Full Length Article

Impact of magnesium on bone health in older adults: A systematic review and meta-analysis

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ABSTRACT

Background: Magnesium plays a key role in bone health and may, therefore, represent an interesting nutrient for the prevention of bone loss and osteoporosis. The aim of this systematic review and meta-analysis was to investigate the impact of magnesium intake from any source on bone mineral density (BMD), bone mineral content (BMC), bone turnover markers, and fracture risk in older adults.

Methods: A systematic search was conducted using Embase, Medline Ovid and Cochrane Central from database inception to October 2020. All studies that related magnesium intake with bone health outcomes among adults aged ≥60 years were included. Two investigators independently conducted abstract and full-text screenings, data extractions, and risk of bias assessments. Authors were contacted for missing data.

Results: Once 787 records were screened, six cohort studies, one case-control study and five cross-sectional studies were included. Qualitative evaluation demonstrated a positive trend between higher magnesium intake and higher hip and femoral neck BMD. Meta-analysis of four studies showed a significant positive association between magnesium intake and hip BMD (pooled beta: 0.03, 95% CI: 0.01–0.06, $p < 0.05$).

Conclusions: This systematic review indicates that a higher magnesium intake may support an increase in hip and femoral neck BMD. Due to limited research no associations with BMD at other sites or fractures were found. There is a need for properly designed cohort studies to determine the association between magnesium intake and bone health in older adults. Next, large and long-term randomized controlled trials in older adults are needed to determine whether an increase in magnesium (supplementation) intake can improve bone health. The combination of several bone nutrients (calcium, vitamin D, protein, magnesium and potentially more) may be needed for the most optimal effect on bone health and to delay or prevent the development of osteoporosis.

1. Introduction

People from the age of 50 years are at risk of developing osteoporosis, a condition which causes 8.9 million osteoporotic fractures each year worldwide [1]. In order for bones to grow and to be maintained, several nutrients are needed [2]. For the prevention of bone loss, and thus the development of osteoporosis, calcium and vitamin D are well known. Another nutrient that plays a role in bone health is magnesium. This nutrient represents a crucial cofactor for enzymes necessary for the synthesis of bone matrix [3] and it plays a role in bone formation by stimulating osteoblast proliferation [4]. In addition, magnesium

deficiency can lead to abnormal hydroxyapatite crystals (a major component of bone), to an increase in the secretion of proinflammatory cytokines which stimulate osteoclast activity, and to lower parathyroid hormone (PTH) and 25-hydroxyvitamin D [25 (OH)D] levels [3–4]. It is yet unclear if magnesium can have the same impact on the development of osteoporosis as calcium and vitamin D.

Results from studies investigating the relation between magnesium intake and bone health have been contradictory, according to the first and only systematic review and meta-analysis on magnesium intake and bone health in 2015 [5]. In this study, no restrictions on the study population were applied. A positive significant correlation between

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magnesium intake with hip bone mineral density (BMD) was found (pooled r: 0.16; 95% CI: 0.00–0.32) as well with femoral neck BMD (pooled r: 0.14; 95% CI: 0.00–0.28). However, no correlations were found between magnesium intake with lumbar spine BMD and risk of total and hip fractures [5]. More studies have been published since 2015, which may lead to new insights on the relation between magnesium and bone health.

In the present study, we addressed our hypothesis that an adequate total magnesium intake (350 mg/day for adult men and 300 mg/day for adult women [6]) results in higher bone mineral content (BMC) and BMD and suppresses bone turnover and subsequently reduces fracture risk in older adults (aged 60 years or older). Older adults specifically can be at risk of a magnesium deficiency due to a decreased absorption and increased excretion of magnesium [7]. In addition, magnesium intakes in older adults in multiple Western countries are found to be lower than the recommended intake for adults [8–9]. Considering the mechanisms by which magnesium can influence bone health, the higher risk of magnesium deficiency and age-related bone loss, we hypothesized that an adequate magnesium intake can contribute to the prevention of osteoporosis. Therefore, the aim of this systematic review and meta-analysis was to examine the impact of magnesium intake from any source on BMC, BMD, bone turnover markers and fracture risk in older adults.

2. Material and methods

The reporting of this systematic review and meta-analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines [10]. This study was registered at Research Registry (identification number 1122).

2.1. Data sources and searches

The databases Embase, Medline Ovid and Cochrane Central were searched to identify relevant studies that examined the relations of magnesium intake (food and/or supplemental sources) with bone health outcomes of interest (Table 1) from database inception to July 2021. The searches were limited to the English language. The complete search strategy per database is available in Supplemental Table A1.

2.2. Eligibility criteria

Studies were eligible for inclusion if they (1) evaluated the relationship between magnesium intake and bone health; (2) had an intervention duration of at least 6 months; (3) included older adults aged ≥60 years (or mean age ≥60 years if also younger individuals were included). There was no restrictive criterion on study design. Studies were excluded if no original data was presented or if published in the form of conference abstracts, letters, reviews, or meta-analyses. Animal studies and in vitro studies were excluded as well. Lastly, studies including solely participants with a diagnosed disease or with a baseline population of which >20% was diagnosed with a disease were also not included.

