using a likelihood ratio test that compared models with and without the interaction term. The values on the y-axis in panel B are differences in probability of survival.
Abbreviation: CI, confidence interval

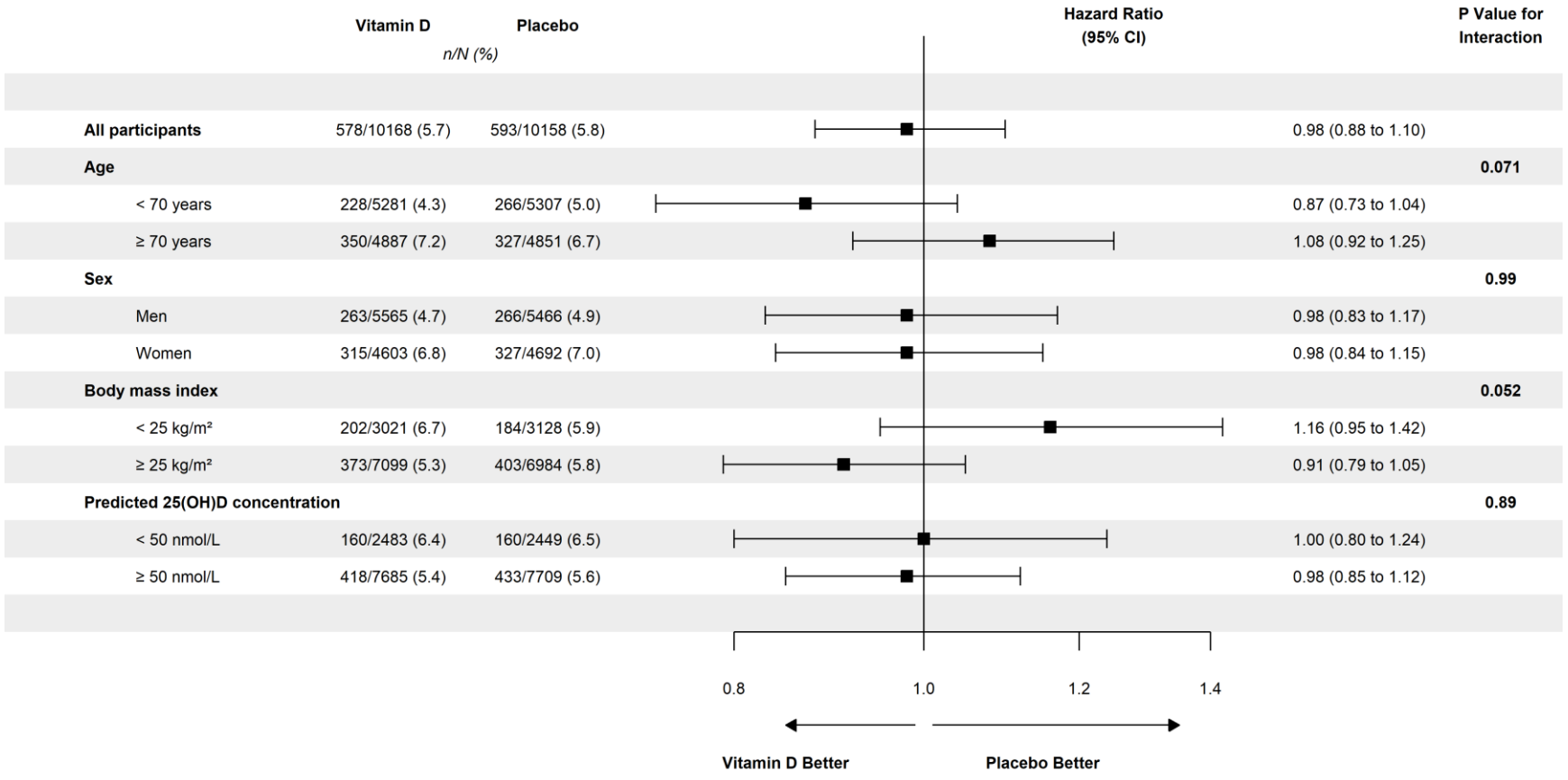


Figure 4. Effect of vitamin D supplementation on total fractures for all participants and by selected baseline characteristics.

The outcome is first fracture following randomisation. Estimates from flexible parametric survival models. Hazard ratios compare vitamin D to placebo. All models include 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, include the characteristic of interest and an interaction between randomisation group and the characteristic of interest. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval

Appendix F – PLANNED SUPPLEMENTARY TABLES

STable 1. Baseline characteristics of D-Health participants according to whether or not they were included in the analysis of fractures.

Characteristic	N (%) Included (N = 20,326)	N (%) Excluded (N = 984)	P-value[a]
Randomisation Group			
Placebo	10158 (50.0)	497 (50.5)	0.74
Vitamin D	10168 (50.0)	487 (49.5)	
Age (years)			
60-64	5020 (24.7)	232 (23.6)	0.81
65-69	5568 (27.4)	266 (27.0)	
70-74	5519 (27.2)	277 (28.2)	
≥ 75	4219 (20.8)	209 (21.2)	
Sex			
Men	11031 (54.3)	499 (50.7)	0.03
Women	9295 (45.7)	485 (49.3)	
Body mass index (kg/m²)			
< 25	6149 (30.4)	268 (27.9)	0.13
25 to < 30	8622 (42.6)	407 (42.4)	
≥ 30	5461 (27.0)	284 (29.6)	
Missing	*94*	*25*	
Predicted 25(OH)D concentration (nmol/L)			
< 50	4932 (24.3)	268 (27.2)	0.03
≥ 50	15394 (75.7)	716 (72.8)	
Ancestry			
British/European	18588 (93.0)	862 (90.6)	0.01
Australian/New Zealander	692 (3.5)	35 (3.7)	
Asian	222 (1.1)	19 (2.0)	
Indigenous	143 (0.7)	8 (0.8)	
Mixed/other	338 (1.7)	27 (2.8)	
Missing	*343*	*33*	
Highest qualification obtained			
None	2019 (10.0)	125 (13.2)	0.0002
School or intermediate certificate	3380 (16.8)	175 (18.5)	
Higher school or leaving certificate	2821 (14.0)	144 (15.2)	
Apprenticeship or certificate	6719 (33.4)	313 (33.1)	
University degree or higher	5161 (25.7)	190 (20.1)	
Missing	*226*	*37*	

Characteristic	N (%) Included (N = 20,326)	Excluded (N = 984)	P-value[a]
Alcohol consumption (drinks/week)			
< 1	4807 (24.6)	240 (26.2)	0.42
1 to 7	8697 (44.4)	407 (44.5)	
> 7 to 14	3587 (18.3)	167 (18.3)	
> 14	2479 (12.7)	101 (11.0)	
Missing	*756*	*69*	
Smoking history			
Never	11059 (54.8)	533 (55.4)	0.91
Ex-smoker	8250 (40.9)	387 (40.2)	
Current	854 (4.2)	42 (4.4)	
Missing	*163*	*22*	
Time outdoors (hours/week)			
Low (< 8)	6549 (33.0)	315 (33.9)	0.38
Moderate (8 to < 18)	6599 (33.3)	289 (31.1)	
High (≥ 18)	6696 (33.7)	326 (35.1)	
Missing	*482*	*54*	
Self-rated overall health			
Excellent or very good	11180 (55.9)	467 (49.1)	<0.0001
Good	7137 (35.7)	381 (40.0)	
Fair or poor	1696 (8.5)	104 (10.9)	
Missing	*313*	*32*	
Self-rated quality of life			
Excellent or very good	13399 (67.4)	561 (59.2)	<0.0001
Good	5331 (26.8)	300 (31.7)	
Fair or poor	1138 (5.7)	86 (9.1)	
Missing	*458*	*37*	
History of osteoporosis[b]			
No	18715 (96.8)	161 (100.0)	0.02
Yes	621 (3.2)	0 (0.0)	
Missing	*990*	*823*	

[a] P-value from chi-squared test

[b] Derived using Pharmaceutical Benefits Scheme (PBS) data. We assumed that a participant had osteoporosis at baseline if they were prescribed a medication for osteoporosis (i.e., PBS items with Anatomical Therapeutic Chemical code of: M05BA; M05BB; M05BX03; M05BX04; G03XC01; H05AA02; H05AA04; M05BX06) within twelve months of randomisation.

STable 2. Effect of supplementation with vitamin D on fractures. Predicted difference in standardised survival and time-varying hazard ratio at 2, and 5 years post-randomisation, and predicted overall hazard ratio.

Years since randomisation	Survival Difference (95% CI)	Hazard Ratio (95% CI)
Total fracture		
2	-0.0020 (-0.0057 to 0.0016)	0.98 (0.86, 1.11)
5	0.0011 (-0.0053 to 0.0075)	0.88 (0.74, 1.06)
Overall HR		0.98 (0.88, 1.10)
Nonvertebral fracture		
2	-0.0008 (-0.0043 to 0.0027)	0.95 (0.83, 1.09)
5	0.0025 (-0.0036 to 0.0086)	0.87 (0.72, 1.06)
Overall HR		0.95 (0.84, 1.08)
Major osteoporotic fracture		
2	-0.0014 (-0.0040 to 0.0012)	1.01 (0.83, 1.23)
5	-0.0029 (-0.0075 to 0.0017)	1.13 (0.86, 1.47)
Overall HR		1.11 (0.94, 1.30)
Hip fracture		
2	-0.0005 (-0.0021 to 0.0011)	1.09 (0.76, 1.56)
5	-0.0004 (-0.0033 to 0.0024)	0.94 (0.61, 1.45)
Overall HR		1.04 (0.80, 1.35)

The outcomes are first fracture at any site, first nonvertebral fracture, first major osteoporotic fracture (hip, wrist, proximal humerus, spine), and first hip fracture following randomisation. Estimates (comparing vitamin D to placebo) from flexible parametric survival models that include randomisation group, age, sex, and state of residence at baseline. Time-varying estimates 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). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort.

STable 3. Sensitivity analysis[a]: Effect of supplementation with vitamin D on fractures. Predicted difference in standardised survival and time-varying hazard ratio at 2, and 5 years post-randomisation, and predicted overall hazard ratio.

Years since randomisation	Survival Difference (95% CI)	Hazard Ratio (95% CI)
Total fracture		
2	-0.0017 (-0.0055 to 0.0022)	0.97 (0.86, 1.10)
5	0.0014 (-0.0054 to 0.0081)	0.90 (0.76, 1.07)
Overall HR		0.98 (0.88, 1.09)
Nonvertebral fracture		
2	-0.0004 (-0.0041 to 0.0033)	0.95 (0.83, 1.08)
5	0.0026 (-0.0038 to 0.0090)	0.90 (0.75, 1.08)
Overall HR		0.96 (0.85, 1.07)
Major osteoporotic fracture		
2	-0.0010 (-0.0039 to 0.0018)	0.99 (0.83, 1.18)
5	-0.0030 (-0.0080 to 0.0021)	1.15 (0.91, 1.47)
Overall HR		1.09 (0.94, 1.26)
Hip fracture		
2	-0.0001 (-0.0022 to 0.0019)	1.04 (0.79, 1.38)
5	-0.0005 (-0.0041 to 0.0032)	1.02 (0.72, 1.45)
Overall HR		1.03 (0.84, 1.26)

[a] Medicare Item Numbers for hip arthroplasty included in the codes used to ascertain hip fractures.
The outcomes are first fracture at any site, first nonvertebral fracture, first major osteoporotic fracture (hip, wrist, proximal humerus, spine), and first hip fracture following randomisation. Estimates (comparing vitamin D to placebo) from flexible parametric survival models that include randomisation group, age, sex, and state of residence at baseline. Time-varying estimates 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). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort.

