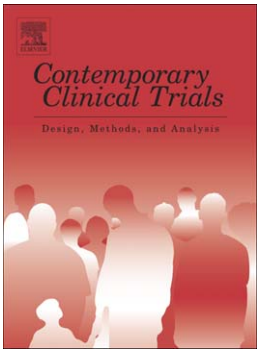

The D-Health Trial: A randomized trial of vitamin D for prevention of mortality and cancer

R.E. Neale, B.K. Armstrong, C. Baxter, B. Duarte Romero, P. Ebeling, D.R. English, M.G. Kimlin, D.S.A. McLeod, R.L. O′Connell, J.C. van der Pols, A.J. Venn, P.M. Webb, D.C. Whiteman, L. Wockner

PII: S1551-7144(16)30055-6
DOI: doi: 10.1016/j.cct.2016.04.005
Reference: CONCLI 1386

To appear in: *Contemporary Clinical Trials*

Received date: 4 February 2016
Revised date: 4 April 2016
Accepted date: 10 April 2016

Please cite this article as: Neale RE, Armstrong BK, Baxter C, Romero B. Duarte, Ebeling P, English DR, Kimlin MG, McLeod DSA, OConnell RL, van der Pols JC, Venn AJ, Webb PM, Whiteman DC, Wockner L, The D-Health Trial: A randomized trial of vitamin D for prevention of mortality and cancer, *Contemporary Clinical Trials* (2016), doi: 10.1016/j.cct.2016.04.005

The D-Health Trial: a randomized trial of vitamin D for prevention of mortality and cancer.

Neale RE[1], Armstrong BK[2], Baxter C[1], Duarte Romero B[1], Ebeling P[3], English DR[4], Kimlin MG[5], McLeod DSA[1], O'Connell RL[6], van der Pols JC[7], Venn AJ[8], Webb PM[1], Whiteman DC[1], Wockner L[1],

[1] Population Health Division, QIMR Berghofer Medical Research Institute, Brisbane, Australia
[2] School of Public Health, University of Sydney, Sydney, Australia
[3] School of Clinical Sciences, Monash University, Melbourne, Australia
[4] Melbourne School of Population Health, University of Melbourne; Cancer Epidemiology Centre, Cancer Council Victoria, Melbourne, Australia
[5] Health Research Institute, University of the Sunshine Coast, Sippy Downs, Australia
[6] NHMRC Clinical Trials Centre, University of Sydney, Sydney, Australia
[7] School of Public Health, The University of Queensland, Brisbane, Australia
[8] Menzies Institute for Medical Research, University of Tasmania, Hobart, Australia

Abbreviated title: The D-Health Trial
Key terms: vitamin D, randomized clinical trial, mortality, cancer
Word Count:
Number of figures and tables: Tables 5; Figures 2

Corresponding author and person to whom reprints requests should be addressed
A/Prof Rachel Neale
QIMR Berghofer Medical Research Institute
Locked Bag 2000, Royal Brisbane Hospital
QLD 4029
Australia
rachel.neale@qimrberghofer.edu.au

Grants and fellowships: The D-Health Trial is funded by a National Health and Medical Research Council (NHMRC) project grant (APP1046681) RE Neale, DSA McLeod, PM Webb and DC Whiteman are supported by fellowships from the NHMRC.

Disclosures: The authors have nothing to disclose.

Clinical Trial Registration Number: Australian New Zealand Clinical Trials Registry: ACTRN12613000743763

ABSTRACT

Background: Vitamin D, specifically serum 25(OH)D has been associated with mortality, cancer and multiple other health endpoints in observational studies, but there is a paucity of clinical trial evidence sufficient to determine the safety and effectiveness of population-wide supplementation. We have therefore launched the D-Health Trial, a randomized trial of vitamin D supplementation for prevention of mortality and cancer. Here we report the methods and describe the trial cohort.

Methods: The D-Health Trial is a randomized placebo-controlled trial, with planned intervention for 5 years and a further 5 years of passive follow-up through linkage with health and death registers. Participants aged 65-84 years were recruited from the general population of Australia. The intervention is monthly oral doses of 60,000 IU of cholecalciferol or matching placebo. The primary outcome is all-cause mortality. Secondary outcomes are total cancer incidence and colorectal cancer incidence.

Results: We recruited 21,315 participants to the trial between February 2014 and May 2015. The participants in the two arms of the trial were well-balanced at baseline. Comparison with Australian population statistics shows that the trial participants were less likely to report being in fair or poor health, to be current smokers or to have diabetes than the Australian population. However, the proportion overweight or with health conditions such as arthritis and angina was similar.

Conclusions: Observational data cannot be considered sufficient to support interventions delivered at a population level. Large-scale randomized trials such as the D-Health Trial are needed to inform public health policy and practice.

INTRODUCTION

The role of vitamin D in preventing rickets and osteomalacia has been established for many years. Laboratory and observational epidemiological studies have suggested that it may also play a role in many other diseases, such as cardiovascular and autoimmune diseases, diabetes, and cancer risk and survival (1). However it is not known whether associations seen in observational studies are causal, or whether supplementing a population would alter health outcomes.

