Recruitment and Results of a Pilot Trial of Vitamin D Supplementation in the General Population of Australia

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Context: The benefits of high serum levels of 25-hydroxyvitamin D [25(OH)D] are unclear. Trials are needed to establish an appropriate evidence base.

Objective: We plan to conduct a large-scale trial of vitamin D supplementation for the reduction of cancer incidence and overall mortality and report here the methods and results of a pilot trial established to inform its design.

Design: Pilot D-Health was a randomized trial carried out in a general community setting with 12 months intervention and follow-up.

Participants: Participants were 60- to 84-yr-old residents of one of the four eastern Australian states who did not have any vitamin D-related disorders and who were not taking more than 400 IU supplementary vitamin D per day. A total of 644 participants were randomized, and 615 completed the study (two persons withdrew because of nonserious adverse events).

Interventions: The interventions were monthly doses of placebo or 30,000 or 60,000 IU vitamin D_3.

Main Outcomes: The main outcomes were the recruitment rate and changes in serum 25(OH)D.

Results: Ten percent of those approached were recruited. At baseline, the mean 25(OH)D was 42 nmol/liter in all three study arms. The mean change in 25(OH)D in the placebo group was 0.12 nmol/liter, compared with changes of 22 and 36 nmol/liter in the 30,000- and 60,000-IU groups, respectively.

Conclusions: The D-Health pilot has shown that a large trial is feasible in Australia and that a dose of 2000 IU/d will be needed to ensure that a large proportion of the population reaches the target serum 25(OH)D level. (*J Clin Endocrinol Metab* 97: 4473–4480, 2012)

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Abbreviation: 25(OH)D, 25-Hydroxyvitamin D.

It has been known for almost a century that vitamin D is essential for bone health. More recently, it has been recognized that vitamin D also affects the growth, differentiation, and apoptosis of cells in multiple organs (1, 2), and epidemiological data are accumulating to suggest that lower levels of vitamin D, estimated by measuring circulating levels of 25-hydroxyvitamin D [25(OH)D], have a number of negative health effects (3–6). However, some, although not all (7), well-conducted cohort studies have shown that people in the highest 25(OH)D category have a substantially increased risk of pancreatic cancer (8, 9), and older women given high annual doses of vitamin D had an increased risk of falls (10). Thus, the full range of potential risks and benefits of high vitamin D levels needs to be understood before we can establish an optimal vitamin D level and recommend supplementation for those below such a level in the general population.

Inferring causality from observational studies is problematic due to the inability to adequately control for confounding, which is a particular issue for studies of vitamin D. Serum 25(OH)D levels are associated with many factors that are risk factors for cancer and death (11, 12), and it is therefore possible that vitamin D deficiency is merely an indicator of poor future health rather than a causal factor for disease. Before a health intervention that is amenable to assessment by randomized trial is recommended to a large proportion of the general population, it is advisable to establish the evidence through conduct of such trials, particularly given the conspicuous failures of other single-nutrient interventions.

Trial evidence for a beneficial effect of vitamin D supplementation on chronic disease is sparse. A meta-analysis of trials, mostly conducted in elderly and/or hospitalized people and designed primarily to examine bone health, suggested a 6% (95% confidence interval 2–9%) reduction in all-cause mortality for those randomized to vitamin D supplementation (13), but the individual trials used highly variable vitamin D doses, different dosing regimens, and different populations. Despite the ongoing debate about optimal vitamin D levels and the widespread recognition of the need for large-scale trials, there has been a marked and rapid increase in vitamin D testing in Australia. The number of vitamin D tests ordered by general practitioners has increased by 10-fold from 22,670 tests in 2000 to 2.2 million tests in 2010, costing Medicare Australia approximately $96 million annually (14). Given the lack of an evidence base to support such use of healthcare funds, and the current lack of knowledge about the risks and benefits of vitamin D supplementation, it is imperative that large-scale trials are conducted as soon as possible.

Large trials require a substantial investment of time and money, so it is essential to test the feasibility of conducting such a trial before beginning. We have therefore conducted a pilot trial in the setting of the Australian population to inform the optimal design of a fully powered trial that would have common cancers and total mortality as the primary outcomes. The primary aims of the pilot trial were to estimate the participation fraction and its determinants (important factors in determining feasibility and generalizability), cost, and compliance with the intervention. We also aimed to determine whether 30,000 or 60,000 IU of cholecalciferol per month would be required to ensure that most people in the study population had a serum level of 25(OH)D of at least 75 nmol/liter, which is the level that some (15), but not all (16), have suggested is necessary to optimize health. We report here the trial methods, recruitment statistics, and results in terms of serum 25(OH)D measured at baseline and after 12 months of intervention.