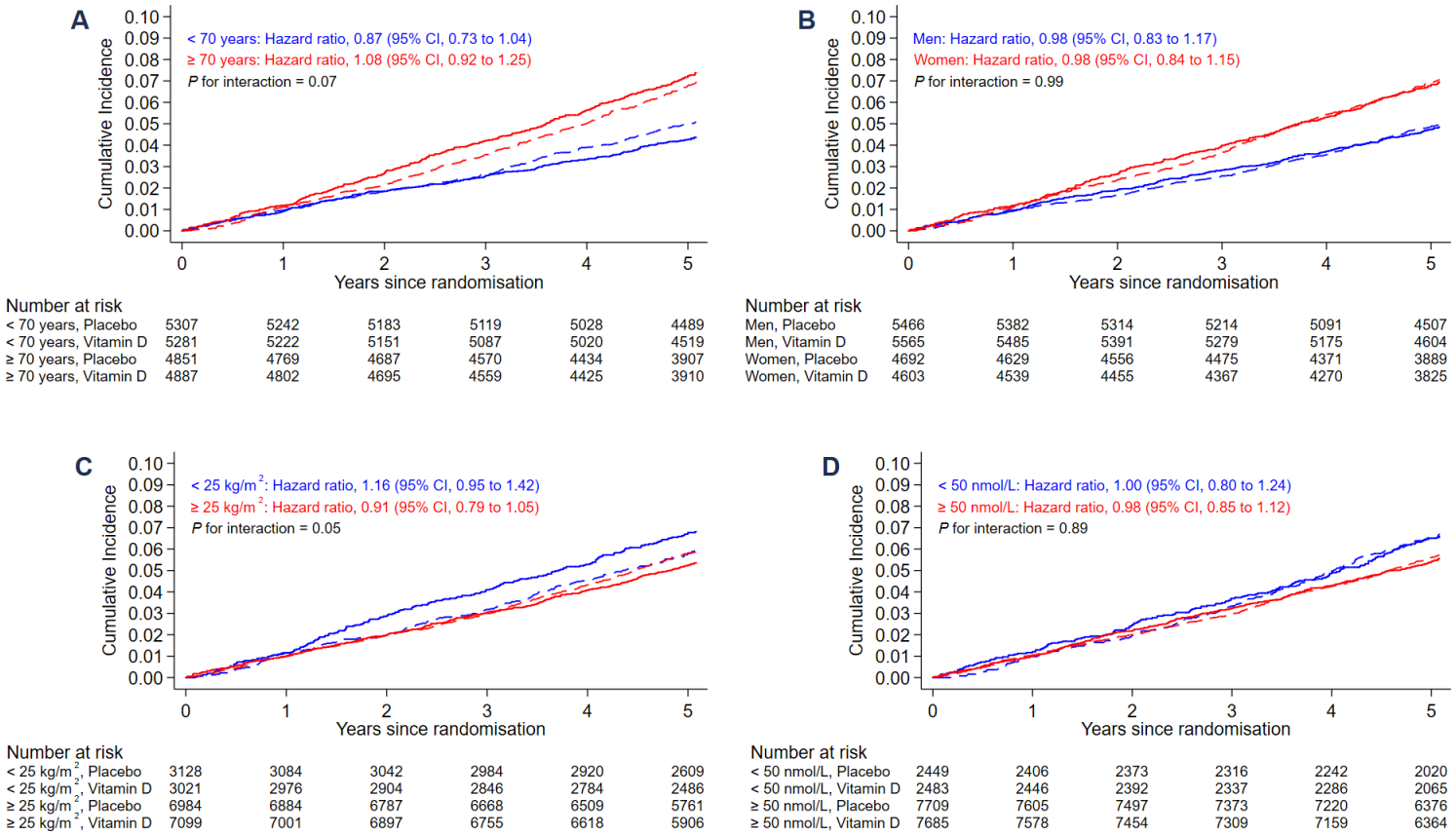
STable 4. Associations between selected baseline characteristics and fractures.

		≥1 fracture		≥1 nonvertebral fracture		≥1 osteoporotic fracture		≥1 hip fracture	
Characteristic	**N**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**
Age (years)									
60-64	5020	233 (4.6)	Ref.	218 (4.3)	Ref.	95 (1.9)	Ref.	28 (0.6)	Ref.
65-69	5568	261 (4.7)	1.03 (0.86 to 1.22)	234 (4.2)	0.98 (0.82 to 1.18)	138 (2.5)	1.34 (1.04 to 1.75)	49 (0.9)	1.61 (1.01 to 2.56)
70-74	5519	336 (6.1)	1.40 (1.18 to 1.66)	282 (5.1)	1.25 (1.05 to 1.50)	181 (3.3)	1.91 (1.49 to 2.45)	64 (1.2)	2.23 (1.43 to 3.48)
≥ 75	4219	341 (8.1)	1.97 (1.67 to 2.33)	309 (7.3)	1.91 (1.60 to 2.27)	168 (4.0)	2.51 (1.95 to 3.23)	81 (1.9)	3.91 (2.54 to 6.03)
Sex									
Men	11031	529 (4.8)	Ref.	466 (4.2)	Ref.	219 (2.0)	Ref.	99 (0.9)	Ref.
Women	9295	642 (6.9)	1.55 (1.38 to 1.75)	577 (6.2)	1.58 (1.40 to 1.79)	363 (3.9)	2.15 (1.82 to 2.55)	123 (1.3)	1.66 (1.27 to 2.17)
Body mass index (kg/m²)									
< 25	6149	386 (6.3)	Ref.	347 (5.6)	Ref.	207 (3.4)	Ref.	91 (1.5)	Ref.
25 to < 30	8622	480 (5.6)	0.93 (0.81 to 1.07)	432 (5.0)	0.94 (0.81 to 1.08)	211 (2.4)	0.79 (0.65 to 0.96)	81 (0.9)	0.67 (0.49 to 0.90)
≥ 30	5461	296 (5.4)	0.89 (0.77 to 1.04)	255 (4.7)	0.86 (0.73 to 1.01)	162 (3.0)	0.92 (0.75 to 1.13)	49 (0.9)	0.64 (0.45 to 0.91)
Predicted 25(OH)D concentration (nmol/L)									
≥ 50	15394	851 (5.5)	Ref.	754 (4.9)	Ref.	415 (2.7)	Ref.	154 (1.0)	Ref.
< 50	4932	320 (6.5)	1.15 (1.01 to 1.31)	289 (5.9)	1.17 (1.02 to 1.34)	167 (3.4)	1.21 (1.01 to 1.45)	68 (1.4)	1.36 (1.02 to 1.81)
Alcohol consumption (drinks/week)									
< 1	4807	319 (6.6)	Ref.	277 (5.8)	Ref.	170 (3.5)	Ref.	68 (1.4)	Ref.
1 to 7	8697	496 (5.7)	0.90 (0.78 to 1.04)	451 (5.2)	0.95 (0.81 to 1.10)	251 (2.9)	0.89 (0.73 to 1.08)	91 (1.0)	0.80 (0.59 to 1.10)
> 7 to 14	3587	184 (5.1)	0.88 (0.73 to 1.06)	163 (4.5)	0.90 (0.74 to 1.10)	86 (2.4)	0.84 (0.65 to 1.09)	30 (0.8)	0.71 (0.46 to 1.09)
> 14	2479	130 (5.2)	1.00 (0.81 to 1.24)	114 (4.6)	1.02 (0.81 to 1.28)	53 (2.1)	0.89 (0.64 to 1.22)	24 (1.0)	0.93 (0.57 to 1.50)

		≥1 fracture		≥1 nonvertebral fracture		≥1 osteoporotic fracture		≥1 hip fracture	
Characteristic	**N**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**	**n (%)**	**HR (95% CI)**
Self-rated overall health									
Excellent/v. good	11180	597 (5.3)	Ref.	545 (4.9)	Ref.	289 (2.6)	Ref.	103 (0.9)	Ref.
Good	7137	407 (5.7)	1.07 (0.94 to 1.22)	357 (5.0)	1.03 (0.90 to 1.18)	211 (3.0)	1.16 (0.97 to 1.39)	88 (1.2)	1.31 (0.99 to 1.75)
Fair or poor	1696	149 (8.8)	1.76 (1.47 to 2.11)	126 (7.4)	1.62 (1.33 to 1.97)	73 (4.3)	1.80 (1.39 to 2.33)	28 (1.7)	1.87 (1.23 to 2.84)
Self-rated quality of life									
Excellent/v. good	13399	683 (5.1)	Ref.	612 (4.6)	Ref.	340 (2.5)	Ref.	117 (0.9)	Ref.
Good	5331	338 (6.3)	1.23 (1.08 to 1.41)	301 (5.6)	1.23 (1.07 to 1.41)	166 (3.1)	1.22 (1.01 to 1.47)	77 (1.4)	1.60 (1.20 to 2.13)
Fair or poor	1138	117 (10.3)	2.16 (1.78 to 2.63)	103 (9.1)	2.11 (1.71 to 2.60)	60 (5.3)	2.22 (1.69 to 2.92)	23 (2.0)	2.41 (1.54 to 3.77)
History of osteoporosis									
No	18715	1032 (5.5)	Ref.	924 (4.9)	Ref.	512 (2.7)	Ref.	193 (1.0)	Ref.
Yes	621	69 (11.1)	1.75 (1.37 to 2.24)	59 (9.5)	1.65 (1.26 to 2.16)	34 (5.5)	1.53 (1.08 to 2.18)	14 (2.3)	1.67 (0.96 to 2.89)

