Clinical Nutrition 38 (2019) 317–323

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Original article

# Cross-sectional associations of dietary and circulating magnesium with skeletal muscle mass in the EPIC-Norfolk cohort

Richard P.G. Hayhoe [a], Marleen A.H. Lentjes [b], Angela A. Mulligan [b], Robert N. Luben [b], Kay-Tee Khaw [b], Ailsa A. Welch [a, *]

[a] Department of Population Health and Primary Care, Norwich Medical School, Faculty of Medicine and Health Sciences, University of East Anglia, Norwich, NR4 7TJ, UK
[b] Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Strangeways Research Laboratory, Worts Causeway, Cambridge, CB1 8RN, UK

ARTICLE INFO

*Article history:*
Received 12 April 2017
Accepted 7 January 2018

*Keywords:*
Sarcopenia
Skeletal muscle
Ageing
Nutrition
General population studies

SUMMARY

*Background:* Maintenance of skeletal muscle in older age is critical to reducing frailty and the risk of falls and fractures. Nutrition has established importance for muscle health in general, but less research has looked at associations of dietary intake of specific micronutrients on skeletal muscle mass in older adults.
*Aims:* This study aimed to investigate the influence of dietary and circulating magnesium on skeletal muscle mass in a UK population of 14,340 middle to older-aged men and women participating in the EPIC-Norfolk cohort study.
*Methods:* Dietary nutrient intakes were estimated from 7-day food diaries and fat-free mass (FFM) by bioelectrical impedance analysis. Multivariable regression was used to investigate associations of FFM-based indices of muscle mass with quintiles of dietary magnesium intake or serum magnesium concentration groups. All analyses were stratified by sex, and regression models were adjusted for relevant covariates.
*Results:* Significant positive trends in FFM measures were evident across magnesium dietary intake quintiles for both sexes (all $p < 0.001$; $n = 6350$ men; $n = 7990$ women) and both <60 and $\geq$ 60 year olds, with all-age quintile 5 *versus* quintile 1 maximal differences of 4.6% in men and 6.3% in women; highly relevant compared to the estimated 1% decline per year after 40 years of age. These observations were not reflected in serum magnesium analyses, where no consistent trends were found across the skeletal muscle mass indices tested.
*Conclusion:* Further investigation will be required to improve our understanding of the relationship between serum magnesium concentration and skeletal muscle mass. However, this study has demonstrated strong associations between dietary magnesium intake and indices of skeletal muscle mass in a UK population of middle to older-aged adults, highlighting the likely importance of dietary magnesium for optimal muscle health in this population.


## 1. Introduction

Sarcopenia is a syndrome characterised by a progressive and generalised loss of skeletal muscle mass and function with age [1]. Significant reduction in skeletal muscle mass and strength impairs static and dynamic balance, which may increase risk of falls and thus the risk of resultant fractures [2]. Indirectly, the maintenance of skeletal muscle is important in protecting against osteoporosis since the mechanical force of muscle contractions stimulates bone modelling and remodelling, which increases bone strength and mass [3]. Previous research has also shown skeletal muscle mass to be positively correlated with both bone mineral content and density [2]. Sarcopenia can therefore have significant implications for affected individuals, placing them at risk of adverse outcomes including physical frailty and falls, and resulting in an increased need for health and social care services [4]. Muscle tissue also has a

*Abbreviations:* BIA, Bioelectrical impedance analysis; CRP, C reactive protein; DINER, Data Into Nutrients for Epidemiological Research; EAR, Estimated Average Requirement; EPIC, European Prospective Investigation into Cancer and Nutrition; FFM, Fat Free Mass; FFM%, Percentage Fat Free Mass; $FFM_{BMI}$, Fat Free Mass standardised by Body Mass Index; FFQ, Food-Frequency Questionnaire; HRT, Hormone Replacement Therapy; RNI, Reference Nutrient Intake.

* Corresponding author.
*E-mail address:* a.welch@uea.ac.uk (A.A. Welch).

https://doi.org/10.1016/j.clnu.2018.01.014
0261-5614/

metabolic role in the body and thus loss of muscle mass may result in other detrimental outcomes, including change to metabolic rate, insulin resistance, and increased risk of hypertension [5].

Sarcopenia is a complex condition, with many contributory factors including hormonal changes, decreased protein synthesis, low-grade inflammation, oxidative stress, mitochondrial dysfunction, and neuromuscular ageing. Nevertheless, interventions targeting modifiable lifestyle behaviours, such as physical activity or diet, provide a potential strategy to reduce severity [4]. It is recognised that appropriate nutrition is critical for normal muscle metabolism, but influences of specific dietary nutrients on sarcopenia are less well defined. Dietary protein has received most attention in the past [6], but more recently the importance of other dietary components, including vitamin D [7] and antioxidant micronutrients vitamins C [8] and E [9,10], has been suggested. Likewise, the mineral magnesium has drawn some attention. Older individuals may be particularly susceptible to developing low magnesium status due to physiological decline in function of the gastrointestinal and renal systems causing a reduction in absorption of dietary magnesium and an increase in urinary excretion [11]. Second only to bone, skeletal muscle acts as a major store of magnesium where it is important for energy metabolism, transmembrane transport, and muscle contraction and relaxation [12]. Magnesium supplementation has been shown to increase the muscle strength young adults gained through exercise [13] and improve physical performance in older individuals [14]. Epidemiological studies have shown higher dietary magnesium intakes associated with greater skeletal muscle mass and function [15] [16,17], and a significant positive association of serum magnesium concentration with muscle performance in older adults [18]. However, a comprehensive population cohort analysis of dietary and circulating magnesium associations with skeletal muscle measures in both men and women is currently lacking. This study therefore aims to address this by exploring the potential associations of dietary magnesium intake and serum magnesium concentration with bio-impedance estimated fat free mass (as a measure of skeletal muscle mass), in a mixed-sex UK population of middle to older-aged individuals.