Subjects and Methods

The D-Health pilot trial is a population-based, randomized, placebo-controlled double-blind chemoprevention trial in which participants were randomized to receive monthly doses of placebo or 30,000 or 60,000 IU vitamin D_3 (cholecalciferol) for 12 months. The trial was conducted under the Australian Therapeutic Goods Administration Clinical Trial Notification scheme (Trial 2010/0423) with ethical approval granted by the Human Research Ethics Committee at the Queensland Institute of Medical Research.

Participant selection and exclusion criteria

Potentially eligible participants were aged between 60 and 84 yr and resident in one of the four eastern states of Australia (from north to south, Queensland, New South Wales, Victoria, and Tasmania; latitude 11° S to 42° S). We aimed to recruit an equal number of people from the capital cities of each state and from regional centers, ensuring that all participants lived within 20 km of a pathology collection center where blood could be collected. We used the Australian Electoral Roll as the sampling frame. Electoral registration is compulsory for Australian citizens aged 18 yr and over, and the register is estimated to be 91% complete. Selection and randomization were stratified by state, sex, age in 5-yr age bands, and capital city or regional residence.

We did not include anybody who was taking more than 400 IU vitamin D per day or who had a history of any of the following conditions: kidney stones, hyperparathyroidism, osteomalacia, osteoporosis, or sarcoidosis. In addition, we excluded anybody who did not speak English sufficiently well to comprehend the patient information and consent forms or who did not have a telephone number on which we could contact them if necessary during the trial.

Sample size

The primary aim of the trial was to estimate participation fractions, but the sample size required to achieve our secondary aim of assessing change in serum concentration of 25(OH)D was substantially larger than that required to estimate the participa-

tion fraction precisely. Thus, our secondary aim formed the basis for our sample size calculations. We aimed to recruit at least 560 participants. Allowing for a dropout rate of approximately 20%, this would result in 450 participants completing the 12-month intervention. This would give over 90% power to detect a 10% increase in the proportion of people with serum levels of 25(OH)D greater than 75 nmol/liter in either of the supplemented groups, assuming a two-sided α-level of 0.05 and baseline proportion of 27% with 25(OH)D greater than 75 nmol/liter. The recruitment invitations were sent in weekly waves, with the number of people approached in later waves being based on the recruitment rate in the earlier waves. Due to a higher response in later waves, we enrolled a greater number of people than planned.

Subject recruitment and randomization

We sent an invitation to selected voters, including a brief information brochure about the study, an expression-of-interest form, and a reply-paid envelope. The expression-of-interest form included a series of questions about supplementary vitamin D intake and medical conditions that would result in exclusion from the study. Respondents were given the option of completing the form online. Half of the selected voters were randomly assigned within strata to receive a second letter if we received no response either in hard copy or electronically within 2 wk of posting the initial invitation.

After receiving an expression-of-interest form and determining eligibility, we sent eligible participants a package containing a comprehensive information booklet, a consent form, a four-page questionnaire, and a blood collection form that included a list of the locations of pathology collection centers of companies with which we had an agreement. Blood was drawn by phlebotomists at the collection centers and sent by courier to a central laboratory in Brisbane, Queensland.

Upon receipt of the consent form, the questionnaire, and the blood, we randomized patients to one of the three trial arms using a telephone randomization service provided by the National Health and Medical Research Council Clinical Trials Centre at the University of Sydney. Participants were randomized in a 1:1:1 ratio using computer-generated random permuted blocks to ensure even randomization within strata. The first participant was randomized on October 12, 2010, and the last on March 15, 2011.

The intervention

The active medication and the placebo were produced as identical gelcaps by Sanofi-Aventis Healthcare (Virginia, Queensland, Australia) and packaged into bottles of six. We posted one bottle at baseline and a second after 6 months. Participants were asked to take the tablet on the first day of each month, and to maximize compliance, we sent participants a text message, e-mail, or postcard reminder to take each tablet.