Vitamin D has a range of potential anti-cancer actions, including regulating inflammation, cell differentiation, apoptosis, proliferation and angiogenesis (2). Observational studies have consistently shown that low serum 25 hydroxy vitamin D (25(OH)D) concentration is associated with increased risk of colorectal cancer (3), but the associations for most other cancers have been less consistent (1). Worse cancer survival has also been associated with lower 25(OH)D (4-6), suggesting possible late stage effects in the course of disease. Despite these suggestive findings, confounding or reverse causality are plausible explanations for the inverse associations between 25(OH)D levels and cancer risk, and randomized trials have largely failed to demonstrate any protective effect of vitamin D supplementation on cancer. The only randomized controlled trial that has been adequately powered to answer this question delivered null findings (7,8) although the apparent lack of effect may be explained by the relatively low dose of vitamin D used (400 IU per day) and by suboptimal compliance.

Observational studies have also consistently associated circulating 25(OH)D with a number of other health outcomes, including cardiovascular disease and diabetes, but the trials have again showed a notable absence of effect (1,9). Meta-analyses of trials do suggest a protective effect of vitamin D supplementation against total mortality, with pooled relative risks ranging from 0.88 to 0.96 (1). However, in most trials mortality was not a primary endpoint and the majority were conducted in highly selected population subgroups, such as in the frail elderly or in people with a particular disease or risk factor, rather than in the general population.

In light of the suggestive observational data and the paucity of population-based trials with adequate power to assess effects on mortality and cancer of public health significance, three large randomized trials have recently been launched, including the Vitamin D and Omega-3 (VITAL) Trial in the United States (10), the Vitamin D Assessment (ViDA) study in New Zealand (11) and our own D-Health Trial, a placebo-controlled trial among elderly residents of Australia. The aim of the D-Health Trial is to determine whether increasing the mean 25(OH)D concentration in the general population through widespread supplementation would result in improved health outcomes. Here we report the methods and describe the characteristics of the trial participants.

METHODS

Funding, sponsor and ethical approval

The funding body is the National Health and Medical Research Council of Australia and the sponsor is the QIMR Berghofer Medical Research Institute (Brisbane, Queensland, Australia).

The protocol was approved by the Human Research Ethics Committee of the QIMR Berghofer Medical Research Institute and all participants gave written consent to participate.

Trial design

The D-Health Trial is a randomized, placebo-controlled, double-blinded superiority trial with two parallel groups. The primary endpoint is all-cause mortality. Participants were allocated in a 1:1 ratio to 60,000 IU vitamin D3 or placebo, taken orally once per month. The first participants were randomized in February 2014 and the last in May 2015.

Participants

D-Health is set in the general population of Australia, with participants recruited from all states and territories with the exception of the Northern Territory. Potential participants were randomly selected from the Australian Electoral Roll; it is compulsory for all people aged 18 years and over to enrol to vote in Australia. We also recruited volunteers who were not randomly selected by promoting the study through the media and encouraging participants to recruit their friends and family.

To be eligible, participants had to be aged between 60 and 79 years at the time that the electoral roll extracts were generated. Volunteers were accepted if they were aged up to 84; people in the 80-84 year age group were not directly invited because our pilot trial showed a very low response rate in people of this age (12). Exclusion criteria were: self-reported previous diagnosis of hypercalcemia, hyperparathyroidism, kidney stones, osteomalacia or sarcoidosis or self-reported intake of more than 500 IU vitamin D per day, which is consistent with Australian recommended daily intakes (https://www.nrv.gov.au/nutrients/vitamin-d). While it is lower than the 800 IU per day recommended for people over 70 in the United States (13), the sun exposure of the Australian population is likely to be higher than the majority of those resident in the United States. The protocol initially specified exclusion of people with osteoporosis due to concerns that they may be taking high doses of vitamin D; this exclusion was removed five months into the recruitment period to increase the recruitment rate, but high vitamin D intake for these participants remained an exclusion criterion.

Enrolment

Potential participants received an initial invitation including a short flyer explaining the study, an expression of interest (EOI) form (which asked about vitamin D intake and health conditions that would result in exclusion) and a reply-paid envelope. Those who returned the EOI form or completed it online and were eligible were then mailed a short survey (which captured information about demographic, lifestyle and health factors), a participant information sheet and two consent forms. The two consent forms sought consent to participate in the study and consent to link study data with Medicare Australia databases (see below for more information). Giving consent to linkage to Medicare data was not a requirement for participation. When the study consent form and survey were completed and returned, either on paper or online, participants were enrolled into the trial and randomized.

Randomization

Participants were randomized to active or placebo tablets within strata of age (60-64; 65-69; 70-74; 75+), sex and state or territory using computer-generated block randomization with randomly permuted block sizes. A statistician unrelated to the study generated the randomization schedule using STATA software, which was uploaded into the study database by the database developers. To ensure that allocation was concealed, the table was visible only to the database developers and not to study staff. Further, the developers were unable to modify the table. Each month the project manager ran a standard procedure that automatically allocated participants who had consented since the previous randomization.

Blinding

Participants and all study staff, including data analysts, are blind to group assignment.

Intervention

The interventions are monthly doses of 60,000 IU of cholecalciferol (vitamin D3) prepared as a gelatin capsule in a soya oil excipient or placebo (manufactured by Lipa Pharmaceuticals Pty Ltd). The placebo contains soya oil and has the same appearance as the active product. A one-year supply of blister-packed capsules is posted to participants at baseline and every 12 months thereafter, with a planned total intervention period for each participant of 5 years.