## 2. Materials and methods

Data analysed in this cross-sectional cohort study were from the Norfolk component of the European Prospective Investigation into Cancer and Nutrition (EPIC). Written informed consent was provided by participants according to the Declaration of Helsinki, and all procedures were approved by The Norfolk District Health Authority Ethics Committee. Full details of recruitment to this cohort and the procedures involved have been described previously [19]. In summary, 25,639 men and women aged 40–79 years old living in the general community in Norfolk, UK, were recruited to the study and participated in a baseline health-check between 1993 and 1997. Of these, 15,028 participants aged 42–82 years had further data recorded at a second health-check between 1997 and 2000, when bioelectrical impedance analysis (BIA) was undertaken.

At both health checks, height and weight were measured according to standard protocols [19]. Height was recorded to the nearest millimetre using a free-standing stadiometer and weight to the nearest 0.1 kg using calibrated digital scales with the participant wearing light clothing and no shoes. BMI was calculated from these measurements (kg/m$^2$). BIA was carried out using a previously validated [20,21] standard technique (Bodystat, Isle of Man, UK). The Tanita TBF-531 BIA analyser calculated body density (BD) from total weight (Wt) in kg, height (Ht) in cm, and impedance (Z) in ohms, using the following standard regression formulae for adults: BD in men = 1.100455−0.109766 × Wt × Z ÷ Ht$^2$ + 0.000174 × Z; BD in women = 1.090343−0.108941 × Wt × Z ÷ Ht$^2$ + 0.00013 × Z. From this, fat free mass (FFM) in kg was calculated: FFM = Wt − ((4.57 ÷ BD − 4.142) × Wt). This estimates the total mass of non-fat compartments of the body, i.e. metabolic tissue, intra- and extra-cellular water, and bone tissue. As a further index for assessment, percentage FFM (FFM%) was calculated as FFM divided by total weight multiplied by 100, and in order to scale for differences in skeletal muscle mass with increasing body weight or stature, FFM standardised by BMI ($FFM_{BMI}$) was calculated as FFM divided by BMI [22].

Health and lifestyle questionnaires, as previously described [19], were completed by all participants to gather data including age, physical activity, social class, smoking status, menopausal status and HRT use, and corticosteroid use. Each participant's physical activity status was categorised, according to a heart-rate data validated method [19,23], as *inactive*, *moderately inactive*, *moderately active*, or *active*. Dietary intakes were assessed using 7 day food diaries completed by each participant detailing all food and drink consumed, together with the portion sizes [24]. DINER (Data Into Nutrients for Epidemiological Research) software was used to enter the dietary information provided by the diaries [25], which was then checked and processed by nutritionists to obtain nutrient data, using DINERMO [26]. Serum magnesium concentration was determined using blood sampled by peripheral venepuncture during the baseline health check. Samples were prepared, using a technique optimised for use in EPIC, and stored in liquid nitrogen at −196 °C until analysed by Quotient Bioresearch, Fordham, UK, using an Olympus AU640 Chemistry Immuno Analyser to perform a xylidyl blue based colorimetric assay (Beckman Coulter, USA). Measurements below 0.2 mmol/L or above 3.3 mmol/L were considered invalid and excluded from analyses.

The High Performance Computing Cluster supported by the Research and Specialist Computing Support service at the University of East Anglia was used for statistical data analysis with STATA software (v.13; Stata Corp., Texas). All analyses were stratified by sex since significant differences in body composition and skeletal muscle mass exist between men and women. Any p values $< 0.05$ were considered to be statistically significant in individual analyses. Multivariable regression with ANCOVA was used to investigate differences in skeletal muscle measures across sex-specific quintiles of dietary magnesium intake. An adjusted model was tested, correcting for the potential effects of physiological (age, menopausal status, HRT status, corticosteroid use, statin use), lifestyle (smoking status, physical activity, social class) and dietary factors (total energy intake, and the percentage of total energy from protein); also included was the energy intake to estimated energy requirement ratio (EI:EER) as a percentage, to help correct for dietary misreporting [27]. Likewise, differences in skeletal muscle measures across sex-specific groups of serum magnesium concentration were investigated using the same covariates, but excluding dietary factors in the adjusted model. Serum magnesium concentration in healthy individuals is kept under tight homeostatic control; published guidance suggests 0.7–1.0 mmol/L should be used as a reference range for healthy individuals [28]. Serum magnesium concentration groups were therefore categorised as <0.7 mmol/L (group 1), 0.7–0.8 mmol/L (group 2), 0.8–0.9 mmol/L (group 3), 0.9–1.0 mmol/L (group 4), and >1.0 mmol/L (group 5). Group 2 has been used as the reference category for inter-group analyses. Participants were excluded from analyses if they had missing or extreme (<300 or >1000 ohms [29]) BIA impedance values (n = 228 and n = 22), FFM < 25 kg (n = 13), BMI ≥ 36 kg/m$^2$ (n = 337), or had missing values for any covariates included in the multivariable model (n = 88 for diet analyses, and n = 48 for serum analyses). Analyses were repeated after stratifying for age (<60 and ≥ 60 years). Correlation between dietary and serum

continuous scale magnesium variables was assessed by Pearson correlation coefficient.