Measurement of 25(OH)D

Nonfasting blood samples were collected at study entry and within 2 wk of the last tablet being taken. They were transported to the Queensland University of Technology (Brisbane, Australia) where serum was stored at −80 C. Serum concentration of 25(OH)D was measured as a single batch using a commercial chemiluminescent immunoassay [LIAISON 25(OH)D vitamin D TOTAL assay; DiaSorin, Inc., Stillwater, MN). This assay measures both 25(OH)D_2 (ergocalciferol) and 25(OH)D_3 (cholecalciferol). Intraassay variability was 3–6% for serum 25(OH)D. Corresponding values for interassay variability were 6–9%. The laboratory

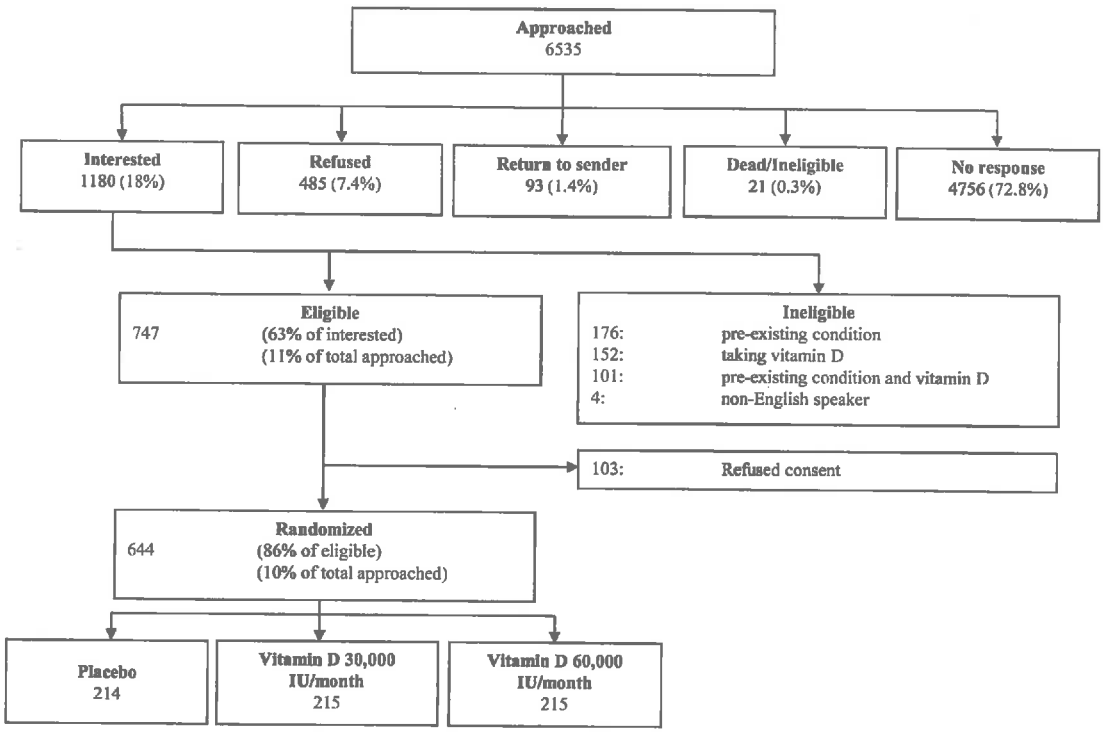

FIG. 1. Recruitment flow chart.

undertaking the testing is a participant in the Vitamin D External Quality Assessment Scheme (DEQAS).

Statistical analysis

The response fractions according to sex, age, and state or region of residence were summarized using simple descriptive statistics. We used Pearson's χ^2 statistics to assess differences in the response fractions between subgroups. Adjusted predicted probabilities of responding according to the selection strata and whether or not participants were randomized to receive a second letter were estimated from a logistic regression model that included all of these factors as predictors. We used Student's paired *t* test to examine the difference in mean serum 25(OH)D before and after supplementation. Differences in the mean change in serum 25(OH)D between the three study arms were assessed using independent *t* tests. All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Recruitment of participants

We approached 6535 people. We received no response from approximately 75% of these and 7% of people declined to participate (Fig. 1). Eighteen percent of participants (n = 1180) returned a completed expression-of-interest form; only 19 participants used the online facility. Of those interested, 433 (37%) were ineligible. After receiving additional information about the study, 103 eligible people chose not to participate. We finally randomized 644 participants (86% of those who initially responded and were deemed eligible and 10% of all those approached).

