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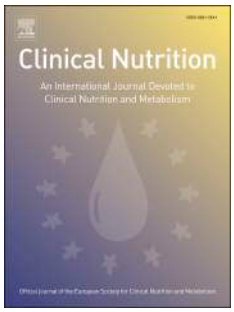

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The effect of active vitamin D supplementation on body weight and composition: a meta-analysis of individual participant data

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Abstract

Background & Aims: Obesity is associated with vitamin D (VitD) deficiency. However, previous studies showed mixed effects of VitD (25-hydroxyVitD/calcidiol) supplementation on body weight. The biological actions of VitD require the hydroxylation of inactive VitD into active VitD (1.25-dihydroxyVitD/calcitriol). This step is highly regulated; therefore, supplementing with inactive VitD might not be sufficient to overcome the potential adverse health effects of VitD deficiency. The objective of this study was to conduct a systematic review and individual participant data (IPD) meta-analysis of data acquired from randomised placebo-controlled calcitriol trials (RCTs) to determine the effects of calcitriol on body weight and weight-related parameters.

Methods: Studies were identified from MEDLINE, EMBASE, and CENTRAL databases up to January 27, 2024, and excluded those involving dialysis or cancer patients. We obtained IPD from eligible trials and assessed bias using the Cochrane Collaboration risk-of-bias tool and methodological quality using the Heyland Methodological Quality Score. The study was prospectively registered with PROSPERO (CRD42017076202).

Results: Although none of the studies reported information regarding our primary objective, we obtained IPD for 411 patients, with 206 randomised to receive calcitriol and 205 to placebo. This dataset enabled us to conduct an IPD meta-analysis with 17,084 person-months of follow-up (median: 11 months). Meta-analysis showed that calcitriol does not alter body weight, BMI, waist circumference, fat mass or lean body mass compared to placebo. Adjusting for age and sex did not alter the outcomes.

Conclusions: In conclusion, this systematic review and IPD meta-analysis indicate that calcitriol does not affect body weight in normal-weight postmenopausal women and lean patients with type 1 diabetes nor in people suffering from obesity, type 2 diabetes and chronic kidney disease. Whether calcitriol lowers body weight in VitD-sufficient people with obesity remains to be elucidated.

Keywords: Body mass index, calcitriol, meta-analysis, systematic review, vitamin D.

Introduction

Obesity, characterised by an excessive accumulation of body fat due to an imbalance between energy consumption and expenditure, is a prevalent and debilitating condition with well-established links to various metabolic disorders, including type 2 diabetes, dyslipidaemia, hypertension, cardiovascular disease and various types of cancer [1, 2]. Obesity is also associated with vitamin D (VitD) deficiency [3-5]. The National Academy of Medicine defines VitD deficiency (VitDD) in adults as a serum 25-hydroxyVitD (calcidiol) concentration below 50 nmol/L [6]. In the National Health and Nutrition Examination Survey, 41.6 per cent of 4.495 adult participants were VitD deficient, demonstrating a high prevalence of VitDD in the general population, with a higher prevalence observed among individuals with obesity (53.8% v. 33.0%) [7]. Cross-sectional data consistently demonstrate an inverse correlation between body fat mass and serum concentrations of 25-hydroxyVitD [3, 5, 7-19]. A meta-analysis of 34 studies corroborated this inverse association, reporting a 4% decrease in 25-hydroxyVitD levels for every 10% increase in BMI [20]. This inverse relationship has been attributed to several factors, including dilution of VitD in adipose tissue, reduced dietary VitD intake or sunlight exposure [5, 21, 22]. However, these observations have also prompted questions about reverse causality: Does VitD metabolism affect long-term energy balance, and could its deficiency contribute to weight gain and obesity?

VitD is a fat-soluble secosteroid hormone primarily recognised for its role in calcium metabolism and bone turnover [23-25]. Recent studies have unveiled its far-reaching physiological properties beyond mineral ion homeostasis, including regulating innate and adaptive immune responses [26]. Epidemiological associations between VitDD and certain types of cancer have been established [8, 27-29], which may be partly attributed to VitD's immunomodulatory effects [30-32]. Moreover, mounting evidence suggests that VitD plays a role in glucose, lipid, and energy metabolism [33-35].