## 3. Results

Selected characteristics of participants are summarised in Table 1 stratified by sex. All variables were significantly different in men and women except for corticosteroid and statin use. The UK Reference Nutrient Intake (RNI) for magnesium is 300 mg per day for men over the age of 18 years and 270 mg per day for women, while the Estimated Average Requirements (EARs) for men and women are 250 mg and 200 mg [30]. In this cohort, mean dietary magnesium intakes were 332 ± 90 mg for men and 275 ± 73 mg for women. The largest contribution of magnesium in the diet of both men and women in this cohort came from cereals and cereal foods (33.7% of total dietary magnesium in men; 32.4% in women). Fruits and vegetables accounted for a further 11.5% in men and 15.0% in women, while hot beverages provided 10.1% in men and 11.4% in women. Further detail of the contribution of foods to magnesium intake is provided in Supplemental Fig. 1. Prevalence of inadequate intakes estimated using the EAR cut-point method [31] was 14.3%, with a greater number of men with inadequate intakes than women (16.1% *vs.* 12.9%; $p < 0.001$; $n = 14340$). No correlation was evident between magnesium dietary intake and serum concentration (Pearson's $r = 0.007$, $p = 0.646$, $n = 4611$ men; $r = -0.030$, $p = 0.020$, $n = 5972$ women).

In dietary model analyses, there were significant positive trends across magnesium intake quintiles in adjusted FFM, FFM%, and $FFM_{BMI}$ for both men and women (all $p < 0.001$; $n = 6350$ men; $n = 7990$ women) (see Supplemental Table 1). These trends were evident in both <60 ($n = 2366$ men; $n = 3535$ women) and ≥60 year olds ($n = 3984$ men; $n = 4455$ women) (see Fig. 1). The largest all-age inter-quintile differences were apparent in women where adjusted FFM for those in quintile 5 was 2.9% greater than in quintile 1, FFM% was 4.2% greater, and $FFM_{BMI}$ was 6.3% greater (all $p < 0.001$; $n = 3196$); quintile 5 *vs.* 1 differences in men were 2.0% for FFM, 2.4% for FFM%, and 4.6% for $FFM_{BMI}$ (all $p < 0.001$; $n = 2540$). For women under 60 years of age, adjusted FFM in quintile 5 was 3.4% greater than in quintile 1, FFM% was 4.6% greater, and $FFM_{BMI}$ was 7.2% greater (all $p < 0.001$; $n = 1394$); in

**Table 1**
Selected characteristics of the EPIC-Norfolk cohort population stratified by sex for the diet analysis group (n = 14,340) and the serum analysis group (n = 10,611).

| Characteristic | Diet analysis group | | *P*[a] | Serum analysis group | | *P* |
|---|---|---|---|---|---|---|
| | Men | Women | | Men | Women | |
| | n = 6350 | n = 7990 | | n = 4628 | n = 5983 | |
| Age (years) | 62.9 ± 9.0[b] | 61.5 ± 9.0 | <0.001 | 62.9 ± 8.7[b] | 61.6 ± 8.9 | <0.001 |
| BMI (kg/m$^2$) | 26.7 ± 3.0 | 26.1 ± 3.7 | <0.001 | 26.7 ± 3.0 | 26.0 ± 3.7 | <0.001 |
| Magnesium intake (mg/day) | 332 ± 90 | 275 ± 73 | <0.001 | – | – | |
| Total energy intake (kcal/day) | 2286 ± 500 | 1735 ± 378 | <0.001 | – | – | |
| Protein % of energy | 14.8 ± 2.4 | 15.5 ± 2.8 | <0.001 | – | – | |
| Serum [Mg] (mmol/L) | – | – | | 0.82 ± 0.11 | 0.80 ± 0.12 | <0.001 |
| FFM (kg) | 61.6 ± 5.9 | 40.6 ± 4.5 | <0.001 | 61.7 ± 5.9 | 40.6 ± 4.5 | <0.001 |
| FFM% | 76.7 ± 5.8 | 60.9 ± 8.3 | <0.001 | 76.8 ± 5.8 | 61.1 ± 8.1 | <0.001 |
| $FFM_{BMI}$ | 2.33 ± 0.26 | 1.58 ± 0.26 | <0.001 | 2.33 ± 0.26 | 1.59 ± 0.26 | <0.001 |
| EI:EER% | 91.1 ± 20.7 | 93.7 ± 21.8 | <0.001 | – | – | |
| Smoking | | | <0.001 | | | <0.001 |
| Current | 542 (8.5) | 696 (8.7) | | 375 (8.1) | 489 (8.2) | |
| Former | 3524 (55.5) | 2551 (31.9) | | 2552 (55.1) | 1909 (31.9) | |
| Never | 2284 (36.0) | 4743 (59.4) | | 1701 (36.8) | 3585 (59.9) | |
| Physical activity | | | <0.001 | | | <0.001 |
| Inactive | 1736 (27.3) | 2070 (25.9) | | 1236 (26.7) | 1537 (25.7) | |
| Moderately inactive | 1595 (25.1) | 2600 (32.5) | | 1164 (25.2) | 1927 (32.2) | |
| Moderately active | 1590 (25.0) | 1933 (24.2) | | 1160 (25.1) | 1445 (24.2) | |
| Active | 1429 (22.5) | 1387 (17.4) | | 1068 (23.1) | 1074 (18.0) | |
| Corticosteroid use | | | 0.391 | | | 0.391 |
| Never (<3 months) | 6086 (95.8) | 7583 (94.9) | | 4444 (96.0) | 5698 (95.2) | |
| Current or former (>3 months) | 264 (4.2) | 407 (5.1) | | 184 (4.0) | 285 (4.8) | |
| Statin use | | | 0.391 | | | 0.391 |
| No | 6003 (94.5) | 7700 (96.4) | | 4389 (94.8) | 5769 (96.4) | |
| Yes | 347 (5.5) | 290 (3.6) | | 239 (5.2) | 214 (3.6) | |
| Menopausal status | | | | | | |
| Pre-menopausal | – | 475 (5.9) | | – | 273 (4.6) | |
| Peri-menopausal (<1 years) | – | 266 (3.3) | | – | 209 (3.5) | |
| Peri-menopausal (1–5 years) | – | 1400 (17.5) | | – | 1106 (18.5) | |
| Post-menopausal | – | 5849 (73.2) | | – | 4395 (73.5) | |
| HRT | | | | | | |
| Current | – | 1704 (21.3) | | – | 1297 (21.7) | |
| Former | – | 1432 (17.9) | | – | 1095 (18.3) | |
| Never | – | 4854 (60.8) | | – | 3591 (60.0) | |
| Social Class | | | <0.001 | | | <0.001 |
| Professional | 523 (8.2) | 547 (6.8) | | 385 (8.3) | 401 (6.7) | |
| Managerial | 2587 (40.7) | 2950 (36.9) | | 1917 (41.4) | 2226 (37.2) | |
| Skilled non-manual | 797 (12.6) | 1554 (19.4) | | 567 (12.3) | 1180 (19.7) | |
| Skilled manual | 1422 (22.4) | 1577 (19.7) | | 1055 (22.8) | 1190 (19.9) | |
| Semi-skilled | 781 (12.3) | 950 (11.9) | | 537 (11.6) | 688 (11.5) | |
| Non-skilled | 149 (2.3) | 267 (3.3) | | 99 (2.1) | 197 (3.3) | |
| Un-coded | 91 (1.4) | 145 (1.8) | | 68 (1.5) | 101 (1.7) | |

