REVIEW

The Effects of Milk Supplementation on Bone Health Indices in Adults: A Meta-Analysis of Randomized Controlled Trials

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ABSTRACT

Milk contains a number of bone-beneficial nutrients. However, milk, due to the D-galactose content, might have unfavorable effects on bone health. A meta-analysis of randomized controlled trials (RCTs) was performed to clarify the effects of milk supplementation on bone mineral density (BMD), bone turnover markers [N-terminal telopeptide of type I collagen (NTx), C-terminal telopeptide of type 1 collagen (CTx), osteocalcin, bone alkaline phosphatase (BALP), and procollagen type 1 N-propeptide (P1NP)], and hormonal indices related to bone metabolism [parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D], and insulin-like growth factor 1 (IGF-1)] in adults. The PubMed and Web of Science databases were searched. A random-effects model was used to estimate the pooled effect sizes. A total of 20 RCTs were included. The trial duration ranged from 1 mo to 36 mo. Milk supplementation resulted in a small but significant increase in BMD at the hip (+0.004 g/cm^2; $n = 9$ RCTs) and lumbar spine (+0.025 g/cm^2; $n = 7$), but did not significantly affect whole-body BMD ($n = 3$) and femoral neck BMD ($n = 7$). Milk supplementation reduced the concentrations of P1NP (–5.20 ng/mL; $n = 9$), CTx (–0.16 ng/mL; $n = 9$), and NTx (–8.66 nmol bone collagen equivalents/mmol creatinine; $n = 3$). The concentrations of osteocalcin ($n = 9$) and BALP ($n = 3$) were not affected by milk supplementation. Reduced parathyroid hormone PTH (–1.01 pg/mL; $n = 13$) concentrations and increased IGF-1 (+1.79 nmol/l; $n = 4$) concentrations were observed with milk supplementation. 25(OH)D (+3.73 ng/mL; $n = 11$) concentrations were increased with vitamin-D fortified milk supplementation. The addition of milk to the diet may potentially increase the likelihood of preventing bone loss by restoring bone homeostasis through the modulation of the calcium-vitamin D-PTH axis, bone remodeling rate, and growth hormone/IGF-1 axis. *Adv Nutr* 2022;13:1186–1199.

Statement of Significance: While milk is often recommended to optimize bone health, limited evidence in the literature has raised concerns regarding the potentially detrimental effects of increased milk consumption on bone health, increasing skepticism regarding the role of milk in bone health. Reassuringly, the present meta-analysis of randomized controlled trials in adults suggests that milk supplementation shows a small but significant increase in BMD at the hip and lumbar spine, and these findings are supported by reduced concentrations of several bone turnover markers and PTH.

Keywords: milk, bone mineral density, bone turnover, bone remodeling, bone mass, calcium

Introduction

Milk is a good source of nutrients [e.g., protein, calcium, phosphorus, vitamin D (if fortified)] that are important for maximizing bone mass accretion during growth and peak bone mass during adulthood to prevent age- or menopause-related bone loss during older age (1). For this reason, milk consumption is often recommended to optimize bone health; however, the recommendation of milk for the optimization of bone health is not without controversy. Paradoxically, hip fracture rates tend to be highest in countries with greater milk consumption (2), although this correlation may not be causal and might be due to confounding by factors such as life expectancy, vitamin D status, and ethnicity. Moreover, it has been hypothesized that milk [but not fermented dairy products (e.g., cheese, yogurt)] may have unfavorable effects on bone health because it is the major dietary source of D-galactose, which has been shown to cause premature aging in animal models through the induction of oxidative stress and chronic inflammation, factors that contribute to age-related bone loss and sarcopenia in humans (3). Although prospective cohort studies generally reported at least neutral, if not inverse, association between milk consumption and

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fracture risk (2), a prospective cohort study found that increased milk consumption was associated with a higher risk of hip fracture in Swedish women (3). Nonetheless, only randomized controlled trials (RCTs) can establish a causal relation between exposure and outcome. Although no RCT data on the effect of milk on fracture risk have been reported, numerous RCTs (4–23) have been performed to investigate the effects of milk on bone mineral density (BMD), bone turnover markers, and hormonal indices related to bone metabolism in adults. However, many of these RCTs were hampered by small sample sizes, resulting in limited statistical power to detect modest but meaningful changes in BMD, bone turnover markers, and hormonal indices. Thus, it is only through meta-analysis that their findings can be understood in aggregate. Given this consideration, we performed a meta-analysis of RCTs to clarify the effects of milk supplementation on BMD, bone turnover markers, and hormonal indices related to bone metabolism in adults.

Methods

The present meta-analysis was prepared and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist (24). The research question was defined by the Participants, Interventions, Comparisons, Outcomes, and Study (PICOS) framework. Two researchers (KH and J-SC) independently performed the literature search, study selection, data extraction, and assessments of the risk of bias (RoB) and certainty of the evidence. Discrepancies between the 2 investigators were resolved by mutual consent.

Search strategy

The PubMed and Web of Science databases were searched for relevant RCTs published in any language from their inception to July 2021, using the following combination of search terms: (milk OR dairy) AND (randomized OR randomly OR trial) AND (bone OR bone remodeling OR bone resorption OR bone formation OR bone turnover OR bone mineral density OR bone mass OR bone loss OR osteoporosis OR vitamin D OR N-terminal telopeptide of type I collagen OR NTx OR C-terminal telopeptide of type 1 collagen OR CTx OR osteocalcin OR alkaline phosphatase OR procollagen type 1 N-propeptide OR P1NP OR parathyroid hormone OR vitamin D OR insulin-like growth factor 1 OR IGF-1). We also screened the reference lists of the retrieved articles to avoid missing studies.

Study selection

The PICOS are shown in **Table 1**. Briefly, parallel or crossover RCTs that enrolled adults were included in the present meta-analysis if they met all of the following inclusion criteria: *1*) 1 or more intervention groups received nonfermented fortified or unfortified fluid or powdered milk and being compared with nondairy control (or placebo) or no intervention; *2*) reported effects on BMD, bone turnover markers [N-terminal telopeptide of type I collagen (NTx), C-terminal telopeptide of type 1 collagen (CTx), osteocalcin, bone alkaline phosphatase (BALP), and procollagen type 1 N-propeptide (P1NP)], and hormonal indices related to bone metabolism [parathyroid hormone (PTH), 25-hydroxyvitamin D [25(OH)D], and insulin-like growth factor 1 (IGF-1)]. For 25(OH)D, we only included the RCTs that assigned vitamin D-fortified milk as the treatment group, as milk does not naturally contain vitamin D. If the RCTs did not specifically mention whether fluid milk was fortified with vitamin D, the judgment on whether fluid milk was fortified with vitamin D was first made based on the vitamin D content of the milk. In this case, the milk must contain ≥100 IU of vitamin D per cup (250 mL). If the vitamin D content of the milk was not available, we assumed that the milk was fortified with vitamin D in the RCTs that were conducted in the countries where fluid milk is routinely fortified with vitamin D (2). For milk powder, the RCTs were expected to mention that vitamin D was added to the milk specifically or the milk must contain ≥100 IU of vitamin D per suggested serving size; otherwise, the milk was considered to not be fortified with vitamin D. If overlapping publications from the same trial participants were identified, we only included the one with the largest sample sizes and longest trial duration or the most complete relevant data. If original main trials and their extension or follow-up studies (e.g., investigating the effects of discontinuation) reported the same outcome data, we only included the former, as the latter generally generated fewer participants than the original main trial. However, we included the extension studies if the relevant outcome was not reported in the main trials (but reported in the extension studies).

Data extraction

From each of the included RCTs, the following information was extracted: first author name; year of publication; participant characteristics including mean age, sex, and health status; trial characteristics including trial design, trial duration, intervention, the number of participants in the intervention or control groups; the dose of milk taken; the amounts of calcium obtained from milk supplementation; whether the milk was fortified with vitamin D; baseline intake of calcium and protein; DXA manufacturers; vitamin D status; and values of BMD, bone turnover markers, and hormonal indices before and after the interventions.

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Supplemental Figure 1, Supplemental Tables 1–3, and the Supplemental Appendix are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
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Abbreviations used: BALP, bone alkaline phosphatase; BMD, bone mineral density; CTx, C-terminal telopeptide of type 1 collagen; IGF-1, insulin-like growth factor 1; NTx, N-terminal telopeptide of type I collagen; P1NP, procollagen type 1 N-propeptide; PICOS, Participants, Interventions, Comparisons, Outcomes, and Study; PTH, parathyroid hormone; RCT, randomized controlled trial; RoB, risk of bias; WMD, weighted mean difference; 25(OH)D, 25-hydroxy-vitamin D.

