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Randomized Control Trials

Effect of sun exposure versus oral vitamin D supplementation on serum 25-hydroxyvitamin D concentrations in young adults: A randomized clinical trial

Hee-Kyung Joh [a, b, c, *], Seung-sik Hwang [d], BeLong Cho [b, e, f, g], Chun Soo Lim [h], Sung-Eun Jung [i]

[a] Department of Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea
[b] Department of Family Medicine, Seoul National University Hospital, Seoul, Republic of Korea
[c] Department of Family Medicine, Seoul National University Health Service Center, Seoul, Republic of Korea
[d] Department of Public Health Sciences, Seoul National University Graduate School of Public Health, Seoul, Republic of Korea
[e] Health Promotion Center, Seoul National University Hospital, Seoul, Republic of Korea
[f] Advanced Institutes of Convergence Technology, Seoul National University, Seoul, Republic of Korea
[g] Institute on Aging, Seoul National University College of Medicine, Seoul, Republic of Korea
[h] Department of Internal Medicine, Seoul National University Boramae Medical Center, Seoul, Republic of Korea
[i] Department of Pediatric Surgery, Seoul National University Children's Hospital, Seoul, Republic of Korea

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SUMMARY

Background: Vitamin D inadequacy is associated with a wide range of diseases. However, optimal strategies to improve vitamin D status, especially in Asian populations, remain unclear. We tested the hypotheses that (1) relevant sun exposure or oral vitamin D supplementation would significantly increase serum 25-hydroxyvitamin D (25OHD) concentrations compared with placebo, (2) sun exposure and supplementary vitamin D would be similar in serum 25OHD increases, and (3) the two interventions may have different effects on cardio-metabolic markers.

Methods: In this 8-week randomized placebo-controlled clinical trial including vitamin D-deficient adults in Seoul (37 °N), Korea, changes in serum 25OHD concentrations were compared between the sun exposure (daily ≥ 20–30 min around noon, $n = 50$), oral vitamin D_3 (500 IU/d, $n = 50$), and control (placebo, $n = 50$) groups.

Results: Both sun exposure and oral vitamin D_3 effectively increased serum 25OHD concentrations. Compared with placebo, the between-group least-squares mean (LSM) differences in changes were 2.2 ng/mL (95% CI: 0.2, 4.2) in the sun exposure group and 8.5 ng/mL (6.5, 10.5) in the oral vitamin D_3 group. Increases in serum 25OHD were greater with oral vitamin D_3 than with sun exposure (LSM difference in changes = 6.3 ng/mL, 95% CI: 4.3, 8.3). More participants in the oral vitamin D_3 group (54.2%) achieved serum 25OHD concentrations ≥20 ng/mL at week 8 than those in the sun exposure (12.2%) or control (4.3%) groups. Compliance with sun exposure advice was relatively low, and only those with adequate compliance had a significant increase in serum 25OHD. Changes in the cardio-metabolic markers were mostly insignificant in all groups.

Conclusions: Enhanced sun exposure and 500 IU/d of oral vitamin D_3 supplementation significantly increased serum 25OHD concentrations. However, our protocol for sun exposure was not as effective as 500 IU/d of oral vitamin D_3 supplementation.

This trial was registered at clinicaltrials.gov as NCT03310242.

Abbreviations: ALT, alanine transferase; AST, aspartate transaminase; BMD, bone mineral density; CLIA, chemiluminescent immunoassay; d, day; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; LSM, least-squares mean; min, minutes; PTH, parathyroid hormone; RR, relative risk; UVB, ultraviolet type B; 25OHD, 25-hydroxyvitamin D.

* Corresponding author. Seoul National University Health Service Center, 1 Gwanak-ro, Gwanak-gu, Seoul 08826, Republic of Korea. Fax: +82 2 880 9274.
E-mail address: hkjoh@snu.ac.kr (H.-K. Joh).

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1. Introduction

Vitamin D has well-established roles in mineral metabolism and musculoskeletal health promotion [1]. There is mounting evidence on the beneficial roles of vitamin D in cancer, cardiovascular disease, diabetes, infections, and mortality [2–4]. The main natural source of vitamin D for humans is exposure to solar ultraviolet type B (UVB) radiation of the skin, where vitamin D is synthesized [1,5]. Other sources include foods or supplements; however, natural foods contain scant amounts of vitamin D without fortification [6]. Vitamin D inadequacy is emerging as a global health problem, with recent estimates indicating that 1 billion people worldwide are vitamin D deficient or insufficient [1]. The vitamin D status in many Asian countries has been deteriorating in recent years [7,8]. Although the causes of the increasing trend in vitamin D inadequacy are not clear, behavioral factors, such as limited sun exposure due to indoor lifestyles or urbanization, active protection against sunlight, and unfavorable dietary habits, may be some reasons [8–11].

To ensure an optimal vitamin D status in the general population, public guidelines on safe and sufficient sun exposure and vitamin D intake are essential. However, the currently available evidence obtained from randomized controlled trials is insufficient to support the guidelines. Most sun exposure advice is based on theoretical models or artificial UV sources [12–14] and the assumption that people are completely exposed to the correct wavelength of sunlight [15]. Furthermore, those recommendations are focused on light-skinned individuals and thus may be inappropriate for other ethnicities [16,17]. In previous studies that used UV radiation simulating casual summer sunlight in the United Kingdom, 90% of the white participants achieved vitamin D sufficiency [12]; however, none of the South Asian participants did [16]. Different sociocultural practices in Asian populations may also contribute to low vitamin D status [18]. They usually avoid sun exposure and adopt sun protection behaviors (e.g., wearing a hat or long sleeved clothing, using an umbrella or sunscreen, staying in the shade when outdoors) [7]. In Asian populations, the amount of sun exposure required for optimal vitamin D synthesis as well as the relative potency of sun-derived and supplementary vitamin D remains unknown [15,17]. It is also unclear if sun exposure guidelines will be successfully adopted in these populations in real-life situations.

We, therefore, conducted a randomized trial in vitamin D-deficient Korean adults. Our principal aims were to (1) evaluate the effects of sun exposure and oral vitamin D supplementation on serum 25-hydroxyvitamin D (25OHD) concentrations compared with placebo and (2) compare the relative effectiveness of sun exposure and oral vitamin D in increasing serum 25OHD concentrations. The secondary aims were to (1) assess the effects of sun exposure and oral vitamin D on cardio-metabolic health markers and (2) determine the feasibility of sun exposure advice in practice. We hypothesized that (1) relevant sun exposure and oral vitamin D will induce significant increases in serum 25OHD levels, (2) the effects of sun exposure and oral vitamin D would be similar with regards to serum 25OHD increases, and (3) the two interventions may have different effects on cardio-metabolic markers.