Firstly, *in vitro* data using human pre-adipocytes and adipocytes have demonstrated that calcitriol treatment significantly diminishes the release of cytokines and chemokines, thereby reducing inflammation [36-38]. Secondly, calcitriol administration in diet-induced obese mice reduced food intake [39], suggesting that

calcitriol treatment could benefit obesity management [39]. Thirdly, limited evidence from human intervention trials supports the notion that cholecalciferol supplementation promotes weight loss and enhances metabolic health: VitD supplementation resulted in a larger reduction in energy intake and improved postprandial insulin sensitivity in individuals with overweight or obesity [40, 41]. However, most studies were small and of short duration. A larger follow-up study of cholecalciferol supplementation in 200 adults with obesity failed to demonstrate any significant effect on body weight or adiposity [42]. Furthermore, a meta-analysis of 12 randomised controlled trials, including two trials involving 66 women with VitDD, found no significant effect of standard-dose cholecalciferol supplementation on body weight [43].

It is imperative to recognise that VitD was administered as the inactive cholecalciferol in these studies, while calcitriol (1.25-dihydroxyVitD) is the active VitD metabolite with VitD receptor (VDR) binding potential and biological action. Hydroxylation of VitD to generate calcitriol is regulated by parathyroid hormone and phosphate in the kidney (Figure 1). We have previously demonstrated that circulating 25-hydroxyVitD levels correlate poorly with calcitriol levels in individuals with obesity [21]. Therefore, cholecalciferol treatment might not sufficiently elevate levels of active VitD, potentially explaining the negative results observed in clinical trials.

To address this research gap, we conducted an individual participant data (IPD) meta-analysis of placebo-controlled calcitriol intervention trials in adults to investigate the effects of calcitriol on body weight, adiposity and composition.

Methods

Study design

The study protocol adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses protocol (PRISMA-P) checklist (Supplemental Figure *S*1; [44]). Specifically, we adhered to the PRISMA-IPD statement in reporting our findings [45]. We prospectively registered the systematic review protocol at

the International Prospective Register of Systematic Reviews (PROSPERO) on September 5, 2017, with registration number CRD42017076202 [46].

Eligibility criteria

Published studies were eligible for inclusion if they were randomised, placebo-controlled clinical trials using intravenous or oral calcitriol treatment in adults for ≥ two weeks. In instances where studies with more than two intervention arms (e.g., comparing calcitriol and ergocalciferol to placebo) were involved, the calcitriol versus placebo comparison was included in the current analysis. Uncontrolled studies, studies involving children or adolescents with a follow-up duration of less than two weeks, and studies involving patients undergoing renal replacement therapy (RRT) or with cancer were excluded, as these conditions can significantly disrupt vitamin D metabolism, confounding the effects of calcitriol per se. No restrictions were applied to other comorbidities.

Outcomes

The study's primary outcome was to assess calcitriol's effect on body weight. We compared the changes in body weight from baseline to end of treatment between the calcitriol and placebo-treated groups. Secondary outcomes included the effects of calcitriol on i. BMI, ii. waist circumference, iii. (total) body fat mass, and iv. lean body mass.

Literature search

To ensure a comprehensive search, an experienced medical information specialist (JL) thoroughly searched MEDLINE, EMBASE, and CENTRAL databases from inception to January 27, 2024, using a search

121 strategy that included relevant search terms for calcitriol (Supplemental Table *S1*). Language restrictions
122 were not applied. Duplicates were removed using EndNote X7 (Clarivate Analytics, Toronto, Ontario,
123 Canada). Search results were stored and analysed using Covidence systematic review software (Veritas
124 Health Innovation, Melbourne, Australia). We manually reviewed reference lists of selected articles to
125 identify additional relevant publications.

126

127 *Study selection*

128 All identified entries from the literature search were independently screened by at least two investigators
129 (SMO, SC and/or IA) based on the predetermined eligibility criteria. For entries accepted by at least one
130 investigator, full-text publications were obtained and assessed independently by the two investigators for
131 eligibility. Disagreements were resolved by consulting a third investigator (KWtH).

132

133 *Data extraction*

134 In addition to advantages concerning data quality and analysis [47], we decided to take the IPD
135 approach because i. the original calcitriol studies were designed with other primary outcomes, ii. the
136 original calcitriol papers often did not describe our outcomes of interest, and iii. we hypothesised that
137 our outcomes of interest were, in fact, available from the selected studies.

138 We retrieved contact information for the corresponding author from a recent publication or through
139 online research. We reached out to corresponding authors by email, requesting their collaboration on this
140 IPD meta-analysis. Non-responders were sent a reminder after six weeks. We also contacted co-authors
141 whenever email addresses could be traced.

142 From authors who agreed to participate, we requested de-identified IPD for baseline and follow-up
143 outcomes of interest, including i. weight, ii. height, iii. body-mass index, iv. waist-circumference, v. fat

mass, vi. total body fat, and/or vii. lean body mass. In addition, we extracted information on i. study characteristics, ii. intervention and control treatments, iii. information to assess the risk of bias, and iv. participants' baseline characteristics. Two reviewers (SMO, SC and/or IA) independently extracted data using standardised forms.