TABLE 1 Participants, Interventions, Comparisons, Outcomes, and Study design

Parameter	Criteria
Participants	Adults
Intervention	Nonfermented fortified or unfortified fluid or powdered milk
Comparison	Nondairy placebo or control or no intervention
Outcome	Bone mineral density, bone turnover markers (N-terminal telopeptide of type I collagen, C-terminal telopeptide of type 1 collagen, osteocalcin, bone alkaline phosphatase, and procollagen type 1 N-propeptide), and hormonal indices related to bone metabolism (parathyroid hormone, 25-hydroxyvitamin D, and insulin-like growth factor 1)
Study design	Parallel or crossover randomized controlled trials

Assessments of the RoB and certainty of the evidence

The RoB among the included RCTs was assessed using the Cochrane Collaboration's tool for assessing the RoB (25) that covers 6 domains of bias (each domain includes 1 or more specific entries), namely selection bias (random sequence generation; allocation concealment), performance bias (blinding of the participants and personnel), detection bias (blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective outcome reporting), and other bias. Based on careful assessment, each entry can be judged as "low risk" of bias, "high risk" of bias, or "unclear risk" of bias. The certainty of the evidence for each outcome was assessed using the NutriGrade (26) scoring system that consists of the following items: *1*) RoB, study quality, and study limitations (maximum 3 points); *2*) precision (maximum 1 point); *3*) heterogeneity (maximum 1 point); *4*) directness (maximum 1 point); *5*) publication bias (maximum 1 point); *6*) funding bias (maximum 1 point); *7*) study design (maximum 2 points). The following total score cut-off points were used to judge the certainty of evidence: 0 to <4 (very low), 4 to <6 points (low), 6 to <8 (moderate), and ≥8 points (high).

Statistical analyses

The 25(OH)D analysis included only vitamin-D fortified milk (see study selection), whereas other analyses included fortified or unfortified milk. If multiple doses of milk were assigned, we included those with the highest dose. If different fortification degrees of calcium or vitamin D were assigned, we included those with the highest dose of additional agents (e.g., milk + 600 g of calcium was chosen over milk + 300 g of calcium) or those with the maximal addition of agents (e.g., milk + calcium + vitamin D was chosen over milk + calcium). For 2-arm RCTs, in which the intervention group received milk and was compared with nondairy placebo/control/no intervention, any RCT was included regardless of the intervention dose and additional agents. The weighted mean difference (WMD) was used as the measure of effect sizes (or treatment effects). The pooled effect sizes and their 95% CIs were estimated using a DerSimonian and Laird random-effects model, which accounts for heterogeneity in treatment effects among the included RCTs (27). Three parameters, namely mean difference, SD change, and sample size, are required to calculate the pooled effect sizes. For parallel RCTs, the effect sizes were calculated by subtracting the mean changes in bone health indices from baseline to the end of the intervention in the control group from the average changes in bone health indices from baseline to the end of the intervention in the milk group. For crossover RCTs, the effect sizes were calculated by subtracting the mean values of bone health indices at the end of the control period from those reported at the end of the milk supplementation period. If not reported, the SD was computed from the reported SE, CI, or *P* value according to the standard formula (25). To standardize results from different DXA manufacturers, the values of BMD at the hip, femoral neck, and lumbar spine obtained by Lunar DXA were converted to Hologic DXA equivalent values using published conversion equations (28–30). Since such conversion equations have not been developed for whole-body BMD, we only included the RCTs that used Hologic DXA in the meta-analysis of whole-body BMD. The low number and relatively similar characteristics [e.g., mostly performed in Asian countries with a relatively low calcium intake, mostly enrolled females (particularly postmenopausal women), mostly enrolled older participants, mostly used vitamin D-fortified milk, mostly completed within either ≥1 y or < 1 y] of the RCTs included in each analysis and the absence of important baseline data (e.g., habitual milk intake, protein intake, vitamin D status) in several RCTs did not allow accurate and unbiased participant and trial characteristics to be performed, as the RCTs could not be evenly distributed across the subgroups. As different manufacturers produced the milk used for the trials, there may be variations in the nutrient content of the milk. For example, some manufacturers may produce milk with higher calcium than others. Therefore, it may not be appropriate to stratify the results according to the dose of milk taken. Instead, we used the amounts of calcium obtained from milk supplementation to better reflect the dose of milk taken. Furthermore, since all or most of the included RCTs enrolled Asian female participants, particularly postmenopausal women, we performed sensitivity analyses restricted to postmenopausal women and Asian participants. The degree of heterogeneity across trials was assessed using I^2 statistics. The I^2 values of <25%, 25–50%, and >50% were used to define low heterogeneity, moderate heterogeneity, and high heterogeneity, respectively (31). The potential

publication bias was assessed using Begg's rank correlation test and Egger's linear regression (32). If publication bias was detected, the trim and fill method was performed to correct the bias (33). All statistical analyses were performed using STATA software, version 11.0 (StataCorp.). All *P* values were 2-sided, and the level of significance was set at <0.05.

Results

Literature search

The study selection process, with reasons for exclusion, is shown in **Supplementary Figure 1**. The initial database searches resulted in 5374 publications. After duplicate removal and title/abstract screening, 101 publications were eligible for full-text review. Of these 101 articles, 81 were excluded for various reasons (**Supplementary Appendix**). Finally, a total of 20 (4–23) publications were included in the present meta-analysis. The characteristics of the included RCTs are summarized in **Supplementary Table 1**. Briefly, the eligible publications were published between 1995 and 2021.

RoB

The RoB assessment is summarized in **Supplementary Table 2**. Only a few RCTs adequately described the methods of random sequence generation (13 of 20 RCTs) and allocation concealment (3 of 20 RCTs). Nearly all of the included RCTs did not blind participants, personnel, and outcome assessors from the knowledge of which intervention a participant received. However, given that the outcome data were based on objective measurements (i.e., BMD, bone turnover markers, and hormonal indices), which are free from human judgment, the outcome measurements were less likely to be influenced by the lack of blinding. Therefore, the risk of performance bias and detection bias in all RCTs was judged as low. For incomplete outcome data, the attrition rates of 20% were used as a cut-off point. The attrition rates in milk and control groups after the randomization were $<20\%$ (low risk) in 16 RCTs, $>20\%$ (high risk) in 1 RCT, and not reported (unclear risk) in 3 RCTs. Since the possibility of selective outcome reporting could not be ruled out due to the unavailability of trial protocols, the risk of reporting bias in all RCTs was judged as unclear. The risk of other bias was judged as unclear in all RCTs, as bias may be present, but the information to assess whether an important RoB across RCTs exists was insufficient.

Meta-analyses

Twenty (4–23) RCTs were performed among generally healthy adults. Only 1 (13) RCT had a crossover design, whereas the remaining RCTs had a parallel design. Fifteen (4–10, 13, 15, 16, 18, 19, 21–23) RCTs enrolled older participants (aged $\geq$56 y), whereas 5 (11, 12, 14, 17, 20) others were conducted in young adults (aged 23–28 y). Sixteen (4, 5, 7–9, 11–15, 17–22) RCTs enrolled only women [mainly postmenopausal women (4, 5, 7–9, 13, 15, 18, 19, 21, 22) aged $\geq$56 y], 2 (10, 16) enrolled only men, and 2 (6, 23) enrolled both men and women. Eleven (4–7, 10, 11, 13, 14, 16, 20, 23) RCTs were performed in Western countries, with 9 (8, 9, 12, 15, 17–19, 21, 22) others conducted in Asian countries. The intervention duration was $\geq$1 y in 8 (4, 5, 8–10, 12, 16, 18) RCTs and $<$1 y in 12 (6, 7, 11, 13–15, 17, 19–23) RCTs. All RCTs assigned participants in the intervention group to supplement their habitual diet with either milk powder (ranging from 40 g/d to 110 g/d) or fluid milk (ranging from 237 mL/d to 1000 mL/d). In 13 (5–7, 9–12, 14–16, 19–21) RCTs, the milk was fortified with vitamin D. The majority of RCTs simply asked the participants in the control group to continue their habitual diet, while a few RCTs used beverages [such as juice (7), maltodextrin drink (14), rice-based drink (15, 19), and soy (22)] or placebo tablets (4, 5) as comparators. Not all RCTs reported information on baseline 25(OH)D concentrations and calcium and protein intake. Baseline protein intake was adequate (ranging from 63.8 g/d to 127 g/d). Baseline calcium intake was lower in Asian participants (ranging from 267 mg/d to 520 mg/d; mostly $\leq$500 mg/d) than in Western participants (ranging from 572 mg/d to 1268 mg/d). Baseline 25(OH)D concentrations varied widely across RCTs (ranging from 12.8 ng/mL to 58.5 ng/mL). Five RCTs either used Hologic DXA (4, 8, 12, 17, 18) or Lunar DXA (5, 9, 10, 16, 23) to measure BMD.

