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The Multi-Ethnic Study of Atherosclerosis Individual Response to Vitamin D trial: building a randomized clinical trial into an observational cohort study

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Abstract

The INdividual response to VITamin D (INVITe) trial was a randomized, placebo-controlled, parallel group trial of vitamin D_3 supplementation (2000 IU daily) designed to determine clinical and genetic characteristics that modify the response to vitamin D supplementation. To enhance internal and external validity and reduce cost, the INVITe trial was nested within the Multi-Ethnic Study of Atherosclerosis (MESA), an ongoing prospective observational cohort study. The INVITe trial enrolled a community-based population of 666 racially and ethnically diverse participants from January 2017 to April 2019. This represents 30% of 2210 MESA participants approached for screening, and 96% of those found to be eligible. Barriers to enrollment included delayed initiation of the trial relative to scheduled MESA study visits, a lower number of available MESA participants than expected, and a high prevalence (18%) of high-dose vitamin D supplementation (>1000 IU daily, an exclusion criterion). The final study visit was attended by 611 participants (92%), and median adherence was 98%. Our experience suggests that integration of a randomized trial into an existing observational cohort study may leverage strengths of the source population and enhance enrollment, retention, and adherence, although with limited enrollment capacity. The INVITe trial will use rigorously-collected data to advance understanding of individual determinants of vitamin D response.

Introduction

Measurement of circulating vitamin D concentrations and vitamin D supplementation have permeated clinical care.[1] Interest in vitamin D as a therapeutic agent stems from the pleiotropic biological effects of vitamin D receptor activation in experimental models and associations of low circulating concentrations of 25-hydroxyvitamin D (25(OH)D) with disease outcomes in observational studies.[1–4] Yet, randomized trials of vitamin D supplementation have found negligible impact of this treatment on cardiovascular, cancer, and other clinical outcomes.[5–9] Heterogeneity in the response to vitamin D treatment may partly explain the minimal net benefit seen in trials and reveal clues regarding basic mechanisms of disease.

The individual response to vitamin D supplementation may plausibly vary by the degree of vitamin D sufficiency (or deficiency) at the time of treatment, bioavailability and its determinants (such as obesity), and differences in the activity of vitamin D metabolic pathways, including genetic variation. For example, race and polymorphisms in genes related to vitamin D metabolism modify the association of low circulating vitamin D concentrations with clinical outcomes.[3,4]

Randomized trials are the most rigorous way to determine individual factors that modify the effects of interventions. However, randomized trials have their own challenges, including enrollment of representative populations, participant retention, and cost. Integration of clinical trials into existing cohort studies may mitigate these challenges, to the extent that

genuine efficiencies can be created.[10] Specifically, established cohort studies offer large populations of engaged participants, community-based enrollment procedures, detailed measurements of participant characteristics, valuable infrastructure, and experienced investigators to support trial activities.[11]

Here, we report our approach to integrating a randomized trial of vitamin D supplementation into the Multi-Ethnic Study of Atherosclerosis, an ongoing prospective cohort study.[12] The goal of the trial was to determine individual clinical and genetic characteristics that modify the biologic response to vitamin D_3 supplementation. Data collection is complete, and results for enrollment and retention and lessons learned from implementing this study design are presented herein. Primary outcomes of the trial will be presented in a separate report.

Materials and methods

Study setting

The Multi-Ethnic Study of Atherosclerosis (MESA) is an ongoing, prospective, community-based cohort study designed to investigate the determinants and outcomes of subclinical cardiovascular disease.[12] Between 2000–2002, MESA enrolled 6,814 participants ages 45–84 years from six U.S. communities: Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA. MESA oversampled by race/ethnicity to create a cohort that was approximately 40% White, 30% African American, 20% Hispanic, and 10% Asian, primarily Chinese. In-person follow-up examinations occurred 1.5, 3, 5, 10, and 15 years after the baseline exam. MESA also enrolled a study of air pollution and cardiovascular disease, MESA Air, which recruited primarily from the MESA Cohort, with an additional 490 participants added from the MESA Family ancillary study and 257 participants explicitly recruited for MESA Air from Los Angeles, California and New York, New York, to enhance the air pollution exposure heterogeneity.[13]

Study design

We designed and conducted the INdividual response to VITamin D (INVITe) trial as a randomized, placebo-controlled, parallel group clinical trial of vitamin D_3 supplementation nested within the ongoing MESA cohort study (Figure 1), organized as an ancillary study to MESA. We primarily recruited MESA participants at the time of their year 15 examination (September 2016 – March 2018). This approach enhanced efficiency of implementing the INVITe trial, compared with performing separate study visits, though with constraints to acceptable additional participant burden, total available sample size, and timing of trial activities (Table 1). The study was approved by the Institutional Review Board of each enrolling site and registered prior to initiation (NCT02925195).