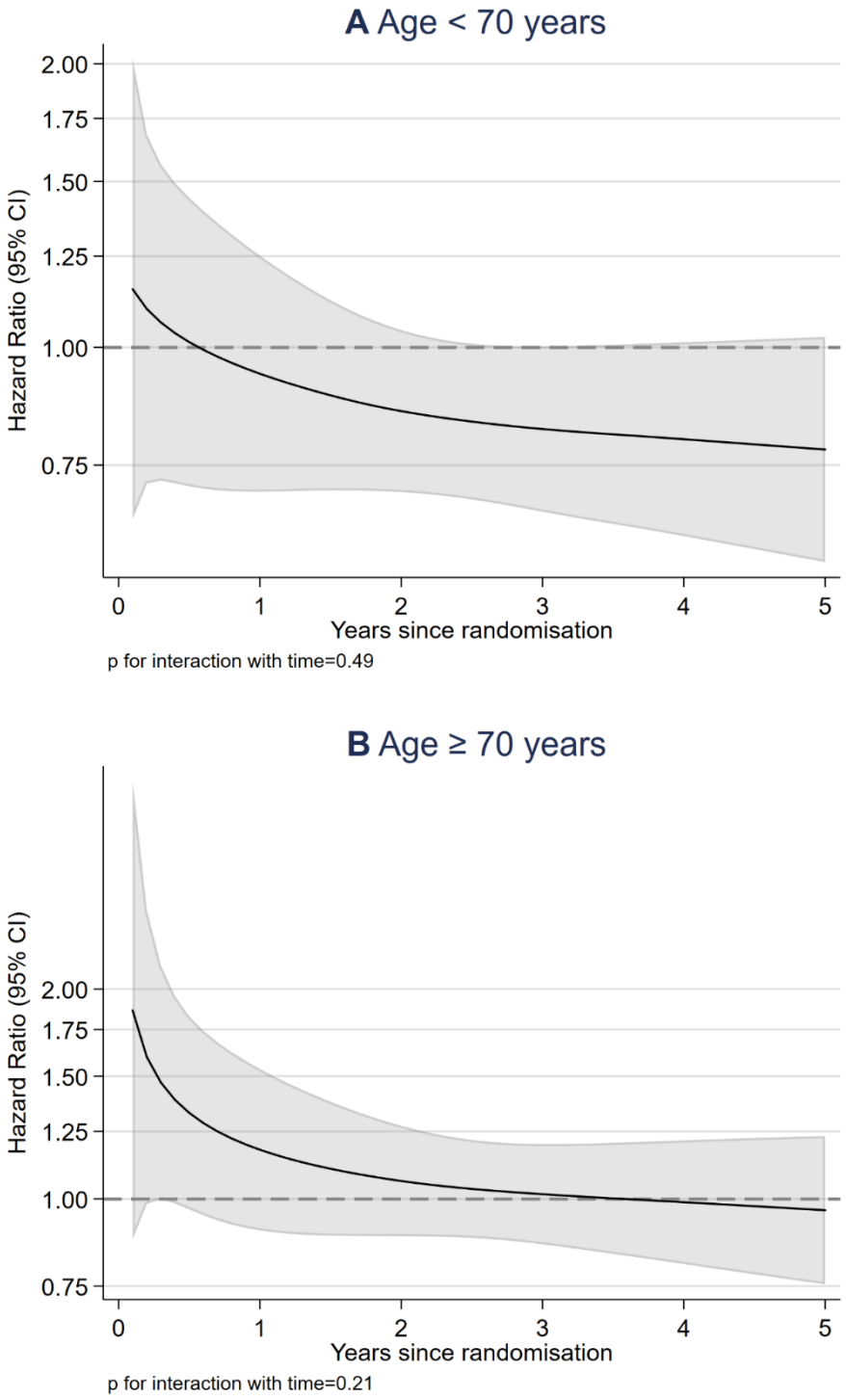
[a] Estimates (comparing vitamin D to placebo) are from flexible parametric survival models, where the baseline log cumulative hazard function is modelled using a restricted cubic spline with two internal knots (placed at the 33rd and 67th percentiles of the uncensored log survival times). All models included age at randomisation, and sex.
Abbreviations: CI, confidence interval; HR, hazard ratio; Ref., reference; v. good, very good

Appendix G – PLANNED SUPPLEMENTARY FIGURES



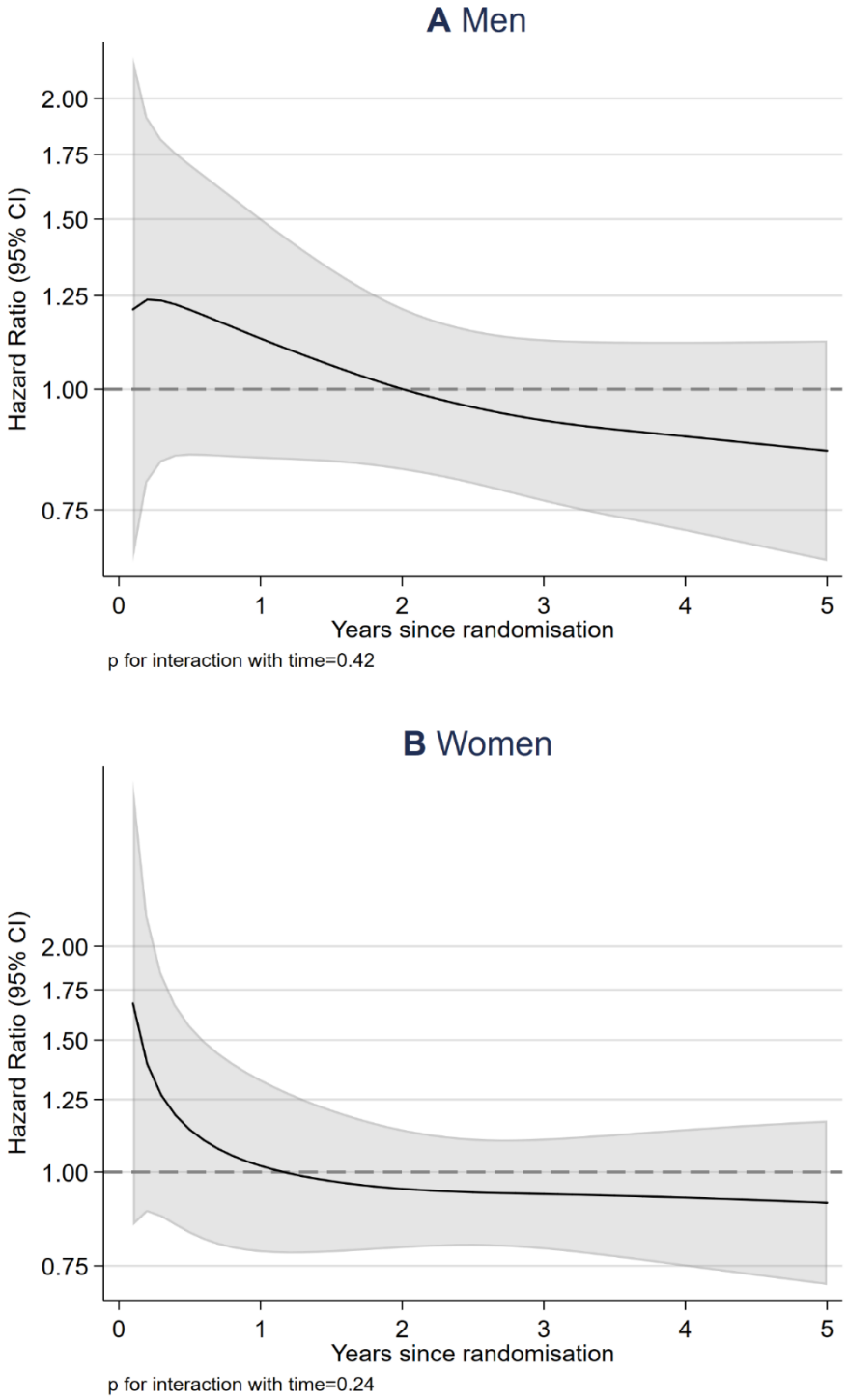
SFigure 1. Cumulative incidence of total fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration.

The outcome is first fracture following randomisation. Curves estimated using Kaplan-Meier methods. Hazard ratios (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, the baseline characteristic of interest, age, sex, and state of residence at baseline, and an interaction between randomisation group and the baseline characteristic of interest. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



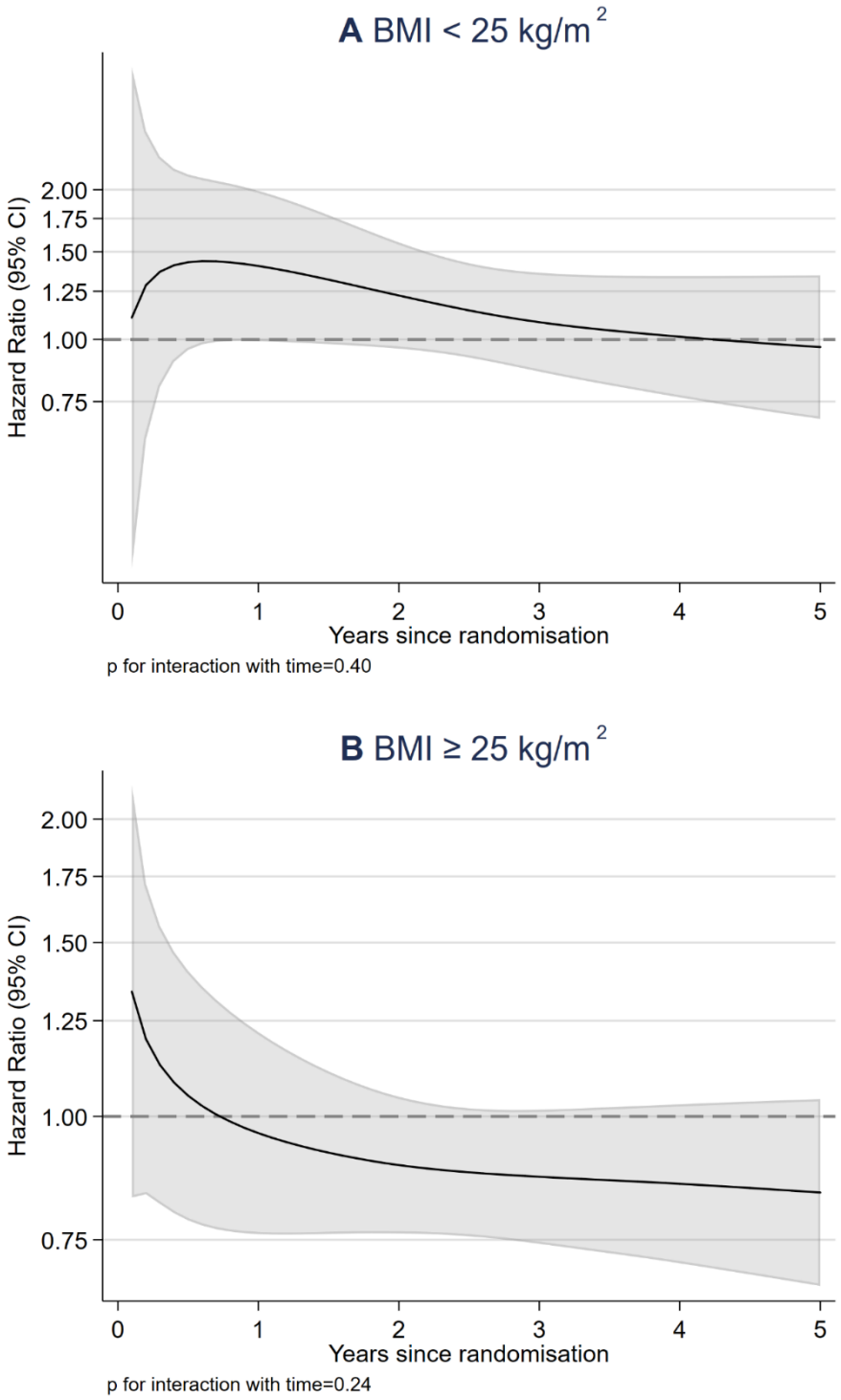
SFigure 2. Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to baseline age (<70 years, ≥70 years).