2. Materials and methods

2.1. Study design

We conducted an 8-week, randomized placebo-controlled clinical trial among vitamin D-deficient young adults at a single clinic in Seoul (37 °N), South Korea. An independent statistician, not involved in participant recruitment or data collection, performed random assignments using a computer-generated randomization code (STATA 8 program). Eligible participants were randomly assigned, in a 1:1:1 ratio, to one of three parallel groups: enhanced sun exposure (sun exposure group), 500 IU/d of oral cholecalciferol (oral vitamin D_3 group), or placebo (control group). The study medications (vitamin D_3 and placebo) were identical in appearance and taste; they were manufactured, packed in bottles, and labeled with sequence numbers by Darim Biotech pharmaceuticals (Seoul, South Korea). An independent pharmacist kept the list linking the randomization code to the medication bottle number in a secure place until the end of the study. Both participants and the research team remained blinded to the treatment assignment. Participants allocated to the sun exposure group could not be blinded to the intervention, but the measurement team and the statistician were blinded to the allocation information. After randomization, all participants visited the Seoul National University Health Service Center every 4 weeks for 8 weeks. The study was approved by the Institutional Review Board of Seoul National University College of Medicine/Seoul National University Hospital (Seoul, South Korea; IRB number, H-1504-112-668). The trial was conducted per the ethical standards of the Helsinki Declaration. All participants provided written informed consent before participation. This trial was registered at clinicaltrials.gov (NCT03310242).

2.2. Participants

Participants were recruited among healthy male and female university students who participated in an annual health checkup that measured various health indicators including serum 25OHD. We sent potential participants, whose serum 25OHD levels were <12 ng/mL, invitation e-mails explaining the rationale behind the trial, an outline of participation, and relevant scientific information. The inclusion criteria were as follows: age 18–39 y; Korean ethnicity; serum 25OHD level <12 ng/mL, as measured within 2 weeks before the screening visit; agreeing to refrain from consuming personal supplemental vitamin D or calcium; and willingness to accept randomization and follow the trial protocol. Exclusion criteria were as follows: photosensitivity or sunlight allergy; a history of skin cancer or other cancers, kidney stones, hypercalcemia, hypercalciuria, or hyperparathyroidism; taking antihypertensive, lipid-lowering, or hypoglycemic medicines; use of supplemental vitamin D (as a single-ingredient or combined with calcium, multivitamins, or medicines) or medications known to induce photosensitivity within 2 months prior to enrollment; intentional UV exposure (e.g., beach, tanning bed) within 2 weeks before enrollment or planned during the trial period; pregnancy or breast-feeding; and unwillingness or inability to comply with the trial protocol.

2.3. Intervention

Participants in the sun exposure group were advised to undergo direct sun exposure between 11 a.m. and 2 p.m. every day for at least 20 min/d during summer (July and August) and at least 30 min/d during fall (September to November), with as much skin exposed as feasible under the circumstances. If longer than 1 h of sun exposure was planned under a UV Index ≥3, use of sun protection was recommended. Otherwise, sunblock application was recommended only on the face. To monitor and estimate the daily amount of sun exposure, we developed a smartphone application (SNU Sun Diary). Participants in the sun exposure group kept records in real time using the application every day throughout the study period; data were transferred to researchers every week. Information on the dates, start and end times of sun exposure (direct sun only), exposed skin area, use of sunscreen, and real-time weather conditions was recorded. When a smartphone was not

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available, a paper diary was permitted. We created a daily sun exposure score as a function of the time of day (to account for diurnal UVB radiation intensity variations), exposure duration, exposed body surface area, sunscreen use, and real-time weather conditions (to account for the UVB transmission of the atmosphere according to cloud cover). The body surface area was estimated as face (5%); face and hands (10%); face, hands, and arms or lower legs (25%); face, hands, arms, legs, and trunk (60%) [15]. Instructions on enhanced sun exposure and smartphone application use were provided via 1:1 education sessions at baseline. To improve compliance, we contacted participants weekly by text messages, emails, or telephone and encouraged them to follow the protocol.

Participants in the oral vitamin D_3 group received 500 IU of cholecalciferol daily, and those in the control group received placebo. They were provided leaflets with general information on vitamin D deficiency and were advised to continue their usual diet and outdoor activities, not to take vitamin D supplements, and not to travel to any sunny area during the study period. Compliance was ascertained by the number of pills returned at each visit. A compliance rate greater than 85% was considered satisfactory.

2.4. Endpoints

The primary outcome was the least-squares mean (LSM) change in the serum 25OHD concentrations from baseline to week 8. Secondary outcomes included the percentages of participants who achieved the cut-off, 20 ng/mL of serum 25OHD concentration and those whose serum 25OHD concentration increases from baseline to week 8 were $\geq$10 ng/mL. The LSM changes in the parathyroid hormone (PTH) levels, whole-body bone mineral density (BMD) and fat %, and cardio-metabolic markers [BMI, waist circumference, systolic (SBP) and diastolic (DBP) blood pressure, blood lipids, fasting glucose, aspartate transaminase (AST), alanine transferase (ALT), and gamma-glutamyl transferase (GGT)] were also included as secondary outcomes. Information on adverse events was collected throughout the trial. Participants were instructed to discontinue their assigned protocol if they were diagnosed with hypercalcemia or kidney stones or they developed other safety-related conditions during follow-up. Blood and urine calcium and creatinine concentrations were measured to assess the potential adverse effects of hypercalcemia or hypercalciuria at week 8.

2.5. Outcome measurements

The blinded measurement team performed all the outcome measurements using the same equipment. At baseline and every 4 weeks, thereafter, anthropometric data were collected, and web-based self-administered questionnaires were completed. Weight and height were measured in light clothing without shoes. Waist circumference was measured around the midpoints between the lowest rib margin and the uppermost borders of the iliac crest. Blood pressure was manually measured using a sphygmomanometer (CK-301, Spirit Medical Co. Taiwan). The self-administered questionnaire comprised items on demographic characteristics, lifestyle (smoking, alcohol use, physical activities, diet, and outdoor time in the sun), medical history (medications, use of non-study drugs or supplements, major illnesses, and potential side effects), and the Fitzpatrick skin phenotypes (baseline only) [19].