Three (8, 12, 17) RCTs were available for the analysis of whole-body BMD (no. of milk group/no. of control group: 313/316), 9 (4, 5, 8–10, 12, 16–18) for hip BMD (637/610), 7 (4, 8–10, 16–18) for femoral neck BMD (415/384), 7 (8–10, 12, 16–18) for lumbar spine BMD (587/560), 9 (5, 9, 11–15, 17, 22) for osteocalcin (529/521), 3 (12–14) for BALP (242/246), 9 (7, 11–13, 15, 19–22) for P1NP (582/592), 9 (7, 11–15, 19, 21, 22) for CTx (538/546), 3 (5, 7, 20) for NTx (124/126), 13 (4, 6, 7, 9, 10, 12–16, 19–21) for PTH (834/838), 11 (5, 6, 9, 11, 12, 14–16, 19–21) for 25(OH)D (716/720), and 4 (6, 11, 13, 23) for IGF-1 (136/138). Most of the analyses were predominantly based on the data from RCTs in Asian women (mostly postmenopausal women). Two (9, 23) RCTs that used Lunar DXA were excluded from the analysis of whole-body BMD (see statistical analyses). Of 11 RCTs included in the analysis of 25(OH)D, 3 (5, 6, 14) RCTs of American adults did not specifically mention whether fluid milk was fortified with vitamin D, and the nutrient content of the milk was not reported. However, the milk was likely to be fortified with vitamin D, as fluid milk is routinely fortified with vitamin D in the USA (2). The analysis was repeated by excluding those 3 (5, 6, 14) RCTs.

Compared with controls, milk supplementation resulted in a small but significant increase in hip BMD (0.004 g/cm^2, 95% CI: 0.002 to 0.007 g/cm^2; **Figure 1**) and lumbar spine BMD (0.025 g/cm^2, 95% CI: 0.005 to 0.045 g/cm^2; Figure 1), but did not affect whole-body BMD (0.005 g/cm^2, 95% CI: −0.006 to 0.016 g/cm^2; Figure 1) and femoral neck BMD (0.002 g/cm^2, 95% CI: −0.003 to 0.007 g/cm^2; Figure 1). There was no difference in the concentrations of osteocalcin (−0.11 ng/mL, 95% CI: −1.23 to 1.00 ng/mL; **Figure 2**) and BALP (0.25 μg/L, 95% CI: −0.39 to 0.89 μg/L; Figure 2) between the milk and control groups. However, the concentrations of

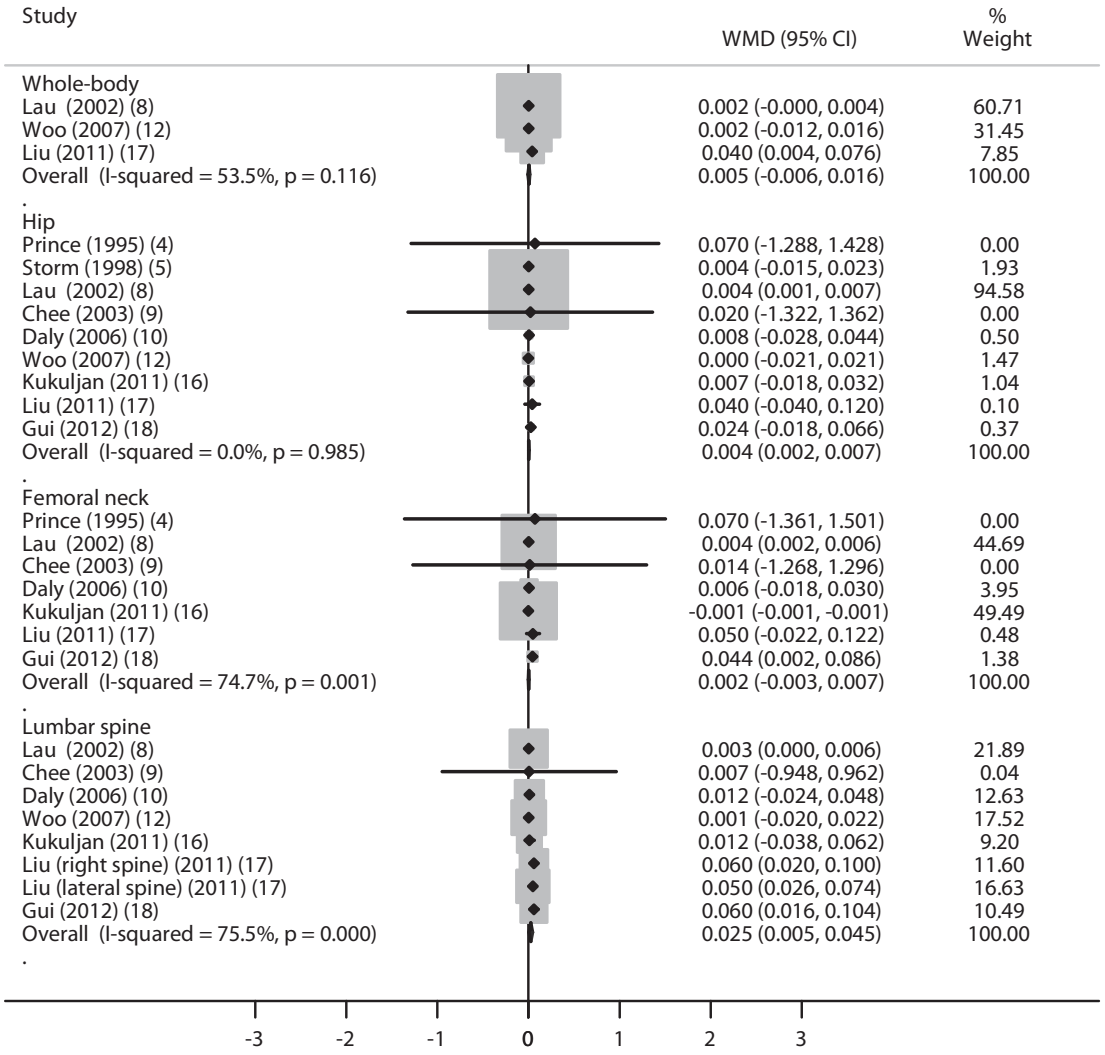

FIGURE 1 Forest plot of the change in bone mineral density (BMD) after milk supplementation in adults. Weighted mean difference: 0.005 (95% CI: −0.005 to 0.016) g/cm^2 for whole-body BMD, 0.004 (95% CI: 0.002 to 0.007) g/cm^2 for hip BMD, 0.002 (95% CI: −0.003 to 0.007) g/cm^2 for femoral neck BMD, and 0.025 (95% CI: 0.005 to 0.045) g/cm^2 for lumbar spine BMD. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

P1NP (−5.20 ng/mL, 95% CI: −9.07 to −1.33 ng/mL; **Figure 3**), CTx (−0.16 ng/mL, 95% CI: −0.23 to −0.10 ng/mL; **Figure 4**), and NTx (−8.66 nmol bone collagen equivalents/mmol creatinine, 95% CI: −13.57 to −3.75 nmol bone collagen equivalents/mmol creatinine; **Figure 5**) were reduced in the milk group relative to the control group. The milk group had a greater decrease in PTH concentrations (−1.01 pg/mL, 95% CI: −1.42 to −0.60 pg/mL; **Figure 6**) and a greater increase in the concentrations of IGF-1 (1.79 nmol/L, 95% CI: 1.03 to 2.56 nmol/L; Figure 6) than the control group. 25(OH)D (3.73 ng/mL, 95% CI: 1.36 to 6.11 ng/mL; **Figure 7**) concentrations were higher in the vitamin D-fortified milk than in the control group; the exclusion of 3 RCTs that did not specifically mention whether the milk was fortified with vitamin D did not materially alter the finding (5.73 ng/mL, 95% CI: 3.94 to 7.51 ng/mL). No heterogeneity was observed in the analyses of hip BMD and IGF-1(all $I^2 = 0\%$), whereas moderate to high heterogeneity was observed in the analyses of other outcomes (all $I^2 \geq 38.2\%$). There was no evidence of publication bias (Egger's test, all $P \geq 0.11$; Begg's test, all $P \geq 0.18$).