[a] P values are for differences between men and women, according to t-test for continuous or chi-square for categorical variables.
[b] Values are mean ± SD or frequency (percentage).

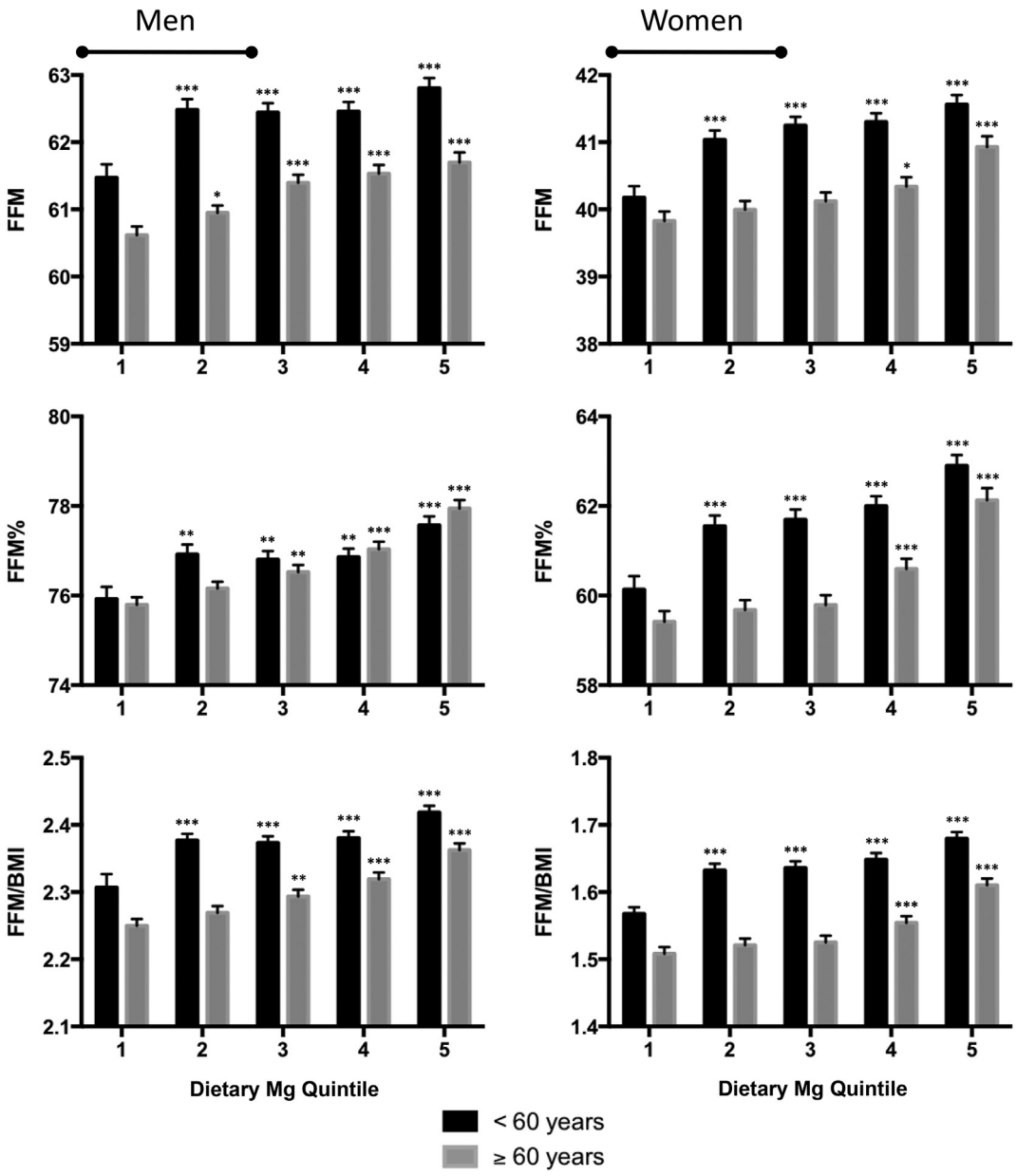


**Fig. 1.** Adjusted skeletal muscle measures for individuals of the EPIC-Norfolk cohort stratified by sex, age group, and quintiles of dietary magnesium intake (n = 14,340). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ *versus* quintile 1, according to ANCOVA. Adjusted for: age, menopausal status, HRT status, corticosteroid use, statin use, smoking status, physical activity, social class, total energy intake, percentage of total energy from protein, and EI:EER. Values are presented as mean ± SE. **Mg intake (mean ± SD; mg/day) by Mg quintiles (Q)**. *Men <60 years:* Mean, 350 ± 92; Q1, 226 ± 30; Q2, 283 ± 12; Q3, 323 ± 11; Q4, 368 ± 15; Q5, 470 ± 73. *Men ≥60 years:* Mean, 322 ± 87; Q1, 223 ± 31; Q2, 282 ± 12; Q3, 322 ± 11; Q4, 366 ± 16; Q5, 465 ± 71. *Women <60 years:* Mean, 285 ± 75; Q1, 187 ± 27; Q2, 235 ± 10; Q3, 268 ± 10; Q4, 305 ± 12; Q5, 385 ± 62. *Women ≥60 years:* Mean, 268 ± 71; Q1, 186 ± 26; Q2, 234 ± 10; Q3, 267 ± 10; Q4, 304 ± 13; Q5, 381 ± 56.

men the differences were 2.2% for FFM, 2.2% for FFM%, and 4.8% for $FFM_{BMI}$ (all $p < 0.001$; $n = 940$). For women 60 years or over, adjusted FFM in quintile 5 was 2.8% greater than in quintile 1, FFM% was 4.6% greater, and $FFM_{BMI}$ was 6.8% greater (all $p < 0.001$; $n = 1802$); in men the differences were 1.8% for FFM, 2.8% for FFM%, and 5.0% for $FFM_{BMI}$ (all $p < 0.001$; $n = 1600$).

In all-age serum model analyses (see Supplemental Table 2) no linear trends were apparent between magnesium serum concentration groups and FFM, FFM%, or $FFM_{BMI}$; likewise, no significant differences were identified between muscle mass measures in the low normal concentration group (group 2) *vs.* other groups. However, stratifying the serum data by age highlighted some significant differences (see Fig. 2). In individuals ≥60 years old, FFM was significantly lower in magnesium concentration group 4 *vs.* group 2 in both men ($p = 0.031$; $n = 1131$) and women ($p = 0.020$; $n = 1311$), and group 5 *vs.* group 2 in women only ($p = 0.029$; $n = 928$).

## 4. Discussion

This study, using data from a large population cohort, has shown that associations between dietary magnesium and indices of skeletal muscle mass exist in both men and women. Significant positive trends in FFM, FFM% and $FFM_{BMI}$ were evident across increasing quintiles of dietary magnesium intake for both sexes, which remained after adjustment for important biological, lifestyle and other dietary covariates. These results corroborate previous smaller-scale studies including the positive relationship between magnesium intake and dual-energy X-ray absorptiometry-assessed