Serum 25OHD concentrations were measured every 4 weeks using chemiluminescent immunoassay (CLIA, LIAISON® 25-OH Vitamin D Total Assay; DiaSorin Inc., Stillwater, MN, USA) at Green Cross Reference Laboratory, Inc. (Yongin, Korea). The quality of the analytical method was evaluated using the international Vitamin D External Quality Assessment Scheme and the National Institute of Standards and Technology vitamin D metabolites quality assurance program. The intra-assay CV was 2.8%, and inter-assay CV ranged from 3.0% to 3.6%. At baseline and week 8, serum PTH concentrations were measured using the electrochemiluminescence immunoassay (intact PTH, Cobas 8000, Roche Diagnostics International Ltd., Rotkreuz, Switzerland); whole-body BMD and fat % were measured using dual-energy X-ray absorptiometry (DPX NT, GE Healthcare, Waukesha, Wisconsin, USA); 12-h fasting concentrations of plasma glucose, total cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, AST, ALT, and GGT were measured (Cobas 6000, Roche Diagnostics International Ltd., Rotkreuz, Switzerland); and low-density lipoprotein (LDL) cholesterol levels were calculated in accordance with the Friedewald equation [20]. Serum and urine calcium concentrations were measured using colorimetry (Cobas 8000, Roche Diagnostics International Ltd., Rotkreuz, Switzerland).

2.6. Statistical analysis

Sample sizes were calculated for the two hypotheses: (1) higher serum 25OHD concentrations in the sun exposure and oral vitamin D_3 groups than in the control group and (2) a similar or non-inferior effect on serum 25OHD with sun exposure relative to oral vitamin D_3. Given that we had two primary outcome comparisons, type I errors were adjusted as 2.5% according to the Bonferroni correction. Assuming an effect size of 5 $\pm$ 5 ng/mL in the serum 25OHD concentrations between the active and control groups, a sample size of 25 per group was required with 90% power and a two-sided α <0.025. We presumed that the two active treatments (SD $\pm$ 5 ng/mL) were considered to be equivalent when the differences in the mean changes of serum 25OHD concentrations were <3 ng/mL; a sample size of 44 per group would provide 80% power (one-sided $\alpha < 0.025$). For the final sample size, we chose the larger number from the calculated sample sizes. Allowing for a 10% drop-out rate, we aimed to recruit 50 participants per group (total 150).

The primary analyses were based on a modified intention-to-treat analysis, which included participants who were randomized and had baseline information, regardless of adherence or loss to follow-up. All continuous variables were examined for normality; values were log-transformed if their distributions were right-skewed. To assess whether balance was achieved by randomization, we compared the baseline characteristics across the treatment groups. Continuous variables were summarized with mean (SD) or median (IQR) values, and between-group differences were tested using ANOVA or the Kruskal–Wallis tests; proportions of categorical variables were compared using chi-square tests. Pearson correlation coefficients were computed between serum 25OHD and secondary outcomes at baseline and each visit.

We estimated the LSM changes in serum 25OHD concentrations within each treatment group and LSM differences in the changes between the groups based on a repeated-measures mixed-effects model, which uses all available follow-up data (including unbalanced data) and takes into account correlations between multiple measurements within one individual. The main model was adjusted for baseline 25OHD concentrations, months of enrollment, time (baseline and weeks 4 and 8), and time $\times$ treatment interaction as fixed effects. We also compared the proportions of those who achieved a serum 25OHD concentration $\geq$20 ng/mL at week 8 and had an increase in 25OHD levels $\geq$10 ng/mL from baseline to week 8 between the treatment groups using chi-square tests and relative risks (RRs).

We performed stratified analyses to test whether the treatment effects were modified by months of enrollment, compliance to the protocol, and baseline BMI. In the sensitivity analyses, we additionally adjusted for age, sex, BMI category, or skin type in the main model to examine any significant differences in fitted outcomes.

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We conducted per-protocol analyses according to the actual treatment received. Safety data were summarized descriptively, and the proportions of drop-outs and side effects were compared using chi-square tests across the groups. Statistical tests were two-sided and P <0.05 was considered significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

3. Results

Of the 2286 adults who were prescreened at an annual health checkup, 479 (21.0%) had serum 25OHD concentrations <12 ng/mL. Of those potential participants, 211 provided consent after receiving invitation emails. A total of 150 participants met the eligibility criteria and were enrolled in the trial after the screening visit (Fig. 1). From July 2, 2015 to October 8, 2015, participants were randomly assigned to a group (50 in the sun exposure group, 50 in the oral vitamin D_3 group, and 50 in the control group). The trial was completed on December 1, 2015. Of the initial participants, 4 withdrew their consent during follow-up, and 144 (96%) completed the trial (49 in the sun exposure group, 48 in the oral vitamin D_3 group, and 47 in the control group). The number of post-randomization visits and proportions of those who completed the 8-week follow-up were similar across the groups.

The baseline characteristics of the study participants ($n = 146$) are shown in Table 1. Of the participants, the mean (±SD) age was 24.3 ± 3.9 years, 59.6% were women, and the mean concentration of serum 25OHD was 9.8 ± 1.6 ng/mL. There were no significant differences in the baseline characteristics across the groups. The hours of sunshine were monitored daily in Seoul, and UVB (W/m^2) was measured from 4 a.m. to 8 p.m. in a meteorological observatory (36.5 °N) near Seoul. Both measurements during the study period were similar to the data from previous years [21]. All participants in the sun exposure group completed the real-time sun diary using the smartphone application. Based on the diary, the median duration of sun exposure was 25.3 (IQR, 17.7–35.9) min/d. Compliance to the enhanced sun exposure protocol was relatively low. Only 38.8% ($n = 19$) had sun exposure ≥30 min/d, while 32.7% ($n = 16$) had an exposure time <20 min/d. When we adjusted for time of day to control for diurnal UVB variations, only 14.3% ($n = 7$) had sun exposure time ≥30 min/d during the time period around noon (between 11 a.m. and 2 p.m.), and 69.4% ($n = 34$) had a sun exposure time <20 min/d. The pill compliance to oral vitamin D_3 and placebo was generally good (median, 94.7% and 95.2%, respectively) without significant between-group differences ($P = 0.27$). In the oral vitamin D_3 group, the number of participants whose compliance exceeded 85% was 42 (85.7%), and the median dose of cholecalciferol consumed was 474 (IQR, 442–500) IU/d. At baseline, serum 25OHD levels were positively correlated with HDL cholesterol ($P = 0.03$), and inversely correlated with BMI, waist circumference, DBP, and whole-body fat % ($P = 0.07$, 0.06, 0.09, and 0.09, respectively). At week 8, only serum PTH was inversely correlated with serum 25OHD levels ($P = 0.09$).