The dose was chosen based on the results of our pilot trial, which showed that the mean serum 25(OH)D in participants supplemented with 60,000 IU was 75 nmol/L (30 ng/ml) after supplementation, compared with 42 nmol/L (17 ng/ml) in the placebo group (12). Approximately half of the participants in the 60,000 IU group attained a 25(OH)D of at least 75 nmol/L and a further 40% had a level between 50 and 74 nmol/L. We also piloted 30,000 IU per month; the post-supplementation mean was 64 nmol/L (26 ng/ml) and only 24% had a 25(OH)D concentration of $\geq$ 75 nmol/L.

Adherence and contamination

All participants are asked to take their capsules on the first day of the month. To maximize adherence we send a reminder on the last day of each month by cellular telephone text message or automated landline message. We also send an email to participants who have provided an email address.

Once enrolled, we allow participants to take up to 2000 IU/day of concomitant vitamin D if requested to do so by their doctor. This limit ensures that participants in the intervention group are unlikely to exceed the tolerable upper limit of 4000 IU/day recommended by the IOM (13). While this can cause contamination, it minimises withdrawal providing more complete capture of patient-reported outcomes.

We measure adherence in two ways. Firstly, at each annual survey we ask participants to report the number of study capsules taken in the previous 12 months. Secondly, each year we are measuring 25(OH)D in a random sample of approximately 600 participants, 300 from each group. While there will be some overlap, a new sample will be selected each year. Participants are mailed a request form and asked to attend a local pathology laboratory collection centre to have a fasting blood sample collected. The 25(OH)D assay will be

performed using an LC-MS/MS assay at the Centre for Metabolomics (University of Western Australia) that is taking part in the international Vitamin D Standardisation Program and shows high accuracy and precision. DNA and remaining serum are being stored.

We ask participants to report their supplementary vitamin D intake in each annual survey. In addition, we ask participants to telephone or email us if they increase or decrease any off-trial vitamin D intake, and each change is recorded in the D-Health Trial database.

Outcomes

The primary outcome is all-cause mortality. Secondary outcomes are total cancer incidence and colorectal cancer incidence. These outcomes will be captured through linkage with the Australian National Death Index and the Australian Cancer Database. These registers provide universal coverage of the Australian population. Data for these outcomes will thus be complete for all participants except those who emigrate from Australia. Linkages are planned for 2017, 2022 and 2025 giving approximately 10 years of follow-up for all participants.

Other proposed outcomes that will be captured through self-report in annual surveys include: cardiovascular events (including high blood pressure, heart failure, arrhythmia, angina, heart attack, stroke, transient ischemic attack), depression (using the Patient Health Questionnaire 9 instrument), anxiety, upper respiratory illnesses, chronic obstructive pulmonary disease, hyper- or hypothyroidism, diabetes, pain, falls in the month prior to survey completion, fractures, arthritis, self-reported health status, number of hospitalisations, glaucoma, cataract, insomnia, sleep apnoea. To minimize missing patient-reported outcome information, we ask participants who withdraw if they would be willing to continue to complete annual surveys. We telephone non-responders on several occasions to maximise return of surveys.

Australia provides universal health cover to all citizens. The Medicare Benefits Database and the Pharmaceutical Benefits Database managed by Medicare Australia hold information about services provided and drugs dispensed, except most of those provided or dispensed in public hospitals. We will link records of individual consenting participants to these databases to capture additional outcomes including: medication use (for example: statins, antibiotics, antihypertensives, immunosuppressants), treatment of nonmelanoma skin cancer, and procedures undergone outside the public hospital system. Data will be near complete for participants who consented to linkage with Medicare Australia databases, including for withdrawn participants unless they have specifically withdrawn consent for linkage.

Stored blood samples from randomly selected participants may be used, subject to funding, to assess the effect of vitamin D supplementation on analytes such as fatty acids, cytokines, glucose and on genetic/epigenetic factors such as leukocyte telomere length and methylation.

Data management

D-Health Trial data are managed using a custom-designed MySQL database. The system has full audit capabilities.

Participants predominantly complete baseline and annual surveys on paper, although an online interface is available and a small proportion of participants complete surveys online. Survey data are entered by Datatime Services Pty Ltd using a combination of automated

capture (using Captiva EMC - Formware v5.0 with manual verification of anomalies) and manual data entry.

Statistical analyses

Analysis of the effect of treatment with vitamin D3 will be based on the intention-to-treat principle. We will use Cox proportional hazards models to assess effects of supplementation on mortality and cancer and on some other outcomes where time-to-event analyses are appropriate (e.g. first diagnosis of diabetes or high blood pressure).

There are a number of outcomes where we will have repeated measures from annual surveys or linkage with health registers, such as falls, upper respiratory tract infections, mood and antibiotic use. For these we will use mixed effects models (linear for continuous variables, negative binomial for count variables and logistic for binary variables) to account for clustering by participant.

We will conduct a number of sensitivity analyses. We will assess the effect of missing participant-reported outcome data by performing multiple imputation. The impact of non-adherence and contamination will be explored using instrumental variable and complier average causal effect analyses which preserve the randomisation (14).

We will assess whether the effect of vitamin D supplementation differs according to predicted baseline vitamin D status. We will first use samples collected from a subset of our placebo group during the trial to validate a model we derived in our earlier pilot study (15), and will then use this to predict baseline vitamin D deficiency in the full cohort. Potential differences in effect according to predicted baseline vitamin D status will then be tested by fitting an interaction between treatment allocation and predicted baseline vitamin D status.