Milk supplementation containing ≥1000 mg of calcium per day reduced the concentrations of osteocalcin (−2.67 ng/mL, 95% CI: −5.99 to −0.65 ng/mL), P1NP (−6.87 ng/mL, 95% CI: −11.02 to −2.71 ng/mL), CTx (−0.15 ng/mL, 95% CI: −0.20 to −0.10 ng/mL), and PTH (−1.06 pg/mL, 95% CI: −1.59 to −0.53 pg/mL). By comparison, milk supplementation containing <1000 mg of calcium per day reduced PTH (−1.67 pg/mL, 95% CI: −2.96 to −0.38 pg/mL) concentrations. Milk supplementation did not significantly affect outcomes other than those mentioned above when the results

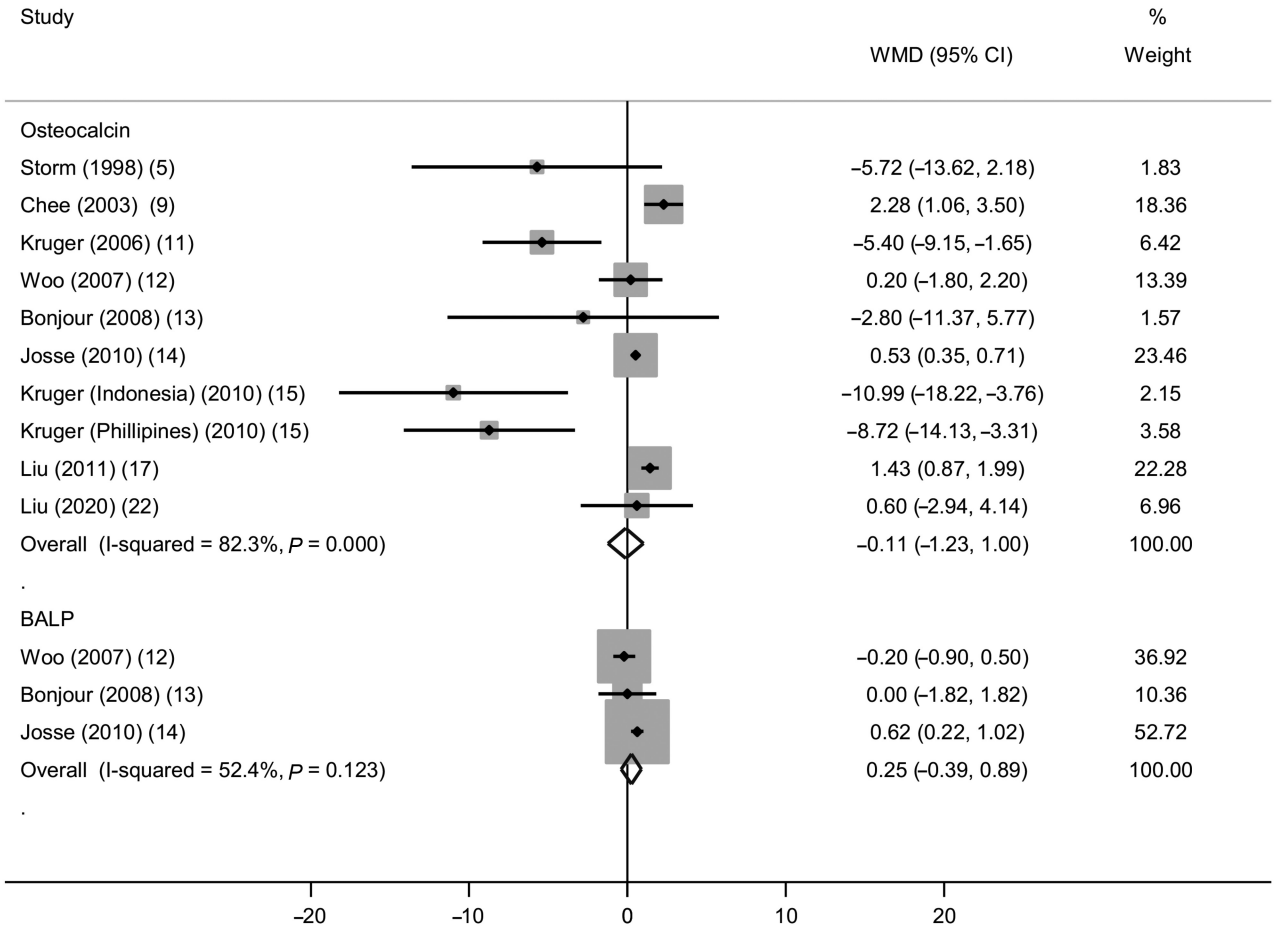

FIGURE 2 Forest plot of the change in the concentrations of serum osteocalcin and BALP after milk supplementation in adults. Weighted mean difference: −0.11 (95% CI: −1.23 to 1.00) ng/mL for osteocalcin and 0.25 (95% CI: −0.39 to 0.89) μg/L for BALP. Weights are from random-effects meta-analysis. BALP, bone alkaline phosphatase; WMD, weighted mean difference.

were stratified by the amounts of calcium in the milk.

When the analyses were restricted to postmenopausal women, the effect sizes of milk versus control were 0.004 (95% CI: 0.002 to 0.007) g/cm^2 for hip BMD, 0.010 (95% CI: −0.008 to 0.028) g/cm^2 for femoral neck BMD, 0.026 (95% CI: 0.004 to 0.046) g/cm^2 for lumbar spine BMD, −3.87 (95% CI: −8.02 to 0.27) ng/mL for osteocalcin, −6.21 (95% CI: −11.06 to −1.37) ng/mL for P1NP, −0.21 (95% CI: −0.28 to −0.14) ng/mL for CTx, −7.94 (95% CI: −11.48 to −4.41) nmol bone collagen equivalents/mmol creatinine for NTx, −0.87 (95% CI: −1.35 to −0.38) pg/mL for PTH, and 4.23 (95% CI: 2.28 to 7.75) ng/mL for 25(OH)D.

When the analyses were restricted to Asian participants, the effect sizes of milk versus control were 0.005 (95% CI: −0.006 to 0.016) g/cm^2 for whole-body BMD, 0.004 (95% CI: 0.001 to 0.007) g/cm^2 for hip BMD, 0.020 (95% CI: −0.008 to 0.049) g/cm^2 for femoral neck BMD, 0.030 (95% CI: 0.005 to 0.055) g/cm^2 for lumbar spine BMD, −0.29 (95% CI: −2.20 to 1.62) ng/mL for osteocalcin, −5.59 (95% CI: −10.91 to −0.26) ng/mL for P1NP, −0.12 (95% CI: −0.24 to −0.01) ng/mL for CTx, and −1.17 (95% CI −1.58 to −0.77) pg/mL for PTH.

Certainty of the evidence

Low certainty of the evidence was evident for BALP, whereas the certainty of the evidence for other outcomes was graded as moderate (**Supplementary Table 3**).