Study population

Eligibility criteria were intentionally broad (Table 2) to maximize recruitment and enhance external validity. Previously collected MESA data were used to assess prior serum calcium concentrations and histories of kidney stones, kidney transplant, and kidney replacement therapy. We did not screen for “vitamin D deficiency” based on serum 25(OH)D

concentrations because one goal of the trial was to determine biomarkers of vitamin D status that robustly inform the degree of response to treatment, including 25(OH)D concentration.

To ensure that total vitamin D intake remained within safe limits as proposed by the Institute of Medicine (tolerable upper intake level, 4000 IU daily),[14] we excluded MESA participants who were taking high dose vitamin D supplements, defined as total dose of vitamins D_2 plus D_3 >1000 IU/day, including multivitamin sources.

We initially restricted enrollment to four MESA field centers due to available funding, selecting sites with the highest numbers of African American participants (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore City and County, MD; and Chicago, IL). Enrollment was subsequently expanded to MESA Air participants from these sites as well as MESA participants from a fifth site (Los Angeles County, CA) (Table 3).

Enrollment procedures

We primarily used the MESA year 15 examination for INVITe trial eligibility assessment, informed consent, baseline data collection, randomization, and study drug dispensing (Figure 1). Information about the INVITe trial was included in materials routinely sent to MESA participants in advance of the year 15 visit, and MESA participants potentially eligible for INVITe were contacted by telephone in advance of their visit to address any questions about trial participation. Potentially eligible participants were asked to undergo screening at the time of their visit. Willing and eligible participants were enrolled, randomized, and provided with study medication on the same day. Because funding for MESA INVITe was awarded after the MESA year 15 examination was initiated, some participants had already completed their year 15 study visit before their site was activated for INVITe. In these cases, a separate baseline visit for the INVITe trial was performed. The year 15 MESA study visits were completed from September 2016 to June 2018, and baseline INVITe visits were completed from January 2017 to April 2019.

Intervention

INVITe trial participants were randomly assigned to oral vitamin D_3 (one 2000 IU softgel daily) or matching placebo. Study medications were provided by Carlsson Labs. The dose of 2000 IU daily was chosen because it is known to effectively raise circulating 25(OH)D concentration (on average) and has been used in larger trials with clinical outcomes.[5,15] Treatments were assigned for a duration of 16 weeks, at which time attained serum 25(OH)D concentrations were expected to be near steady-state concentrations observed with indefinite treatment.[16] Participants using non-study supplements that contain vitamin D (≤1000 IU daily) were asked to continue these throughout the study.

Vitamin D_3 or placebo were assigned in a 3:1 ratio because variability in response was expected to be larger among participants assigned to vitamin D_3. A random allocation sequence was generated centrally by the MESA data coordinating center in blocks of four, stratified by MESA site. Site personnel, study participants, and study investigators were blinded to treatment assignments by using medication bottles that were labeled with unique identifiers known only to the coordinating center and Carlsson Labs. Participants were

unblinded when they completed the study so that treatment assignments and selected laboratory results could be reported and applied to clinical care in a timely manner.

Follow-up

Participants were contacted by telephone two weeks after enrollment, at which time study staff inquired about adverse effects and general questions. Participants were scheduled for a single trial-specific study visit 16 weeks after randomization, during which adherence (by pill count), adverse events, and medication changes were assessed and blood pressure (three measurements while sitting), blood samples, and urine samples were obtained using standard MESA protocols.

Outcomes

Co-primary outcomes were changes in serum concentrations of 1,25-dihydroxyvitamin D and parathyroid hormone from baseline to 16 weeks. Generation of 1,25-dihydroxyvitamin D and suppression of parathyroid hormone are proximate effects of vitamin D supplementation that can be observed over a short period of time, reflect functional changes in the vitamin D endocrine system, and may plausibly be modified by relevant clinical and genetic factors. In addition, higher circulating 1,25-dihydroxyvitamin D concentration and lower circulating parathyroid hormone concentration have each been associated with lower risks of cardiovascular events.[17,18] Secondary outcomes included changes in blood pressure, urine calcium excretion, and serum calcium concentration. 1,25-dihydroxyvitamins D_3 and D_2 were measured by immunoaffinity and liquid chromatography-tandem mass spectrometry (interassay coefficients of variation 4.3–12.3% at 14–46 pg/mL) and summed to measure total 1,25-dihydroxyvitamin D.[19] Parathyroid hormone was measured using an automated two-site sandwich immunoassay on the Beckman-Coulter Dxl 800 platform (interassay coefficient of variation 4.9–5.3%% at 82–250 pg/mL).[20]

Data analysis

We described MESA participants screened, enrolled, and completing the INVITe trial according to CONSORT guidelines. Participants were analyzed according to their randomly assigned treatment. Adherence, defined as the percentage of pills the participant used out of the number they should have used, was estimated from pill counts as:

$$(\text{N pills dispensed} - \text{N pills returned}) / \text{minimum}(\text{N pills dispensed}, \text{N days between baseline and follow-up study visits}) \times 100.$$