Sample size

We based our sample size calculations on cumulative risk of death over a 10-year period. We used sex- and age-specific (by single year of age) death rates in the general Australian population to estimate the expected risk for trial participants. Figure 1 shows the detectable relative risk (80% power and significance 0.05) with different sample sizes, based on a logrank test, allowing the mortality rate for the trial participants to vary between 60% and 100% of the population mortality rate (i.e. standardised mortality ratio (SMR) of 0.6 – 1).

Monitoring and adverse event reporting

An independent data safety monitoring board (DSMB) has been established, consisting of experts in clinical trials, vitamin D, endocrinology, statistics and epidemiology. The DSMB meets biannually to review study progress in order to make recommendations about modification of the study protocol or termination of the trial. Evaluation of interim results will be underpinned by Haybittle-Peto rules (16,17) applied to mortality and cancer endpoints. The DSMB will also consider other endpoints and new scientific data that may become available during the supplementation period of the D-Health Trial.

An independent organisation employed by the QIMR Berghofer Medical Research Institute carries out biannual monitoring to assess compliance with the approved protocol.

We ask participants to contact us by telephone or email if they experience an adverse event. We record all adverse events in the D-Health database and classify their relation to the study medication as unrelated, unlikely, possible, probable, or definite. The study physician reviews all events to ensure this assignment is correct. We code events using the medical dictionary for regulatory activities (MedDRA) which enables systematic reporting to the DSMB and the sponsor. All events captured through the annual surveys (including hospitalisations and reasons for these) are also reported biannually.

RESULTS

Recruitment began in January 2014. The first participants were randomized in February 2014 and the final participants in May 2015. We invited 421207 people randomly selected from the Australian Electoral Roll to participate (Figure 2). Nine percent expressed interest in participating and, additionally, 1896 volunteers submitted an expression of interest form. Just over two-thirds of those interested were eligible and we enrolled approximately three-quarters of these. Including volunteers, 21,315 people were enrolled.

Table 1 shows the power to detect a range of hazard ratios (alpha=0.05) for total mortality, total cancer incidence and colorectal cancer incidence, assuming that the trial cohort experiences events at 0.8 of rate of the general Australian population. Assuming 10% departure from randomized treatment in both groups, the true relative risks are also given. As used here, a 10% departure corresponds to a 20% departure over the full intervention period because we assume that, on average, people become non-adherent at the midpoint.

The proportion of those invited who were enrolled varied across age, sex and state strata (Table 2). People over 75 years were the least likely to both express interest in participating and to be eligible. Thus only 3% of people this age invited were enrolled (excluding volunteers) compared with at least 6% in those younger than 70 years. Men were marginally more likely to express interest and considerably less likely to be ineligible. People from Tasmania, the most southerly state, were the most likely to be interested. Although they also had the greatest proportion of people ineligible, almost 6% of those invited were enrolled compared with less than 4% from Victoria, the state with the lowest enrolment.

Just under 8% of all participants are volunteers (N=1658, 7.7%). Approximately 10% of those younger than 70 years are volunteers compared with 3.5% for participants aged 75-79. Compared with men, a greater proportion of women are volunteers (10% vs 5%). Almost 17% of Queensland participants are volunteers, compared with between 3.5% and 7.5% in other states, presumably because the sponsor is located in Queensland.

The primary reason for ineligibility was consumption of greater than 500 IU of supplementary vitamin D per day (63%) (Table 3). Women were more likely than men to be ineligible due to pre-existing vitamin D supplementation. A past history of kidney stones was the most commonly reported pre-existing health condition (28% of those excluded due to a health condition), followed by hypercalcemia (22%) (note that these are not mutually exclusive).

The distributions of selected baseline characteristics are shown in Table 4 and all factors examined are well balanced across the two trial arms. Approximately one quarter of

participants are in each of the four five-year age categories (60-64; 65-69; 70-74; 75-84) and just over half of all participants are men. The vast majority (91%) of participants gave their ancestry as British/European. High cholesterol and high blood pressure each occurred in almost half of participants, and two-thirds had a body mass index in the overweight/obese category. Approximately 15% of participants in both groups were taking 500 IU or less of supplementary vitamin D per day.

Our cohort is somewhat healthier than the Australian population (18). D-Health participants are less likely than the Australian population to report having fair or poor health, less likely to be a current smoker and less likely to report having diabetes (Table 5). However, similar proportions of D-Health participants and Australian Health Survey respondents report a history of angina and arthritis and slightly more D-Health participants report psoriasis. The distribution of body mass index of men is very similar in the two populations and more D-Health women are obese compared with the Australian population.

DISCUSSION

The D-Health Trial is one of the largest trials of vitamin D to be conducted and has adequate power to detect small to moderate effects of oral vitamin D supplementation on overall mortality and cancer incidence. Its design enables assessment of the effect of increasing the mean serum 25(OH)D concentration in the Australian population and reducing the proportion of people who are vitamin D deficient. The results of the D-Health Trial will inform decisions about mandatory food fortification or advice regarding supplementation.

For largely pragmatic reasons, participants in the D-Health Trial are aged over 60 years and we are supplementing people for only five years. Thus we will not be able to address the issue of whether vitamin D supplementation of younger people or for a longer period of time has health benefits. However, the actions of vitamin D reported in *in vitro* and animal studies, suggest that it may act later in carcinogenesis (19) and cardiovascular disease (20) processes, consistent with our design aiming to measure health effects during and after a five-year treatment period in older age.