Data verification

Upon receiving the IPD, two investigators (SMO, SC and/or IA) verified the integrity of the data by replicating the baseline characteristics table presented in the published trial report. We contacted the study authors to address any missing data or queries arising from these integrity checks. Once all queries were resolved, the clean and de-identified IPD were uploaded to a central study database in IBM® SPSS Statistics for Windows, Version 28.0. (Armonk, NY: IBM Corporation).

Data synthesis and statistical analysis

We adhered to established guidelines for data synthesis and meta-analysis of IPD [48]. Initially, we performed a separate reanalysis of data from all included studies to verify the accuracy of the obtained outcome data. If necessary, we contacted the original authors to authenticate the reanalysis and address any discrepancies.

In the subsequent phase, we employed a one-stage approach to conduct an IPD meta-analysis with a two-level structure (i.e., repeated measures were clustered within patients). Data were analysed using linear mixed model analysis, reported as mean differences with 95% confidence intervals and associated *p*-values. All models incorporated treatment and prespecified confounders (i.e., baseline value of the outcome of interest, study, sex and age). Thereafter, we commenced the analysis with a model including time, treatment and time-by-treatment interaction.

In this context, mixed model analysis is recommended as it accounts for the dependency of observations and possesses favourable properties regarding missing data [49]. Time was introduced as a categorical variable and represented by dummy variables to assess treatment effects at different time points.

Data were analysed using IBM SPSS Statistics for Windows, Version 28.0. (Armonk, NY: IBM Corporation). Pooled IPD outcomes are presented as mean differences (MD) with 95% confidence intervals (CI) and associated p values. The reported p values are two-tailed, and statistical significance was considered when $p < 0.05$.

Risk of bias assessment

The revised Cochrane Collaboration risk-of-bias tool for randomised trials [50] was used to assess bias arising from the: i. randomisation process, ii. blinding process (of participants, investigators, and outcome assessors), iii. (missing) outcome data, iv. outcome measurement, and v. selection of the reported results. We evaluated the methodological quality of individual studies using the Heyland Methodological Quality Score (MQS) [51]. Studies with an MQS ≥ 8 were regarded as having high methodological quality. Reporting bias was assessed by contacting study authors to inquire if all prespecified outcomes were reported. Two investigators (SMO, SC, and/or IA) independently evaluated study quality, and consensus resolved disagreements.

Results

Selection process and general characteristics

Through electronic and manual searches, we assessed 3554 original records, identifying 93 studies that potentially met our predefined eligibility criteria. Upon further evaluation, none of these studies contained information relevant to our outcomes of interest. Additional information was acquired from the authors

190 to refine our search results. The study selection process is depicted in Figure 2. Ultimately, ten studies met
191 the eligibility criteria for inclusion in the final analysis.

192 The twelve included studies provided data from three unique study populations (Table 1). We obtained
193 IPD outcomes for 411 participants, of whom 206 were randomly allocated to calcitriol treatment and 205
194 to placebo. One study was conducted in the USA [52-58], and the other two were conducted in Western
195 Europe [59-61]. One study enrolled only postmenopausal women, although the other two enrolled both
196 men and women but with comorbid conditions (i.e., diabetes and/or chronic kidney disease). Baseline
197 serum 25-hydroxyVitD concentrations were determined in the postmenopausal women only,
198 demonstrating that 237 of these 246 women (96.3%) had VitDD prior to randomisation. In all studies,
199 calcitriol treatment was administered as oral Rocaltrol®, with daily doses ranging from 0.25 – 0.50 µg.
200 The duration of follow-up ranged from nine to 36 months.

201 To ensure the integrity of the obtained IPD, we replicated the primary analyses in the published papers,
202 where applicable. The risk-of-bias assessment and Heyland MQS are provided in Supplemental Tables *S2*
203 and *S3*, respectively. All RCTs demonstrated a low risk of bias and MQS ≥ 8, indicating high
204 methodological quality.

205

206 *Primary outcome: effect of calcitriol on body weight*

207 The effect of calcitriol on total body weight, was not statistically significant different from the effect of
208 placebo in any of the included studies (Table 2). Meta-analysis of pooled IPD, adjusted for participants'
209 age and sex, confirmed that calcitriol treatment had no significant effect on total body weight (MD: -0.59
210 kg, 95% CI: -1.55 – 0.37 kg, P=0.224; Figure 3). In line, calcitriol did not affect BMI significantly in individual
211 studies (Table 2) or overall IPD meta-analysis (MD: -0.78 kg/m^2, 95% CI: -1.69 – 0.127 kg/m^2, P=0.092;
212 Figure 3).