2.3. Study selection

First, duplicates across the three literature searches were removed. Second, titles and abstracts were independently screened for eligibility by two researchers, which were blinded to each other's decisions. Lastly, for articles that had passed the first screening, the full texts were retrieved to further verify eligibility. This was also done independently by two researchers and reasons for exclusion were collected in Excel. Disagreements between individual judgements were resolved by a third researcher.

2.4. Data extraction

From all eligible studies, the following information was extracted: study characteristics, intervention details, relevant outcomes and their assessment methods, data details and confounders. This information was organized by study type in a data extraction sheet in Excel. One researcher extracted the data, which was reviewed and confirmed by another researcher.

2.5. Risk of bias in individual studies

To assess risk of bias of included cohort studies and case-control studies, the Newcastle-Ottawa Scale (NOS) was used [11]. The NOS evaluates three parameters: selection, comparability and outcome/exposure. Each study was awarded with a score from 0 to 9 with higher scores reflecting lower risk of bias. Risk of bias in cross-sectional studies was assessed using an adapted version of the AXIS-tool, following the example of Weeda et al. [12], with only questions focusing on study design and conduct [13]. Each study was assigned a score from 0 to 8 with higher scores reflecting lower risk of bias. Two investigators independently assessed the risk of bias in included studies. Disagreements were discussed and resolved via group consensus.

2.6. Data synthesis

All eligible studies were summarized in tables including first author, publication year, cohort name (if applicable), participant characteristics, baseline mean age or age range, exposure assessment, mean magnesium intake, source of magnesium, follow-up period, relevant outcomes, and effect sizes. Summary tables were organized by study type (cohort, case-control and cross-sectional). Results were qualitatively and, if possible, quantitively summarized by study type and outcome of interest.

2.7. Meta-analysis

The Cochrane Handbook for conducting meta-analyses was pursued when adequate data were accessible [14]. If required data were not reported, authors of relevant publications were contacted. Both the chi-square test and the I-squared statistic were used to address statistical heterogeneity across studies. A value ≥50% was used as a threshold for indicating statistical heterogeneity [14–15]. When heterogeneity was present, a random-effects model was applied, if not then a fixed-effect model was used. Results were pooled with standardized mean differences for continuous outcomes and hazard ratios (HR) for binary outcomes. Sensitivity analyses were conducted to identify the effect of a single study on the total estimate and of studies that were judged to be at high risk of bias. Meta-analysis was performed using R (v4.0.3; R Foundation for Statistical Computing, Vienna; packages meta and metafor).

Table 1
Bone health outcomes of interest.

Outcome	Sites
BMC	Total body
BMD	Total body, hip, femoral neck, lumbar spine
Bone turnover markers	Bone formation and resorption markers
Fracture risk	Hip and total

Note: BMC = Bone Mineral Content; BMD = bone mineral density.

3. Results

3.1. Search results

The search resulted in 988 records (Fig. 1). After removal of duplicates and exclusion based on abstract and title, a total of 62 publications were found eligible for full-text review. In total eleven articles were included for data extraction (five cohort studies, one case-control study and five cross-sectional studies). The characteristics of the included studies are presented in Table 2 (cohort), Table 3 (case-control) and Table 4 (cross-sectional). Two cohort studies reported cross-sectional data as well and are, therefore, included in both Tables 2 and 4 [16–17].

3.2. Risk of bias

The assessment of risk of bias in the selected cohort studies is presented in Table 5. Risk of bias was classified as high (score 1–3), some concerns (score 4–6), or low (score 7–9). Three cohort studies had some concerns [16,18,20] and two cohort studies were classified as having a low risk of bias [17,19]. With respect to controlling for important confounders, one point was given if the study controlled for age, gender, weight or BMI, energy intake, physical activity, smoking, alcohol, vitamin D, and calcium. A second point was given if family history of osteoporosis, fractures, and illnesses were included. None of the cohort studies controlled for all these factors, but four studies adjusted for a large part of the relevant confounders [16–18,20]. Dropout rates varied from 6% to 31%. A dropout above 20% and without a description of those lost was considered as high, which applied to two studies [16,20].

The assessment of risk of bias in the selected case-control study is presented in Table 6 [21]. Overall risk of bias was classified as 'some concerns', multiple important confounders were not included and there was no information about hip fracture history for the controls.

For the cross-sectional studies (Table 7), only one scored 5 out of 8 points [24] and the other 6 studies scored 6 or 7 points. All cross-sectional studies failed on justification of sample sizes. In addition, half of the studies failed to receive points for the fact that the selection process was not likely to select participants that were representative of target/reference population under investigation [17,23–24,26].

3.3. BMC

No eligible studies were found investigating the effect of magnesium intake on BMC in older adults.