The outcome is first fracture following randomisation. Time-varying hazard ratios (comparing vitamin D to placebo) are from flexible parametric survival models that included randomisation group, sex, 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). Models were fitted separately to data from participants within each subgroup of age. The p value for the interaction with time is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



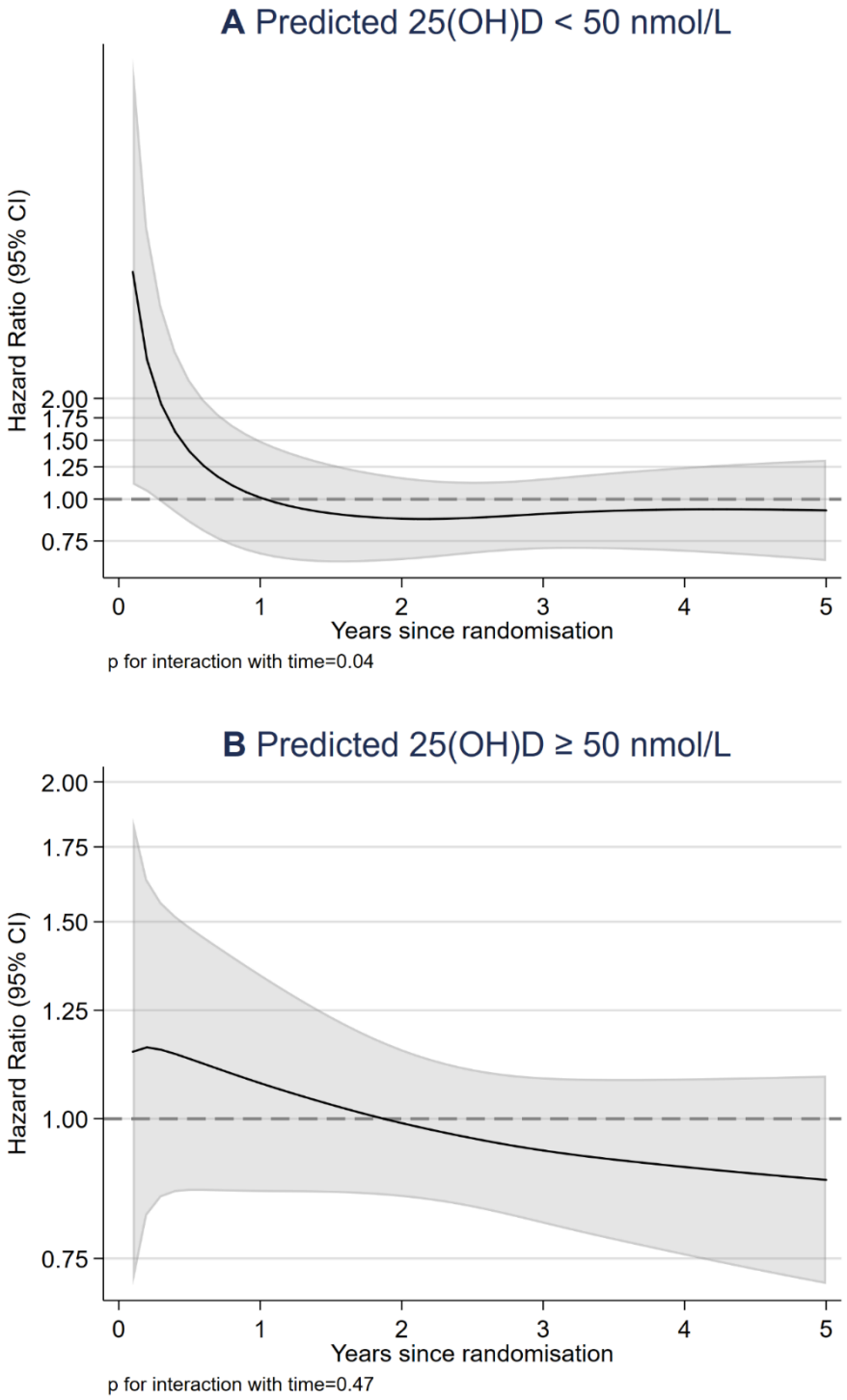
SFigure 3. Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to sex (men, women).

The outcome is first fracture following randomisation. Time-varying hazard ratios (comparing vitamin D to placebo) are from flexible parametric survival models that included randomisation group, age, 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). Models were fitted separately to data from men and women. The p value for the interaction with time is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



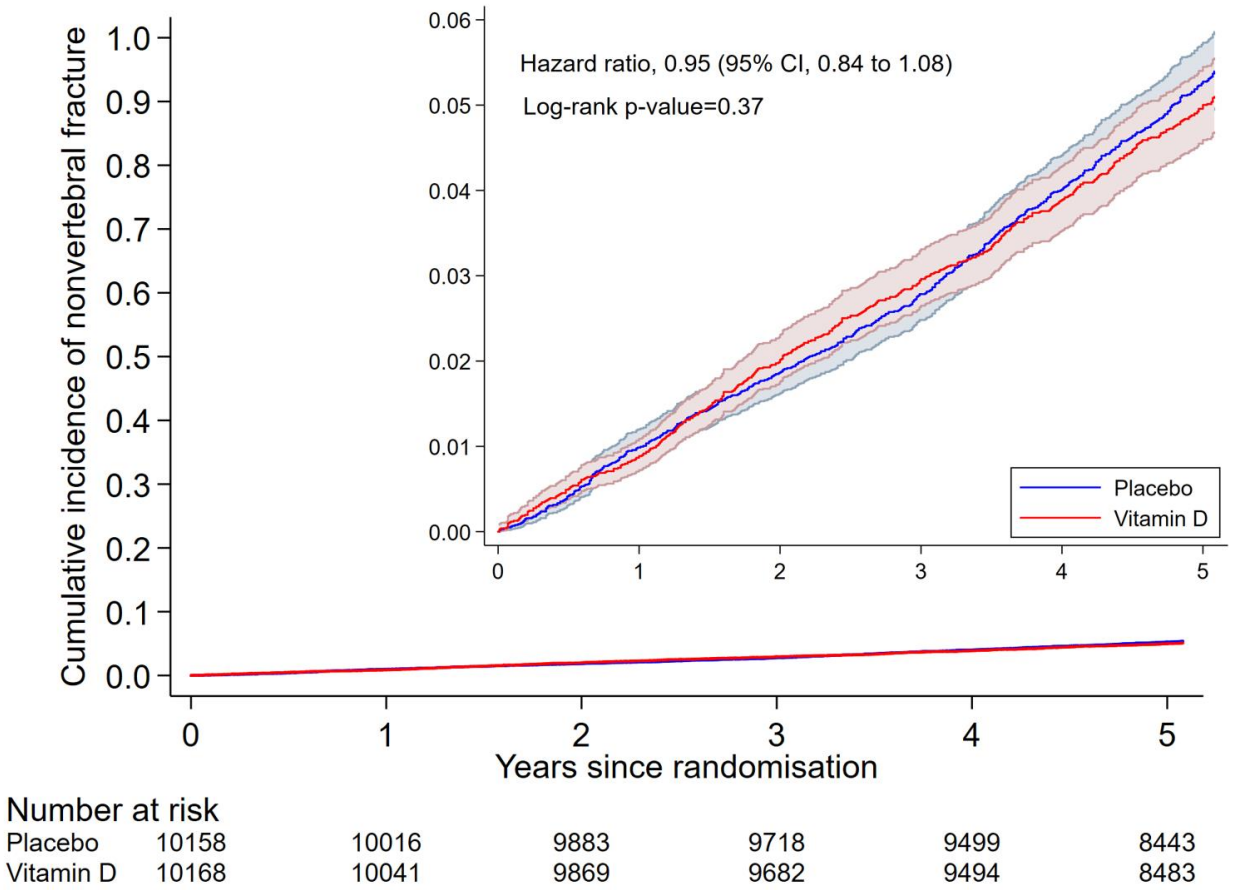
SFigure 4. Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to baseline body mass index (<25 kg/m^2, ≥25 kg/m^2).

The outcome is first fracture following randomisation. Time-varying hazard ratios (comparing vitamin D to placebo) are from flexible parametric survival models that included randomisation group, age, sex, 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). Models were fitted separately to data from participants within each subgroup of body mass index. The p value for the interaction with time is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



SFigure 5. Time-varying hazard ratio (vitamin D versus placebo) for total fractures according to predicted deseasonalised baseline 25(OH)D concentration (<50 nmol/L, ≥50 nmol/L).

The outcome is first fracture following randomisation. Time-varying hazard ratios (comparing vitamin D to placebo) are from flexible parametric survival models that included randomisation group, age, sex, 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). Models were fitted separately to data from participants within each subgroup of predicted 25(OH)D concentration. The p value for the interaction with time is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval

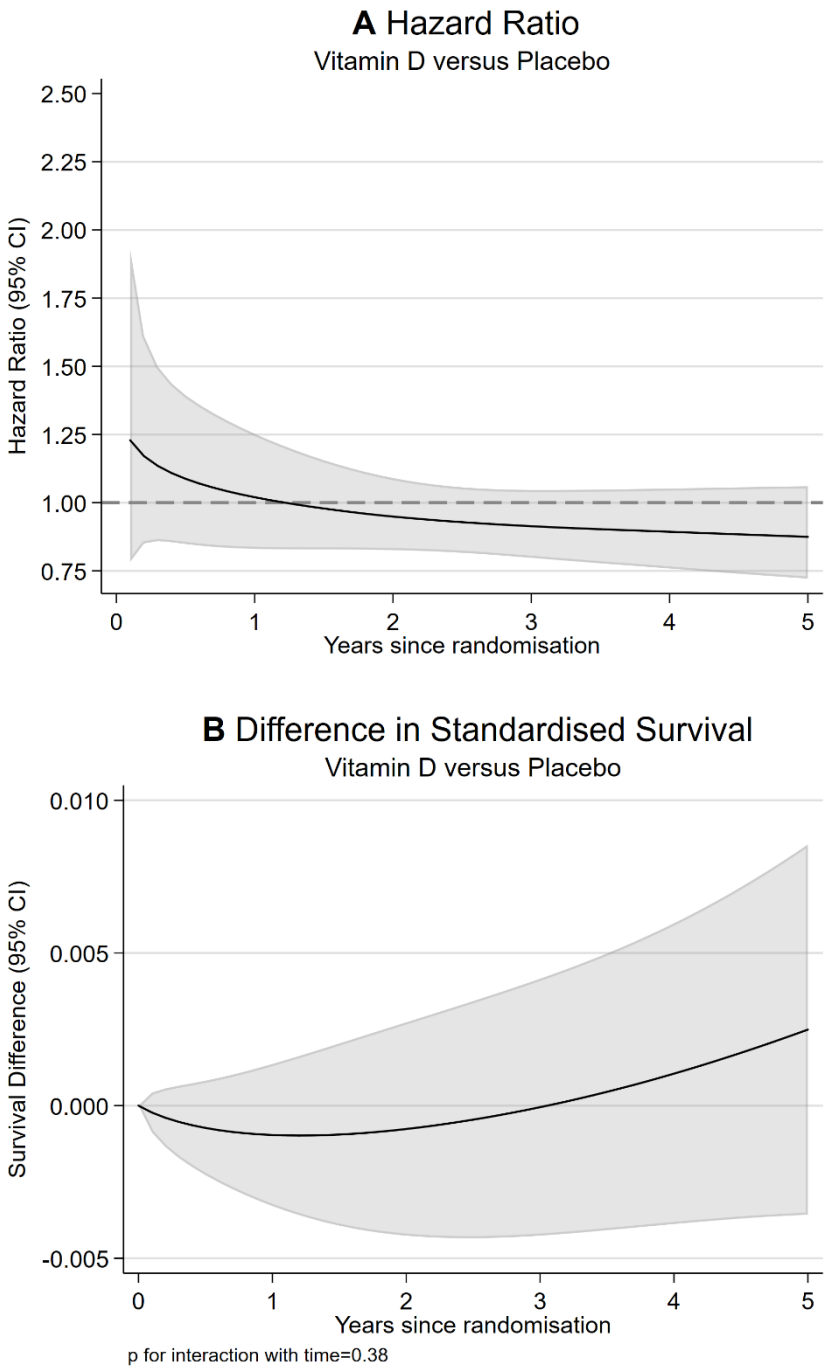


Number at risk

Placebo	10158	10016	9883	9718	9499	8443
Vitamin D	10168	10041	9869	9682	9494	8483