Discussion

In the present meta-analysis of RCTs in adults, milk supplementation resulted in a small but significant increase in BMD at the hip and lumbar spine. Milk supplementation reduced the concentrations of several bone turnover markers (P1NP, CTx, NTx) and PTH and increased IGF-1 concentrations. Vitamin D-fortified milk increased 25(OH)D concentrations. Milk supplementation did not significantly affect the concentrations of osteocalcin and BALP. Stratification by the amounts of calcium obtained from milk supplementation revealed the significant changes in bone turnover markers were more consistently observed with milk supplementation containing ≥1000 mg calcium per day;

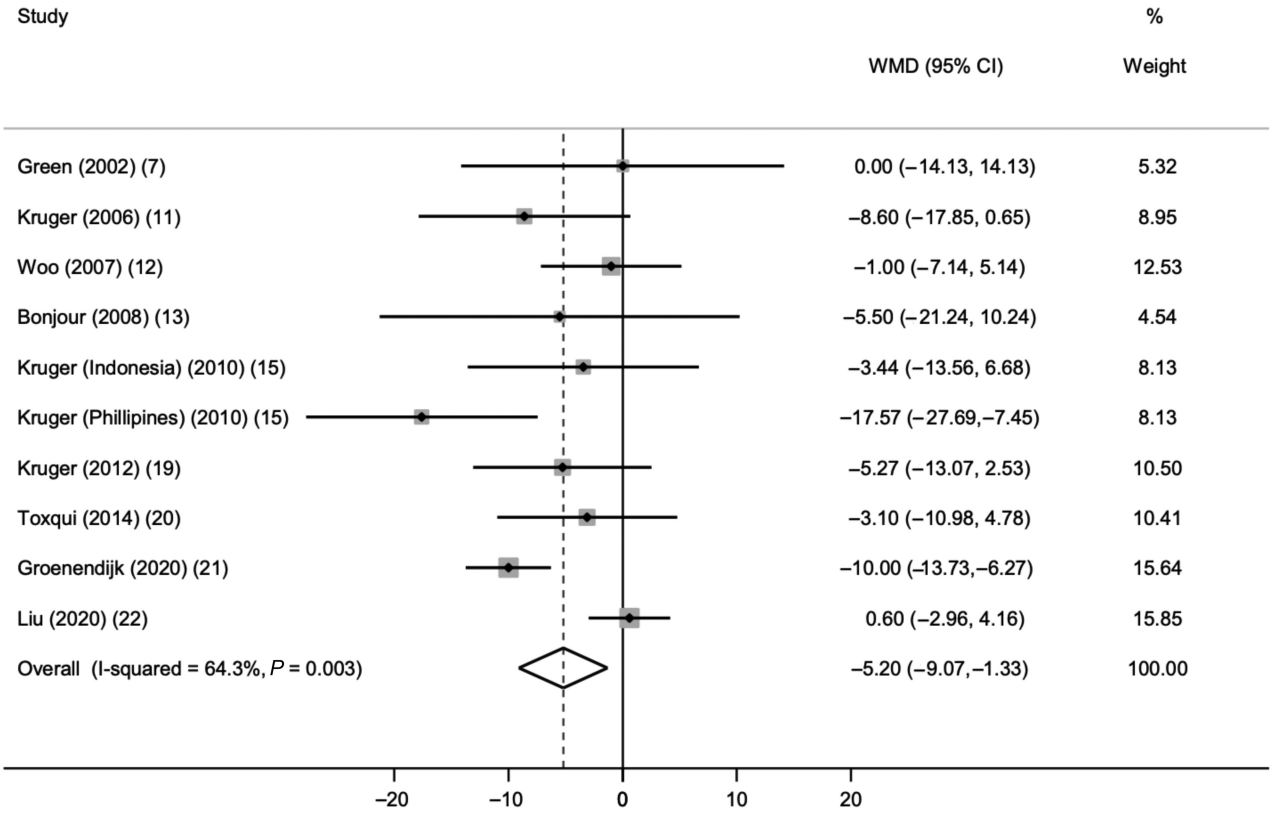

FIGURE 3 Forest plot of the change in serum procollagen type 1 N-propeptide (P1NP) concentrations after milk supplementation in adults. Weighted mean difference: −5.20 (95% CI: −9.07 to −1.33) ng/mL. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

however, such changes were less consistently observed with milk supplementation containing <1000 mg calcium per day. The results of sensitivity analyses that restricted the analyses to postmenopausal women and Asian participants generally mirrored those of the main analyses. The certainty of the evidence was judged as low for BALP and moderate for other outcomes.

Consistent with our findings, dairy supplementation has been shown to increase BMD in a meta-analysis (34) of RCTs in postmenopausal women. However, our meta-analysis differs from the previous meta-analysis in several important aspects. First, unlike the previous meta-analysis, which combined different dairy products, the present meta-analysis is specific to milk. Dairy products represent a diverse class of foods, and their effects on bone health may also vary by specific product type. Therefore, it may not be appropriate to combine different dairy products in the same analysis. Second, we did not restrict our inclusion criteria to postmenopausal women, which allowed more RCTs to be included and more generalizable results. Third, our meta-analysis focused not only on BMD but also on other important bone health indices, namely bone turnover markers and hormonal indices related to bone metabolism. The additional data of bone turnover markers and hormonal indices related to bone metabolism can aid the interpretation of the findings on BMD. Fourth, our meta-analysis used WMD rather than standardized mean difference, which was used in the previous meta-analysis, to measure effect size. The main difference between WMD and the standardized mean difference is that the former measure of effect size is used in the meta-analysis of studies that use the same measurement scales and expressed in units of the measurement scales (e.g., g/cm^2, pg/mL, nmol/L, ng/mL). In contrast, the latter measure of effect size is used in the meta-analysis of studies that use different measurement scales and expressed in units of SD, making the overall intervention effect difficult to interpret. All in all, our meta-analysis is arguably more comprehensive, generalizable, and easily interpreted than the previous meta-analysis.

Mechanistically, the potential skeletal benefits of milk could, to a certain extent, be explained by its potential antiresorptive and anabolic effects (**Figure 8**). Our results indicate that milk may potentially prevent PTH-mediated bone loss, as manifested by PTH suppression and the concomitant reduction in bone resorption markers and increase in BMD. PTH maintains calcium balance in the circulation by promoting the resorption of minerals, such as calcium, from the bone in response to low blood concentrations of calcium. Milk contains considerable amounts of calcium

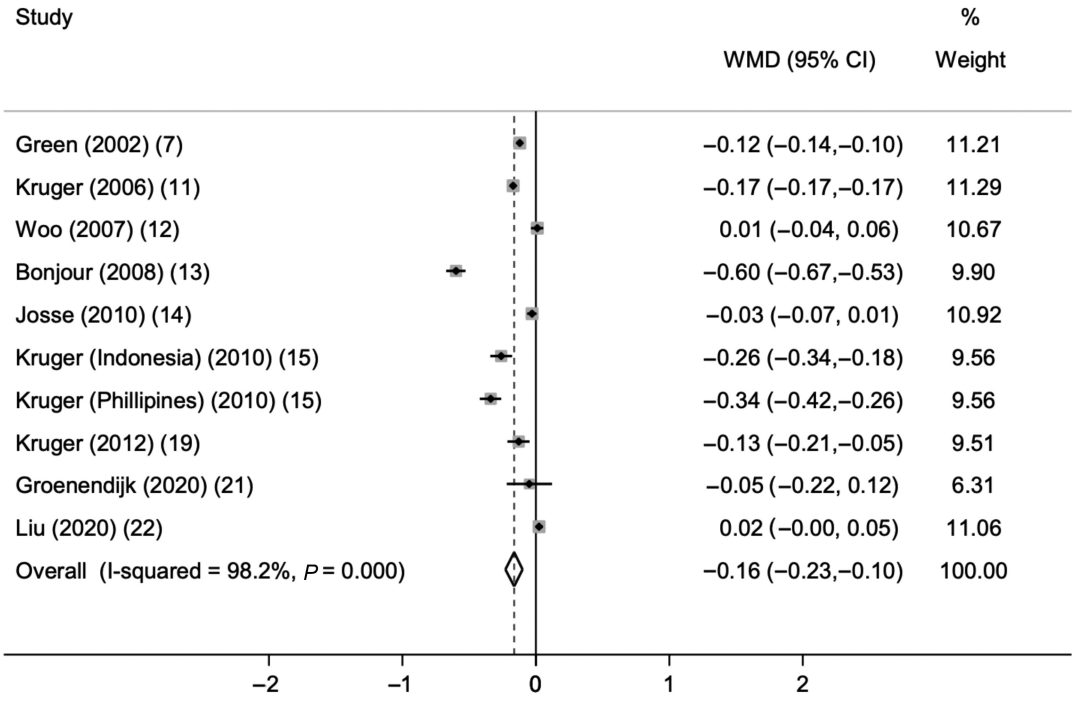

FIGURE 4 Forest plot of the change in serum C-terminal telopeptide of type 1 collagen concentrations after milk supplementation in adults. Weighted mean difference: −0.16 (95% CI: −0.23 to −0.10) ng/mL. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

and, when fortified, vitamin D, which improves calcium absorption (1, 2). Increased calcium intake from dietary sources or supplements produces a modest increase in BMD (35). In the present meta-analysis, the improvement in vitamin D status [reflected by increased 25(OH)D concentrations] in adults was consistent with the increased intake of vitamin D from vitamin D-fortified milk supplementation. Supplementation with either calcium-fortified foods (36) or