Secondary outcomes: effect of calcitriol on waist circumference, body fat mass, and lean body mass

Secondary outcomes, waist circumference, body fat mass, and lean body mass, were only available in Gallagher's cohort [52-58]. In these postmenopausal women, calcitriol did not significantly affect these secondary outcomes (Table 2). Adjustments for participants' age and sex did not alter these results (Figure 3).

Discussion

This systematic review and IPD meta-analysis demonstrate that calcitriol treatment does not significantly reduce body weight or alter body composition. These results were consistent across different study populations, including non-obese postmenopausal women, individuals with type 2 diabetes and chronic kidney disease and lean young adults with type 1 diabetes.

The relationship between obesity and VitDD is well-established. Volumetric dilution, low dietary intake, and/or sunlight exposure may contribute to the increased prevalence of VitDD in humans with obesity. However, it is unclear whether VitDD plays a causal role in the development of obesity. In this regard, VitD supplementation (cholecalciferol) has been investigated as a potential therapy for metabolic disorders. Studies have yielded conflicting results, with overall negative findings [62-64]. However, these trials primarily examined the effects of inactive VitD or cholecalciferol, whereas emerging preclinical evidence suggests that active VitD/calcitriol may benefit food intake and body weight [39]. Nonetheless, our human findings indicate that calcitriol alone may not be a major, effective strategy to reduce body weight or improve body composition in standard dosages. However, we acknowledge that the strength and generalisability of this conclusion remain limited due to the limited available data.

This study has several strengths. Incorporating unpublished, original data from three independent clinical cohorts allowed us to analyse a substantial amount of novel data from a relatively large number of participants. In this regard, using IPD meta-analysis methods is another key strength of this study. This approach enabled us to thoroughly verify the quality of the original data, standardise outcome parameters across studies and adjust for baseline outcome values, resulting in a more robust and precise meta-analysis than traditional methods. Furthermore, we only included placebo-controlled trials; all included trials used a clinically relevant calcitriol dose within the recommended therapeutic range, and all had sufficiently long follow-up durations.

This study also has some limitations. Although we successfully obtained IPD from three unique trials with 411 participants, despite repeated efforts, we could not contact the authors of 33 of the 90 potentially eligible studies (37%). This may have introduced some non-response bias. However, this is not a major source of concern for two reasons: i. the available data shows little heterogeneity, suggesting that the studies included in our analysis represent the broader body of literature; ii. it seems conceptually unlikely that authors of studies where calcitriol affected body weight would be less willing to share IPD than authors of 'negative' or 'neutral' studies. In addition, the limited number of studies in our analysis prevented us from conducting a subgroup analysis to formally investigate the specific effects of calcitriol on weight change in individuals with obesity. Although Karalliedde et al. [59] included a substantial number of participants with obesity (BMI 32.4 [28.0-37.9] and 32.5 [27.7-36.2] for calcitriol and placebo, respectively), no significant effect of calcitriol on body weight was observed in this population. However, it is important to note that the included participants in that study had type 2 diabetes and chronic kidney disease (CKD) stage 3. CKD is associated with impaired calcitriol production, and calcitriol treatment in these patients restores low calcitriol levels. Therefore, it remains to be determined whether treatment with calcitriol affects body weight of individuals with obesity, normal kidney function, and normal VitD status. In this regard, data from rodent models of obesity are encouraging [39] .

Furthermore, baseline cholecalciferol levels were only available from one cohort, limiting our ability to assess whether pre-treatment VitD status affected the effect of calcitriol treatment on body weight. Additionally, we could not perform Funnel plot analysis to evaluate publication bias because the number of included studies was less than ten [65]. This limitation prevented us from formally assessing whether the absence of significant effects in our meta-analysis is due to publication bias or true effects. Finally, we did not perform sensitivity analyses due to the small number of studies with little heterogeneity with respect to the outcome of interest.

Conclusion

In conclusion, this systematic review and IPD meta-analysis shows that in postmenopausal women, in patients with type 1 diabetes without obesity and in adults with overweight/obesity, type 2 diabetes and CKD stage III, calcitriol treatment does not affect body weight or composition. Whether calcitriol treatment reduces body weight in individuals with obesity who are VitD sufficient remains to be elucidated.

Funding statement

No funding was received for this study.

Conflict of interest

We declare that there are no conflicts of interest regarding this manuscript.

Author Contribution

SMO conducted data curation, formal analysis, investigation, methodology, resource management, validation, and visualisation and contributed to the original draft, review, and editing. IA and SC were involved in data curation, validation, and editing. JL conducted the search. JWT provided methodology and statistical guidance. CW, CG and JK contributed to data sharing and editing. JAR and MJS provided supervision and participated in editing. KWtH contributed to supervision, data curation, validation, and editing. All authors have read and approved the published version of the manuscript.