3.4. BMD – total body

Two cross-sectional studies assessed the effect of magnesium intake (food and supplements) on total body BMD, showing beneficial effects [16,25]. Orchard et al. [16] found that total body BMD was 2% higher ($p < 0.001$), in women who consumed >422.5 mg/day compared with
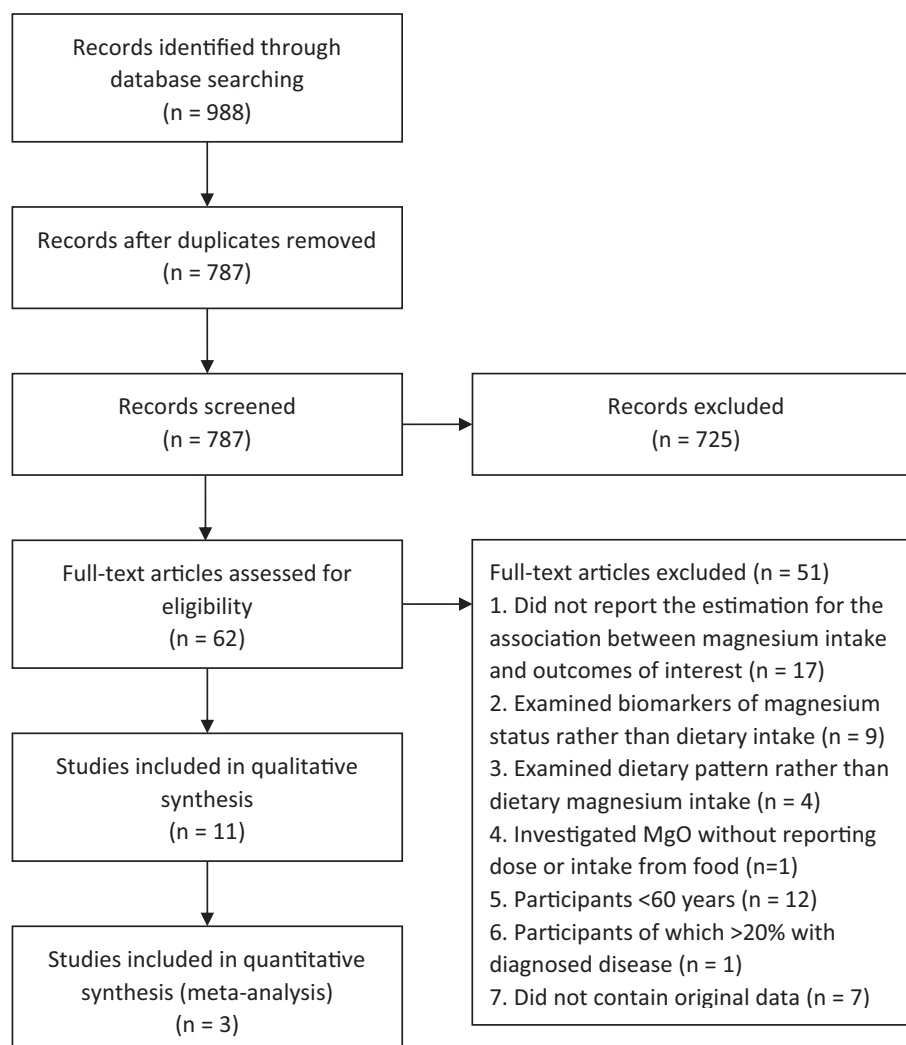

Fig. 1. Flow diagram of study selection.

Table 2

Summary table of cohort studies included in the analysis.

First Author, year (ref)	Cohort name (country)	Participants	N baseline/ analyzed	Baseline mean age(SD) (y)	Exposure assessment	Mean Mg intake[1]	Sources	Follow-up (y)	Relevant outcomes	Effect sizes[2]	
Chan, 2011 [18]	- (China)	Men and women ≥65 y	2944/ 2217 (1225 men, 992 women)	Men: 71.6(4.6); women: 72.0(5.1)	FFQ	Men: 390; women: 387	Food	4	Hip BMD	Men: B -0.0002 SE 0.029 p 0.782 Women: B 0.036 SE 0.035 p 0.237	○ ○
									FN BMD	Men: B 0.001 SE 0.001 p 0.200 Women: B 0.022 SE 0.001 p 0.487	○ ○
Kaptoge, 2003 [19]	EPIC-Norfolk Study (US)	Men and women ≥65 y	944/ 892 (450 men, 442 women)	Mean (95%CI): Men: 72.0 (68.0, 77.4); women: 71.9 (67.9, 77.0)	7 d food records	Men: 304; women: 255	Food	2.8	Hip BMD	Men: B 0.082 SE 0.076 p 0.279 Women: B -0.020 SE 0.084 p 0.814	○ ○
Orchard, 2014 [16]	WHI Observational Study (US)	PM women 50-79 y	93,676/ 73,684	63	FFQ	<207, 207-270, 270-334, 334-422, ≥422 (quintiles)	Food and supplements	7.6	Hip fracture	Q2 vs Q1: HR 1.1 (0.90, 1.36); Q3 vs Q1: HR 0.90 (0.71, 1.12); Q4 vs Q1: HR 0.90 (0.71, 1.14); Q5 vs Q1: HR 1.04 (0.81, 1.34); p-trend 0.563	○
									Total fracture	Q2 vs Q1: HR 1.02 (0.96, 1.08); Q3 vs Q1: HR 1.01 (0.95, 1.07); Q4 vs Q1: HR 1.00 (0.94, 1.06); Q5 vs Q1: HR 1.01 (0.95, 1.08); p-trend >0.999	○
Tucker, 1999 [17]	Framingham Heart Study (US)	Men and women 69-97 y	907/ 628 (229 men, 399 women)	Men: 75.1(4.9); women: 75.3(4.8)	Semi-quantitative FFQ	Men: 300; women: 288	Food and supplements	4	FN BMD	Per 100 mg increase in Mg intake: Men: B 0.018 SE NR p<0.01 Women: B 0.002 SE NR p ns	⊕ ○
Veronese, 2017 [20]	Osteoarthritis Initiative Study (US)	Men and women	4796/ 3765 (1577 men, 2071 women)	60.6(9.1)	FFQ	Men: 161, 239, 299, 359, 491; women: 144, 225, 281, 338, 454 (quintiles)	Food and supplements	6.2	Total fracture	Men: Q2 vs Q1: HR 0.53 (0.31, 0.90) p 0.02; Q3 vs Q1: HR 0.56 (0.33, 0.97) p 0.04; Q4 vs Q1: HR 0.65 (0.36, 1.17) p 0.15; Q5 vs Q1: HR 0.47 (0.21, 1.00) p 0.05; Women: Q2 vs Q1: HR 077 (0.52, 1.14) p 0.20; Q3 vs Q1: HR 0.62 (0.39, 0.99) p 0.05; Q4 vs Q1: HR 0.56 (0.32, 0.98) p 0.04; Q5 vs Q1: HR 0.38 (0.17, 0.82) p 0.01	⊕ ⊕