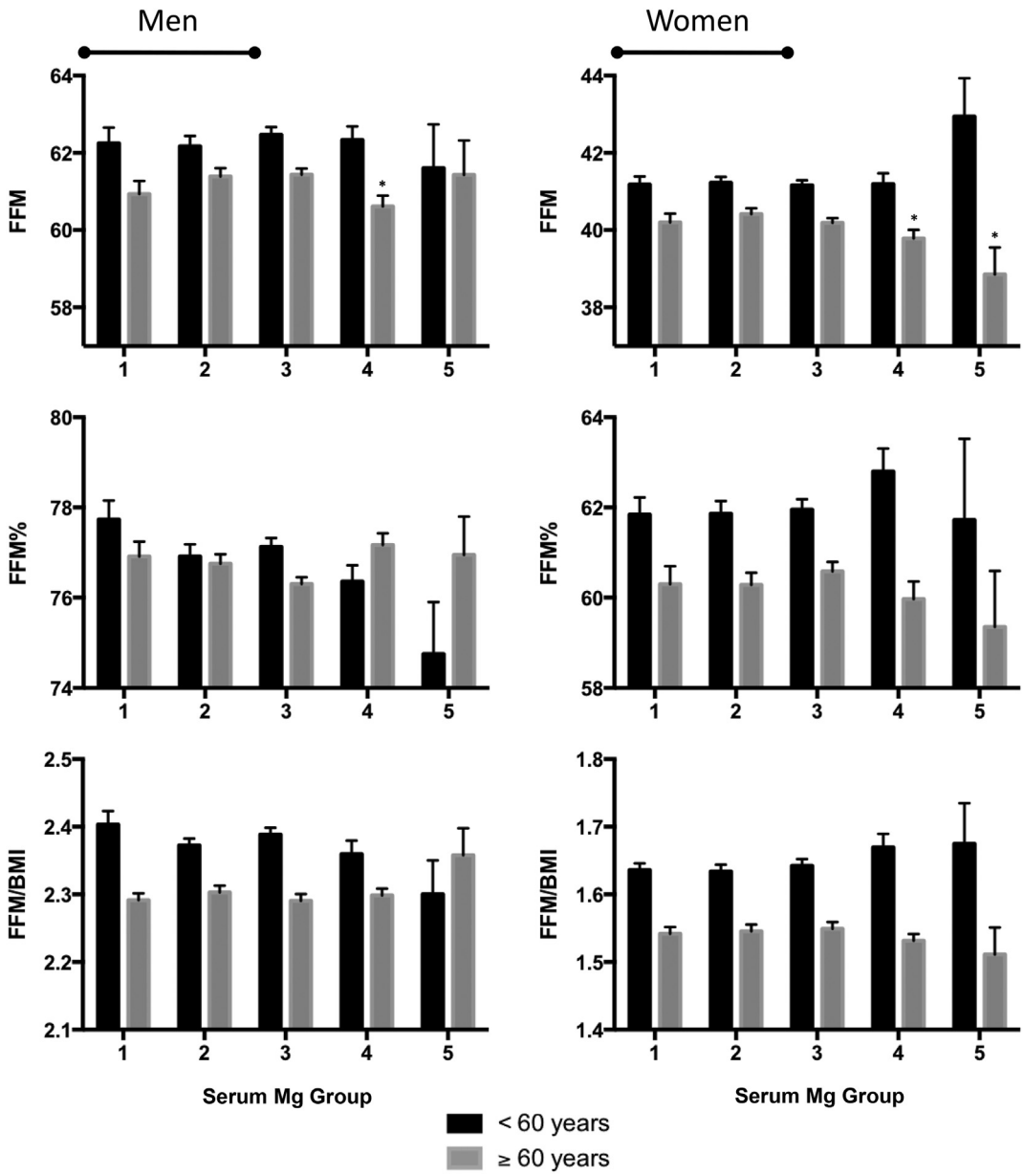


**Fig. 2.** Adjusted skeletal muscle measures for individuals of the EPIC-Norfolk cohort stratified by sex, age group, and serum concentration groups (n = 10,611). $^{*}p < 0.05$; $^{**}p < 0.01$; $^{***}p < 0.001$ *versus* group 2, according to ANCOVA. Adjusted for: age, menopausal status, HRT status, corticosteroid use, statin use, smoking status, physical activity, and social class. Values are presented as mean ± SE. **Serum Mg concentration groups:** <0.7 mmol/L (group 1), 0.7–0.8 mmol/L (group 2), 0.8–0.9 mmol/L (group 3), 0.9–1.0 mmol/L (group 4), and >1.0 mmol/L (group 5).

appendicular lean mass in individuals aged 50–79 years in the Tasmanian Older Adult Cohort Study [15], the greater FFM seen with higher intakes of dietary magnesium in a UK study of women aged 34–83 years from the TwinsUK cohort [16], and the more recent large-scale cross-sectional analysis of FFM% and $FFM_{BMI}$ using UK Biobank data [17]. Associations between serum magnesium concentration groups and skeletal muscle mass indices are less clear, although this is unsurprising considering the tight homeostatic control of circulating magnesium and the fact that less than 1% of total body magnesium is present in the blood [32]. This homeostatic control makes it less likely that a serum magnesium concentration outside the normal range represents an extreme dietary intake of magnesium, and more likely that it is the result of a pathological problem (e.g. abnormal renal wasting) or diuretic medication [32]. Indeed, our results showed correlation of magnesium serum concentration with dietary intake in the EPIC-Norfolk cohort was negligible. Previous studies have demonstrated that despite presenting with normal serum magnesium concentration, some individuals may be severely magnesium deficient, with low concentrations in bone and muscle due to long-term compensatory release of magnesium to maintain serum concentration when dietary intake has been low for a long period of time [33]. This may partly explain the inconsistent associations between serum magnesium concentrations and skeletal muscle mass indices apparent in this study.

It is important to appreciate the magnitude of the differences seen with the dietary analyses. Indeed, considering that the effect of age on skeletal muscle mass is already well-established [34], and confirmed in this dataset where $FFM_{BMI}$ was 5.4% lower in those ≥60 years *versus* those <60 years (data not shown), the differences