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Table 1. Study characteristics. Data are presented in median [IQR].

Study	Number of participants	Population (% female)	Age (years)	Baseline serum [25(OH)D] (in nmol/L)	Intervention (daily dose in µg)	Duration of follow-up (months)	Country
Gallagher et al.*	246	Postmenopausal female (100)	71.4 [68.5-74.3]	78.8 [61.3-92.5]	Rocaltrol (0.50)	36	USA
Karalliedde et al. **	127	Type 2 diabetes and chronic kidney disease stage III (29.9)	67.0 [60.0-70.0]	not available	Rocaltrol (0.50)	11	UK
Walter et al. (2010)	40	Type 1 diabetes mellitus (27.5)	27.7 [22.4-32.8]	not available	Rocaltrol (0.25)	9	Germany

* Seven articles published between 1980 and 2011

** Four articles published between 2022 and 2023

Table 2. The effect of calcitriol supplementation on body composition. Data are presented as median [IQR] or mean ± standard deviation, the Mann-Whitney Test and t-test were used to analyse the data.

Study	Parameter	Calcitriol				Placebo				*p*	
		Baseline		Follow-up		Baseline		Follow-up		Baseline	Follow-up
		n		n		n		n			
Gallagher group*	Weight (kg)	123	64.1 [57.2-71.1]	101	62.3 [54.9-71.7]	123	63.6 [57.0-73.3]	112	64.0 [56.9-74.0]	0.606	0.340
Walter et al. (2010)		22	69.8 ± 10.8	20	70.4 ± 10.6	18	72.9 **± 15.3**	18	74.9 ± 15.2	0.478	0.300
Karalliedde group **		61	94.6 [80.2-107.0]	61	95.4 [77.3-108.6]	64	92.4 [79.8-106.0]	64	92.8 [79.0 - 111.3]	0.838	0.876
Gallagher group*	BMI (kg/m^2)	123	24.7 [22.6-28.4]	101	24.2 [21.3-27.8]	123	25.5 [22.6-28.6]	112	24.7 [22.6-28.4]	0.598	0.278
Walter et al. (2010)		22	22.2 [20.7-24.2]	20	22.9 [20.9-24.8]	18	21.9 [20.2-24.3]	18	22.8 [21.0-24.1]	0.925	0.942
Karalliedde group **		61	32.4 [28.0-37.9]	61	32.2 [28.2-37.0]	64	32.5 [27.7-36.2]	64	33.0 [27.0-36.3]	0.730	1.000
Gallagher group*	Waist circumference (cm)	122	86.0 [77.5-91.6]	101	83.5 [75.5-89.8]	122	83.3 [77.5-93.1]	111	84.0 [77.5 - 91.8]	0.669	0.455
Gallagher group*	Body fat mass (kg)	123	27.0 [21.2-33.4]	101	27.1 [20.3-34.7]	123	27.8 [21.1-34.3]	112	27.6 [21.5 - 34.6]	0.643	0.371
Gallagher group*	Lean body mass (kg)	123	35.1 [32.8-38.6]	101	34.7 [32.2-36.9]	123	35.1 [32.8-38.6]	112	34.7 [32.2 - 36.9]	0.666	0.437

* Seven articles published between 1980 and 2011

** Four articles published between 2022 and 2023

Figure 1. Ultraviolet B (UVB) light converts 7-dehydroxycholesterol in the skin to cholecalciferol. Ingested vitamin D, transported in chylomicrons, reaches the liver. Vitamin D Binding Protein (DBP) carries free VitD to tissues. In the liver, cholecalciferol becomes 25-hydroxyvitamin D, then travels to the kidneys. There, under the influence of parathyroid hormone (PTH), it transforms into its active form—1.25-dihydroxyvitamin D. This active form has several effects: it boosts bone mineralization, increases calcium and phosphate reabsorption in the kidneys and enhances calcium absorption from the intestine. The process is regulated by PTH, responding to low blood calcium.