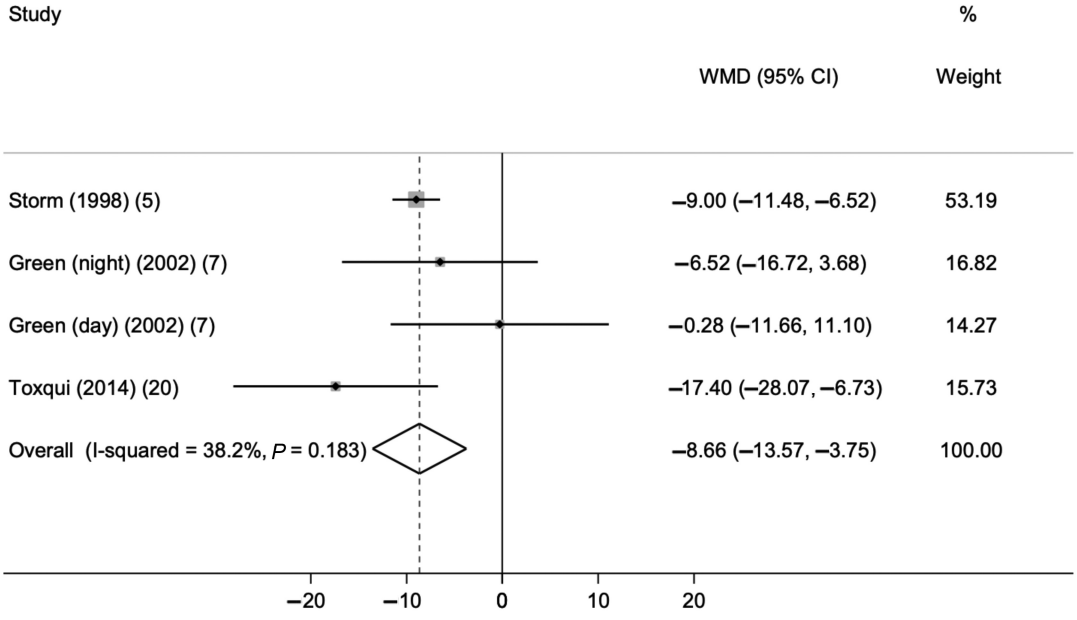

FIGURE 5 Forest plot of the change in urine N-terminal telopeptide of type 1 collagen concentrations after milk supplementation in adults. Weighted mean difference: −8.66 (95% CI: −13.57 to −3.75) nmol bone collagen equivalents/mmol creatinine. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

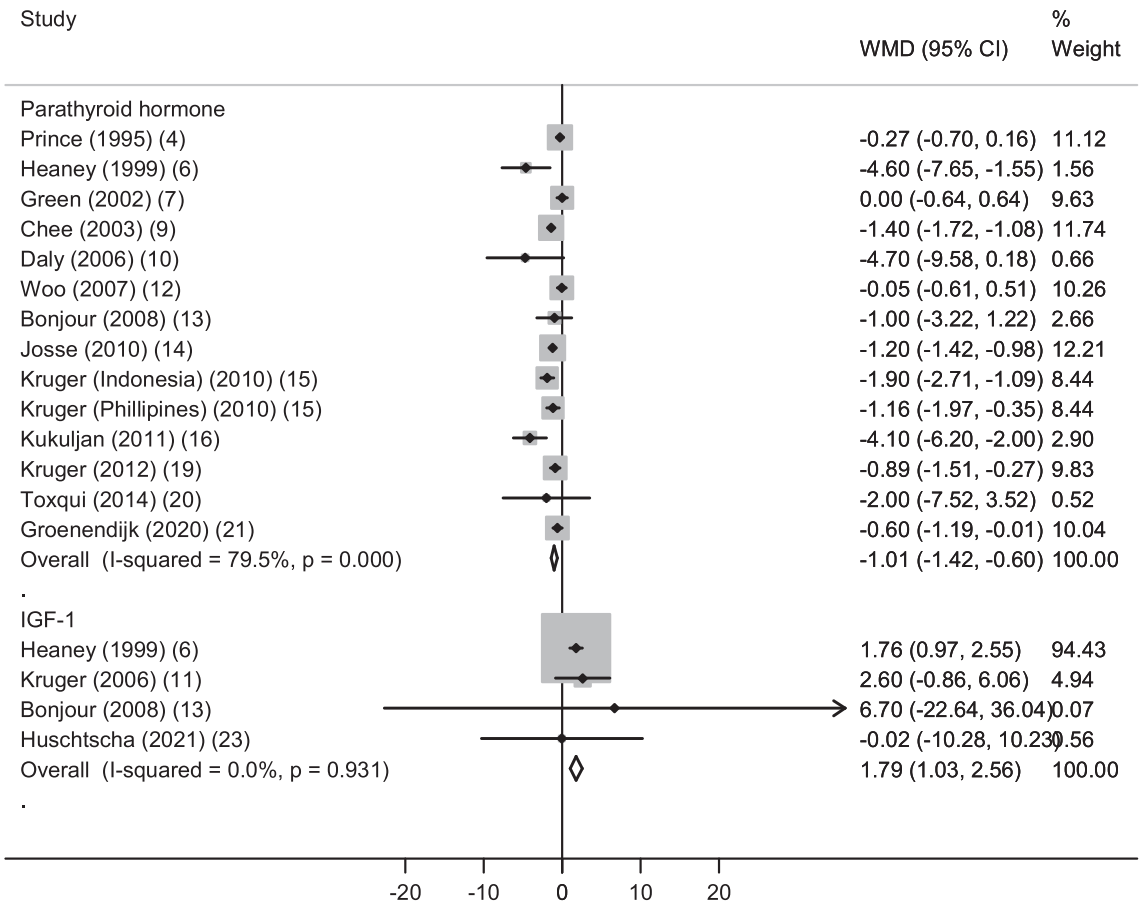

FIGURE 6 Forest plot of the change in the concentrations of serum parathyroid hormone and insulin-like growth factor-1 (IGF-1) after milk supplementation in adults. Weighted mean difference: −1.01 (95% CI: −1.42 to −0.60) pg/mL for parathyroid hormone and 1.79 (95% CI: 1.03 to 2.56) nmol/L for IGF-1. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

vitamin D supplement (37, 38) has been shown to reduce the concentrations of PTH. Adequate calcium intake (from any milk supplementation) and improved vitamin D status (from vitamin D-fortified milk supplementation) would suppress PTH secretion, leading to a reduction in bone resorption (39, 40). In addition to the contents of calcium and, if fortified, vitamin D, milk is also a good source of high-quality protein. High protein intake has been shown to stimulate intestinal calcium absorption that is accompanied by reduced PTH concentrations, which possibly results from a compensatory response to increased calcium absorption (41, 42), supporting our findings of the reduction in PTH concentrations with milk supplementation.

