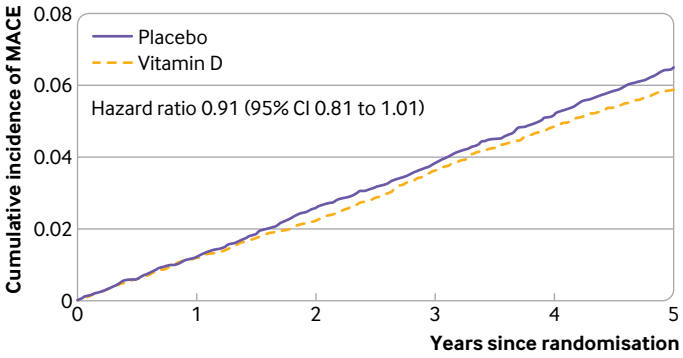

Fig 2 | Cause specific cumulative incidence of major cardiovascular events according to randomisation group and time since randomisation. Curves estimated using Aalen-Johansen methods, treating death without previous major cardiovascular event as a competing risk. Hazard ratio (vitamin D *v* placebo) was estimated using a flexible parametric survival model that included randomisation group, age, sex, and state of residence at baseline. 95% CI=95% confidence interval; MACE=major cardiovascular event

vitamin D group. The incidence of adverse events was similar in the two groups.[17]

Baseline characteristics of participants included in the current analysis, including use of statins and cardiovascular drugs, were well balanced between groups (table 1, supplementary table 3). Fifty four per cent of participants were men and the mean age was 69 years (standard deviation 5). The median follow-up was five years.

Major cardiovascular events

There were 1336 major cardiovascular events during follow-up (vitamin D, n=637 (6.0%); placebo, n=699 (6.6%)). Compared with the placebo group, the rate of major cardiovascular events was lower in the vitamin D group (hazard ratio 0.91, 95% confidence interval 0.81 to 1.01), although the upper bound of the confidence interval is consistent with there being no effect (fig 2, table 2). The hazard ratio did not change with time (supplementary fig 1, supplementary table 4). The difference in the standardised cause specific cumulative incidence at five years was −5.8 events per 1000 participants (95% confidence interval −12.2 to 0.5 per 1000 participants), resulting in a number needed to treat to avoid one major cardiovascular event of 172.

No effect modification was found according to baseline age, sex, or body mass index (fig 3, supplementary figs 2-7). The hazard ratio was lower in people with predicted baseline 25(OH)D concentration ≥50 nmol/L than in those with predicted baseline 25(OH)D <50 nmol/L (hazard ratio 0.87, 95% confidence interval 0.76 to 0.98 *v* 1.04, 0.84 to 1.27; P for interaction=0.14; fig 3, supplementary figs 8 and 9). The hazard ratio was also lower in people using statins at baseline versus those who were not (0.83, 0.71 to 0.97 *v* 0.98, 0.84 to 1.13; P for interaction=0.14), and in those who were using cardiovascular drugs at baseline versus those who were not (0.84, 0.74 to 0.97 *v* 1.01, 0.84 to 1.20; P for interaction=0.12; fig 3, supplementary figs 10-13). In exploratory analyses within subgroups defined according to use of statins or cardiovascular drugs at baseline versus no use, similar patterns were observed (supplementary table 5). In an exploratory analysis requested by reviewers, we performed analyses within subgroups defined by self-report of a major cardiovascular event before baseline. In contrast to the above findings, the effect was stronger in people who did not report a history of major cardiovascular event (0.89, 0.78 to 1.01) versus those who did report an event (0.95, 0.79 to 1.15; supplementary table 5). However, the confidence interval for those reporting an event was wide and the P value for interaction high (0.53).

Table 2 | Hazard ratios for vitamin D in relation to major cardiovascular events

Outcome*	Vitamin D (n=10 658)	Placebo (n=10 644)	HR (95% CI)¶
Major event†	637 (6.0)	699 (6.6)	0.91 (0.81 to 1.01)
Myocardial infarction	194 (1.8)	238 (2.2)	0.81 (0.67 to 0.98)
Coronary revascularisation‡	413 (3.9)	462 (4.3)	0.89 (0.78 to 1.01)
Stroke§	172 (1.6)	173 (1.6)	0.99 (0.80 to 1.23)
Haemorrhagic stroke	40 (0.4)	41 (0.4)	0.97 (0.63 to 1.50)
Ischaemic stroke	116 (1.1)	113 (1.1)	1.03 (0.79 to 1.33)

Data are numbers (%).
95% CI=95% confidence interval.
*The number (%) of people with at least one event.
†Composite endpoint including myocardial infarction, stroke, and coronary revascularisation. The number of people who experienced at least one major event is less than the total of the numbers presented for myocardial infarction, stroke, and coronary revascularisation because participants could experience more than one type of event.
‡Composite endpoint including percutaneous coronary intervention (insertion of stent or balloon, artherectomy, thromboectomy, and endarterectomy) or coronary artery bypass grafting.
§Stroke includes diagnosis code I64 (unspecified) and therefore exceeds the total number of ischaemic and haemorrhagic strokes.
¶Estimated using flexible parametric survival models that included age, sex, and state of residence at baseline. The baseline log cumulative hazard function was modelled using restricted cubic spline with two internal knots (placed at the 33rd and 67th percentiles of the uncensored log survival times).

Specific cardiovascular events

The cumulative incidence and hazard of myocardial infarction were lower in the vitamin D group (hazard ratio 0.81; 95% confidence interval 0.67 to 0.98; table 2, supplementary figs 14 and 15). The same was true of coronary revascularisation, although the confidence interval for the hazard ratio included the null (0.89, 0.78 to 1.01; table 2, supplementary figs 16 and 17). There was no interaction with elapsed time for these outcomes (supplementary figs 15 and 17). The intervention had no apparent effect on stroke (0.99, 0.80 to 1.23; table 2, supplementary fig 18-23). In exploratory analyses of myocardial infarction and coronary revascularisation, we did not find evidence of interactions with baseline statin and other cardiovascular drug use (supplementary table 6).

Discussion

Principal findings

In this analysis of data from the D-Health Trial we found some evidence that supplementation with 60 000 IU of vitamin D_3 per month for up to five years reduced the incidence of major cardiovascular events, particularly myocardial infarction and coronary revascularisation. The absolute differences were small, and the confidence intervals for total major cardiovascular events and coronary revascularisation were consistent with null findings. For total major cardiovascular events, there was some indication of a stronger effect in those who were using statins or other cardiovascular drugs at baseline, or who had higher