Figure 2 illustrates the LSM changes in serum 25OHD concentrations from baseline to week 8 by treatment group. In all groups, serum 25OHD significantly increased at week 4 and 8 from baseline; changes from baseline to week 4 were greater than those observed between week 4 and 8. From baseline to week 8, the within-group LSM increases (±SE) in serum 25OHD were 4.6 ± 0.7 ng/mL with sun exposure, 10.9 ± 0.7 ng/mL with oral vitamin D_3, and 2.5 ± 0.7 ng/mL with placebo ($P < 0.01$ for all within-group differences) (Table 2). Both sun exposure and oral vitamin D_3 were effective in improving serum 25OHD levels. Compared with placebo, the between-group LSM differences in changes (95% CIs) were 2.2 ng/mL (0.2, 4.2) for sun exposure and 8.5 ng/mL (6.5, 10.5) for oral vitamin D_3. The increases in serum 25OHD were greater with oral vitamin D_3 than sun exposure (LSM difference in changes = 6.3 ng/mL, 95% CI: 4.3, 8.3). More participants in the oral vitamin D_3 group (54.2%) achieved a serum 25OHD concentration ≥20 ng/mL at week 8 than in the sun exposure (12.2%) or control (4.3%) groups; the corresponding RRs (95% CIs) were 4.7 (2.2, 10.1) and 12.8 (3.3, 50.2). Similarly, 62.5%, 10.2% and 4.3% of those in the oral vitamin D_3, sun exposure, and placebo groups, respectively, had an increase in serum 25OHD levels ≥10 ng/mL from baseline to week 8.

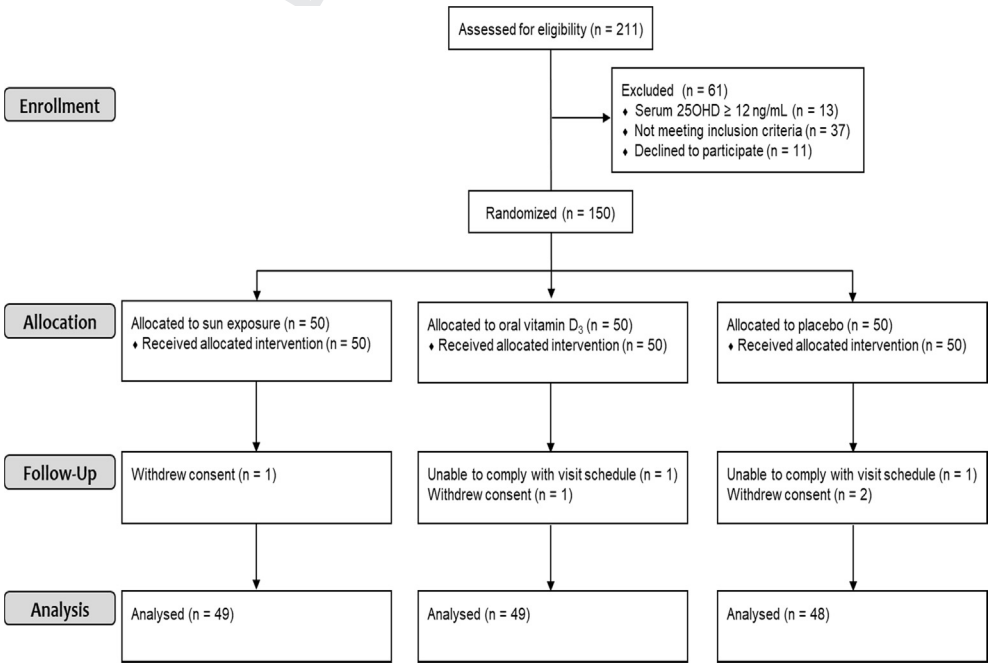

Fig. 1. Flow diagram of the participants showing the processes of enrollment, randomization, follow-up, and data analysis in the study. 25OHD: 25-hydroxyvitamin D.

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We further examined the relationships between compliance to each treatment protocol and changes in serum 25OHD levels (Fig. 3). In the sun exposure group, only those whose sun exposure scores were ranked in the top tertile had a significant increase in serum 25OHD levels compared with placebo (LSM difference = 5.03 ± 1.38 ng/mL, $P < 0.01$), but changes in the other tertiles were not significant ($P \geq 0.33$). Similarly, after adjustment for the time of day, those with average sun exposure durations ≥30 min/d around noon exhibited a significant increase in serum 25OHD concentrations from baseline compared with placebo (LSM difference = 5.09 ± 1.73 ng/mL, $P < 0.01$); however, the increase was smaller than that of oral vitamin D_3 (LSM difference = −3.40 ± 1.73 ng/mL, $P = 0.05$). Subgroups with sun exposure durations <30 min/d around noon did not have a significant increase ($P \geq 0.10$).

In the oral vitamin D_3 group, we found no significant differences in the LSM changes in serum 25OHD concentrations across the compliance tertiles ($P \geq 0.63$).

To take into account seasonal effects on vitamin D status, we stratified participants based on the month of enrollment (Fig. 4). The greatest increases in serum 25OHD levels were observed among those enrolled in July, and the changes consistently decreased after that month in all three groups. Compared with those enrolled in October, participants enrolled in July had significantly greater increases in serum 25OHD levels (LSM difference = 3.41 ± 0.73 ng/mL, $P < 0.01$). The interaction term, month of enrollment × treatment, was not significant

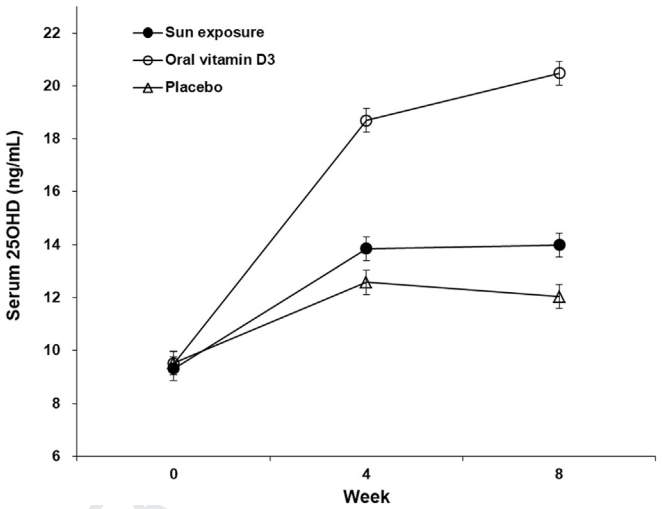

Fig. 2. The LSM ± SE changes in serum 25OHD concentrations from baseline to week 8 by treatment group. In all the groups, serum 25OHD concentrations significantly increased at week 4 and 8 from baseline ($P < 0.01$ for all within-group differences). Compared with placebo, both sun exposure and oral vitamin D_3 were effective in improving serum 25OHD concentrations; however, the increases in serum 25OHD were greater with oral vitamin D_3 than sun exposure. In the sun exposure group, $n = 49$ at week 0–8. In the oral vitamin D_3 group, $n = 49$ at week 0, and $n = 48$ at week 4–8. In the control group, $n = 48$ at week 0, $n = 47$ at week 4–8. LSM, least-square means; 25OHD, 25-hydroxyvitamin D.