The bone mass changes are dependent on the balance of the remodeling process that involves the resorption of the mineralized matrix of old bone (bone resorption), followed by the deposition of equal amounts of unmineralized bone matrix, which would eventually form new mineralized bone (bone formation) (43). If bone resorption exceeds bone formation, bone mass decreases; if bone formation exceeds bone resorption, bone mass increases. Bone resorption and bone formation can be estimated by measuring relevant biomarkers (43). In the present meta-analysis, the concentrations of bone formation (P1NP) and resorption (NTx and CTx) markers were reduced with milk supplementation in adults. Since bone formation is tightly coupled with bone resorption (44, 45), bone formation declines whenever bone resorption falls. Thus, we believe that the observed inhibition in bone formation with milk supplementation was secondary to the reduction in bone resorption. Notably, nearly all (if not all) RCTs included in the analyses of bone resorption and formation markers in adults enrolled only postmenopausal women. The rate of bone remodeling increases after menopause (due to the depletion in estrogen production) and with aging in both sexes (40, 44–47). Accelerated remodeling may lead to more fragile bone tissues that are susceptible to fracture because the newly formed bone is less densely mineralized (as older, more densely mineralized bone is resorbed), the resorption cavities remain temporarily unfilled (owing to the delay in the initiation and slower completion of bone formation that is coupled with resorption), and the isomerization and maturation

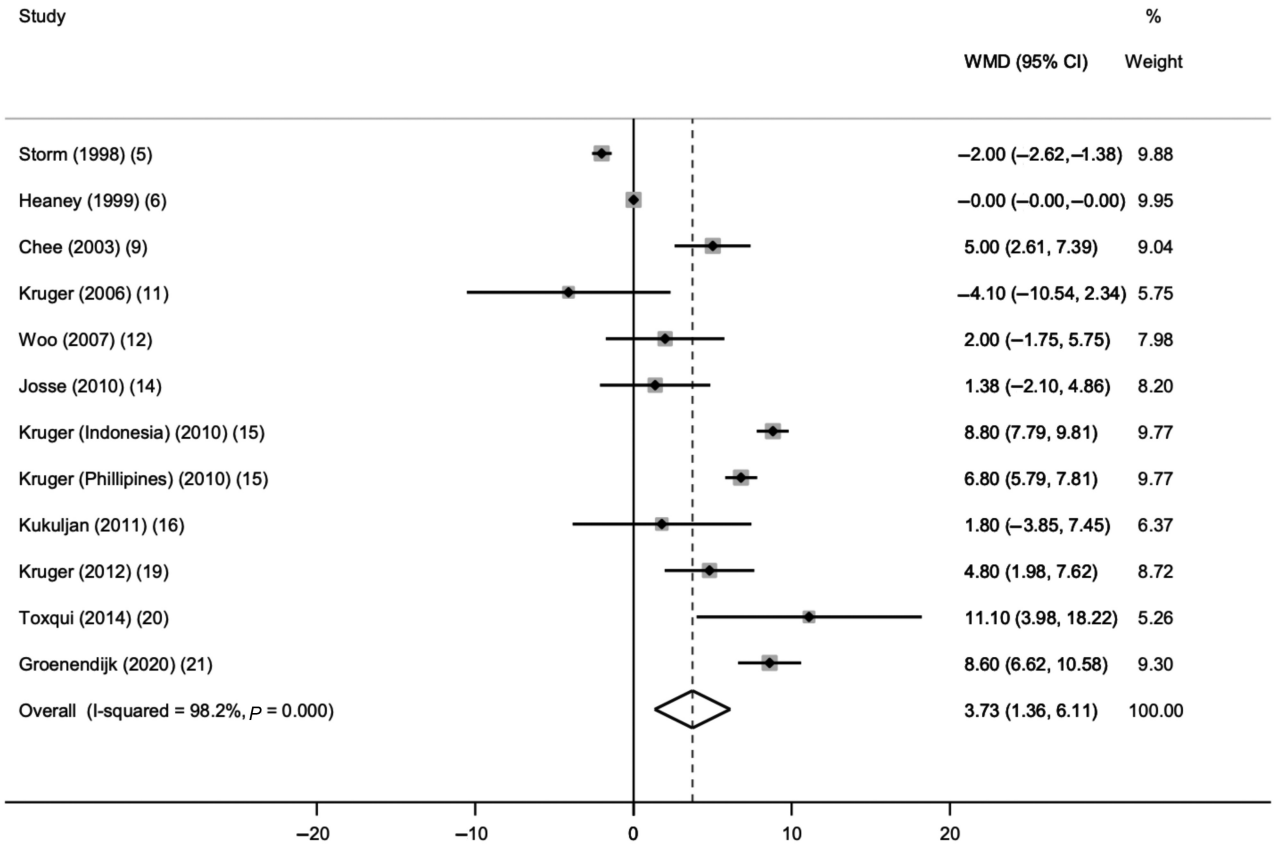

FIGURE 7 Forest plot of the change in serum 25-hydroxyvitamin D concentrations after vitamin D-fortified milk supplementation in adults. Weighted mean difference: 3.73 (95% CI: 1.36 to 6.11) ng/mL. Weights are from random-effects meta-analysis. WMD, weighted mean difference.

of collagen are impaired (46, 47). Thus, the observed concomitant reduction in bone resorption and formation markers with milk supplementation can be arguably seen as beneficial.

Milk may exert skeletal effects beyond modulating the calcium-vitamin D-PTH axis. Dietary protein, particularly from animals, has been suggested to affect the IGF-1/growth hormone axis (48). In accordance with this notion, there is evidence that high protein intake increases IGF-1 concentrations (41, 49–51), providing a scientific basis for the increased IGF-1 concentrations with milk supplementation. IGF-1 is central for longitudinal bone growth, skeletal maturation, and bone mass acquisition during childhood/adolescence and the maintenance of bone mass in adults (48, 52). Reduced IGF-1 concentrations have been linked with a higher risk of fracture (53, 54); therefore, the increase in IGF-1 concentrations with milk supplementation is presumed to have favorable anabolic effects on bones.

Milk contains a number of nutrients that are important for maximizing bone mass accretion during growth and peak bone mass during adulthood with the aim of reducing osteoporosis and bone fractures in older age (1). However, milk, due to the D-galactose content, has been hypothesized to have unfavorable effects on bone health (3). In support of this hypothesis, a large prospective cohort study of Swedish women found that increased milk consumption was associated with higher risks of any fracture and hip fracture (3). In any case, if milk can truly precipitate fracture, it is expected that milk also has an unfavorable effect on bone mass. However, the results of the present meta-analysis suggest that milk supplementation does not adversely affect BMD. Similarly, prospective cohort studies do not support a positive association between milk consumption and fracture risk (2).

Although the accumulating evidence from RCTs and prospective cohort studies is in agreement that consuming milk does not appear to have adverse effects on bone health, the extent of potential skeletal benefits conferred by consuming milk is less defined. According to the results of a recent meta-analysis of observational studies (2), increased milk consumption was not consistently associated with a lower risk of hip fracture across the study populations. However, there was an indication that milk consumption may be inversely associated with a lower risk of hip fracture in certain populations (2). Based on our findings, milk supplementation only resulted in a small increase in BMD at the hip (+0.004 g/cm^2) and lumbar spine (+0.025 g/cm^2) in adults. It remains unknown whether such a modest