Power

An initial sample size of 1,600 was planned to yield high power to detect interactions of a broad range of clinical and genetic characteristics with vitamin D treatment, examining changes in serum 1,25-dihydroxyvitamin D and parathyroid hormone as outcomes. Partway through enrollment, it became clear that enrolling 1,600 participants would not be possible. At that time, we revised the analytic plan and repeated sample size calculations with the goal of providing adequate power to detect clinically meaningful associations of individual clinical and genetic factors with the co-primary outcomes. We calculated a revised sample

size of 682, which provided 80% power for prioritized pharmacogenetic studies. Specifically, a sample size of 682 provided 80% power in stratified analyses among white participants only or African American participants only to detect a difference of 7.5 pg/mL in the effect of vitamin D treatment on change in parathyroid hormone per minor allele, with a significance level of 0.05. This assumed a minor allele frequency of 30%, standard deviation of 32 pg/mL for parathyroid hormone and a within participant correlation of 0.63. Similarly, for 1,25(OH)2D the study with revised sample size was powered to detect a change of 3.6 pg/mL assuming a standard deviation of 14 pg/mL and within participant correlation of 0.52. The change in sample size was approved by the study sponsor and registered at clinicaltrials.gov.

Results

Enrollment

Recruiting first focused on 3,095 MESA participants who completed the preceding MESA study visit (five years prior to the year 15 visit at one of four initial INVITe sites (Figure 2). Of these, 2,160 participants (70%) attended the year 15 study visit, 1,901 (61%) were eligible for INVITe after screening of MESA data, and 1,728 (59%) were approached for screening. Because the INVITe trial started after the year 15 MESA study visit began, 561 of these 1,728 participants (32%) were screened at a separate INVITe-specific study visit or telephone call. In order to expand the pool of potential participants, MESA Air participants and MESA participants from a fifth MESA site were additionally assessed (Table 3), all at a separate INVITe-specific study visit, bringing the total MESA participants approached for screening to 2,210 (Figure 2).

Of 2,210 participants approached, 829 (38%) declined to complete screening, 408 (18%) were excluded for mean vitamin D supplement intake >1000 IU per day, and 278 (13%) were excluded for other reasons (Figure 2). Participants excluded for high-dose vitamin D supplementation were offered the option of reducing intake to ≤1000 IU for 16 weeks followed by re-screen, but only 19 such participants elected this option (Table 3).

In total, 695 participants (31% of those approached for screening) were eligible for INVITe, and 666 (30%) were enrolled. This included 323 of 1,167 MESA participants screened at the year 15 study visit (28%), 301 of 820 MESA participants screened at a separate INVITe-specific study visit (37%), and 42 of 223 MESA Air participants screened at a separate INVITe-specific study visit (19%).

Participant characteristics

The mean age of enrolled participants was 72.2 years and 53% were women, with characteristics well balanced across treatment assignment (Table 4). Proportions of participants with self-described White or African American race/ethnicity were each >30%, with smaller proportions citing Hispanic or Chinese-American race/ethnicity. Prevalence of diabetes was 20%, hypertension 64%, and a prior cardiovascular event adjudicated during MESA observation 5%. Mean baseline serum 25(OH)D concentration was 29.9 ng/mL.

Characteristics of enrolled participants were similar to those who were screened but not enrolled (Table 4).

Retention

All 666 enrolled participants were randomly assigned to a treatment group (499 vitamin D, 167 placebo), and all received study medications. During the 16-week trial follow-up, 1 participant died and 54 were lost to follow-up (Figure 3). 611 participants (92% of those enrolled) attended the final study visit.

Adherence

Among 600 participants with completed pill counts, median (IQR) adherence to study medications was 98% (90–100%), and adherence was within 20% of that directed (80%–120% of pills) for 515 participants (86%). Distribution of adherence by pill count was similar according to treatment assignment (Figure 4).

Discussion

Integration of the INVITe trial into the ongoing MESA observational cohort study offered a number of distinct advantages. Enrollment of screened MESA participants (30% of those approached for screening, and 96% of those found to be eligible), retention (92% attending final study visit), and adherence (median 98%) were all high. These results suggest that INVITe benefited substantially from the commitment of MESA study participants, likely built over the preceding 15 years of engagement, and enhance internal validity of the study. In addition, the community-based, multi-ethnic population of MESA likely provides greater external validity than that of trial populations recruited from clinics or specialized health care settings. The established infrastructure and expertise of the MESA field centers and data coordinating center facilitated efficient conduct of the trial. Trial implementation utilized previously accumulated high-quality data for assessment of eligibility, and available genetic data will be used in upcoming analyses. The trial used study visits already scheduled by MESA in many cases to reduce participant and coordinator burden and cost.

We also experienced unanticipated challenges. Chief among these were multiple barriers to enrollment. First, initiation of the trial was delayed relative to the start of the planned year 15 MESA study visits, resulting in the need to re-contact participants and conduct separate trial-specific screening. Second, attrition of the MESA cohort from the year 10 to year 15 visit was greater than anticipated, leaving fewer available participants for screening. This fall-off was attributable largely to nonparticipation in the year 15 study visit, sometimes due to death. Third, 18% of potentially eligible individuals were excluded due to high-dose vitamin D supplementation (>1000 IU daily), which was not expected at the time the INVITe trial was initially conceived given the absence of convincing evidence for clinical benefits of vitamin D supplementation.