Of those deemed ineligible, 64% had a preexisting condition that precluded participation and 58% were taking a vitamin D supplement. Approximately one quarter had both a preexisting condition and were taking supplements (Fig. 1).

A similar proportion of men and women expressed interest in taking part in D-Health (19 and 17%, respectively), but women were much more likely than men to be ineligible (44% compared with 28% of those interested, $P < 0.001$) (Table 1). Overall, 21% of those who expressed an interest in the study were already taking vitamin D, and this proportion was substantially higher for women (28%) than men (13%). The adjusted predicted probability of men taking part was slightly higher than for women (11 *vs.* 8%) (Fig. 2).

People aged 65–69 yr were most likely to express interest in participating, and approximately 70% of those interested were eligible (Table 1). Almost half of those over 75 who were interested in taking part were ineligible. The overall effect was that the probability of people taking part in D-Health declined considerably with age, from an age of around 70 (Fig. 2).

Voters from Queensland and Tasmania (the most northerly and southerly states) were more likely to respond than those from New South Wales or Victoria, but there were no clear differences in the proportions of those interested who

TABLE 1. Recruitment statistics according to selection variables

	Approached	Interested (% of those approached)	*P* value	Eligible (% of those interested)	*P* value	Randomized (% of those eligible)	*P* value	Randomized (% of those approached)	*P* value
Total	6535	1180 (18)		747 (63)		644 (86)		644 (10)	
Sex			0.145		<0.001		0.520		<0.001
Male	2899	546 (19)		393 (72)		343 (87)		343 (12)	
Female	3636	634 (17)		354 (56)		301 (85)		301 (8)	
Age group (yr)			<0.001		<0.001		0.242		<0.001
60–64	1110	216 (20)		165 (76)		148 (90)		148 (13)	
65–69	1065	245 (23)		172 (70)		148 (86)		148 (14)	
70–74	1245	247 (20)		156 (63)		135 (87)		135 (11)	
75–79	1504	261 (17)		144 (55)		121 (84)		121 (8)	
80–84	1611	211 (13)		110 (52)		92 (84)		92 (6)	
State			<0.001		0.318		0.322		<0.001
Queensland	1434	285 (20)		190 (67)		163 (86)		163 (11)	
New South Wales	1841	284 (15)		181 (64)		149 (82)		149 (8)	
Victoria	1776	265 (15)		167 (63)		145 (87)		145 (8)	
Tasmania	1484	346 (23)		209 (60)		187 (90)		187 (13)	
Region			0.069		0.112		0.348		0.010
Metro	3330	573 (17)		349 (61)		297 (85)		297 (9)	
Regional	3205	607 (19)		398 (66)		347 (87)		347 (11)	
Randomized to second letter			<0.000		0.122		0.487		<0.001
Yes	3286	670 (20)		443 (66)		373 (84)		373 (11)	
No	3249	510 (16)		315 (62)		271 (86)		271 (8)	

Values are n (percent).