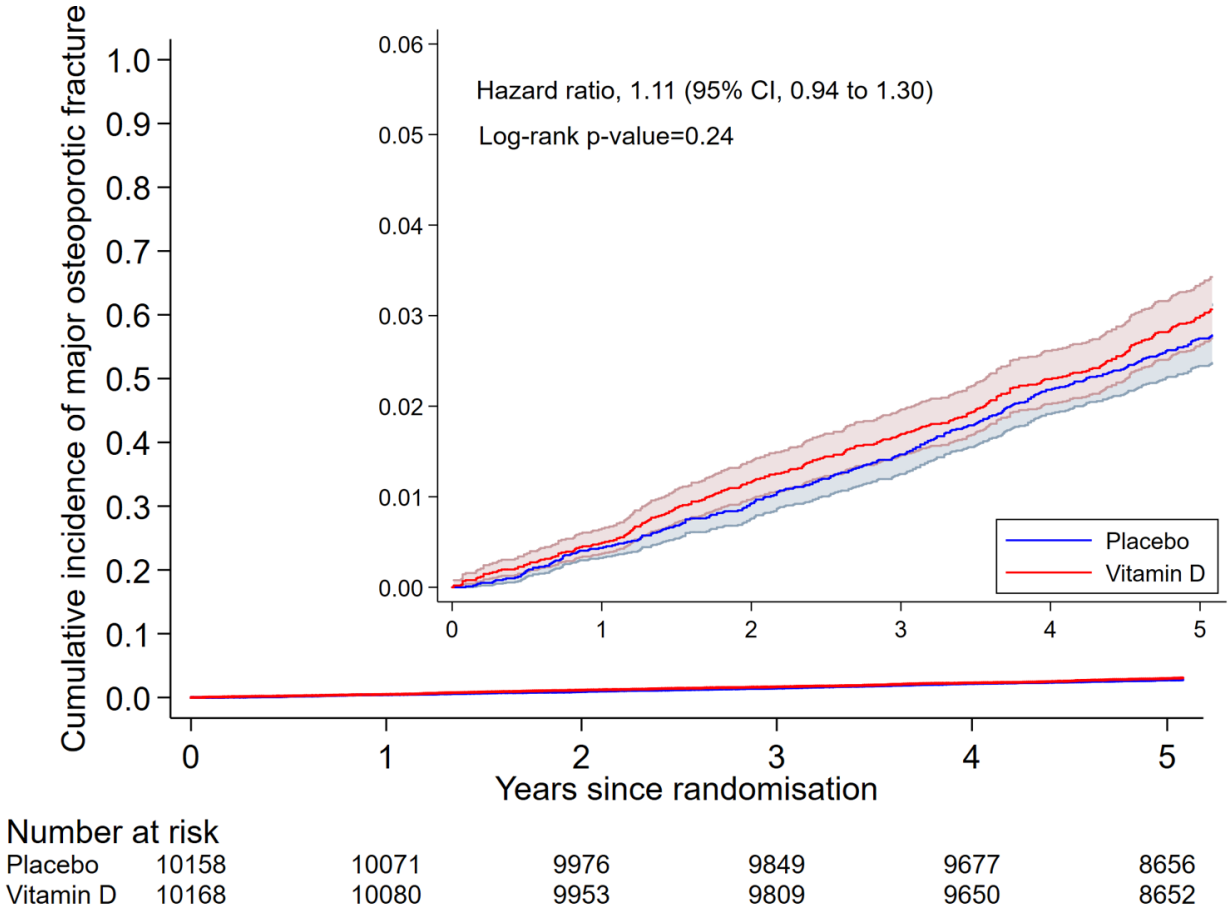
SFigure 6. Cumulative incidence of nonvertebral fractures according to randomisation group and time since randomisation.

Curves estimated using Kaplan-Meier methods and hazard ratio (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The inset shows the same data on an enlarged y axis.
Abbreviation: CI, confidence interval



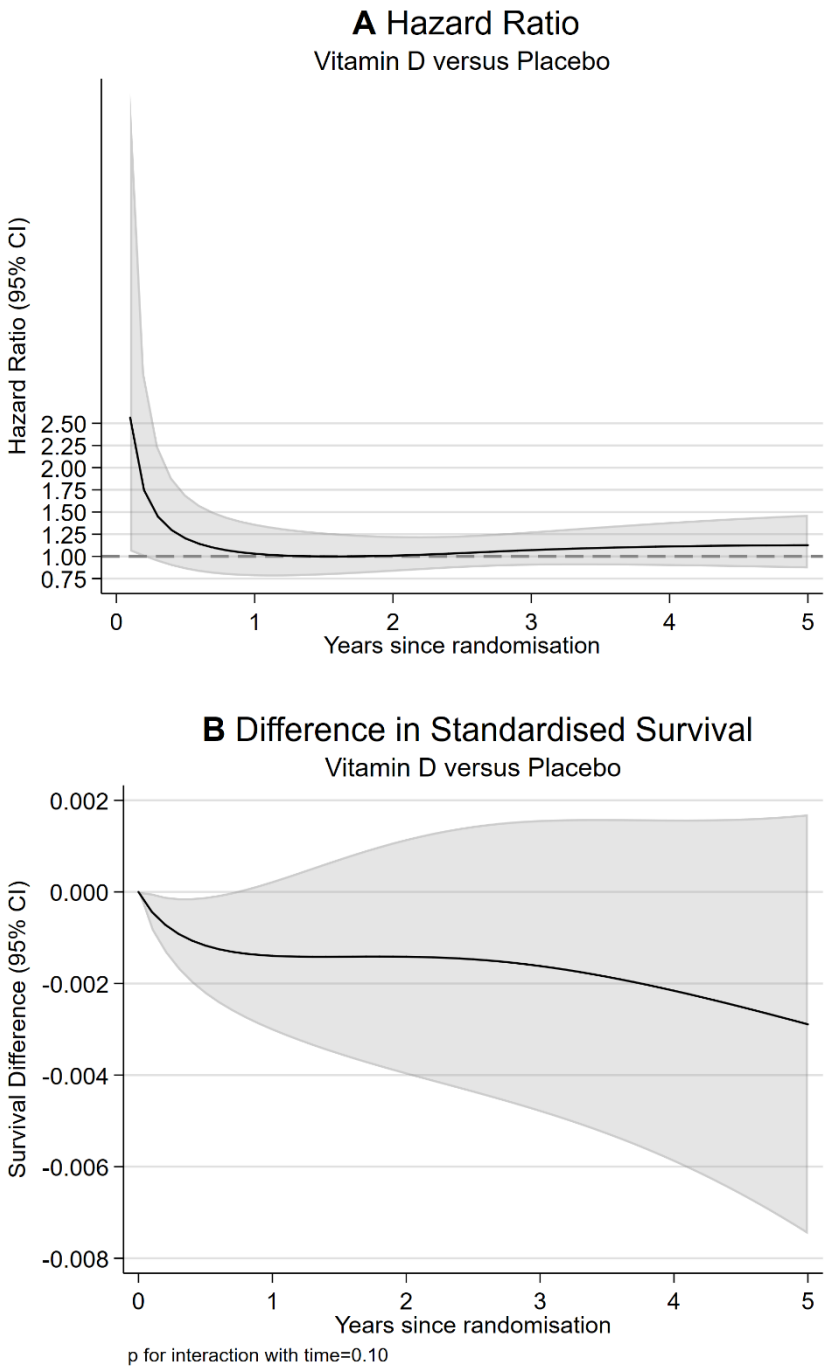
SFigure 7. Time-dependent effect of vitamin D supplementation on nonvertebral fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation.

The outcome is first nonvertebral fracture following randomisation. 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 time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. The interaction between randomisation group and time since randomisation was assessed using a likelihood ratio test that compared models with and without the interaction term. The values on the y-axis in panel B are differences in probability of survival.
Abbreviation: CI, confidence interval



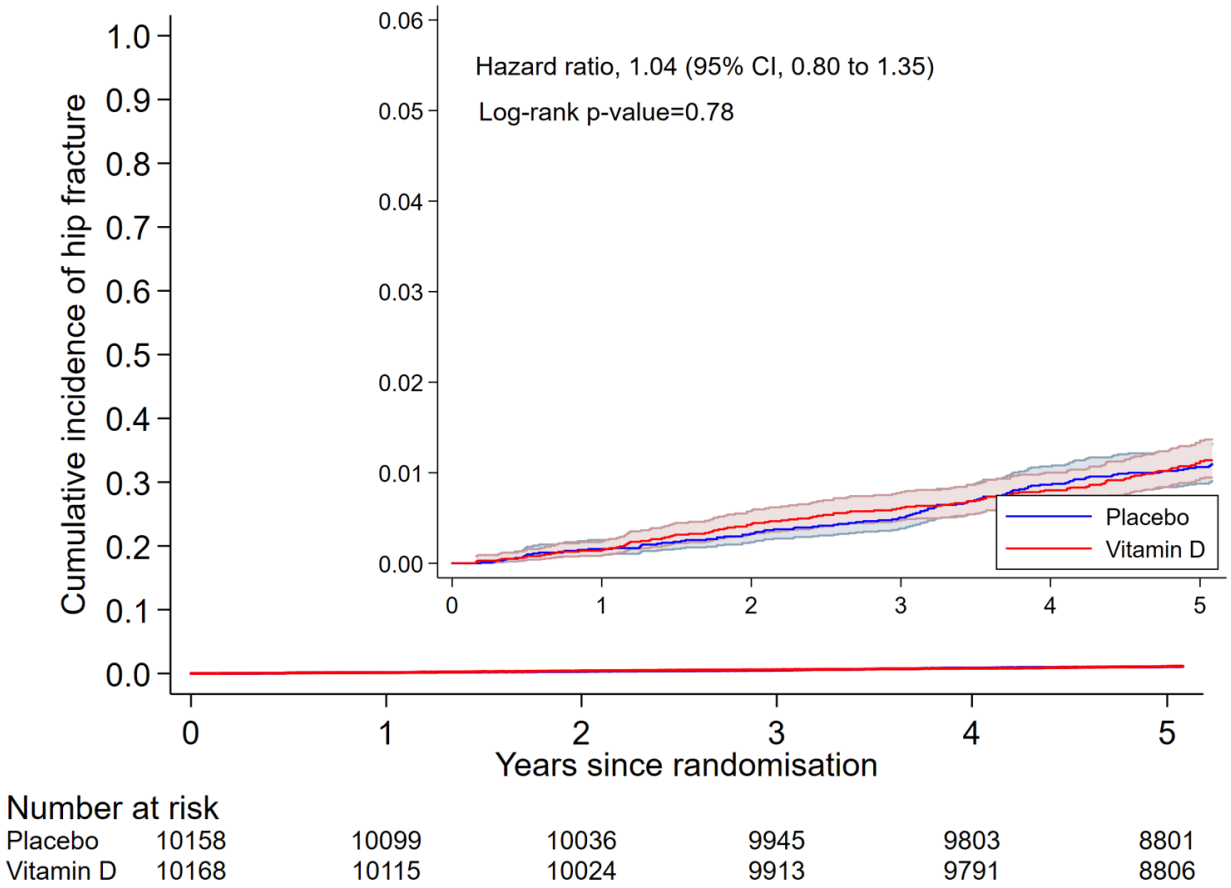
SFigure 8. Cumulative incidence of major osteoporotic fractures according to randomisation group and time since randomisation.