We implemented several solutions to address these challenges, with variable success. First, we asked participants who completed their year 15 MESA study visit prior to initiation of INVITe to return for a trial-specific screening and baseline visit. This approach yielded a large additional enrollment, including a higher proportion of screened participants than that

of participants screened at the year 15 MESA study visit itself. Second, we expanded to include participants in a related, parallel observational cohort (MESA Air), which had less recent contact with study participants, at our same initial field centers. This approach was less successful. Together, these observations suggest that recent participant engagement may be more important for enrollment from an existing cohort study than coordinated study visits. Third, we expanded to a fifth MESA field center, which added a large number of additional participants. Fourth, we allowed MESA participants who were using high-dose vitamin D to "wash out" of high doses for 16 weeks, an option that did not substantially boost enrollment. Regardless of effectiveness for enrollment, all of these solutions increased study complexity and cost, compared to activities originally planned and budgeted.

Our enrollment experience is consistent with prior clinical trials recruiting from cohort studies in that moderate numbers of participants were readily enrolled, but numbers were limited by the fixed size of the source population(s). For example, a clinical trial (N=303) testing the effect of a polypill on intermediate cardiovascular outcomes was fully recruited from the Southern Community Cohort Study.[21] Notably, in this trial, retention and adherence were high (91% attended the final 12-month visit, and median pill count was 86% of expected), similar to the INVITe trial. However, the Ginkgo Evaluation of Memory (GEM) Study enrolled only 249 participants from the Cardiovascular Health Study (10% of 2,409 eligible), and recruitment was expanded to source communities outside the primary cohort to fully enroll 3,027 total participants.[22,23] Similarly, the Vitamin D and Omega-3 Trial (VITAL) recruited approximately 10% of its study population (total N=25,871) from the Women's Health Study,[5] and the COSMOS trial is recruiting in part from the large Women's Health Initiative and VITAL populations, with additional participants sought outside the existing cohort studies.[24]

Our experience offers guidance for future clinical trials leveraging observational cohort studies. Trials may draw on specific strengths of the source cohort, such as the diverse population, strong infrastructure, and relevant available clinical data that were leveraged in our study. Perhaps the most important advantage of this approach is the opportunity to draw from an engaged, committed group of existing participants, reflected in our study by high enrollment, retention, and adherence rates. We learned that it is critical to design a streamlined protocol that minimizes participant and coordinator burden, anticipate unexpected use of supplements not routinely captured during medication inventories, avoid overestimation of numbers of participants available from the source population, and maintain flexibility to adapt to unforeseen barriers.

The INVITe trial generated rigorous, high-quality data to determine clinical, biomarker, and genetic determinants of the biologic response to vitamin D supplementation. While smaller in size than initially envisioned, the diversity, available data characterizing participants (including genetic data), and high retention and adherence will facilitate effective evaluation of study aims. This may help identify better biomarkers of vitamin D status (that relate to functional response rather than static intermediates), more appropriate thresholds to identify vitamin D deficiency, and new insights into mechani sms governing vitamin D response. These results may in turn facilitate subgroup analyses of larger trials to more robustly evaluate the clinical benefits and risks of vitamin D supplementation.

Limitations of applying our experience to future studies include the short duration of the trial and the substantial previous engagement of participants in the MESA cohort. Enrollment, retention, and adherence may differ for longer trials or trials integrated into less established cohorts. Moreover, while there was only minimal concern that the short-term INVITe intervention would adversely affect broader MESA participation (through increased participant burden) or outcomes (through effects on future behavior or health outcomes), this could be a larger concern with other interventions.

In conclusion, integration of clinical trials into existing observational cohort studies offers both advantages and challenges. The MESA INVITe trial will use rigorously collected data to advance understanding of individual determinants of vitamin D response, with a goal to inform larger trials with clinical outcomes and improve identification and treatment of vitamin D deficiency. Lessons from INVITe may help design effective future trials.