seen according to magnesium intake are highly relevant. For example, the difference in adjusted $FFM_{BMI}$ between magnesium quintile 5 and quintile 1 for women was 6.3%. Furthermore, the difference in median daily dietary intake between quintiles 1 and 5 for women was 173 mg, a difference which should be achievable as part of a normal diet (for example, by ½ cup boiled spinach, ¼ cup roasted peanuts, and a medium-sized banana [35]). However, since a typical Western diet containing a high proportion of processed foods and limited whole grains and green vegetables is often deficient in magnesium [36], more needs to be done to promote an adequate diet and avoid adverse musculoskeletal consequences.

Although sarcopenia is a particular issue in individuals aged 60 years old or older, loss of skeletal muscle mass has been documented to progress from the age of 30 years onwards [4]. Age stratification of our dietary magnesium analyses demonstrated largely similar effects for those less than 60 years of age, and those 60 years or older, albeit with lower values for muscle mass indices in the older age group. This highlights the potential benefits of dietary magnesium for musculoskeletal health in all ages of this cohort, and raises the possibility that optimal dietary magnesium intake could help preserve skeletal muscle before sarcopenia becomes problematic later in life.

While previous research has demonstrated magnesium status to be strongly correlated with muscle performance in both young and old individuals [13,14], the mechanisms by which magnesium may influence muscle are not yet fully understood. Magnesium is critical for basic mitochondrial function: cell-culture and animal studies have demonstrated that magnesium depletion can cause structural damage to muscle cells due to oxidative stress and disrupted calcium homeostasis [37]. In addition, magnesium also has a postulated role in protecting against the chronic low-grade inflammation associated with ageing and a known risk factor for sarcopenia [4]. Indeed, circulating concentrations of inflammatory cytokines, including C-reactive protein (CRP), interleukin-6, and tumour necrosis factor-$\alpha$, have been negatively associated with skeletal muscle measures of both mass and function in a number of studies [16,38–40], and systematic review evidence indicates that dietary magnesium intake is inversely associated with serum CRP concentration [41].