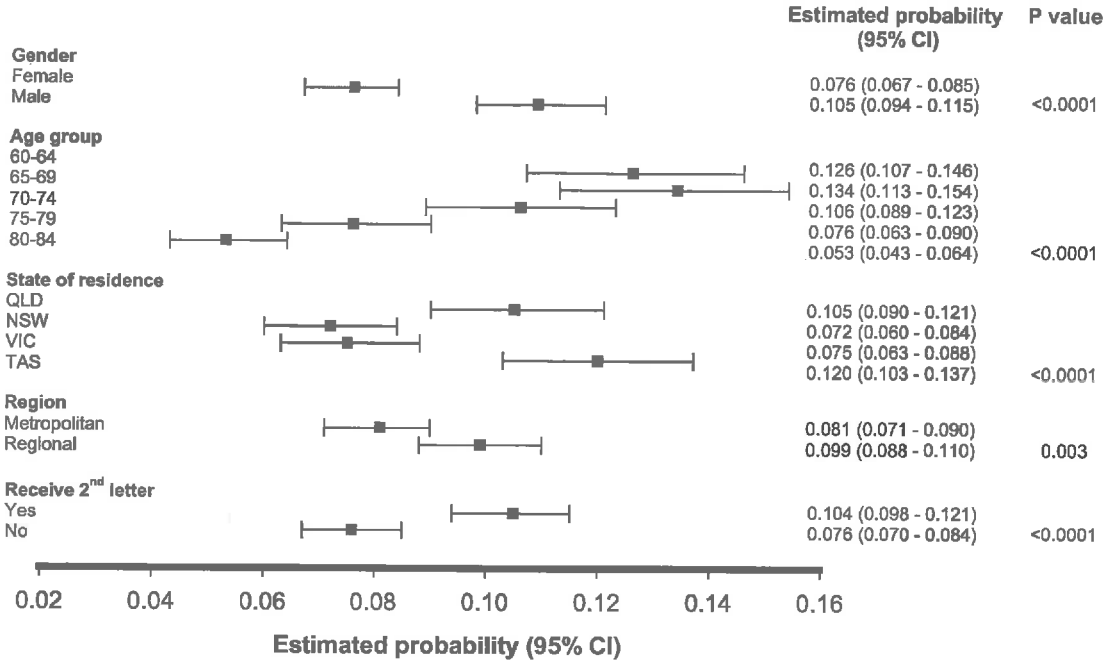

FIG. 2. Adjusted estimated probability of people being randomized to receive capsules *vs.* those invited stratified by gender, age group, state, residential region, and receiving second invitation letter. CI, Confidence interval.

were eligible. We randomized over 11% of Queenslanders and Tasmanians approached, but only 8% of those from New South Wales and Victoria. Slightly higher proportions of people living in regional than in metropolitan areas were both interested in participating and eligible, resulting in a higher final recruitment rate from regional areas (11% compared with 9%, $P = 0.01$) (Table 1), although after adjustment for age, sex, and state, the difference in the predicted probabilities was smaller (Fig. 2).

People randomized to receive a second letter were more likely to express interest in participation than those who were not randomized to receive a second letter and were ultimately more likely to participate in the trial (Table 1 and Fig. 2), but the difference was small.

TABLE 2. Concentration of 25(OH)D at baseline and after intervention

	25(OH)D (nmol/liter), mean (SD)		Mean change (95% CI)	Mean relative change (95% CI)[a]
	Baseline	After intervention		
Treatment group				
Placebo	41.9 (13.4)	41.9 (14.5)	−0.12 (−1.54–1.31)	1.38 (−1.99–4.74)
30,000 IU	41.6 (12.9)	63.9 (16.8)	22.3 (20.0–24.6)	65.2 (56.8–73.5)
60,000 IU	41.7 (14.3)	77.9 (19.7)	36.1 (33.3–38.9)	107.5 (94.7–120.3)
State				
Queensland				
Placebo	46.4 (14.9)	47.3 (16.9)	0.90 (−2.04–3.83)	2.32 (−3.72–8.36)
30,000 IU	45.7 (11.0)	67.1 (17.3)	21.6 (16.7–26.6)	54.5 (40.2–68.8)
60,000 IU	44.9 (16.1)	78.7 (23.8)	33.4 (27.2–39.5)	91.3 (66.4–116.1)
New South Wales				
Placebo	42.3 (11.8)	42.9 (12.1)	0.32 (−2.18–2.82)	2.50 (−3.85–8.85)
30,000 IU	44.7 (12.0)	63.4 (18.8)	19.0 (13.7–24.2)	48.5 (34.2–62.8)
60,000 IU	44.7 (14.7)	78.6 (15.9)	34.0 (29.4–38.5)	94.0 (72.3–115.6)
Victoria				
Placebo	40.3 (13.2)	38.4 (12.9)	−2.05 (−5.60–1.51)	−1.10 (−8.81–6.62)
30,000 IU	38.5 (10.8)	60.8 (16.6)	21.9 (16.8–27.0)	65.2 (49.4–81.1)
60,000 IU	41.3 (12.9)	73.5 (18.7)	32.0 (25.7–38.4)	96.4 (70.4–122.5)
Tasmania				
Placebo	39.0 (12.5)	39.1 (14.2)	0.12 (−2.52–2.76)	1.56 (−5.50–8.63)
30,000 IU	38.0 (15.1)	63.9 (14.4)	26.0 (22.4–29.6)	89.2 (69.2–109.1)
60,000 IU	36.6 (11.8)	80.0 (19.3)	43.2 (38.1–48.4)	141.0 (113.2–168.8)

CI, Confidence interval.