Note: BMD = bone mineral density, HR = hazard ratio, Mg = magnesium, NR = not reported, ns = not significant, PM = postmenopausal, FFQ = food frequency questionnaire, FN = femoral neck, SE = standard error, US = United States, ⊖ = results show a significantly increased fracture risk, ⊕ = results show a significant positive association, ○ = results show no association.

[a]Unit is mg/day. Values presented as mean or range.

[b]Values presented as mean(SE) or HR (95% CI), BMD in g/cm^2.

Table 3

Summary table of the case-control study included in the analysis.

First Author, year (ref)	Country	Participants	N	Mean age (y)	Exposure assessment	Mean Mg intake[1]	Sources	Relevant outcomes	Effect sizes[2]	
Michaëlsson, 1995 [21]	Sweden	Women born in 1914-1948	1140 (247 fracture; 893 no fracture)	Fracture: 67.6; no fracture: 67.7	FFQ	<219, 219-256, 257-306, >306 (quartiles)	Food and supplements	Hip fracture	Q2 vs Q1: OR 1.48 (0.84-2.58) Q3 vs Q1: OR 2.65 (1.35-5.21) Q4 vs Q1: OR 2.74 (1.25-6.04) p-trend 0.007	⊖

Note: FFQ = food frequency questionnaire, Mg = magnesium, OR = odds ratio, ⊖ = results show a significantly increased fracture risk.

[a]Unit is mg/day. Values presented as range.

[b]Values presented as OR (95% CI).

<206.5 mg/day (Q5 vs Q1) and Ryder et al. [25] found in white, but not black, men and women, that magnesium intake was significantly positively associated with total body BMD (white men: beta = 0.039, SE unknown; white women: beta = 0.052, SE = 0.019). For every 100 mg/day increase in magnesium intake, the total body BMD increased approximately with 2%. Furthermore, BMD was 0.04 g/cm^2 higher in white women and 0.02 g/cm^2 higher in white men in the highest compared to the lowest quintile of magnesium intake (247.8 and 394.2 mg/day, respectively; $p < 0.001$).

3.5. BMD – hip

Six studies assessed the effect of magnesium intake on hip BMD, including two cohort studies and four cross-sectional studies, of which three found beneficial effects [16,24–25] and three found no association [18–19,26]. Regarding the cohort studies, Chan et al. [18] found that dietary magnesium intake was not associated with % change in hip BMD in men and women after 4 years of follow-up. Kaptoge et al. [19] found

no significant effect of dietary magnesium intake on hip BMD in both men and women after 2.8 years of follow-up (beta = 0.082, SE = 0.076 for men; beta = −0.020, SE = 0.084 for women). Four cross-sectional studies evaluated the effect of magnesium intake, from food only [24,26] and combined with supplements [16,25], on hip BMD. Orchard et al. [16] found that hip BMD was 3% higher ($p < 0.001$), in postmenopausal women who consumed >422.5 mg/day compared with <206.5 mg/day (Q5 vs Q1). Ryder et al. [25] found that magnesium intake was significantly positively associated with BMD at the hip in white women (beta = 0.044, SE = 0.020, $p = 0.03$), whereas in white men, the relationship was not as strong (beta = 0.032, SE = 0.024, $p = 0.19$). This association was not found in black men and women. McCabe et al. [24] found a significantly positive relation between magnesium intake and hip BMD for men (partial $r = 0.180$; $p < 0.05$). However, no correlation between hip BMD and magnesium intake was found in the women. Woo et al. [26] showed that magnesium intake was not associated with hip BMD in men and women.

Table 4

Summary table of cross-sectional studies included in the analysis.