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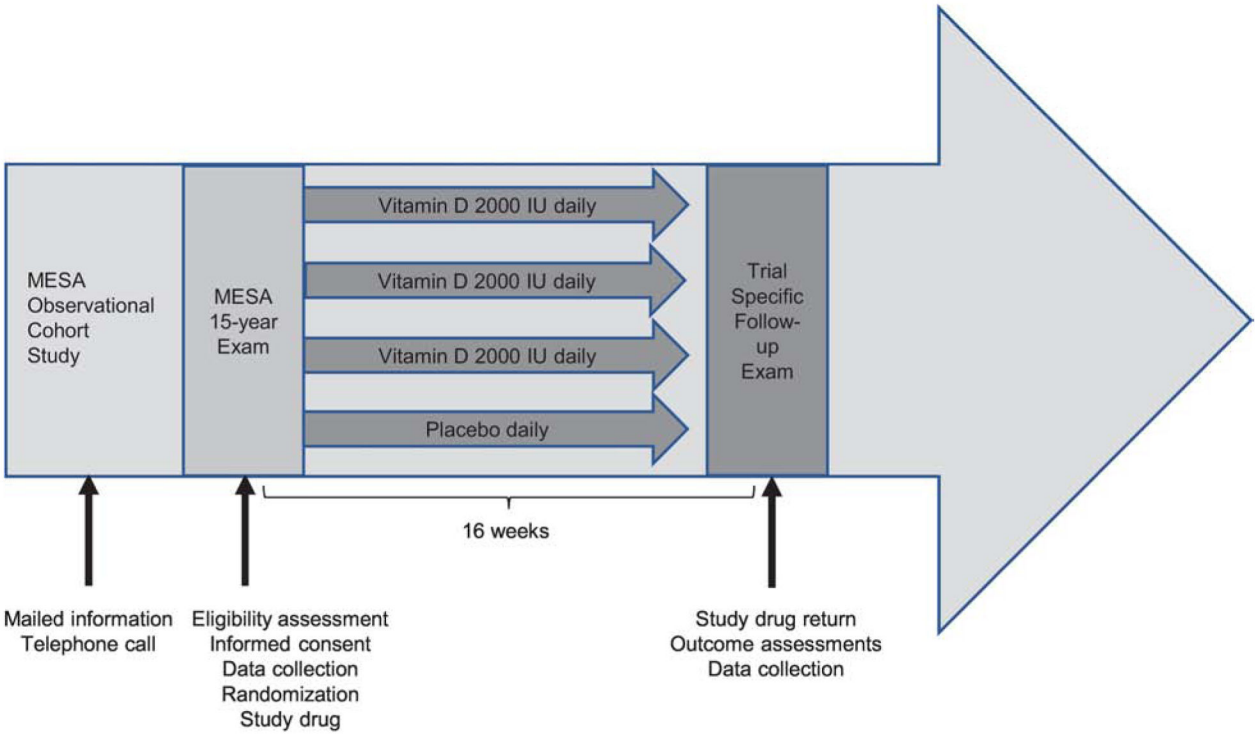