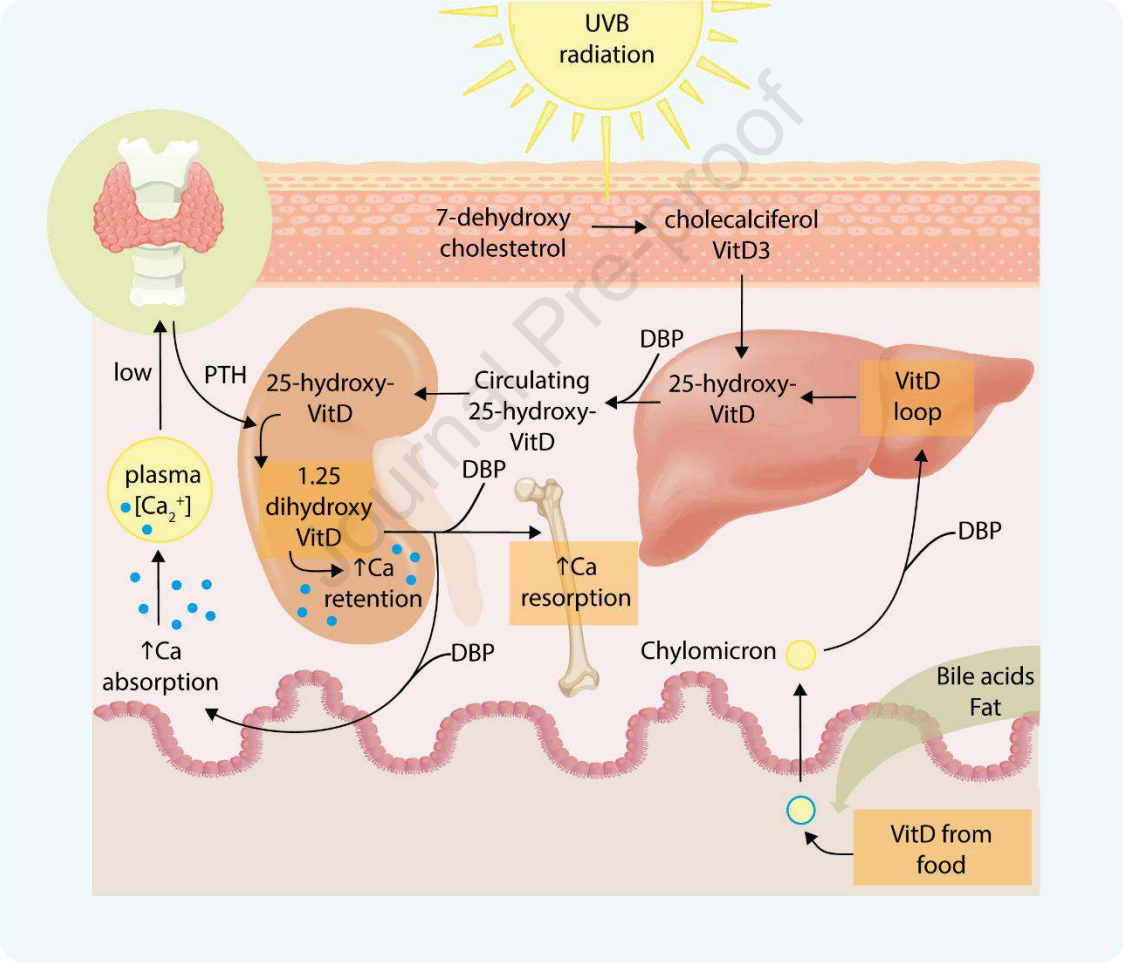