Major osteoporotic fracture includes fractures of the hip, wrist, proximal humerus, and spine. Curves estimated using Kaplan-Meier methods and hazard ratio (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The inset shows the same data on an enlarged y axis.
Abbreviation: CI, confidence interval



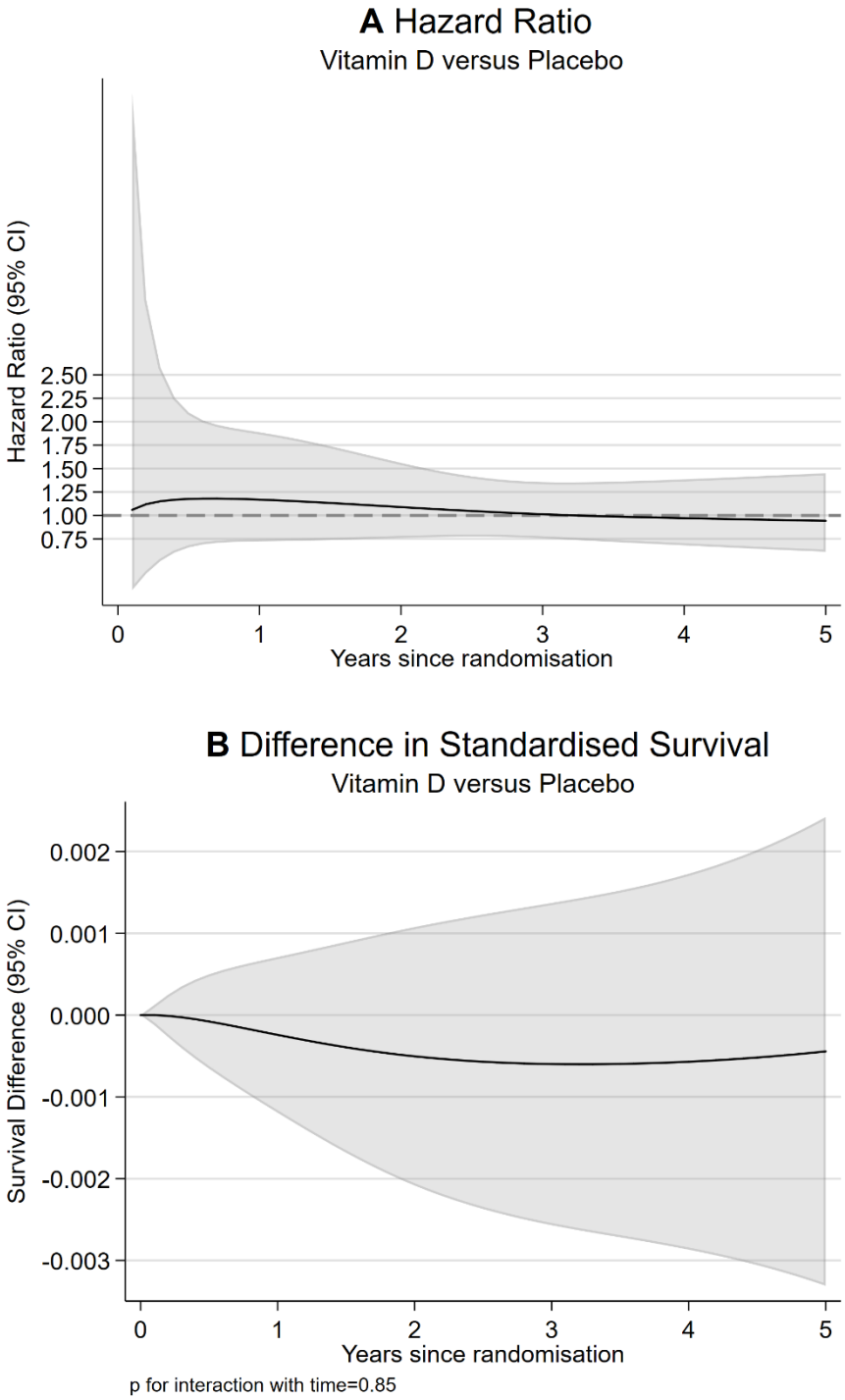
SFigure 9. Time-dependent effect of vitamin D supplementation on major osteoporotic fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation.

The outcome is first major osteoporotic (hip, wrist, proximal humerus, spine) fracture following randomisation. 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 time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. The interaction between randomisation group and time since randomisation was assessed using a likelihood ratio test that compared models with and without the interaction term. The values on the y-axis in panel B are differences in probability of survival.
Abbreviation: CI, confidence interval



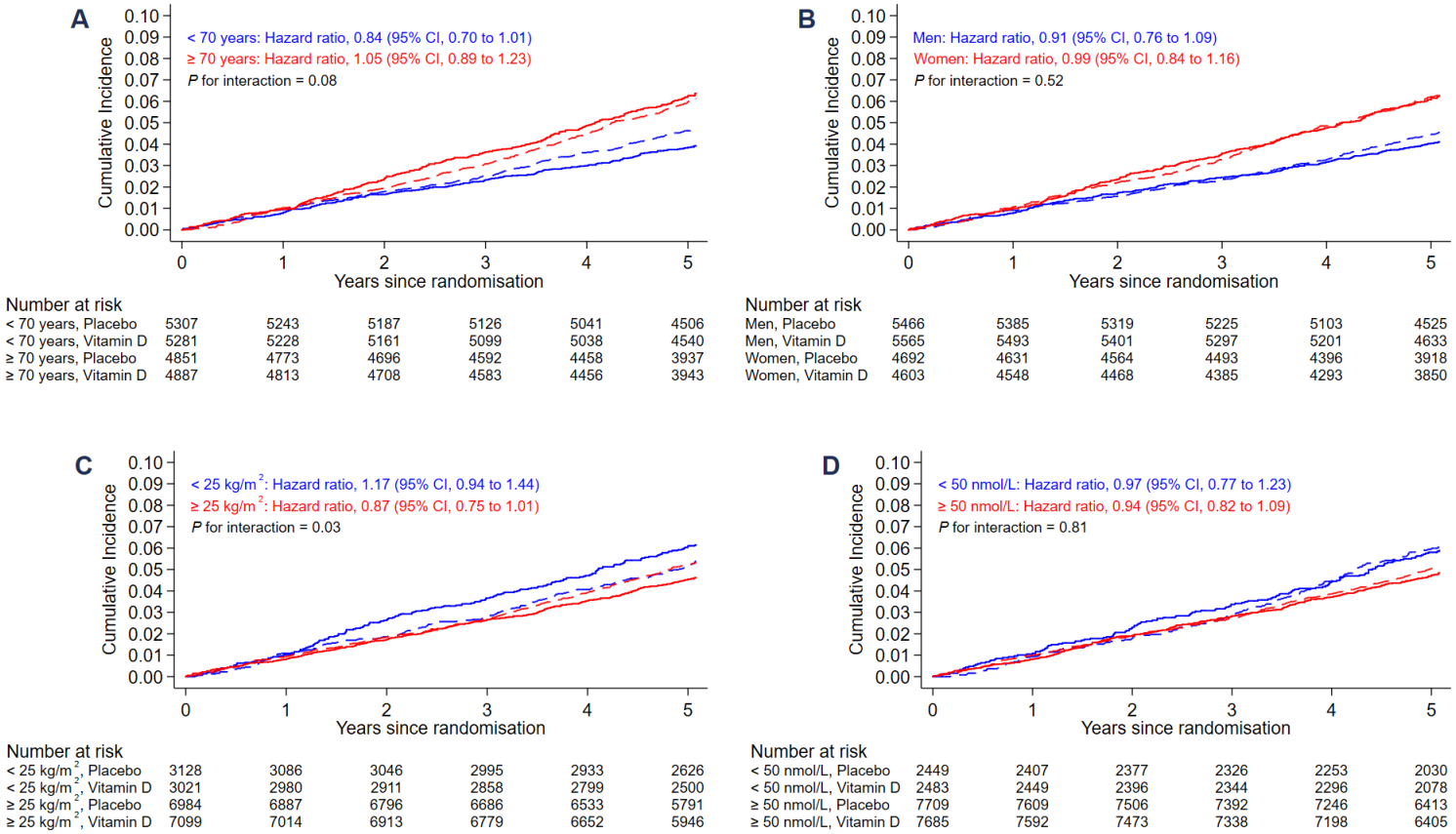
SFigure 10. Cumulative incidence of hip fractures according to randomisation group and time since randomisation.

Curves estimated using Kaplan-Meier methods and hazard ratio (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The inset shows the same data on an enlarged y axis.
Abbreviation: CI, confidence interval



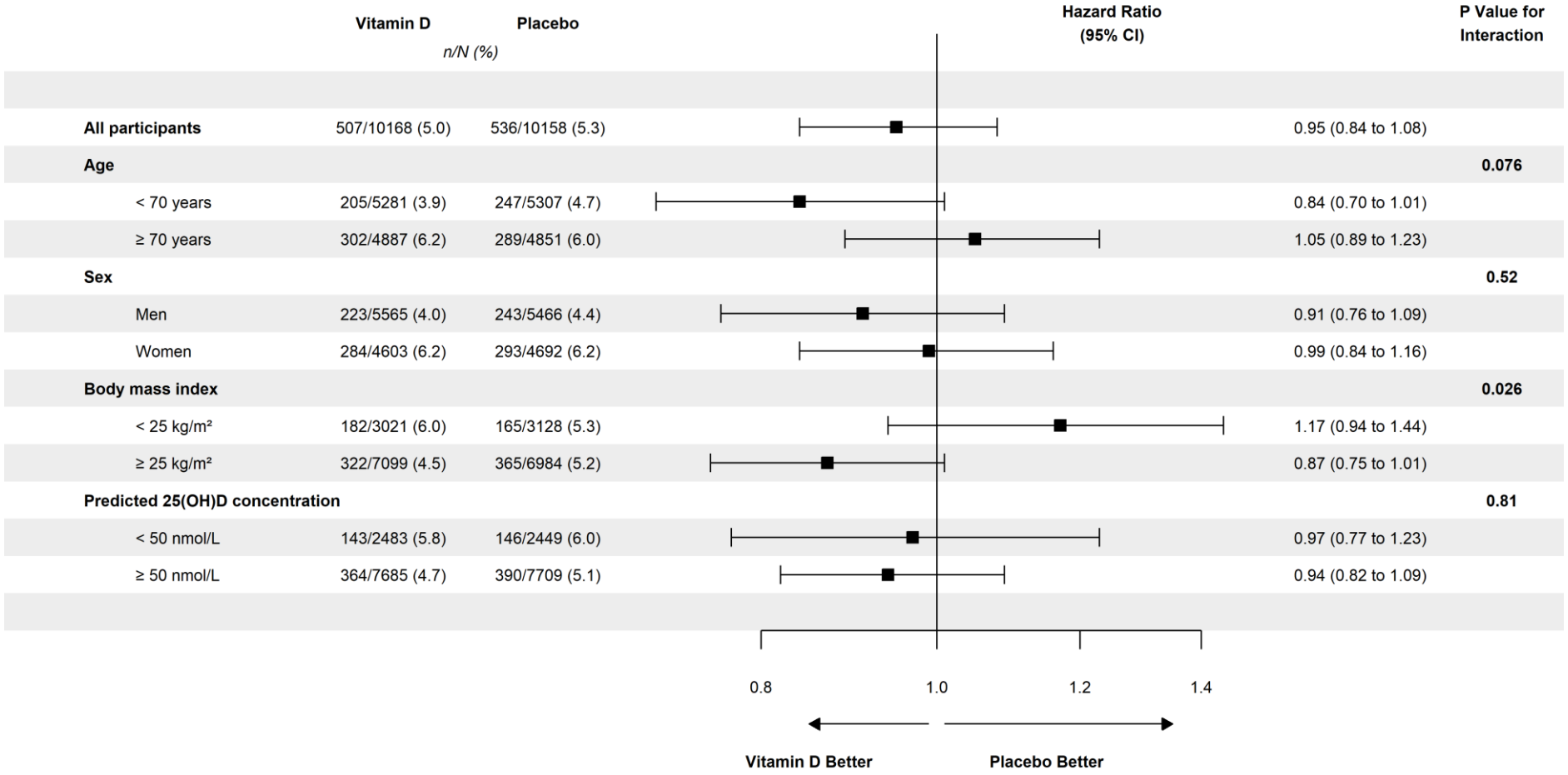
SFigure 11. Time-dependent effect of vitamin D supplementation on hip fractures. Panel A shows the time-varying hazard ratio and panel B shows the difference in standardised survival as a function of time since randomisation.