Figure 1.
Design of the Individual Response to Vitamin D trial

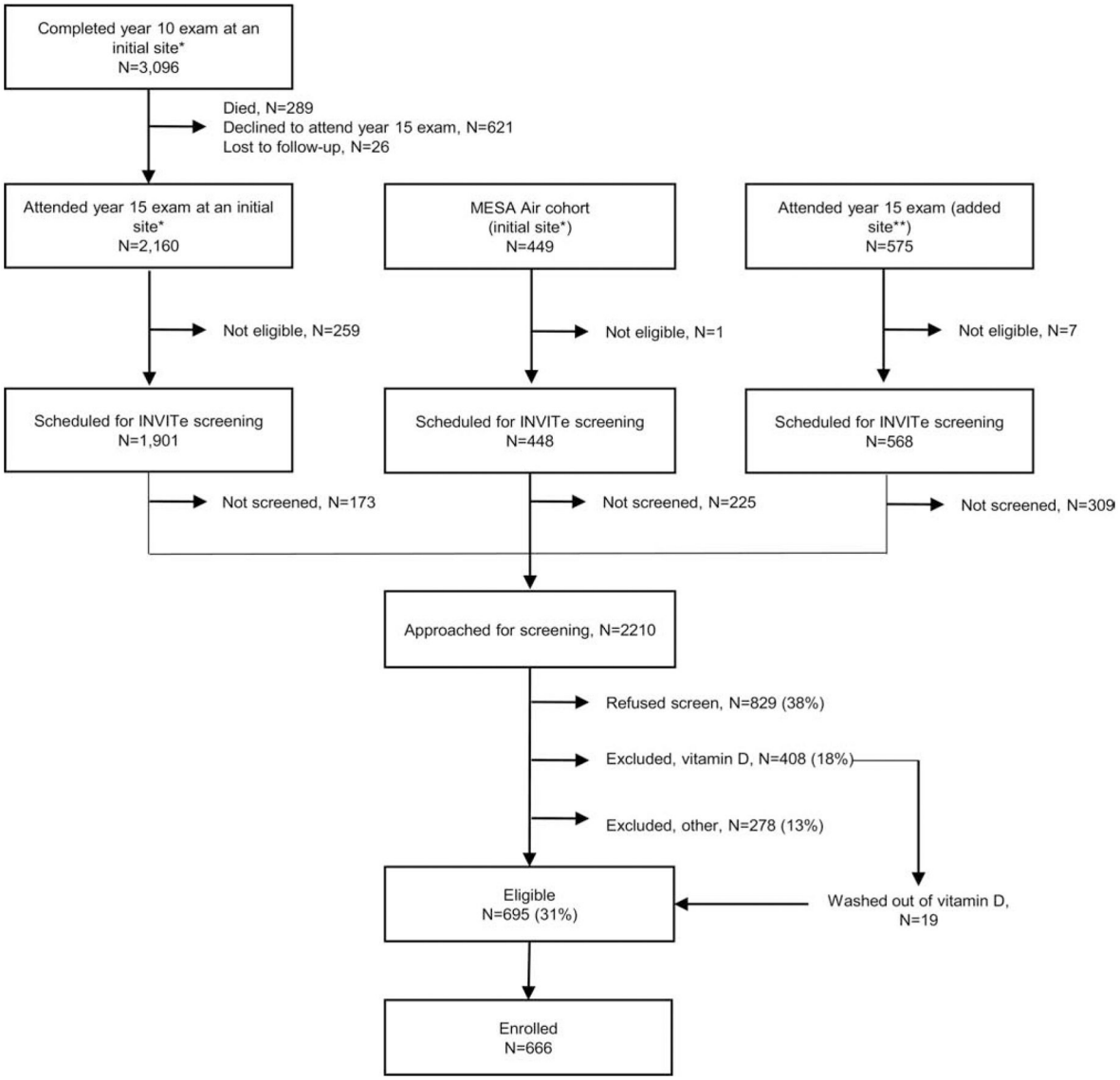

Figure 2.
Study enrollment

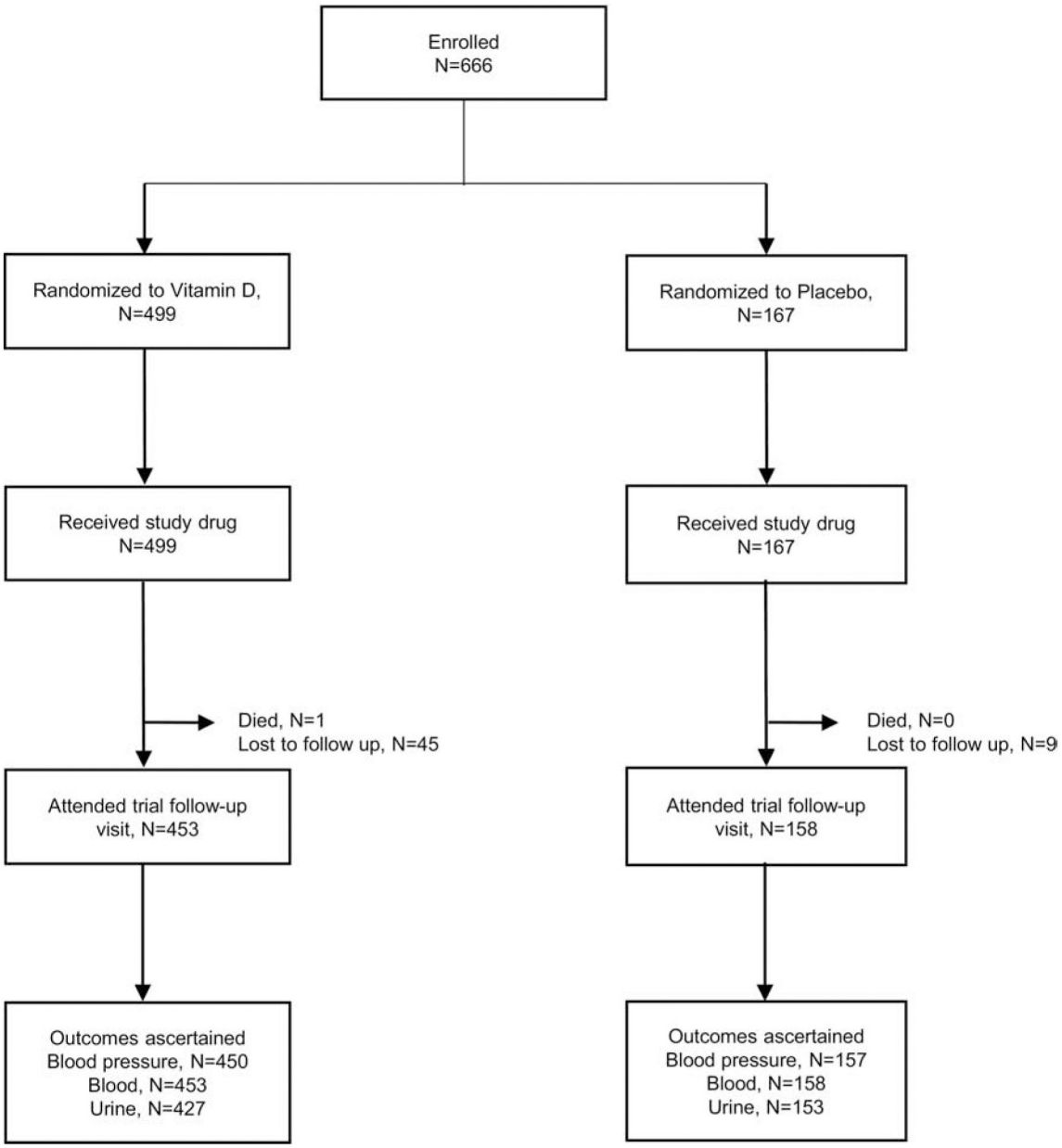

Figure 3.
Study retention and completion

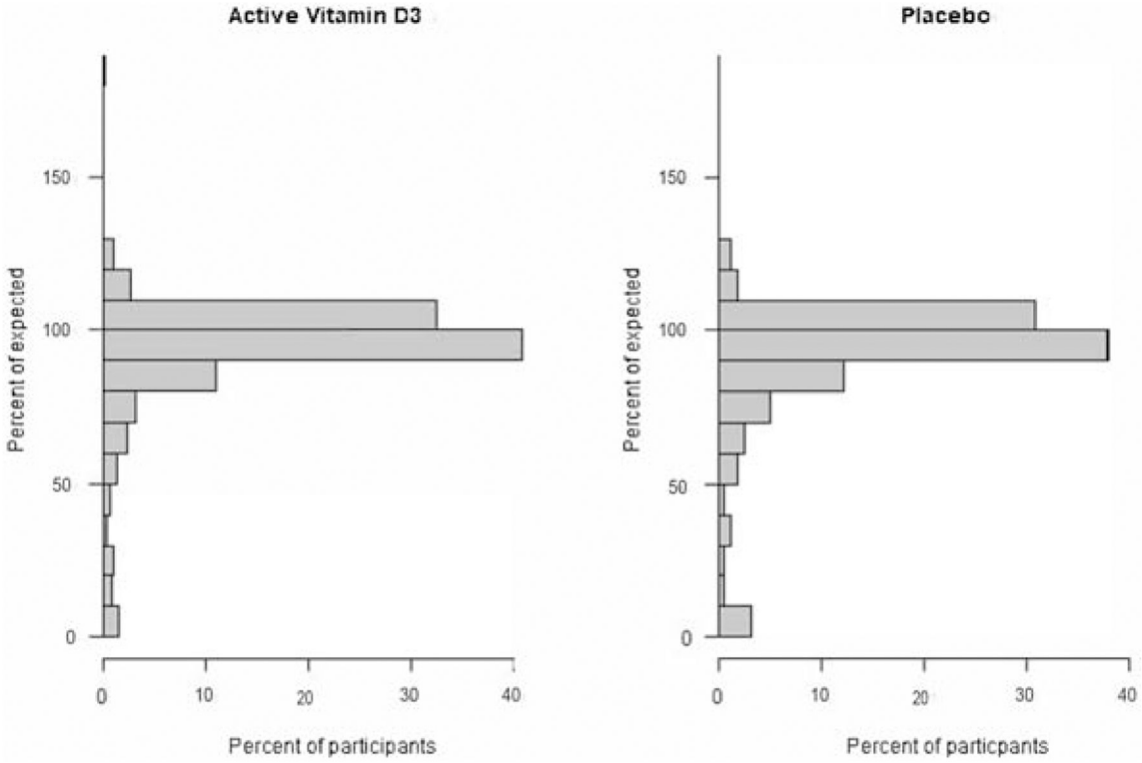

Figure 4.
Study adherence

Table 1.

Advantages and disadvantages of integrating a randomized clinical trial of vitamin D supplementation into the ongoing observational Multi-Ethnic Study of Atherosclerosis

Advantages	Disadvantages
Established field centers and central coordinating center with committed infrastructure for recruitment and retention	Imperative to minimize study burden
Committed participants who have already consented to and followed through with a long-term research study	Constrained total number of people to approach for enrollment
Availability of participants at scheduled in-person parent study visits	Timeline less flexible, tied to parent study procedures
Community-based sampling strategy that maximizes external validity of study findings	Results may not generalize to populations not selected for long-term participation in research
Extensive characterization of study participants already completed, including 15 years of clinical data and extensive genetic data (screening, response predictors)	
Racial and ethnic diversity to enable investigation of possible race/ethnicity-related differences in the response to vitamin D_3 treatment and increase external validity of results	

Table 2.

Eligibility criteria for the Individual Response to Vitamin D trial

Inclusion criteria
Existing MESA participant *
Exclusion criteria
High-dose vitamin D supplementation (>1000 IU daily)
Taking calcitriol or a calcitriol analogue
Clinical diagnosis of primary hyperparathyroidism or sarcoidosis
Kidney stone within the last 5 years
Kidney transplant or kidney replacement therapy
Serum calcium >11 mg/dL at baseline MESA examination (2000–2002)
Self-reported history of elevated serum calcium concentration
Current participation in another interventional study
Inability to provide written informed consent

* Initially required attendance at year 15 in-person examination at one of 4 MESA field centers; later expanded to include MESA Air participants from these sites and a fifth MESA field center

Table 3.