We are using an intermittent dosing regimen due to better compliance over daily dosing (21). In our one-year pilot study 95% of participants reported taking at least 10 of the 12 monthly tablets, a finding which underscores the success of the monthly reminder system we have implemented. Some have criticised intermittent dosing as not being sufficiently physiological (22); however, intermittent dosing is as effective at raising 25(OH)D as daily dosing (23,24). Moreover, because we are delivering vitamin D in excess of daily requirements the unused component will be stored in fat and this will even out oscillations in serum vitamin D3, which may be important. To avoid the potential adverse consequences of such oscillations Vieth recommended that dosing intervals of more than two months should be avoided but that monthly dosing would be an acceptable way to optimize compliance (25). Finally, our dose of 60,000 IU is lower than the estimated capacity of vitamin D binding protein, avoiding displacement of 1,25(OH)D and 25(OH)D in the days after supplementation (22). A meta-analysis of trials of vitamin D supplementation and mortality found that the estimates of effect did not differ according to dosing regimen (26), suggesting that this approach is unlikely to increase mortality. A recent study among people with a prior fall found that

60,000 IU of supplementary vitamin D per month increased falls compared with 24,000 IU per month (27). Further studies are needed to determine if this occurs in other populations and this will be monitored in the D-Health Trial.

The presence of suboptimal 25(OH)D at baseline was not an inclusion criterion, contrary to some recommendations (28). The D-Health Trial was not established to determine whether correction of vitamin D deficiency leads to improved health. Rather the aim of the D-Health Trial is to determine whether increasing the mean 25(OH)D concentration in the population would result in better population health outcomes. A null finding could not be interpreted to indicate that identifying and treating vitamin D deficiency would have no benefit. It would, however, suggest that interventions at a population level, such as increased mandatory food fortification, would not be would not achieve improvements in the health outcomes measured in the D-Health Trial. Further, any evidence of harm would highlight the need for supplements / food fortification to be used with caution.

In keeping with the pragmatic trial design, we did not collect baseline blood samples from participants. With our sample size the power to detect effects in subgroups will be limited. In light of this we could not justify the extra ~$3M AUD that collecting, storing and analysing samples would have cost. Indeed, such a requirement would have prevented the trial from occurring. While we will not be able to analyse data according to baseline 25(OH)D concentration, we used data from our pilot study data to develop a model to predict vitamin D deficiency (15). We will validate this model in the samples from the placebo group that we collect during the trial and this model will then be applied to the entire population to enable exploratory subgroup analyses. The characteristics of participants in the two groups were very similar at baseline so the 25(OH)D concentration in the placebo group participants will provide a measure of the distribution in the population prior to the intervention. While the first blood samples were collected one year after recruitment any temporal change is likely to have been small.

We recruited only about 5% of the people we approached which raises the question of whether our results will be generalizable to the broader population. Our comparison with the Australian Health Survey data suggests that on a number of parameters that may be related to vitamin D status our cohort is very similar to the source population. If the proportion of people who are vitamin D deficient in our population is lower than expected we may underestimate the effect of supplementation. Our proposed subgroup analyses will help to elucidate this issue.

The D-Health Trial has a number of strengths. The large sample size gives sufficient power to analyse mortality and cancer, along with many other health outcomes. We are using a vitamin D dose that we have shown results in an increase in the mean 25(OH)D concentration of 36 nmol/L (15 ng/ml) compared with an unsupplemented placebo group (12). Moreover, the trial's access to linked data through Australia's system of universal health insurance (Medicare and the Pharmaceutical Benefits Scheme) ensures that other endpoints such as nonmelanoma skin cancer and antibiotic use can be assessed.

We are aware of only two other trials of high doses of vitamin D in the general population with greater than 5,000 participants (10,11). The interventions in the VITAL and ViDA Trials

are 2,000 IU / day and 100,000 IU / month respectively but both include similar age groups to D-Health. Other general population trials with over 1,000 participants include the Finnish Vitamin D Trial (FIND) (ClinicalTrials.gov identifier NCT01463813) and the United Kingdom Vitamin D and Longevity (VIDAL) Trial (ISRCTN 46328341) (currently in the pilot phase recruiting 1,600 participants but will potentially be much larger). Characteristics of these trials have recently been summarized (29). Pooling of the data from these general population trials will enable analysis of outcomes such as specific cancers for which each individual trial has inadequate power, along with a variety of subgroup analyses which will be pre-specified prior to pooling.

In conclusion, there has been an exponential expansion in the vitamin D literature and there is now considerable data from observational studies to support an association between circulating 25(OH)D and many disease conditions. However, in these studies it is not possible to separate vitamin D derived from supplements versus sunlight so it is not clear that supplementation would have any benefit. Furthermore, due to the problems of confounding and reverse causation, data from observational studies should not be used to support population-wide interventions designed to be used in healthy people for disease prevention. Randomized trials are required to inform decisions about increased mandatory food fortification and/or recommendations to routinely take a supplement, and the D-Health Trial has been established to meet this need.

Acknowledgements

We would like to acknowledge the D-Health Trial staff who do an extraordinary job: Jill Wood, Kate Bailey, Melissa Brown, Kaitlyn Ford, Linda Rosengren, Kym Watson. We also extend our thanks to the D-Health Trial participants who have committed to this research.