The outcome is first hip fracture following randomisation. 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 time since randomisation, fitted as a restricted cubic spline with one internal knot (placed at the median of uncensored log survival times). Survival functions were standardised to the distribution of age, sex, and state of residence at baseline in the entire cohort. The interaction between randomisation group and time since randomisation was assessed using a likelihood ratio test that compared models with and without the interaction term. The values on the y-axis in panel B are differences in probability of survival.
Abbreviation: CI, confidence interval



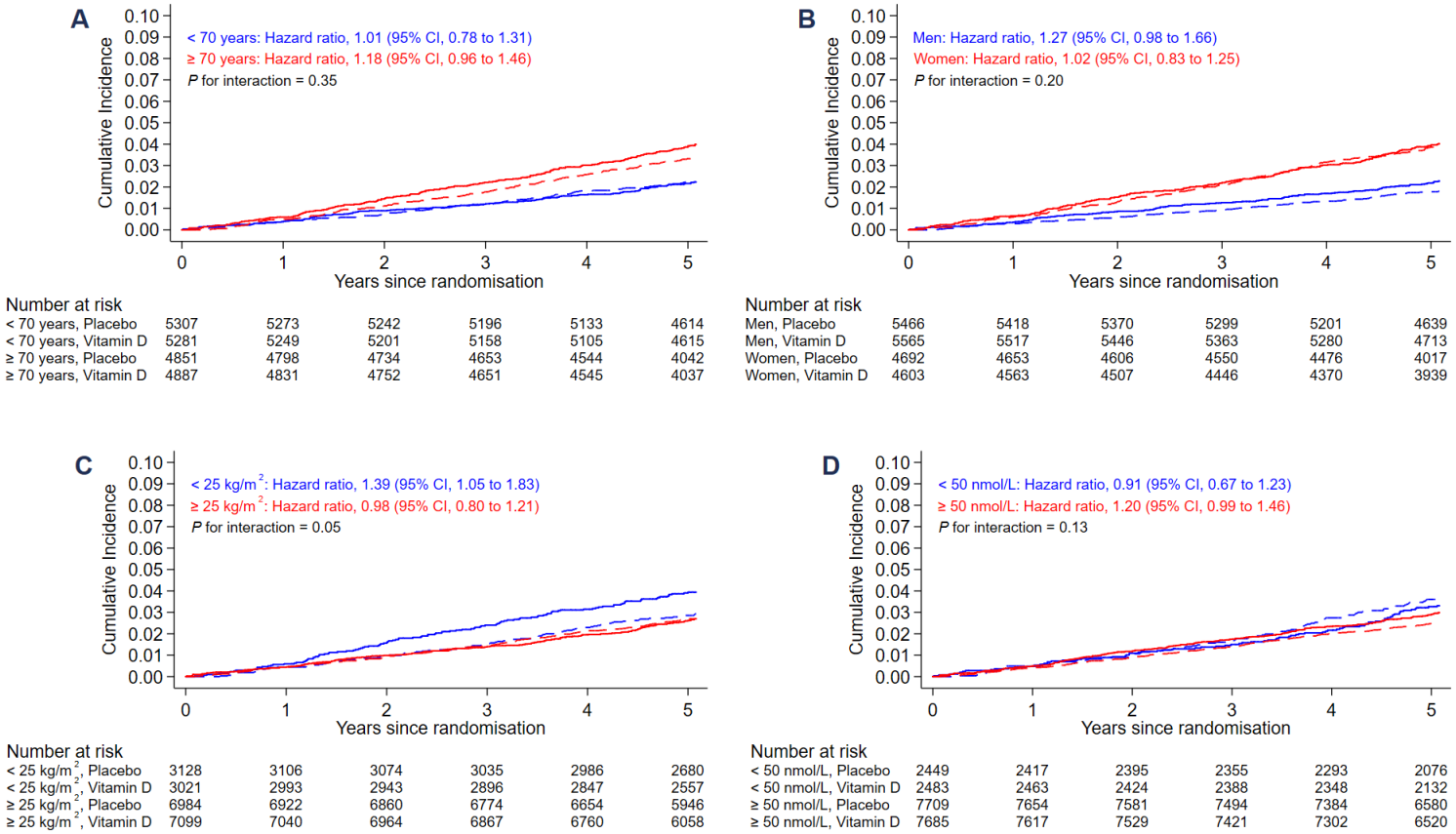
SFigure 12. Cumulative incidence of nonvertebral fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration.

The outcome is first nonvertebral fracture following randomisation. Curves estimated using Kaplan-Meier methods. Hazard ratios (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, the baseline characteristic of interest, age, sex, and state of residence at baseline, and an interaction between randomisation group and the baseline characteristic of interest. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



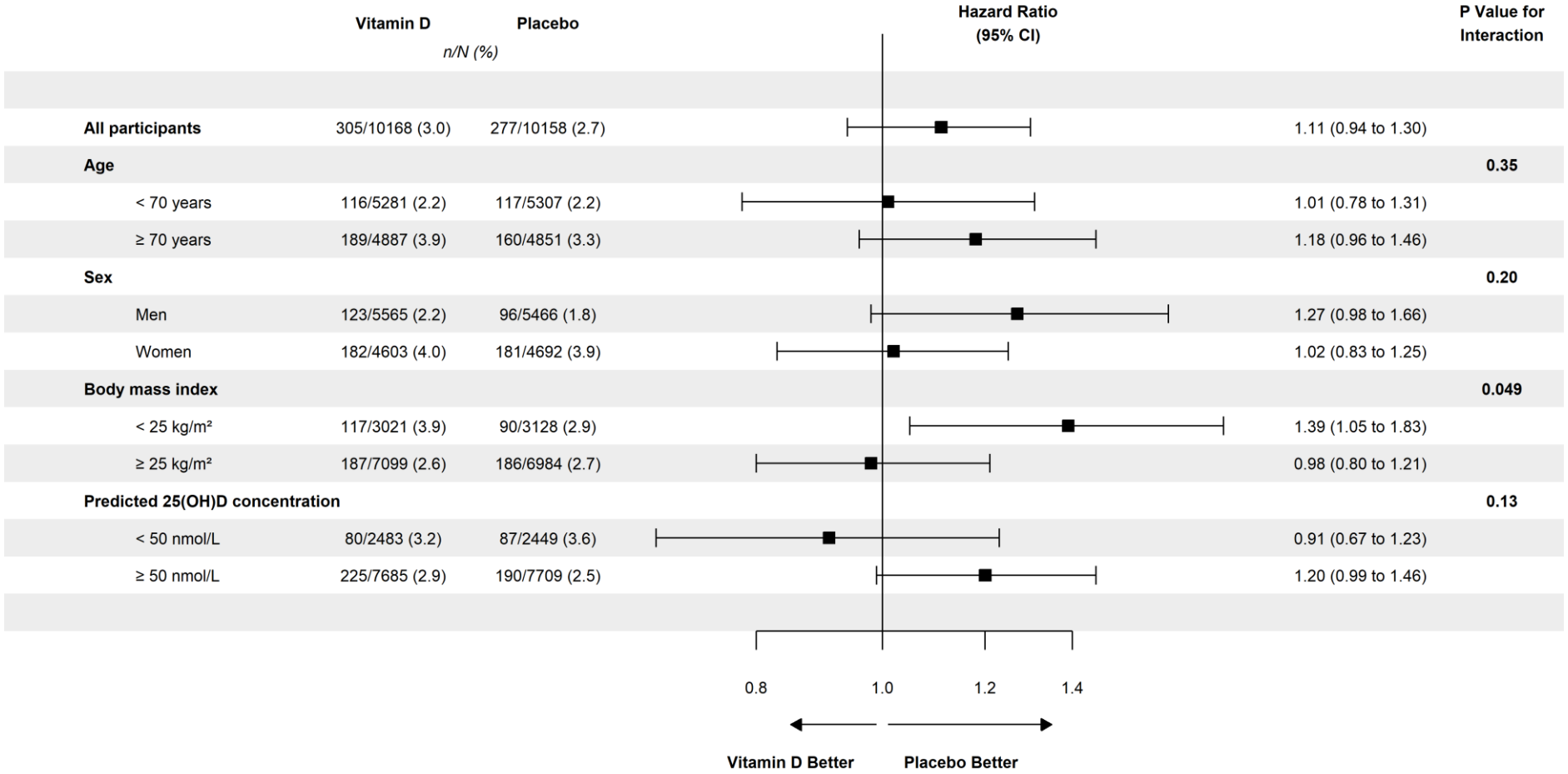
SFigure 13. Effect of vitamin D supplementation on nonvertebral fractures for all participants and by selected baseline characteristics.

The outcome is first nonvertebral fracture following randomisation. Estimates from flexible parametric survival models. Hazard ratios compare vitamin D to placebo. All models include 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, include the characteristic of interest and an interaction between randomisation group and the characteristic of interest. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



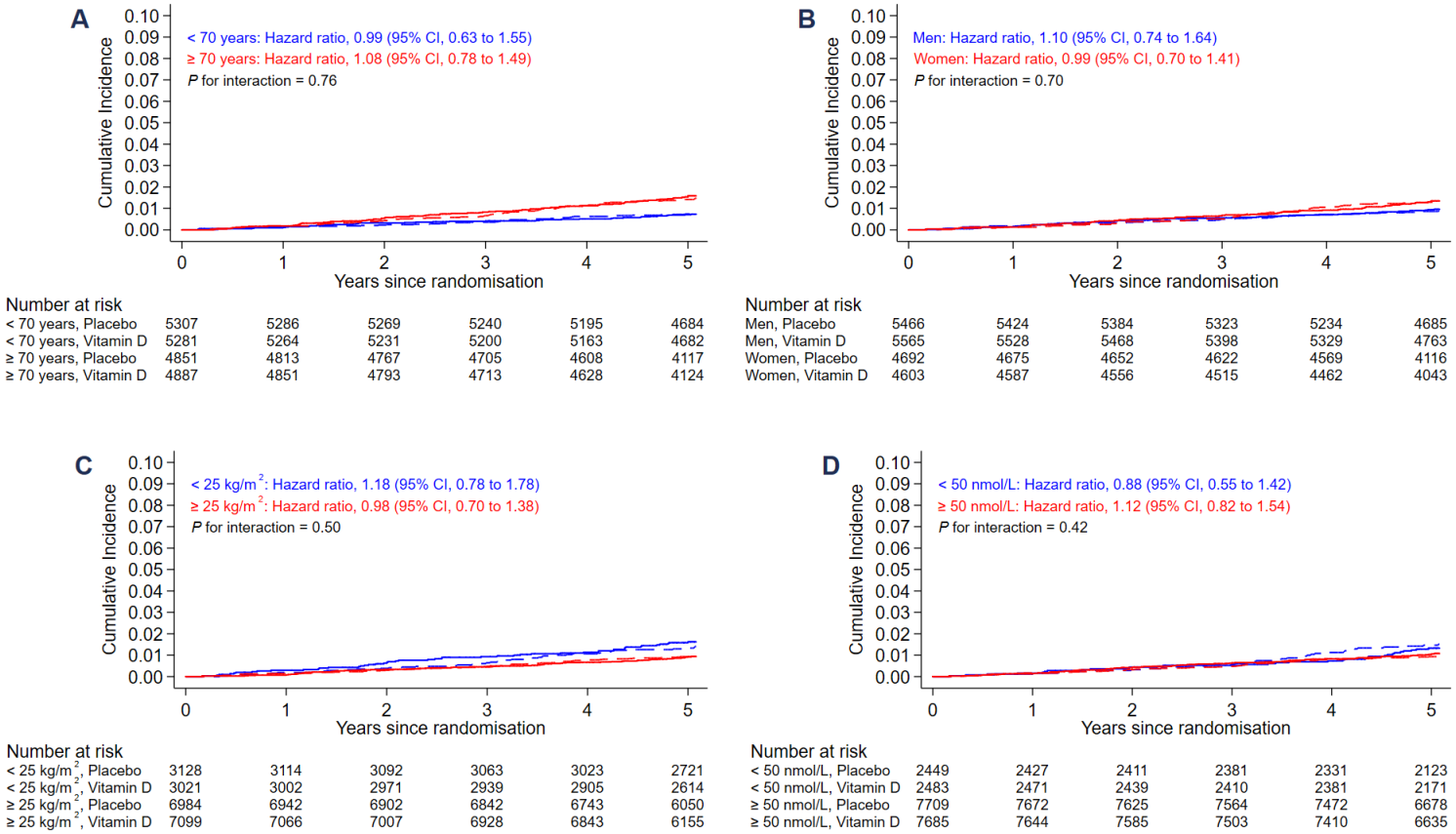
SFigure 14. Cumulative incidence of major osteoporotic fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration.