First Author, year (ref)	Country	Participants	N	Mean age(SD) (y)	Exposure assessment	Mean Mg intake[1]	Sources	Relevant outcomes	Effect sizes[2]	
Ilich, 2003 [22]	US	PM women	136	68.7(7.1)	3 d food records and FFQ	345	Food and supplements	FN BMD	B 0.000094 SE NR p 0.046	⊕
Gunn, 2014 [23]	New-Zealand	PM women	142	60.4; range 50-70	3 d food records	350	Food	FN BMD	r 0.14 p<0.05	⊕
								CTX	r -0.09 p ns	○
								P1NP	r -0.20 p<0.05	⊖
McCabe, 2004 [24]	India	Men and women ≥60 y	745 (116 white men, 75 black men, 289 white women, 265 black women)	72.8(7.5)	Health Habits and History Questionnaire + (frozen) yogurt	White men: 317; black men: 262; white women: 326; black women: 212	Food	Hip BMD	Black and white men: r 0.18 p<0.05 Black and white women: r 0.03 p ns	⊕ ○
								FN BMD	Black and white men: r 0.21 p<0.05 Black and white women: r 0.03 p ns	⊕ ○
Orchard, 2014 [16]	US	PM women 50-79 y	4778	63	FFQ	<207, 207-270, 270-334, 334-422, ≥422 (quintiles)	Food and supplements	Hip BMD	Q5 vs Q1: 3% higher p<0.001 (adjusted least-squares mean: 0.830 vs 0.855)	⊕
								TB BMD	Q5 vs Q1: 2% higher p<0.001 (adjusted least-squares mean: 1.003 vs 1.021)	⊕
Ryder, 2005 [25]	US	Men and women 70-79 y	2038 (716 white men, 352 black men, 534 white women, 436 black women)	White men: 73.9(2.8); black men: 73.5(2.8); white women: 73.6(2.6); black women: 73.6(2.7)	Semi-quantitative FFQ	White men: 331; black men: 305; white women: 308; black women: 279	Food and supplements	TB BMD	White men: B 0.039 SE NR p 0.05 Black men: effect size NR p 0.55 White women: B 0.052 SE 0.019 p 0.005 Black women: effect size NR p 0.83	⊕ ○ ⊕ ○
								Hip BMD	White men: B 0.032 SE 0.024 p 0.19 Black men: NR White women: B 0.044 SE 0.020 p 0.03 Black women: NR	○ ⊕
Tucker, 1999 [17]	US	Men and women 69-97 y	907 (345 men, 562 women)	Men: 75.1(4.9); women: 75.3(4.8)	Semi-quantitative FFQ	Men: 300; women: 288	Food and supplements	FN BMD	Per 100 mg increase in Mg intake: Men: B 0.023 SE NR p<0.1 Women: B 0.012 SE NR p ns	○ ○
Woo, 2009 [26]	China	Men and women ≥65 y	1098 (289 men, 809 women)	72.3(5.3)	7 d FFQ	380	Food	Hip BMD	% difference per 196 mg increase in Mg intake: 0.1% (-0.9, 1) p ns	○
								LS BMD	0.5% (-0.8, 1.7) p ns	○

Note: BMD = bone mineral density, CTX = C-terminal telopeptide of type I collagen, HR = hazard ratio, LS = lumbar spine, Mg = magnesium, NR = not reported, ns = not significant, P1NP = procollagen type I N propeptide, PM = postmenopausal, FFQ = food frequency questionnaire, FN = femoral neck, SE = standard error, TB = total body, US = United States, ⊖ = results show a significant negative association, ⊕ = results show a significant positive association, ○ = results show no association.

[a]Unit is mg/day. Values presented as mean or range.

[b]Values presented as mean (95% CI), partial r or HR (95% CI), BMD in g/cm².

Table 5

Newcastle - Ottawa quality assessment scale for selected cohort studies.

First author, year (ref)	Selection				Comparability	Outcome			Total points out of 9	Risk of bias
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of the exposure	Outcome of interest absent at baseline	Control for important confounders	Outcome assessment	Adequate follow-up duration	Completion of cohort follow-up		
Chan, 2011 [18]	0	1	0	1	1	1	1	1	6	Some concerns
Kaptoge, 2003 [19]	1	1	1	1	0	1	1	1	7	Low
Orchard, 2014 [16]	1	1	0	0	1	1	1	0	5	Some concerns
Tucker, 1999 [17]	1	1	0	1	1	1	1	1	7	Low
Veronese, 2017 [20]	1	1	0	1	1	0	1	0	5	Some concerns

Note. A study receives a maximum of one point for each item within the category's 'selection' and 'outcome'. A maximum of two points can be awarded for the item within the comparability category.

3.6. BMD – femoral neck

Six studies assessed the impact of magnesium intake on femoral neck BMD, including two cohort studies and four cross-sectional studies, of which four studies found significant effects [17,22–24] and two studies found no effect [17–18]. Tucker et al. [17] found a significant positive association between magnesium intake, from both food and supplements, and change in femoral neck BMD in men after 4 years of follow-up (beta = 0.018, SE unknown, $p < 0.01$). In contrast with men, there was no association between magnesium intake and change in femoral

Table 6
Newcastle-Ottawa quality assessment scale for the selected case-control study.

First author, year (ref)	Selection				Comparability	Exposure			Total points out of 9	Risk of bias
	Adequate case definition	Representativeness of the cases	Selection of controls	Definition of controls	Control for important confounders	Ascertainment of exposure	Same method of ascertainment	Non-response rate		
Michaëlsson, 1995 [21]	1	1	1	0	0	0	1	0	4	Some concerns

Note. A study receives a maximum of one point for each item within the category's 'selection' and 'outcome'. A maximum of two points can be awarded for the item within the comparability category.