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Figure Legends

Figure 1: Sample size needed to identify different relative risks under a range of different standardised mortality ratio assumptions (SMR for the trial population compared with the general population)

Figure 2: Recruitment flow chart. *Expression of interest

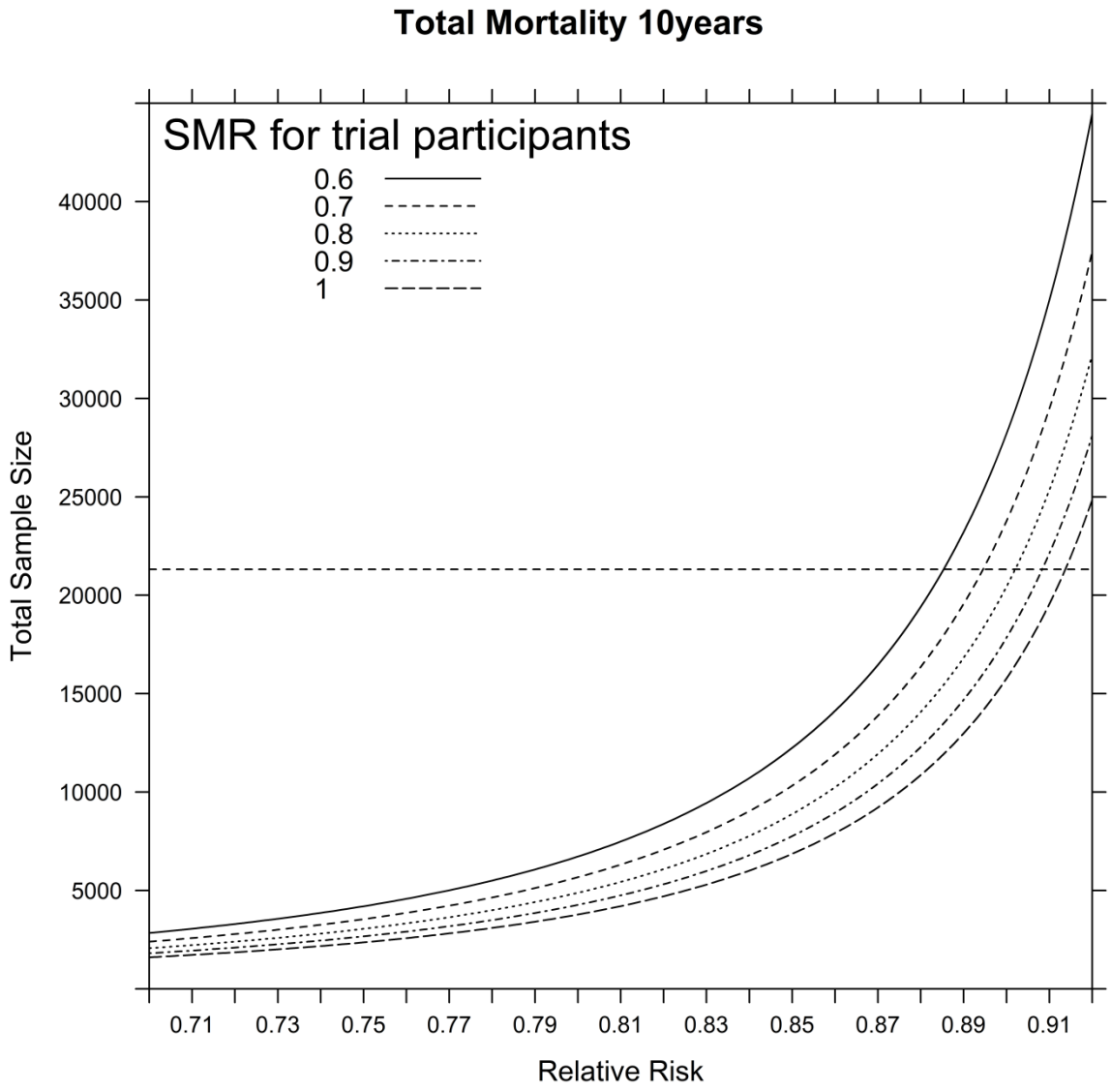

Figure 1

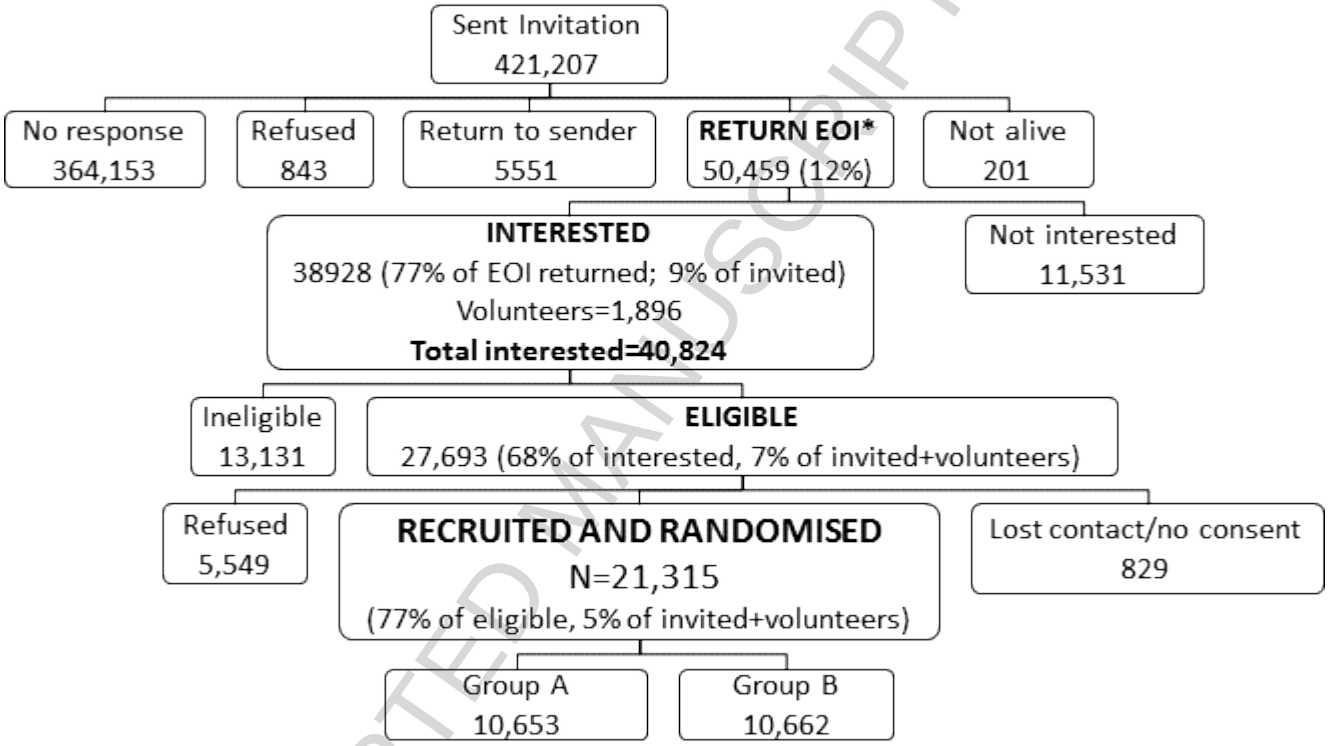

Figure 2

Table 1: Power to detect a range of hazard ratios (alpha=0.05) for total mortality, total cancer and colorectal cancer incidence, assuming the trial population experiences 0.8 of the event rate of the general population and that there is 10% departure from randomized treatment.

HAZARD RATIO		POWER		
Observed	**True[1]**	**Total Mortality**	**Total Cancer**	**Colorectal Cancer**
0.91	0.88	0.80	0.78	0.31
0.90	0.87	0.87	0.86	0.37
0.85	0.81	>95	>95	0.69
0.80	0.75	>95	>95	0.90
0.75	0.69	>95	>95	>95
0.70	0.63	>95	>95	>95
0.65	0.58	>95	>95	>95
0.60	0.52	>95	>95	>95

[1] Represents the hazard ratio under conditions where there was no departure from randomized treatment.

Table 2: Recruitment statistics within strata of age, sex and state

	Invited	Interested (N, % of invited)	Eligible (N, % of interested)	Enrolled (N, % of invited)	Enrolled (inc. volunteers)
Age Group					
60-64	75117	8222 (11.0)	5977 (72.7)	4737 (6.3)	5255
65-69	86423	9703 (11.2)	6680 (68.8)	5217 (6.0)	5835
70-74	117404	11112 (9.5)	7179 (64.6)	5453 (4.6)	5797
75+	142263	9891 (7.0)	5961 (60.3)	4250 (3.0)	4428
Sex					