The outcome is first major osteoporotic (hip, wrist, proximal humerus, spine) fracture following randomisation. Curves estimated using Kaplan-Meier methods. Hazard ratios (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, the baseline characteristic of interest, age, sex, and state of residence at baseline, and an interaction between randomisation group and the baseline characteristic of interest. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



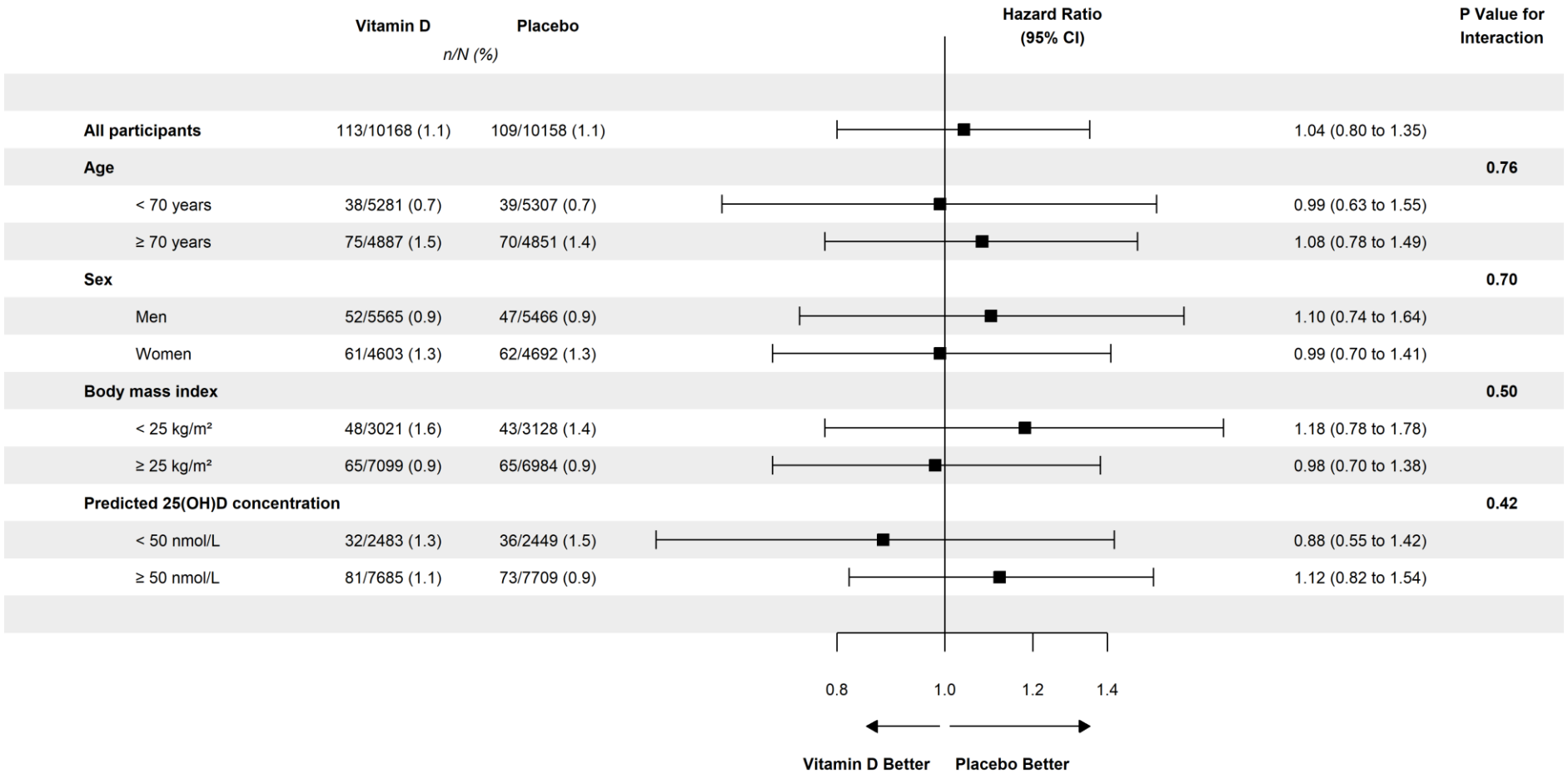
SFigure 15. Effect of vitamin D supplementation on major osteoporotic fractures for all participants and by selected baseline characteristics.

The outcome is first major osteoporotic (hip, wrist, proximal humerus, spine) fracture following randomisation. Estimates from flexible parametric survival models. Hazard ratios compare vitamin D to placebo. All models include 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, include the characteristic of interest and an interaction between randomisation group and the characteristic of interest. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



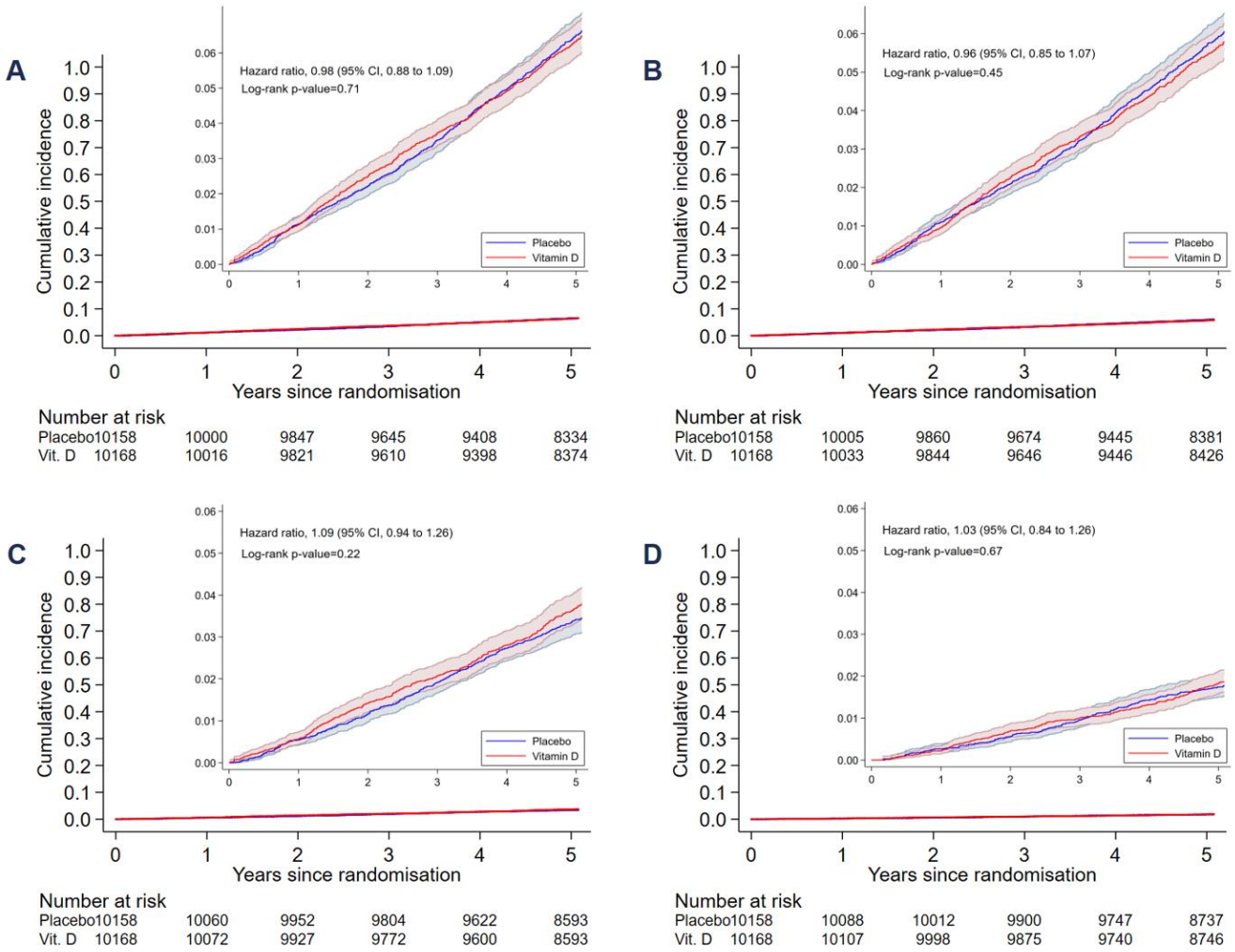
SFigure 16. Cumulative incidence of hip fractures according to randomisation group (vitamin D, solid line; placebo, dashed line) and time since randomisation, stratified by baseline (A) age, (B) sex, (C) body mass index, and (D) predicted deseasonalised 25(OH)D concentration.

The outcome is first hip fracture following randomisation. Curves estimated using Kaplan-Meier methods. Hazard ratios (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, the baseline characteristic of interest, age, sex, and state of residence at baseline, and an interaction between randomisation group and the baseline characteristic of interest. P value for the interaction is from a likelihood ratio test comparing models with and without the interaction term. Abbreviation: CI, confidence interval



SFigure 17. Effect of vitamin D supplementation on hip fractures for all participants and by selected baseline characteristics.

The outcome is first hip fracture following randomisation. Estimates from flexible parametric survival models. Hazard ratios compare vitamin D to placebo. All models include 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, include the characteristic of interest and an interaction between randomisation group and the characteristic of interest. P value for interaction is from a likelihood ratio test comparing models with and without the interaction term.
Abbreviation: CI, confidence interval



SFigure 18. Sensitivity analysis[a]: Cumulative incidence of fractures according to randomisation group and time since randomisation. Panel A – total fracture; panel B – nonvertebral fracture; panel C – major osteoporotic fracture; panel D – hip fracture.

[a] Medicare Item Numbers for hip arthroplasty included in the codes used to ascertain hip fractures.

The outcomes are first fracture (panel A), first nonvertebral fracture (panel B), first major osteoporotic fracture (panel C), and first hip fracture (panel D) following randomisation. Curves estimated using Kaplan-Meier methods and hazard ratio (vitamin D versus placebo) estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. The inset shows the same data on an enlarged y axis. Abbreviation: CI, confidence interval