It is interesting to consider how results for the alternative skeletal muscle indices translate into clinical importance for sarcopenia. $FFM_{BMI}$ may provide a more useful measure than unstandardised FFM or FFM% to assess change in skeletal muscle mass while correcting for differences attributable to body size. This index has recently been used to define cutpoints in the Foundation for the National Institutes of Health Biomarkers Consortium Sarcopenia Project [42], and as it is used in more studies of different populations we will gain a greater understanding of how it describes body composition in both normal and sarcopenic individuals.

This is the first study to have investigated associations between both dietary intake and circulating magnesium, and measures of skeletal muscle in a mixed-sex UK cohort of older adults. However, we recognise there are a number of limitations. These include the observational and cross-sectional study design which precludes us from attributing causal links between magnesium dietary intake or serum concentration and skeletal muscle measures, and reliance on self-reported measures for diet and physical activity data. Nevertheless, the quantitative 7-day food diaries developed for use in EPIC have been validated previously and are expected to provide more precise dietary intake figures compared to alternative FFQ or 24-h recall methods [26]. Magnesium dietary data analysed here were derived from food intake only, and therefore may underestimate total nutrient intakes. However, the supplements consumed by this cohort provide a relatively small contribution to total magnesium intake and thus are likely to have a negligible effect on our results [43]. We assessed magnesium status using serum magnesium concentrations which may not be the most reliable marker of Mg status as discussed earlier. However, the preferred alternative of timed 24 h urine collection which linearly reflects dietary intake may be even less reliable for older individuals due to problems with urine collection and complications of diuretic use [11]. Magnetic resonance measurement of ionised magnesium within skeletal muscle could provide useful data [44], but this method was not practical for our large population sample, and thus serum magnesium measurement remains a useful indicator of magnesium status for this type of study [45]. Indices of skeletal muscle mass were calculated from weight, height, and bioelectrical-impedance measurements, rather than the potentially more accurate and precise methods of dual-energy X-ray absorptiometry, computer tomography, or magnetic resonance imaging [46]. However, bio-electrical impedance assessment has the advantage of avoiding accessibility issues, costs, and radiation, associated with other methods. Consequences of loss of skeletal muscle mass may extend beyond a reduction in strength and function due to the metabolic role of muscle, and may include changes to metabolic rate, insulin resistance, and increased risk of hypertension [5]. While in this study it has not been possible to analyse functional muscle measures in relation to magnesium we believe it is important to have considered the fundamental body composition information provided by BIA data.

## 5. Conclusions

This study has highlighted strong positive associations between dietary magnesium intake and indices of skeletal muscle mass in both men and women of the EPIC-Norfolk cohort, with the scale of effects highly relevant in comparison to age-related losses. The results for circulating magnesium are less patent, potentially due to the tight homeostatic control of blood magnesium concentrations. These findings, which being observational in nature require confirmation by clinical trial, support a hypothesis that dietary magnesium is beneficial to skeletal muscle health in older individuals.

## Funding

The EPIC-Norfolk study was supported by funding from the Medical Research Council (G9502233) and Cancer Research UK (SP2024-0201 and SP2024-0204).

## Author contribution

AAW developed the research question together with RPGH who performed the data analyses and drafted the manuscript. AAW organised data collection in conjunction with RNL who implemented the record linkage. MAHL and AAM prepared dietary and supplemental data for statistical analysis. K-TK is principal investigator of the EPIC-Norfolk Study. All authors read and approved the final manuscript.

## Conflict of interest

None declared.

## Acknowledgements

We thank all the EPIC-Norfolk study participants and coordination staff.

## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.01.014.