Female	216822	19782 (9.1)	11806 (59.7)	8750 (4.0)	9780
Male	204386	19146 (9.4)	13991 (73.1)	10907 (5.3)	11535
State					
New South Wales	103953	8107 (7.8)	5381 (66.4)	4044 (3.9)	4342
Queensland	62511	6462 (10.3)	4555 (70.5)	3494 (5.6)	4207
South Australia	60849	5815 (9.6)	3894 (67.0)	3016 (5.0)	3121
Tasmania	40992	5049 (12.3)	3111 (61.6)	2419 (5.9)	2515
Victoria	89382	7240 (8.1)	4486 (62.0)	3428 (3.8)	3702
Western Australia	6249	6255 (9.9)	4370 (69.9)	3256 (5.1)	3428
Total	421207	38928 (9.2)	25797 (66.3)	19657 (4.7)	21315

Table 3: Reasons for lack of eligibility within strata of age, sex and state

	N (Row %)				
	Health condition	Taking vitamin D>500 IU	Health condition and vitamin D>500 IU[1]	Osteoporosis[2]	Other[3]
Age Group					
60-64	543 (24.2)	1427 (63.6)	178 (7.9)	81 (3.6)	16 (0.7)
65-69	694 (23.0)	1928 (63.8)	256 (8.5)	135 (4.5)	10 (0.3)
70-74	916 (23.3)	2474 (62.9)	320 (8.1)	196 (5.0)	27 (0.7)
75-79	829 (21.1)	2445 (62.2)	338 (8.6)	249 (6.3)	69 (1.8)
Sex					
Female	1125 (14.1)	5565 (69.8)	665 (8.3)	566 (7.1)	55 (0.7)
Male	1857 (36.0)	2709 (52.6)	427 (8.3)	95 (1.8)	67 (1.3)
State					
New South Wales	681 (25.0)	1645 (60.3)	243 (8.9)	121 (4.4)	36 (1.3)
Queensland	568 (29.8)	1035 (54.3)	156 (8.2)	133 (7.0)	15 (0.8)
South Australia	435 (22.6)	1199 (62.4)	174 (9.1)	102 (5.3)	11 (0.6)
Tasmania	343 (17.7)	1346 (69.5)	142 (7.3)	95 (4.9)	12 (0.6)
Victoria	496 (18.0)	1892 (68.7)	244 (8.9)	92 (3.3)	30 (1.1)
Western Australia	459 (24.4)	1157 (61.4)	133 (7.1)	118 (6.3)	18 (1.0)
Total	2982 (22.7)	8274 (63.0)	1092 (8.3)	661 (5.0)	122 (0.9)