[a] Calculated as the difference (after intervention − baseline) divided by the baseline value.

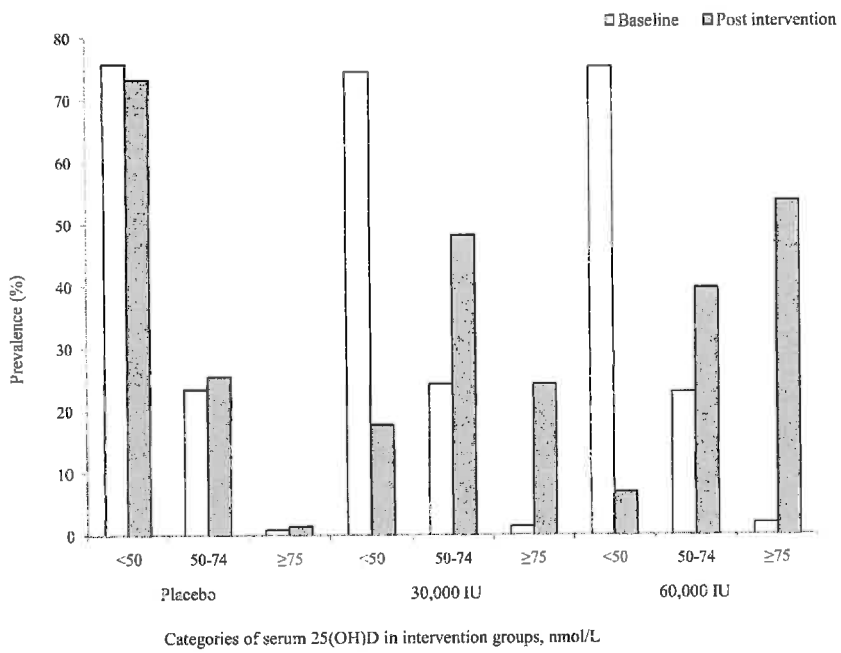

FIG. 3. Proportion of participants in different 25(OH)D categories at baseline and after intervention in different treatment groups.

Follow-up and serum 25(OH)D results

Six hundred fifteen people (95%) completed the study and provided a post-intervention blood sample. Ninety-six percent of participants reported taking at least 10 of the 12 study tablets. Almost 82% of participants said they would have been happy to continue for another 5 yr (the minimum intervention period that would be required in a fully powered trial), despite having been informed at the outset that they would be enrolled for 1 yr only. Those over 80 yr old were less likely to say they would continue than younger participants (70% of people over 80 said they would continue compared with 84% of those under 80, $P = 0.0002$).

At baseline, the mean serum 25(OH)D was 42 nmol/liter in all three study arms. Approximately 75% of participants had a concentration of less than 50 nmol/liter, and less than 2% of participants had a level of over 75 nmol/liter (Table 2 and Fig. 3). After 12 months supplementation, there was essentially no change in the placebo group but an average increase of 22 nmol/liter in those randomized to 30,000 IU vitamin D (comparison with placebo, $P < 0.0001$). Those in the 60,000-IU supplementation group had an average increase of 36 nmol/liter, which was significantly greater than in those randomized to the lower dose ($P = 0.0067$). In the 30,000-IU group, only 18% of people had a level of less than 50 nmol/liter after supplementation and 24% had reached a level of over 75 nmol/liter (Fig. 2). In the 60,000-IU group, over half of the participants had reached a level of 75 nmol/liter. Only 12% of this group had a level of over 100 nmol/liter, and none of these experienced an adverse event or hypercalcemia. Supplementation of people living in Tasmania, where the starting level of serum 25(OH)D was lowest, resulted in a higher mean change in serum 25(OH)D than those living in the mainland states, although there was not a sharp statistical separation (Table 2).

Discussion

There is increasing evidence for the health benefits of vitamin D, and some proponents now advocate supplementation to reduce rates of chronic disease. However, there are also reports suggesting that high vitamin D levels may increase the risks of some fatal cancers and of falls in older women. Thus, it is imperative we understand the full range of health consequences associated with different levels of vitamin D. Recent reports from the International Agency for Research on Cancer and the Institute of Medicine have emphasized the need for large-scale trials of vitamin D with mortality and chronic disease as endpoints to guide public health recommendations (17, 18). Pilot D-Health was designed to test the feasibility of such a trial in Australia.