Enrollment barriers and solutions

Barrier	Solution attempted	Additional N screened	Additional N enrolled
Delayed start relative to parent study examination	Asked participants to return for additional enrollment visit	561	184 (33)%
Attendance at parent study examination lower than forecast	Expanded recruiting to MESA Air cohort (not tied to scheduled in-person examination)	223	42 (19%)
	Added additional MESA field center	259	101 (39%)
High prevalence of high-dose vitamin D supplements (exclusion criterion)	Allowed participants to wash out of supplements and re-screen	408	19 (5%)

Table 4.

Characteristics of screened and enrolled participants

	Screened and enrolled		Screened	
	Vitamin D_3 (N = 499)	**Placebo (N = 167)**	**Enrolled (N=666)**	**Not enrolled (N=1544)**
Demographic characteristics				
Age (years)	72.4 (8.0)	71.6 (7.8)	72.2 (8.0)	74.6 (8.7)
Male	227 (45.5)	86 (51.5)	313 (47.0)	657 (42.6)
Race/ethnicity				
African American	184 (36.9)	61 (36.5)	245 (36.8)	587 (38.0)
White	169 (33.9)	58 (34.7)	227 (34.1)	547 (35.4)
Hispanic	82 (16.4)	29 (17.4)	111 (16.7)	199 (12.9)
Chinese-American	64 (12.8)	19 (11.4)	83 (12.5)	211 (13.7)
Site				
Wake Forest	57 (11.4)	19 (11.4)	76 (11.4)	195 (12.6)
Columbia	140 (28.1)	46 (27.5)	186 (27.9)	351 (22.7)
Johns Hopkins	96 (19.2)	32 (19.2)	128 (19.2)	294 (19.0)
Northwestern	130 (26.1)	45 (26.9)	175 (26.3)	548 (35.5)
UCLA	76 (15.2)	25 (15.0)	101 (15.2)	156 (10.1)
Income				
< $20K	78 (15.6)	19 (11.4)	97 (14.6)	268 (17.4)
$20K – <$35K	91 (18.2)	36 (21.6)	127 (19.1)	240 (15.5)
$35K – <$75K	163 (32.7)	49 (29.3)	212 (31.8)	509 (33.0)
≥ $75K	167 (33.5)	63 (37.7)	230 (34.5)	523 (33.9)
Smoking status				
Current	34 (6.8)	10 (6.0)	44 (6.6)	91 (5.9)
Former	220 (44.1)	81 (48.5)	301 (45.2)	698 (45.2)
Never	245 (49.1)	76 (45.5)	321 (48.2)	752 (48.7)
Comorbidities				
Diabetes	105 (21.0)	33 (19.8)	138 (20.7)	342 (22.2)
Hypertension	332 (66.5)	95 (56.9)	427 (64.1)	989 (64.1)
Prior cardiovascular event	29 (5.8)	5 (3.0)	34 (5.1)	62 (4.0)
Medications				
Antihypertensive medications	306 (61.3)	94 (56.3)	400 (60.1)	911 (59.0)
Vitamin D from non-study supplements *				
None	303 (61.1)	112 (67.9)	415 (62.8)	723 (46.8)
1–400 IU daily	26 (5.2)	13 (7.9)	39 (5.9)	37 (2.4)
401–1000 IU daily	167 (33.7)	40 (24.2)	207 (31.3)	133 (8.6)
>1000 IU daily	0 (0.0)	0 (0.0)	0 (0.0)	493 (31.9)
Physical examination				

	Screened and enrolled		Screened	
	Vitamin D_3 (N = 499)	**Placebo (N = 167)**	**Enrolled (N=666)**	**Not enrolled (N=1544)**
Body mass index (kg/m^2)	29.1 (5.9)	28.4 (5.3)	28.9 (5.7)	28.2 (5.8)
Systolic blood pressure (mmHg)	126.3 (19.2)	126.9 (20.3)	126.4 (19.4)	128.0 (20.6)
Diastolic blood pressure (mmHg)	69.6 (10.0)	70.3 (9.8)	69.8 (10.0)	69.4 (10.2)
Laboratory data				
eGFR (mL/min/1.73m^2)	76.9 (17.7)	80.1 (14.6)	77.7 (17.0)	75.5 (17.8)
Urine ACR (mg/g), median (IQR)	5.0 (2.8, 14.4)	4.4 (2.8, 13.8)	4.9 (2.8, 14.1)	6.1 (3.3, 15.4)
25-hydroxyvitamin D (ng/mL)	30.1 (10.8)	29.3 (10.2)	29.9 (10.6)	N/A
1,25-dihydroxyvitamin D (pg/mL)	50.3 (18.5)	50.2 (16.9)	50.3 (18.1)	N/A
Parathyroid hormone (pg/mL)	49.3 (29.0)	43.5 (20.4)	47.8 (27.1)	N/A

Cell contents are mean (SD) or n (% of non-missing), except for urine albumin-creatinine ratio (median, interquartile range). Data for BMI and diabetes are unavailable for 2 and 1 participants in the enrolled population, respectively and in the screened and not enrolled missingness was less than 2% for all covariates.

*Mean daily intake from all reported supplements, missing for 5 enrolled participants. N/A = not available (not collected).