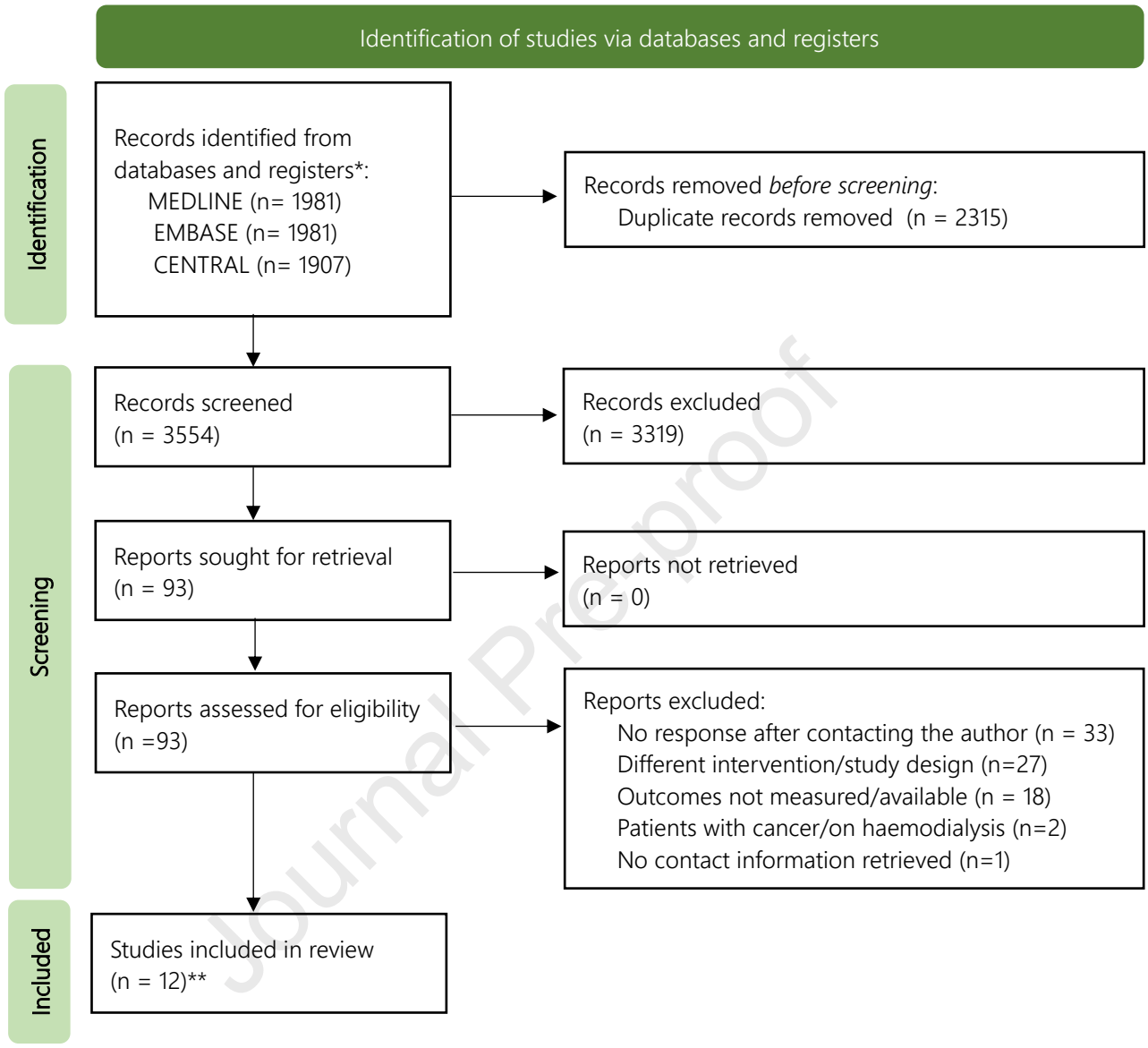