Recruitment of people into population-based trials is challenging. The proportion of people expressing interest in D-Health participation was higher than that reported in previous trials conducted in general populations (19–21). Despite the positive response, many people were either taking vitamin D supplements or had a preexisting condition that precluded them from participating. The proportion of participants with an insufficient vitamin D level was considerably higher than that reported by the largest population-based study conducted in Australia, where the proportion insufficient in older adults ranged from 22–57%, depending on the age and sex group (22). This may be due to laboratory differences in measurement of 25(OH)D but could also be due to selection bias, suggesting that we should be cautious about drawing inferences from this study about the vitamin D intake or status of the general population. However, there is no reason to think that the biological effect of vitamin D supplementation would differ between respondents and nonrespondents, allowing for baseline serum 25(OH)D levels. Nevertheless, optimizing the participation proportion in a large-scale trial would be important for practical reasons.

Given the rapidly increasing rates of vitamin D testing in the general population, it is likely that the proportion of Australians taking vitamin D supplements will have increased since D-Health was launched. There was a 10-fold increase in vitamin D testing over the preceding decade, presumably followed by increased supplementation (14). The prevalence of testing and supplementation will make conducting a large-scale trial in Australia even more challenging. General population screening for vitamin D deficiency or insufficiency is not well supported by current evidence, and further education of the medical workforce may be required (23). However, even if the frequency of testing is reduced, the media coverage of the vitamin D issue and the launch of several high-dose vitamin D supplements, supported by extensive advertising campaigns, may further increase the proportion of the population who would be ineligible to participate in a trial.

To ensure a sufficient number of health events to enable a robust statistical analysis, and because vitamin D may play a role in survival as well as etiology of chronic disease, it is pragmatic to conduct a trial among older members of the population. However, the recruitment and follow-up in the pilot study indicates that a large-scale trial should be restricted to people less than 80 yr old. Approximately 34% of the Australian population lives outside the capital cities (24). D-Health has shown that recruitment of residents of these regions was marginally more successful than in metropolitan areas. If vitamin D supplementation continues to be lower in regional areas, targeting a greater number of people from this population may improve the randomization rate in a future trial, at the potential cost of some loss of generalizability.

The randomization rate was higher in those who were randomized to receive a second letter. However, the small difference suggests that a protocol requiring sending a second letter may not be cost-effective. If the aim of a large-scale trial was to randomize 20,000 participants, using a single-letter protocol, we would need to approach approximately 263,000 people based on the predicted randomization rate of 7.6%. If we used a two-letter protocol, we would need to approach approximately 192,000 people. However, 80% of these would be sent a second letter. Hence, this protocol would result in mailing a total of 346,000 letters at a cost of almost $50,000 more than the single-letter protocol. Other measures to improve response rate, such as an intensive media campaign, recruiting through general practitioners, supplementing the population with volunteers, and calling for enlisted participants to encourage friends and family to join are all measures that could be considered in a large-scale trial, although previous studies have found direct mail to be the most effective approach (19, 20).

We tested two different doses of cholecalciferol. Although the lower dose showed a substantial increase in mean serum 25(OH)D, only 24% of participants had a post-supplementation level of over 75 nmol/liter, the level proposed by some to be optimal for human health. In comparison, approximately half of those randomized to the higher dose achieved this level. Thus, in a large-scale trial, this higher dose of 60,000 IU should be considered to be a minimum. Even if participants in the placebo group were allowed to take a higher dose than the 400 IU allowed in the pilot, this would result in a substantial difference in vitamin D levels between the two arms of the trial. Monthly dosing results in variable serum cholecalciferol levels but stable levels of 25(OH)D (25), and given the likely higher compliance resulting from this dosing regimen compared with daily dosing (26), we believe this to be appropriate.

In conclusion, the D-Health pilot trial has shown that recruitment is feasible and that randomization to cholecalciferol led to a marked difference in 25(OH)D between placebo and active groups. Follow-up and compliance were excellent. A large-scale trial will be possible but somewhat challenging due to the high proportion of people already taking vitamin D. It is crucial that general practitioners and the public are better educated about the lack of evidence to support routine population screening and supplementation to enable the establishment of an appropriate evidence base.

Acknowledgments

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