Table 1
Baseline characteristics of the participants by intervention group.[a]

	Sun exposure group ($n = 49$)	Oral vitamin D_3 group ($n = 49$)	Control group ($n = 48$)	P
Age, year	24.2 (4.3)	24.4 (3.7)	24.2 (3.7)	0.96
Female sex, n (%)	32 (65.3)	28 (57.1)	27 (56.3)	0.60
Weight, kg	59.7 (11.9)	62.1 (12.2)	59.9 (12.7)	0.58
BMI, kg/m^2	21.5 (3.3)	22.0 (3.4)	21.0 (3.2)	0.38
Waist circumference, cm	74.8 (9.7)	76.0 (8.9)	74.0 (9.8)	0.58
Body fat, %	31.9 (8.2)	32.2 (8.8)	29.8 (8.5)	0.32
Whole body BMD, g/cm^2	1.2 (0.1)	1.2 (0.1)	1.2 (0.1)	0.43
SBP, mmHg	108.1 (12.1)	108.3 (11.6)	108.3 (11.0)	0.99
DBP, mmHg	66.4 (8.7)	63.8 (8.2)	65.5 (8.5)	0.31
25OHD, ng/mL	9.6 (1.7)	9.7 (1.6)	10.2 (1.4)	0.13
PTH, pg/mL	35.1 (10.9)	35.2 (12.1)	35.1 (10.9)	0.99
Total cholesterol, mg/mL	176.7 (28.2)	177.6 (29.6)	179.7 (27.3)	0.87
Triglycerides, mg/mL	86.1 (59.2)	89.5 (47.9)	80.8 (28.4)	0.66
HDL cholesterol, mg/mL	66.7 (15.7)	63.5 (17.2)	66.5 (13.5)	0.52
LDL cholesterol, mg/mL	92.9 (27.6)	96.1 (25.5)	97.1 (25.5)	0.71
Fasting glucose, mg/mL	91.3 (6.8)	91.9 (6.1)	91.2 (6.5)	0.86
AST, mg/mL	18.6 (13.3)	17.8 (5.7)	18.8 (11.1)	0.88
ALT, mg/mL	15.0 (11.5)	15.3 (12.2)	15.4 (17.7)	0.99
GGT, mg/mL	15.7 (8.2)	17.6 (11.3)	17.5 (16.9)	0.69
Fitzpatrick skin type, n (%)				0.21
I or II	8 (16.3)	4 (8.2)	3 (6.3)	
III	24 (49.0)	30 (61.2)	29 (60.4)	
IV	16 (32.7)	12 (24.5)	14 (29.2)	
V or VI	1 (2.0)	3 (6.1)	2 (4.2)	
Month of enrollment				0.92
July	19 (38.8)	19 (38.8)	20 (41.7)	
August	15 (30.6)	11 (22.5)	11 (22.9)	
September	9 (18.4)	10 (20.4)	8 (16.7)	
October	6 (12.2)	9 (18.4)	9 (18.8)	
Current smoker, n (%)	1 (2.0)	1 (2.0)	2 (4.1)	0.21
Alcohol intake, drink/week	3.8 (7.8)	3.6 (5.5)	3.8 (5.0)	0.98
Physical activity, MET-h/week	1187 (1085)	1469 (1339)	1350 (1102)	0.50
Outdoor time in the sun, min/d	13.9 (7.7–32.4)	13.9 (7.7–23.1)	11.6 (9.3–27.8)	0.65
Dairy intake, serving/week	4.1 (3.1)	3.6 (2.9)	2.8 (2.2)	0.07
Dark-meat fish intake,[b] serving/week	1.0 (1.2)	0.9 (1.3)	0.6 (0.6)	0.26

[a] Values are means ± SDs or median (IQR) unless otherwise indicated. P values for between-group differences were assessed using ANOVA, the Kruskal–Wallis tests, chi-square tests, or Fisher exact test, as appropriate. AST, aspartate transaminase; ALT, alanine transferase; BMD, bone mineral density; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; MET, metabolic equivalent; SBP, systolic blood pressure; PTH, parathyroid hormone; UVB, UV type B; 25OHD, 25-hydroxyvitamin D.

[b] Included mackerel, salmon, sardines, bluefish, swordfish, and tuna.

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Table 2
Changes in serum 25OHD concentrations and secondary outcome variables.[a] Q1.2