Table 7
Risk of bias in the selected cross-sectional studies based on the AXIS-tool.

First author, year [ref]	Study design	Justified sample size	Appropriate population base	Representative population	Appropriate measurements	Correctly usage of instruments	Discussion/ conclusion	Ethical approval	Total points out of 8
Ilich, 2003 [22]	1	0	1	1	1	1	1	1	7
Gunn, 2014 [23]	1	0	1	0	1	1	1	1	6
McCabe, 2004 [24]	1	0	0	0	1	1	1	1	5
Orchard, 2014 [16]	1	0	1	1	1	1	1	1	7
Ryder, 2005 [25]	1	0	0	1	1	1	1	1	6
Tucker, 1999 [17]	1	0	1	0	1	1	1	1	6
Woo, 2009 [26]	1	0	1	0	1	1	1	1	6

Note. A study receives a maximum of one point for each item.

neck BMD in women after 4 years of follow-up. Chan et al. [18] showed that dietary magnesium intake was not associated with % change in femoral neck BMD in men and women, after 4 years of follow-up. Four cross-sectional studies assessed the effect of magnesium intake, from food only [23–24] and combined with supplements [17,22], on femoral neck BMD. Gunn et al. [23] found that magnesium intake was significantly positively associated with femoral neck BMD in postmenopausal women (partial $r = 0.140$; $p < 0.05$). McCabe et al. [24] found a significantly positive relation between magnesium intake and femoral neck BMD in black and white men (partial $r = 0.210$; p < 0.05) but not in black and white women. Ilich et al. [22] found a significant positive association between magnesium intake and femoral neck BMD in postmenopausal women (beta = 0.00094, SE unknown, $p = 0.046$). Tucker et al. [17] found no significant association in both men and women.

3.7. BMD – lumbar spine

Only one cross-sectional study by Woo et al. [26] looked at lumbar spine BMD and found that magnesium intake (from food only) was not associated with lumbar spine BMD in both men and women.

3.8. Bone turnover markers

Only Gunn et al. [23] looked at the association between dietary magnesium intake and the bone turnover markers C-terminal telopeptide of type I collagen (CTX) and procollagen type I N propeptide (P1NP) in postmenopausal women, in a cross-sectional study design. Magnesium intake was significantly inverse associated with P1NP (partial $r = -0.20$, $p < 0.05$), but not with CTX (partial $r = -0.09$, p ns).

3.9. Fractures

Two cohort studies looked at the association between magnesium intake and total fracture risk and reported different results [16,20].

Veronese et al. [20] found that men and women in the highest quintile of magnesium intake (food and supplements) reported a significant lower risk for fractures, taking those in the first quintile as reference, after 6.2 years of follow-up (men: 491 vs 161 mg/day, HR 0.47, 95% CI 0.21–1.00, p 0.05, women: 454 vs 144 mg/day, HR 0.38, 95% CI 0.17–0.82, p 0.01). Orchard et al. [16] found no significant differences in HRs of total fractures across the quintiles of magnesium intake (food and supplements) (Q5 ≥ 422.5 mg/day vs Q1 < 206.5 mg/day, HR 1.01, p-trend>0.99) in postmenopausal women after 7.6 years of follow up.

Regarding hip fracture risk specifically, one case-control study and one cohort study examined this outcome. Michaëlsson et al. assessed the relation between magnesium intake (from food and supplements) and hip fracture risk in women, in a case-control study [21]. The study showed that high intakes of magnesium was significantly associated with an increased risk of hip fracture. The highest risk was calculated for the highest quartile of magnesium intake, taking the first quartile as reference (>306 mg/day vs <219 mg/day, OR 2.74, 95% CI 1.25–6.04, p-trend 0.01). Orchard et al. [16] found no significant differences in HRs of hip fractures across quintiles of magnesium intake (food and supplements) (Q5 ≥ 422.5 mg/day vs Q1 < 206.5 mg/day, HR 1.04, p-trend 0.56) in postmenopausal women after 7.6 years of follow up.