[1] Conditions include kidney stones, high calcium, hyperparathyroidism, osteomalacia, sarcoidosis; [2]Excluded prior to protocol change; [3]Non-English speaking, cognitively impaired, out of age range

Table 4: Distribution of selected baseline characteristics in the two study arms

		N (%)	
Variable	**Categories**	**Arm A**	**Arm B**
Age	60-64	2627 (24.7)	2628 (24.6)
	65-69	2915 (27.4)	2920 (27.4)
	70-74	2894 (27.2)	2903 (27.2)
	75-84	2217 (20.8)	2211 (20.7)
Sex	Male	5765 (54.1)	5770 (54.1)
	Female	4888 (45.9)	4892 (45.9)
State	New South Wales	2170 (20.4)	2172 (20.4)
	Queensland	2102 (19.7)	2105 (19.7)
	South Australia	1558 (14.6)	1563 (14.7)
	Tasmania	1258 (11.8)	1257 (11.8)
	Victoria	1850 (17.4)	1852 (17.4)
	Western Australia	1715 (16.1)	1713 (16.1)
Ancestry	British/European	9698 (92.9)	9716 (93.0)
	Australian/New Zealand	362 (3.5)	365 (3.5)
	Asian	127 (1.2)	114 (1.1)
	Indigenous	71 (0.7)	80 (0.8)
	Mixed / Other	183 (1.8)	176 (1.7)
	Missing	*212*	*211*
Qualifications	None	1046 (9.9)	1098 (10.4)
	Intermediate school certificate	1756 (16.7)	1798 (17.1)
	Higher school certificate	1530 (14.6)	1435 (13.6)
	Trade / apprenticeship	1325 (12.6)	1226 (11.6)
	Certificate Diploma	2251 (21.4)	2227 (21.1)
	University degree	2607 (24.8)	2748 (26.1)
	Missing	*138*	*130*
Smoking	Never	5761 (54.6)	5816 (55.0)
	Past	4305 (40.8)	4346 (41.1)
	Current	485 (4.6)	411 (3.9)
	Missing	*102*	*89*
Skin tanning	No tan	794 (7.5)	773 (7.3)
	Tan lightly	2661 (25.2)	2703 (25.6)
	Tan moderately	4981 (47.2)	4900 (46.5)
	Tan deeply	2107 (20.0)	2164 (20.5)
	Missing	*110*	*122*
High blood pressure	Yes	5014 (47.5)	5150 (48.8)
	No	5541 (52.5)	5405 (51.2)
	Missing	*98*	*107*
Diabetes	Yes	1218 (11.5)	1252 (11.8)
	No	9343 (88.5)	9312 (88.2)
	Missing	*92*	*98*
High cholesterol	Yes	4770 (45.3)	4743 (45.0)
	No	5766 (54.7)	5796 (55.0)
	Missing	*117*	*123*
Body mass index	Underweight / normal weight	3167 (30.1)	3257 (30.9)
	Overweight / obese	7365 (69.9)	7272 (69.1)
	Missing	*121*	*133*
Self-rated overall health	Excellent	1311 (12.5)	1261 (12.0)
	Very good	4482 (42.7)	4592 (43.8)
	Good	3782 (36.1)	3737 (35.7)
	Fair	836 (8.0)	805 (7.7)

Variable	Categories	N (%) Arm A	Arm B
	Poor	79 (0.8)	81 (0.8)
	Missing	*163*	*186*
Taking vit D supplement[1]	Yes	9061 (85.1)	9101 (85.4)
	No	1590 (14.9)	1561 (14.6)

Table 5: Comparison between selected D-Health baseline characteristics (for 65-74 year olds) and data from the 2011 Australian Health Survey (AHS) for 65-74 year olds.

	%					
	Men		Women		Persons	
	D-Health	AHS	D-Health	AHS	D-Health	AHS
Diabetes	14.6	18.2	8.7	15.1	11.9	16.6
Angina[1]					5.0	4.6
Psoriasis[1]					5.3	3.6
Arthritis[1]					46.4	45.2
Self-rated health						
Excellent / very good	53.9	41.4	59.7	43.9	56.6	42.7
Good	37.1	34.4	33.1	31.5	35.2	32.9
Fair / Poor	9.0	24.2	7.2	24.5	8.2	24.4
Smoking						
Never	46.9	35.1	62.4	58.8	54.2	47.2
Past	48.7	53.6	34.1	33.8	41.8	43.5
Current	4.4	11.3	3.6	7.4	4.0	9.3
Body mass index[2]						
Under/ normal weight	25.0	26.7	34.8	40.5	29.6	33.5
Overweight	48.1	47.1	35.6	34.6	42.3	41.0
Obese	26.9	26.2	29.6	24.9	28.1	25.5

[1] AHS data not available by age and sex within specific age categories

[2] AHS data from the 2007/2008 survey