	Within-group change						Between-group difference					
	Sun exposure group	*P*	Oral vitamin D_3 group	*P*	Control group	*P*	Δsun exposure − Δcontrol	*P*	Δoral vitamin D_3 − Δcontrol	*P*	Δoral vitamin D_3 − Δsun exposure	*P*
25OHD, ng/mL			ΔLSM[b] ± SE						Mean (95% CI)[b]			
Week 4	4.5 ± 0.5	**<0.01**	9.2 ± 0.5	**<0.01**	3.0 ± 0.5	**<0.01**	1.5 (0.2, 2.9)	**0.04**	6.2 (4.8, 7.5)	**<0.01**	4.7 (3.3, 6.0)	**<0.01**
Week 8	4.6 ± 0.7	**<0.01**	10.9 ± 0.7	**<0.01**	2.5 ± 0.7	**<0.01**	2.2 (0.2, 4.2)	**0.03**	8.5 (6.5, 10.5)	**<0.01**	6.3 (4.3, 8.3)	**<0.01**
25OHD ≥ 20 ng/mL			*n*/total *n* (%)						RR (95% CI)[c]			
Week 4	4/49 (8.2)		23/48 (47.9)		2/47 (4.3)		1.8 (0.4, 9.5)	0.47	11.4 (2.9, 45.1)	**<0.01**	6.2 (2.4, 16.4)	**<0.01**
Week 8	6/49 (12.2)		26/48 (54.2)		2/47 (4.3)		2.7 (0.6, 12.8)	0.20	12.8 (3.3, 50.2)	**<0.01**	4.7 (2.2, 10.1)	**<0.01**
Δ25OHD ≥ 10 ng/mL from baseline			*n*/total *n* (%)						RR (95% CI)[c]			
Week 4	4/49 (8.2)		18/48 (37.5)		3/47 (6.4)		1.2 (0.3, 5.1)	0.79	5.9 (1.9, 18.4)	**<0.01**	4.8 (1.8, 13.1)	**<0.01**
Week 8	5/49 (10.2)		30/48 (62.5)		2/47 (4.3)		2.3 (0.5, 11.4)	0.30	14.7 (3.8, 57.6)	**<0.01**	6.3 (2.7, 14.7)	**<0.01**
Changes at week 8			ΔLSM[b] ± SE						Mean (95% CI)[b]			
BMI, kg/m^2	−0.1 ± 0.1	0.15	0.0 ± 0.1	0.94	0.1 ± 0.1	0.30	−0.2 (−0.5, 0.0)	0.08	−0.1 (−0.3, 0.2)	0.49	0.1 (−0.1, 0.4)	0.29
Waist circumference, cm	−0.2 ± 0.5	0.63	0.6 ± 0.6	0.34	0.0 ± 0.4	0.92	−0.2 (−1.3, 1.0)	0.77	0.6 (−0.7, 2.0)	0.36	0.8 (−0.5, 2.1)	0.21
Body fat, %	0.1 ± 0.3	0.77	0.3 ± 0.3	0.37	−0.2 ± 0.3	0.55	0.3 (−0.5, 1.1)	0.52	0.4 (−0.4, 1.3)	0.29	0.2 (−0.6, 1.0)	0.67
Whole body BMD, g/cm^2	0.010 ± 0.002	**<0.01**	0.006 ± 0.002	**0.01**	0.006 ± 0.002	**0.01**	0.004 (−0.002, 0.010)	0.22	−0.001 (−0.007, 0.006)	0.87	−0.004 (−0.011, 0.002)	0.16
PTH, pg/mL	1.6 ± 1.3	0.22	1.0 ± 1.3	0.45	1.7 ± 1.3	0.20	0.0 (−3.7, 3.6)	0.98	−0.7 (−4.3, 2.9)	0.70	−0.7 (−4.3, 2.9)	0.72
SBP, mmHg	−11.4 ± 1.5	**<0.01**	−10.6 ± 2.1	**<0.01**	−8.2 ± 1.4	**<0.01**	−3.2 (−7.2, 0.7)	0.11	−2.4 (−7.0, 2.2)	0.30	0.8 (−3.4, 5.1)	0.70
DBP, mmHg	0.8 ± 1.1	0.47	4.2 ± 1.1	**<0.01**	3.2 ± 1.1	**<0.01**	−2.6 (−5.7, 0.5)	**0.01**	1.0 (−2.2, 4.1)	0.54	3.4 (0.3, 6.5)	**0.03**
Total cholesterol, mg/mL	−1.7 ± 2.5	0.49	0.9 ± 2.5	0.71	−2.7 ± 2.5	0.29	1.0 (−6.1, 8.0)	0.78	3.7 (−3.4, 10.7)	0.31	2.7 (−4.3, 9.7)	0.45
Triglycerides, mg/mL	−0.3 ± 4.3	0.94	−4.7 ± 4.3	0.28	−2.4 ± 4.3	0.57	2.1 (−9.8, 14.1)	0.73	−2.2 (−14.2, 9.8)	0.71	−4.4 (−16.3, 7.6)	0.47
HDL cholesterol, mg/mL	0.4 ± 1.2	0.70	1.3 ± 1.2	0.27	−0.1 ± 1.2	0.92	0.6 (−2.7, 3.9)	0.73	1.4 (−1.9, 4.8)	0.39	0.9 (−2.4, 4.2)	0.61
LDL cholesterol, mg/mL	−2.2 ± 1.8	0.21	0.7 ± 1.8	0.71	−2.2 ± 1.8	0.22	0.0 (−5.0, 5.0)	0.99	2.9 (−2.1, 7.8)	0.26	2.9 (−2.1, 7.8)	0.25
Fasting glucose, mg/mL	0.6 ± 1.1	0.61	2.1 ± 1.4	0.12	1.6 ± 1.0	0.12	−1.1 (−3.9, 1.8)	0.46	0.5 (−2.6, 3.7)	0.74	1.6 (−1.4, 4.6)	0.30
AST, mg/mL	−1.7 ± 1.2	0.13	−0.1 ± 1.2	0.93	−1.4 ± 1.2	0.22	−0.3 (−3.5, 2.9)	0.85	1.3 (−1.9, 4.6)	0.42	1.6 (−1.6, 4.8)	0.32
ALT, mg/mL	−2.7 ± 1.3	**0.04**	−1.7 ± 1.5	0.25	−0.8 ± 1.3	0.56	−2.0 (−5.5, 1.6)	0.28	−1.0 (−4.7, 2.8)	0.61	1.0 (−2.6, 4.6)	0.59
GGT, mg/mL	0.1 ± 1.0	0.92	0.8 ± 1.0	0.42	−0.2 ± 1.0	0.87	0.3 (−2.6, 3.1)	0.85	1.0 (−1.9, 3.9)	0.50	0.7 (−2.1, 3.6)	0.62

[a] Values are least-squares mean (LSM) changes and LSM differences in changes between groups based on a repeated-measures mixed-effects model with treatment group, time (baseline, week 4, week 8), and time × treatment interaction, baseline 25OHD concentrations, and month of enrollment as fixed effects, unless otherwise indicated. AST, aspartate transaminase; ALT, alanine transferase; BMD, bone mineral density; DBP, diastolic blood pressure; GGT, gamma-glutamyl transferase; SBP, systolic blood pressure; PTH, parathyroid hormone; RR, relative risk; 25OHD, 25-hydroxyvitamin D.
[b] Change from baseline.
[c] Calculated using log-binomial regression.

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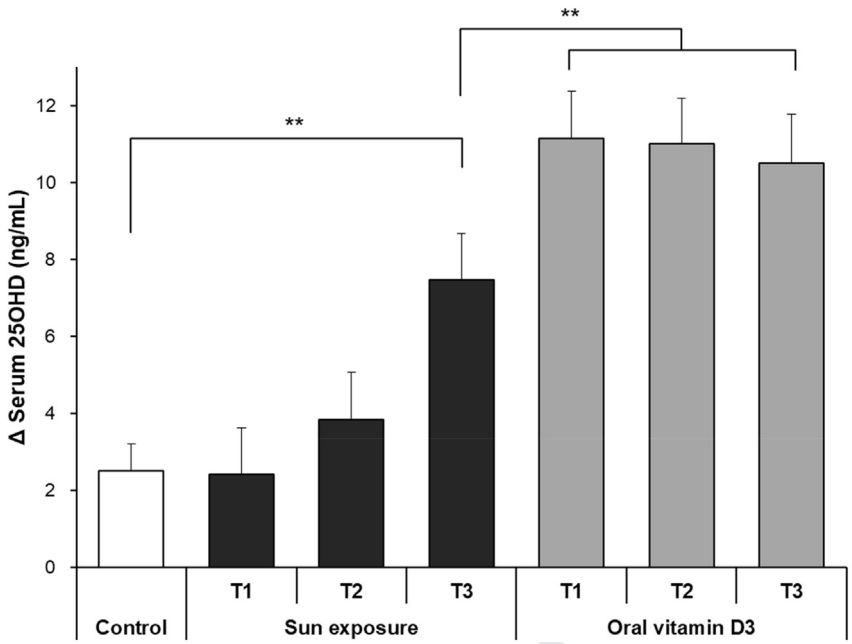