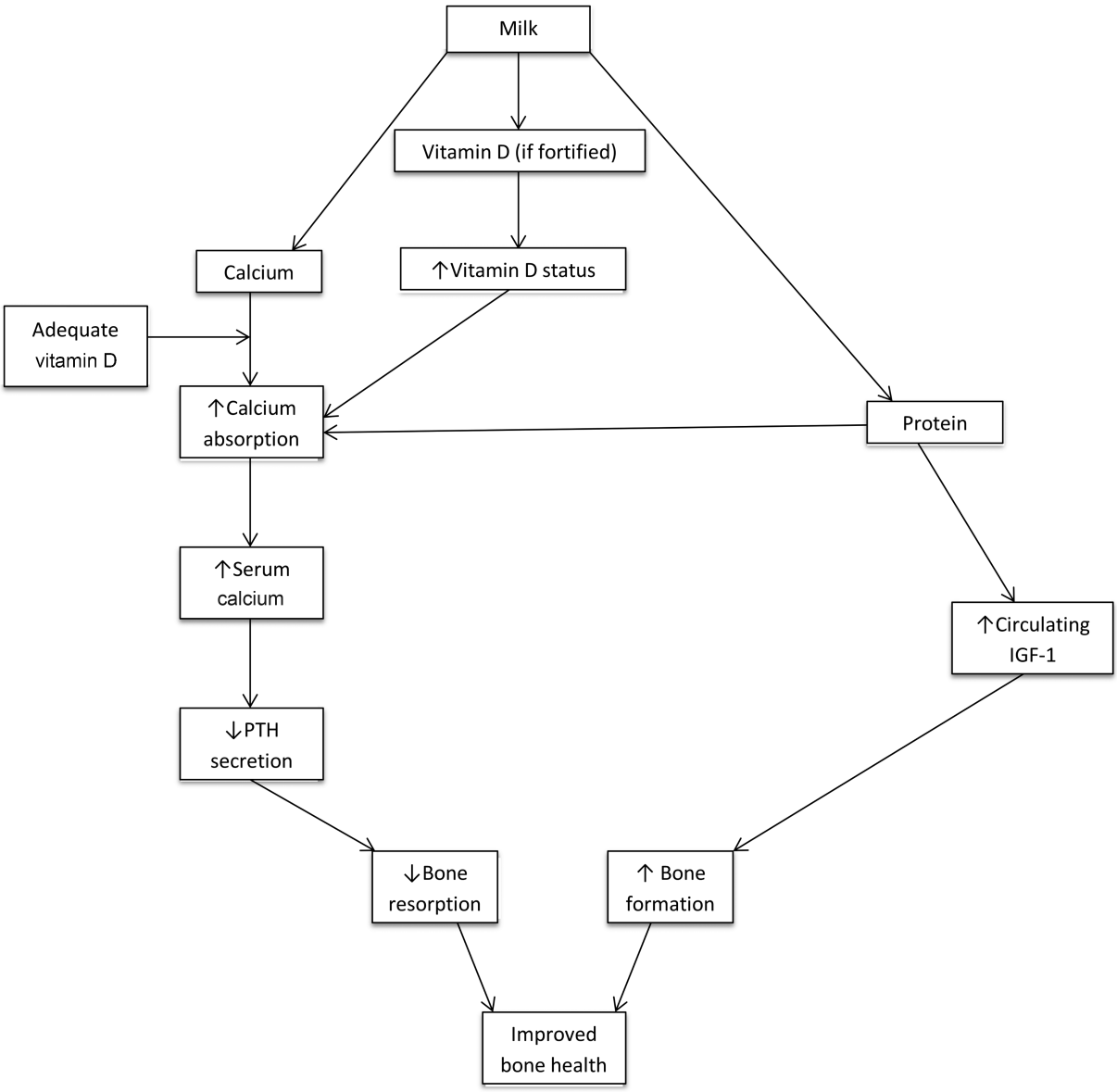

FIGURE 8 The potential mechanisms by which milk may improve bone health in adults. IGF-1, insulin-like growth factor-1; PTH, parathyroid hormone.

magnitude of improvement confers potent antiosteoporotic effects. However, it is important to acknowledge that the duration of milk supplementation may be too short to produce potent antiosteoporotic effects. Moreover, there were other factors that could have attenuated the effects of milk supplementation. First, most of the included RCTs simply asked the participants in the milk group to supplement their habitual diet with milk, while those in the control group maintained their habitual diet. Therefore, it would be more difficult to detect statistically significant effects because even those in the control group might also consume similar or even higher amounts of milk from their habitual diet, although this may not be the case in Asian countries where milk consumption is relatively low. Unfortunately, baseline and postintervention data on milk intake from the habitual diet in those who were or were not supplemented with milk were not available. Second, our analyses were largely based on the data from the RCTs that were performed in Asian countries (mostly in China), where lactose (a sugar found in milk and its derived products) intolerance is highly prevalent (55). In adults with lactose intolerance, the absorption of calcium may be blunted in the presence of lactose (56), although further research is needed.

There is indicative evidence that the skeletal benefits of increased calcium intake are conditional upon low calcium intake (57) and, to a certain extent, sufficient vitamin D (2, 58, 59). Unfortunately, with the current data sets, we were unable to fully capture the potential effect modification by calcium

intake and vitamin D status. However, there are relevant findings worth discussing. We observed that the small but significant increase in hip BMD (+0.004 g/cm^2) and lumbar spine BMD (+0.030 g/cm^2) remained significant when the analyses were restricted to Asian adults who typically had a relatively low baseline calcium intake (≤500 mg/d), partly supporting the view that milk may improve BMD in individuals with low calcium intake. Nonetheless, we could not determine whether the improvement in BMD is specific to individuals with calcium deficiency. Baseline 25(OH)D concentrations varied widely (ranging from 12.8 ng/mL to 58.5 ng/mL) across the RCTs. In humans, vitamin D can be naturally synthesized through sun exposure. However, owing to the current modern lifestyle, which is characterized by more indoor activities, the amount of sun exposure required for optimal vitamin D synthesis is often insufficient. Therefore, dietary intake of vitamin D is also important to ensure sufficient intake of this vitamin. Since only a few foods naturally contain considerable amounts of vitamin D, the fortification of widely consumed foods with vitamin D offers a solution to this issue (2). Indeed, vitamin D-fortified milk supplementation improved vitamin D status.

The beneficial effects of milk supplementation must be sustained to result in a reduction in fracture incidence. There is evidence that some of the skeletal benefits of increased calcium intake from dairy foods (60, 61) or calcium supplement (62–65) are transient and that the improvement in BMD disappears after the supplemental calcium intake is discontinued, possibly due to the shift in bone remodeling towards its original higher rate once calcium intake is not maintained at the higher levels. Conversely, several RCTs suggest increased calcium intake from milk (66, 67) or milk-extracted calcium phosphate (68) may have sustained effects on BMD, although the reasons for this are unclear. Interestingly, in 1 (67) of those RCTs, the dietary calcium intake remained high during the nonsupplemented period in the previously supplemented group. Altogether, it appears that adequate calcium intake must be continuously maintained to have lasting benefits on bone mass.

It has been suggested that the potential skeletal benefits of higher protein intake may only be apparent when calcium intake is adequate (69). In the present meta-analysis, although baseline protein intake was generally adequate (ranging from 63.8 g/d to 127 g/d), baseline calcium intake was relatively low in Asian participants (mostly ≤500 mg/d). However, the observed small increase in BMD at the hip and lumbar spine in Asian participants was not surprising, as the low baseline calcium intake was improved by the supplementation of milk, which provided 500–1200 mg of calcium a day to the habitual diet.

Some caveats need to be considered when interpreting our findings. First, although our results are encouraging, BMD and bone turnover markers are only surrogate endpoints that may not truly reflect fracture incidence. Second, comprehensive subgroup analyses could not be performed owing to the low number and relatively similar characteristics [e.g., mostly performed in Asian countries with a relatively low calcium intake, mostly enrolled females (particularly postmenopausal women), mostly enrolled older participants, mostly used vitamin D-fortified milk, mostly completed within either ≥1 y or <1 y] of the RCTs included in each analysis and the absence of important baseline data (e.g., habitual milk intake, protein intake, vitamin D status) in several RCTs. Consequently, the influence of potentially important effect modifiers (e.g., age, sex, habitual milk intake, calcium intake, protein intake, vitamin D status, fortification) on the intervention effects could not be investigated, hampering the robustness of our findings. Although stratification by the amounts of calcium obtained from milk supplementation was performed, the results were unreliable due to the low number of RCTs, which led to the uneven distribution of RCTs in each subgroup comparison. Notably, the effects of milk supplementation on BMD at the hip and lumbar spine were no longer significant when the results were stratified by the amounts of calcium obtained from milk supplementation, possibly due to limited statistical power to detect weak intervention effects. Third, high heterogeneity was observed in most of the analyses, and again, we were unable to perform extensive subgroup analyses to identify the source of heterogeneity. Fourth, the potential biases on the intervention effects could not be fully ruled out, as most of the included RCTs failed to make the trial protocol available and provide sufficient relevant information for the assessment of RoB.

Conclusions

The addition of milk to the habitual diet may potentially increase the likelihood of preventing bone loss by restoring bone homeostasis through the modulation of the calcium-vitamin D-PTH axis, bone remodeling rate, and growth hormone/IGF-1 axis. Although milk and its derived dairy products are not necessary for optimal health, they offer the most practical way to meet the dietary calcium requirements, as they are generally superior to most nondairy foods in terms of calcium bioavailability and the amount of calcium per serving (1). Nonetheless, it is safe to say that it requires more than milk to improve bone health. The inclusion of various bone-beneficial nutrient-rich foods into the habitual diet together with regular physical activity, smoking cessation, and alcohol abstinence may facilitate a solid approach to improve bone health. Large, long-term, well-designed RCTs (or a multicenter collaborative RCT) that allow subgroup comparisons by calcium intake, protein intake, vitamin D status, fortification, ethnicity, and sex are warranted to provide deeper insights into the impact of milk supplementation on bone health endpoints.

Acknowledgments

The authors' responsibilities were as follows—KH: designed the research and wrote the manuscript; KH and J-SC: performed the literature search, data extraction, and data

analyses; KH: interpreted the data; T-CW and Y-JS: created figures and tables; KH, T-CW, and Y-JL: revised the manuscript; KH, Y-JS, H-WS, BL, and L-QQ: take primary responsibility for the final and intellectual content; and all authors: read and approved the final manuscript.

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