Figure 2. The PRISMA flow diagram of the literature search.



* From inception to 27 January, 2024.

** Eleven out of the twelve included studies contain data from only three unique study populations.

Figure 3. Combining intervention estimates from calcitriol supplementation uncorrected (A) and corrected (B) for age and sex.

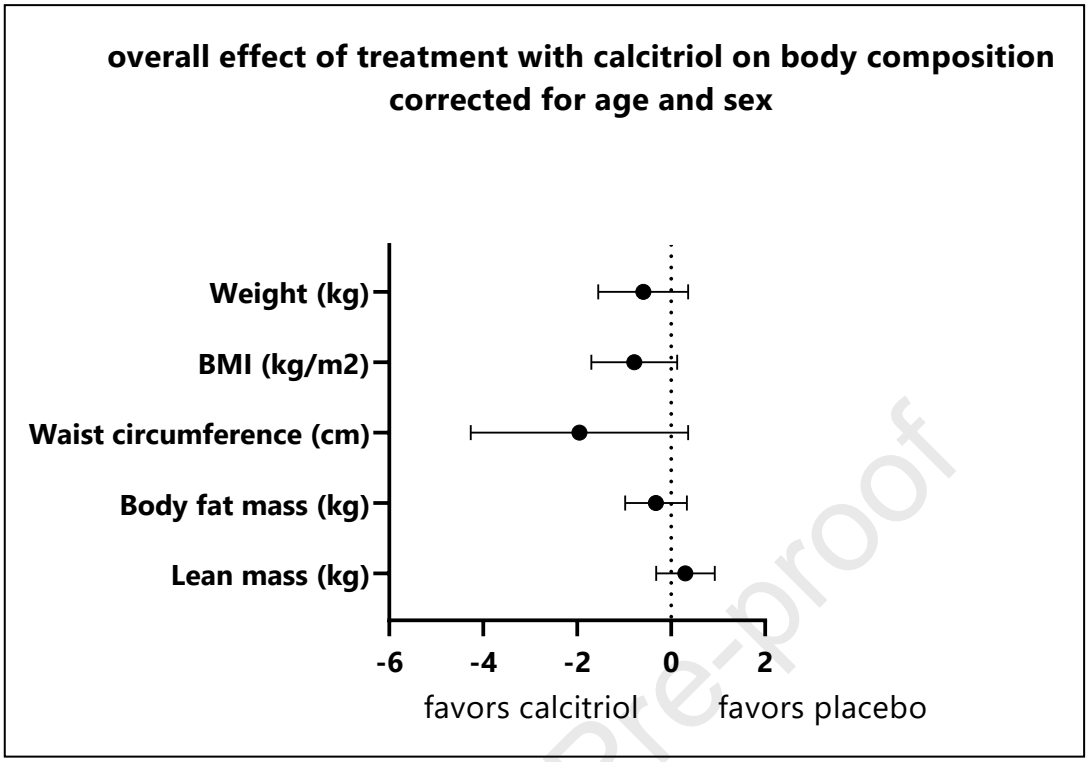
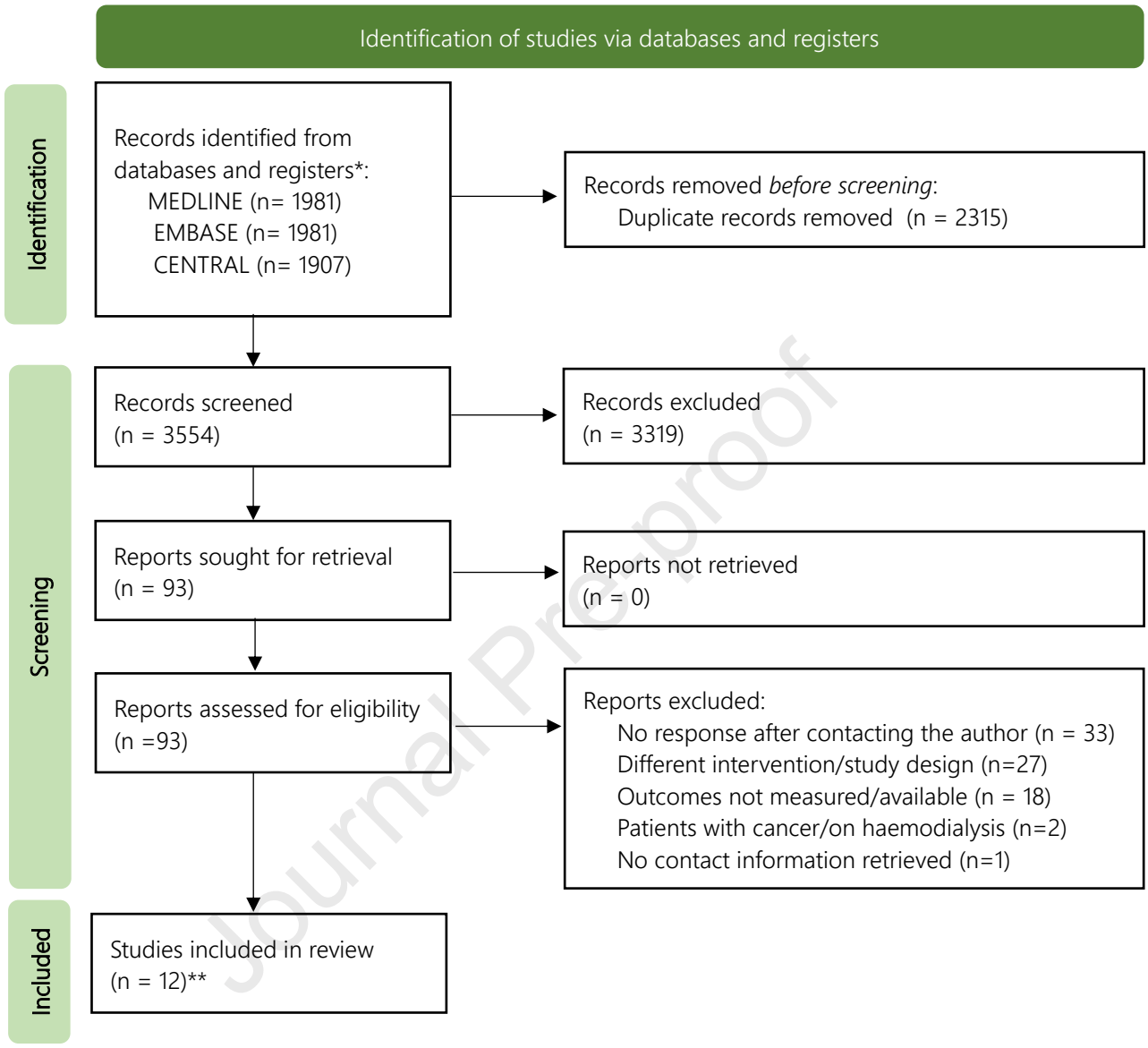


Figure 2. The PRISMA flow diagram of the literature search.



* From inception to 27 January, 2024.

** Eleven out of the twelve included studies contain data from only three unique study populations.