Fig. 3. The LSM ± SE changes in serum 25OHD concentrations from baseline to week 8 according to compliance to each treatment protocol. In the sun exposure group, only those whose sun exposure scores were ranked in the top tertile had a significant LSM increase in serum 25OHD concentrations compared with placebo (LSM difference: 5.03 ± 1.38 ng/mL; $P < 0.01$), but the changes in the other tertiles were not significant ($P \geq 0.33$). In the oral vitamin D_3 group, we found no significant differences in the LSM changes in serum 25OHD concentrations across the compliance tertiles ($P \geq 0.63$). LSM, least-square means; T, tertile of the compliance to the treatment protocol (T1: bottom tertile, T3: top tertile); 25OHD, 25-hydroxyvitamin D; $^{**}P \leq 0.01$.

($P_{interaction} = 0.21$). We also found no significant interaction with BMI status (<23, ≥23 kg/m^2) ($P_{interaction} = 0.43$). When we additionally adjusted for age, sex, or skin type in the main model, those factors were not significant ($P \geq 0.12$) and no material difference in the fitted outcomes was observed. The results of per-protocol analyses were similar to those of the modified intention-to-treatment analyses.

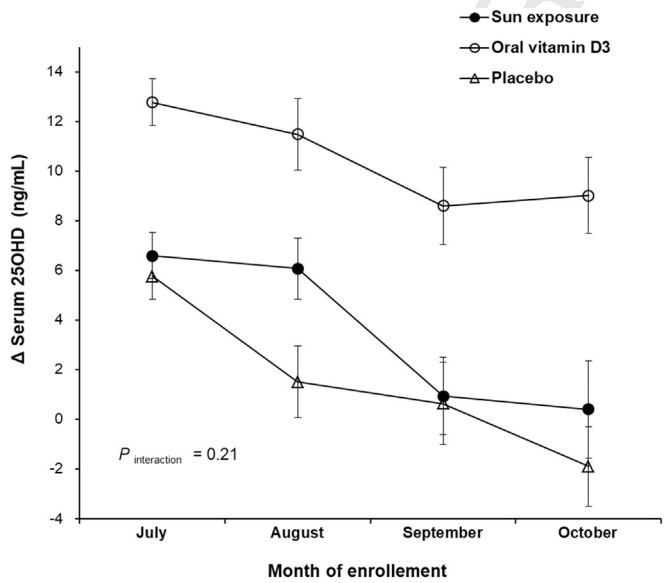

Fig. 4. The LSM ± SE changes in serum 25OHD concentrations from baseline to week 8 according to the months of enrollment. The greatest increases in serum 25OHD concentrations were observed among those enrolled in July, and the changes consistently decreased after that month in all three groups. The interaction term between the month of enrollment and treatment was not significant ($P_{interaction} = 0.21$). LSM, least-square means; 25OHD, 25-hydroxyvitamin D.

Despite the significant between-group differences in the changes of serum 25OHD concentrations, we found no differences in the changes of the secondary outcomes except for DBP (Table 2). After 8 weeks, DBP increased in the oral vitamin D_3 and control groups, but not in the sun exposure group, with significant between-group differences ($P \leq 0.03$). In the subgroup analyses of those who achieved serum 25OHD concentrations ≥20 ng/mL at week 8, we found no significant between-group differences in the changes of the secondary outcomes.

No participants discontinued treatment or withdrew from the trial due to adverse events. After 8 weeks, we found no significant differences in the serum and urine calcium concentrations across the groups; no participant developed hypercalcemia or hypercalciuria.

4. Discussion

In this trial, both sun exposure and 500 IU/d of supplemental vitamin D_3 significantly increased serum 25OHD concentrations compared with placebo. The mean increase of serum 25OHD levels and those who achieved 25OHD concentrations ≥20 ng/mL were greater in the oral vitamin D_3 group than in the sun exposure group. The compliance to enhanced sun exposure advice, however, was relatively low, and only those with adequate adherence had a significant increase in serum 25OHD. A few studies have directly compared the effects of sun (or artificial UV) exposure and supplemental vitamin D, and the results were mixed. Artificial UVB exposure was superior to 800 or 1600 IU/d of oral vitamin D_3 [13,22] and similar to 2000 IU/d [23] among white adults. In contrast, 800 or 1520 IU/d of oral vitamin D_3 was more effective than advised sun exposure [18]. In our study, the estimated doses of sun-derived vitamin D, on the bases of a comparison of the results from oral supplementation, were approximately 130 IU/d for the entire sun exposure group and 300 IU/d for those with sun exposure durations ≥30 min/d around noon, although the relationship

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between the UVB dose and the resulting changes in serum 25OHD may not be linear [24].

Most current health messages suggest a few short sessions of sun exposure during summer to ensure sufficient vitamin D production [1]. Guidelines suggest that exposure of 25% of the body skin area for 5–30 min between 10 a.m. and 3 p.m. two or three times per week can satisfy vitamin D requirements in those with skin type II or III [1]. Several clinical studies examined the efficacy of UVB irradiation on 25OHD levels [13,23,25–27]. A recent meta-analysis concluded that even partial exposure of the skin to moderate UV doses was effective in maintaining an adequate vitamin D status [24]. Conversely, other studies found that the current sun exposure practices of the general population do not provide sufficient amounts of vitamin D [10,12], suggesting that longer exposure durations than currently recommended ones might be needed to reach an optimal level of 25OHD (≥32 ng/mL) [10,28]. Furthermore, the sun-exposure time needed for a sufficient vitamin D status greatly varies between skin types [23,29]. As melanin reduces UVB penetration of the epidermis, limiting cutaneous vitamin D synthesis [1], dark-skinned individuals require longer durations of sun exposure than light-skinned ones for the same amount of vitamin D [5,17,18]. In our study of Korean adults, 20–30 min of daily sun exposure during summer and fall was not effective in achieving an adequate vitamin D status. Although sun exposure can be a simple and safe public health strategy, compliance is an important problem in real-world settings. Previous trials reported poor compliance or high drop-out rates with sun exposure [18,30]. In our study, despite our support to improve adherence, compliance to sun exposure was much lower than that to oral supplementation. Given the sun-avoiding culture in Korea, we suppose that adherence to sun exposure in the general population in real-life conditions would be much lower than our results. Therefore, for effective public adoption of sun-exposure guidelines, it is essential to take into account the widespread cultural practices in Asian countries.