3.10. Meta-analysis

A meta-analysis could be performed for hip BMD among two cohort studies and two cross-sectional studies including seven different groups (Fig. 2). Two cross-sectional studies could not be included because they reported the relation in a different effect size. Heterogeneity was not significantly present for hip BMD ($I^2 = 0.0\%$, heterogeneity chi-squared $p = 0.88$). However, a random-effects model was used since different study designs were included. The meta-analysis showed a significant positive association between magnesium intake and hip BMD (pooled beta: 0.03, 95% CI 0.01, 0.06, $p < 0.05$). Sensitivity analyses demonstrated that there was no single study influencing the overall estimate
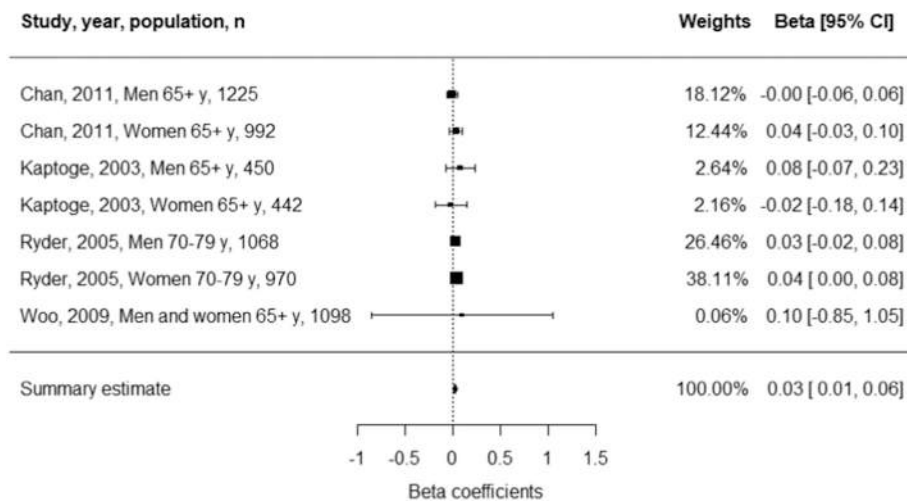
Fig. 2. Forest plot illustrating the impact of dietary magnesium intake on hip BMD.

substantially.

Since missing quantitative data could not be provided for each relevant publication after contact with authors, meta-analyses with other outcomes of interest could not be conducted.

4. Discussion

The aim of this systematic review and meta-analysis was to examine the impact of magnesium intake from any source on BMC, BMD, bone turnover markers and fracture risk in older adults. Qualitative evaluation showed a positive trend between higher magnesium intake and higher hip and femoral neck BMD (Table 8). Meta-analysis of four studies including seven different groups showed a significant positive association between higher magnesium intake and higher hip BMD. No conclusions could be drawn regarding BMC, total body and lumbar spine BMD, bone turnover markers and fracture risk due to a limited number of studies assessing these outcomes.

Comparison of the included studies is complicated because varying

Table 8
Summary of the evidence for the impact of magnesium intake on bone health.

Outcome	Number of studies	Positive impact	No impact	Negative impact	Conclusion
BMC	0	0	0	0	Not enough evidence
TB BMD	2	2	0	0	Not enough evidence
Hip BMD	6	3	3	0	Higher Mg intake potentially beneficial
FN BMD	6	4	2	0	Higher Mg intake potentially beneficial
LS BMD	1	0	1	0	Not enough evidence
BTM	1	1	1	0	Not enough evidence
Total fracture risk	2	1	1	0	Not enough evidence
Hip fracture risk	2	0	1	1	Not enough evidence

Note. BMC = bone mineral content, BMD = bone mineral density, BTM = bone turnover markers, LS = lumbar spine, Mg = magnesium, FN = femoral neck, TB = total body.

levels of magnesium intake were studied and some looked at magnesium intake from both food and supplements, while others only took dietary magnesium into account. In studies reporting magnesium intake as a mean value, the intake ranged from 212 to 390 mg/day [17–19,22–26]. Three studies divided the magnesium intake in quintiles with the highest magnesium category varying from 306 mg/day [21] to 422 mg/day [16] to 491 mg/day for men and 454 mg/day for women [20]. However, no difference in the number of significant results were seen in studies including participants with higher intakes or studies taking magnesium intake from both supplements and food into account.

Besides the different amounts of magnesium intake between the studies, the bioavailability of magnesium should also be considered. Magnesium absorption takes places in the small intestine, which can be affected by several factors, for example the dose, food matrix and dietary factors. Impairing dietary factors include high doses of other minerals, partly and non-fermentable fibers, phytate and oxalate [27]. Dietary factors enhancing magnesium uptake include protein, medium-chain-triglycerides, and low- or indigestible carbohydrates [27]. Factors that can increase magnesium requirements are gastrointestinal diseases [27], chronic alcohol abuse [28] and diseases that results in malabsorption, for example type 2 diabetes [29]. In addition, several drugs including proton pump inhibitors (PPI), diuretics and chemotherapeutic agents can lead to a magnesium deficiency [30]. Only two studies took drug use into account, but the investigated populations were mainly healthy older adults.

One study in the current review found that high intakes of magnesium were associated with an increased risk of hip fractures [21]. However, this case-control study had a higher risk of bias (scored 4 out of 9 points on the NOS) and they did not control for all important confounders. Only one other study investigated the impact on hip fractures and they found no association [16]. Hence, the impact of magnesium intake on hip fracture risk remains unclear.

There were some variations in the associations between magnesium intake and bone health outcomes between men and women across the studies. Veronese et al. found that the impact of magnesium on fracture risk was more important in women than in men (62% and 53% reduction, respectively) [20]. This pattern is in line with the findings of Ryder et al., who concluded that the associations between magnesium intake and total body BMD as well as hip BMD in men were not as strong as they were in women [25]. However, two studies found a significant association between magnesium intake and femoral neck and/or hip BMD for men, while no significant association was found for women [17,24]. It is known that women, particularly after menopause, have lower intakes of micronutrients than men have, making them more susceptible to the effects of nutritional deficiencies [31]. Furthermore, the prevalence of

osteoporosis is higher in women than in men [32]. More research is needed to understand whether the effect of magnesium on bone health outcomes is gender specific.