Dietary requirement for vitamin D in healthy adults is not clear yet and may differ by subgroups of the population [18] and health outcomes [31]. In white adults with sunlight deprivation, 800 IU/d of vitamin D maintained serum 25OHD >25 ng/mL [32], but the same dose failed to increase serum 25OHD to >20 ng/mL in dark-skinned ethnicities [18]. Another study involving old adults reported that 1000 IU/d of oral vitamin D_3 increased serum 25OHD concentrations by 6.3 ng/mL after 1 year [33]. In our trial, 8 weeks of 500 IU/d of vitamin D_3 increased serum 25OHD levels by 10.9 ± 0.7 ng/mL from baseline and by 8.5 ± 1.0 ng/mL compared with placebo. Because we did not strictly limit background sun exposure, the former may be attributed to the combined effect of supplementation and background sunlight, and the latter would be closer to the supplementation effect only. Despite the wide safety margin, long-term safety data on high-dose vitamin D supplementation are lacking [34]. Notably, photosynthesis of vitamin D in the skin is self-regulated. Since excess sun exposure transforms previtamin D_3 and cholecalciferol into inert products (e.g. tachysterol), toxic levels of vitamin D cannot be reached through sun exposure [23,24]. In contrast, high-dose vitamin D supplementation is potentially toxic as the gut-absorption of this fat-soluble vitamin is high and no regulatory mechanism exists [15]. Previous studies reported that serum 25OHD levels increased linearly with the dose of supplementary vitamin D without a ceiling effect [35,36]. A very high dose of oral vitamin D increased the risks of falls and fractures [37]. Therefore, a thorough understanding of potential adverse outcomes is essential before recommending high-dose vitamin D supplementation in large populations [15].

Epidemiologic studies suggested that even mild vitamin D deficiency increases PTH levels and may deteriorate bone health [1], but evidence from clinical trials is lacking. In accordance with previous studies [38,39], we found no significant changes in serum PTH concentrations and whole-body BMD after intervention. In many observational studies, low 25OHD levels were associated with high blood pressure [40], diabetes mellitus [41], fatty liver disease [42], cardiovascular disease [3], and all-cause mortality [43]. However, data from randomized trials were mixed. A meta-analysis [44] and a recent large randomized trial [45] found no significant reduction in cardiovascular deaths with vitamin D supplementation. In our results, despite the correlations between serum 25OHD and several cardio-metabolic markers at baseline, the increases in serum 25OHD levels with either sun exposure or oral vitamin D_3 had few beneficial effects on cardio-metabolic markers. The discrepancy between epidemiologic and intervention-based data can be attributed to several reasons. First, short durations of interventions might have led to the null findings. A low vitamin D status may cause cardio-metabolic outcomes in the long term [46]. Second, sun exposure may affect health through both vitamin D and non-vitamin D pathways; thus, sun-derived and supplemental vitamin D may have different metabolic effects [6,47,48]. For instance, many vasodilators (e.g., carbon monoxide and nitric oxide) are produced only through sun exposure [49,50], which may explain the effect of sun exposure on DBP in our results. In addition, UVB irradiation increased the circulating levels of $1,25(OH)_2D$ (calcitriol) as well, which was not observed after vitamin D_3 supplementation [48]. Third, there might be subgroups benefiting from vitamin D replenishment. Low vitamin D status was a stronger predictor of cardiovascular events in hypertensive individuals than in normotensive ones [51]. Lastly, results of observational studies may be biased due to reverse causation or confounding [52].

Our study had several limitations. First, the sample size was relatively small, especially for the secondary outcomes. Second, the trial period was short to observe the long-term effects of the interventions on the outcomes, although it is known that it takes approximately 7 days for serum 25OHD to peak after UVB exposure [14] and 30 days to reach a plateau after oral supplementation [53]. The half-life of serum 25OHD varies widely according to various factors [9,54,55], and the sources of vitamin D (e.g., sunlight, oral supplementation) possibly affect it. As the serum 25OHD concentration is influenced by its half-life, it is difficult to predict how the results observed in this study will change over time. Third, because our trial was conducted between July and early December, dermal vitamin D synthesis in the sun exposure group might have been less effective after November at the latitude of Seoul (37 °N) [5,50]. In addition, we were not able to control for other environmental factors (e.g., air pollution), which are known to influence UVB reaching the earth's surface [50]. We measured serum 25OHD using CLIA, which is reported to underestimate the absolute values of 25OHD compared with liquid chromatography–tandem mass spectrometry. However, a high degree of relative concordance between the two methods exists [56]. Lastly, our results will not be applicable to those living at different latitudes or with different skin types.

This study has several strengths. To our knowledge, this is one of the few randomized clinical trials comparing the effects of sun exposure and oral vitamin D supplementation on serum 25OHD and various cardio-metabolic markers in Asian populations. Our results may be useful in better understanding the optimal amounts of sun exposure and vitamin D intake in Asian countries with similar climatic conditions and cultural practices. Vitamin D trials conducted among healthy young adults on cardio-metabolic effects are quite scarce worldwide. We used real-time records of individuals' sun exposure to assess the amount more precisely. To control for background sunlight effects, we used a placebo. The high retention rate minimized a risk of selection bias.

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In conclusion, both sun exposure and 500 IU/d of oral vitamin D_3 supplementation significantly raised serum 25OHD levels in young Korean adults. However, the mean increase of serum 25OHD was greater with oral vitamin D_3 supplementation than with sun exposure. Compliance to sun exposure advice was relatively low, and only those with adequate compliance achieved a significant increase in serum 25OHD levels. We found little beneficial effect on cardio-metabolic markers with either sun exposure or oral vitamin D_3. For evidence-based public messages to ensure a sufficient vitamin D status in Asian populations, larger and longer trials with different sun exposure protocols and supplementary doses are warranted.

Author contributions

H-KJ and BC conceptualized and designed the research; H-KJ and BC conducted research and contributed to data collection; H-KJ and S-sH analyzed data; H-KJ, BC, and CSL supervised the progress of the investigation; H-KJ drafted and revised the manuscript; H-KJ, BC, CSL, and SEJ contributed to manuscript review and critically revised the manuscript; all authors are responsible for the veracity and precision of the data analysis. All authors have read and approved the final manuscript.

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Conflicts of interest

There are no conflicts of interest to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2019.03.021.

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