The meta-analysis showed a significant positive association between magnesium intake and hip BMD (pooled beta: 0.03, 95% CI 0.01, 0.06) and is in line with the meta-analysis of Farsinejad-Marj et al. (2015) which included a younger population as well (r 0.16, 95% CI 0.001, 0.32) [5]. They also found that high intakes of magnesium were not associated with increased risk of hip and total fractures. In addition, they observed a positive marginally significant association between magnesium intake and BMD in femoral neck (r 0.14, 95% CI 0.001, 0.28), but no significant association was found with lumbar spine BMD. In comparison with current review, there was not enough data to assess femoral neck and lumbar spine BMD. Note that the results of the meta-analysis should be interpreted with caution due to the low number of included studies.

Since nutrients interact with each other, relationships among nutrients should also be considered. A review by Erem et al. (2019) looked at the interaction between magnesium and vitamin D in older adults [33]. They explained that magnesium is needed by several enzymes involved in vitamin D metabolism, for example for those involved in the conversion of vitamin D to the biological active form. Magnesium also interacts with calcium. As high calcium intake complicates magnesium retention and low magnesium levels can lead to excess calcium excretion, there is an optimal calcium-to-magnesium ratio (suggested to be 2–2.8: 1) [33]. Future studies are warranted to further explore the mechanisms.

Based on the current evidence, calcium and vitamin D remain the most important nutrients for the prevention of bone loss. However, magnesium may play an additional role, which also applies to protein [34]. For older adults, it is recommended to have a calcium intake of 1000 mg/d (inclusion of supplements only if needed), take vitamin D supplementation (800 IU cholecalciferol) to maintain serum 25(OH)D levels >50 nmol/L and have a dietary protein intake of 1.0–1.2 g/kg body weight/d [35–36]. Regarding magnesium, it is advised to avoid of a low intake via the diet, the adequate intake is set at 350 mg/day for adult men and 300 mg/day for adult women on the basis of balance studies [6].

This recommendation is not met for all older adults. The mean magnesium intake in healthy older adults in Western countries varies from 274 to 421 mg/d for males and 227 to 373 mg/d for females. This is lower in more frail older adults [37–38]. Dietary sources rich in magnesium include green leafy vegetables, legumes, nuts, seeds, and whole grains; the magnesium content in these products is presented in Fig. 3 [39]. Moreover, legumes, nuts and seeds also contain high amounts of protein and calcium and thus consist of multiple nutrients that have a positive effect on bone health. There is some more overlap between food products high in key bone nutrients. For example, dairy is rich in protein and calcium and although dairy is not in the top 5 of magnesium rich products, it still contributes to your daily magnesium intake. This makes clear that the effects of nutrients on bone health cannot be considered in isolation.

A strength of this review was that only publications studying older adults (aged ≥60 years) were eligible, making the recommendation specific for this more vulnerable group. Consequently, the review did not contain any randomized controlled trials, as existing human intervention studies with magnesium were focused on a younger population. However, a trial in twenty postmenopausal osteoporotic women found that oral magnesium supplementation (daily oral dose of 1830 mg magnesium citrate for 30 days) suppressed bone turnover [40]. All in all, this makes clear that large and long-term randomized controlled trials in older adults are needed to determine whether an increase in magnesium (supplementation) intake can improve bone health.
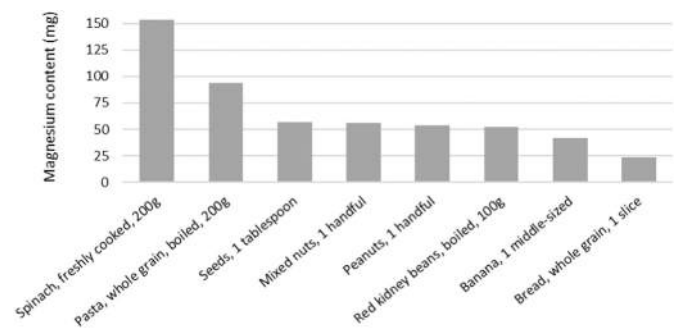

Fig. 3. Food products rich in magnesium with content per portion size. Value for seeds is an average of pumpkin seeds, sunflower seeds and pine nuts.

5. Conclusions

This systematic review indicates that a higher magnesium intake may support an increase in hip and femoral neck BMD. Due to limited research no associations with BMD at other sites or fractures were found. We still miss properly designed cohort studies investigating the association between magnesium intake and bone health, adjusted for all relevant confounding factors. Understanding the relationship between magnesium and bone health is an important step toward finding preventive measures for age-related bone loss and prevention of osteoporosis. Moreover, we hypothesize that the combination of several bone nutrients (calcium, vitamin D, protein, magnesium and potentially more) are needed for the most optimal effect on bone health.

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CRediT authorship contribution statement

Inge Groenendijk: Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft, Visualization, Project administration. **Marieke van Delft:** Conceptualization, Methodology, Formal analysis, Investigation, Writing – original draft. **Pieter Versloot:** Investigation. **Luc J.C. van Loon:** Writing – review & editing. **Lisette C. P.G.M. de Groot:** Conceptualization, Writing – review & editing, Supervision.

Declaration of competing interest

None.

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