## References


[1] Cruz-Jentoft AJ, Baeyens JP, Bauer JM, Boirie Y, Cederholm T, Landi F, et al. Sarcopenia: European consensus on definition and diagnosis: report of the European working group on sarcopenia in older people. Age Ageing 2010;39(4):412–23.
[2] Szulc P, Beck TJ, Marchand F, Delmas PD. Low skeletal muscle mass is associated with poor structural parameters of bone and impaired balance in elderly men–the MINOS study. J Bone Miner Res 2005;20(5):721–9.
[3] Russo CR. The effects of exercise on bone. Basic concepts and implications for the prevention of fractures. Clin Cases Miner Bone Metab 2009;6(3):223–8.
[4] Welch AA. Nutritional influences on age-related skeletal muscle loss. Proc Nutr Soc 2014;73(1):16–33.
[5] Karakelides H, Nair KS. Sarcopenia of aging and its metabolic impact. Curr Top Dev Biol 2005;68:123–48.
[6] Paddon-Jones D, Short KR, Campbell WW, Volpi E, Wolfe RR. Role of dietary protein in the sarcopenia of aging. Am J Clin Nutr 2008;87(5):1562S–6S.
[7] Arik G, Ulger Z. Vitamin D in sarcopenia: understanding its role in pathogenesis, prevention and treatment. Eur Geriatr Med 2016;7(3):207–13.
[8] Cesari M, Pahor M, Bartali B, Cherubini A, Penninx BW, Williams GR, et al. Antioxidants and physical performance in elderly persons: the Invecchiare in Chianti (InCHIANTI) study. Am J Clin Nutr 2004;79(2):289–94.
[9] Khor SC, Abdul Karim N, Ngah WZ, Yusof YA, Makpol S. Vitamin E in sarcopenia: current evidences on its role in prevention and treatment. Oxid Med Cell Longev 2014;2014:914853.
[10] Mulligan AA, Lentjes MAH, Luben RN, Khaw KT, Welch AA. Dietary vitamin E intake is associated with greater fat-free mass and percentage fat-free mass in the EPIC-Norfolk cohort. Proc Nutr Soc 2016;75(OCE3).
[11] Veronese N, Zanforlini BM, Manzato E, Sergi G. Magnesium and healthy aging. Magnes Res 2015;28(3):112–5.
[12] Jahnen-Dechent W, Ketteler M. Magnesium basics. Clin Kidney J 2012;5(Suppl. 1):i3–14.
[13] Brilla LR, Haley TF. Effect of magnesium supplementation on strength training in humans. J Am Coll Nutr 1992;11(3):326–9.
[14] Veronese N, Berton L, Carraro S, Bolzetta F, De Rui M, Perissinotto E, et al. Effect of oral magnesium supplementation on physical performance in healthy elderly women involved in a weekly exercise program: a randomized controlled trial. Am J Clin Nutr 2014;100(3):974–81.
[15] Scott D, Blizzard L, Fell J, Giles G, Jones G. Associations between dietary nutrient intake and muscle mass and strength in community-dwelling older adults: the Tasmanian Older Adult Cohort Study. J Am Geriatr Soc 2010;58(11):2129–34.
[16] Welch AA, Kelaiditi E, Jennings A, Steves CJ, Spector TD, MacGregor A. Dietary magnesium is positively associated with skeletal muscle power and indices of muscle mass and may attenuate the association between circulating C-Reactive protein and muscle mass in women. J Bone Miner Res 2016;31(2):317–25.
[17] Welch AA, Skinner J, Hickson M. Dietary magnesium may be protective for aging of bone and skeletal muscle in middle and younger older age men and women: cross-sectional findings from the UK Biobank cohort. Nutrients 2017;9(11).
[18] Dominguez LJ, Barbagallo M, Lauretani F, Bandinelli S, Bos A, Corsi AM, et al. Magnesium and muscle performance in older persons: the InCHIANTI study. Am J Clin Nutr 2006;84(2):419–26.
[19] Day N, Oakes S, Luben R, Khaw KT, Bingham S, Welch A, et al. EPIC-Norfolk: study design and characteristics of the cohort. European prospective investigation of cancer. Br J Canc 1999;80(Suppl. 1):95–103.
[20] Shanholtzer BA, Patterson SM. Use of bioelectrical impedance in hydration status assessment: reliability of a new tool in psychophysiology research. Int J Psychophysiol 2003;49(3):217–26.
[21] Simpson JA, Lobo DN, Anderson JA, Macdonald IA, Perkins AC, Neal KR, et al. Body water compartment measurements: a comparison of bioelectrical impedance analysis with tritium and sodium bromide dilution techniques. Clin Nutr 2001;20(4):339–43.
[22] Studenski SA, Peters KW, Alley DE, Cawthon PM, McLean RR, Harris TB, et al. The FNIH sarcopenia project: rationale, study description, conference recommendations, and final estimates. J Gerontol A Biol Sci Med Sci 2014;69(5):547–58.
[23] Wareham NJ, Jakes RW, Rennie KL, Schuit J, Mitchell J, Hennings S, et al. Validity and repeatability of a simple index derived from the short physical activity questionnaire used in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Public Health Nutr 2003;6(4):407–13.
[24] Bingham SA, Welch AA, McTaggart A, Mulligan AA, Runswick SA, Luben R, et al. Nutritional methods in the European prospective investigation of cancer in Norfolk. Public Health Nutr 2001;4(3):847–58.
[25] Welch AA, McTaggart A, Mulligan AA, Luben R, Walker N, Khaw KT, et al. DINER (Data Into Nutrients for Epidemiological Research) - a new data-entry program for nutritional analysis in the EPIC-Norfolk cohort and the 7-day diary method. Public Health Nutr 2001;4(6):1253–65.
[26] Lentjes MA, McTaggart A, Mulligan AA, Powell NA, Parry-Smith D, Luben RN, et al. Dietary intake measurement using 7 d diet diaries in British men and women in the European Prospective Investigation into Cancer-Norfolk study: a focus on methodological issues. Br J Nutr 2013;111(3):1–11.
[27] Murakami K, Livingstone MB. Prevalence and characteristics of misreporting of energy intake in US adults: NHANES 2003–2012. Br J Nutr 2015;114(8):1294–303.
[28] Ayuk J, Gittoes NJ. Contemporary view of the clinical relevance of magnesium homeostasis. Ann Clin Biochem 2014;51(Pt 2):179–88.
[29] Fish RM, Geddes LA. Medical and bioengineering aspects of electrical injuries. Tucson: Lawyers & Judges; 2003.
[30] Department of Health. Dietary reference values for food energy and nutrients for the United Kingdom. London: HSMO; 1991.
[31] Sobiecki JG, Appleby PN, Bradbury KE, Key TJ. High compliance with dietary recommendations in a cohort of meat eaters, fish eaters, vegetarians, and vegans: results from the European Prospective Investigation into Cancer and Nutrition-Oxford study. Nutr Res 2016;36(5):464–77.
[32] Wu J, Carter A. Magnesium: the forgotten electrolyte. Aust Prescr 2007;30:102–5.
[33] de Baaij JH, Hoenderop JG, Bindels RJ. Magnesium in man: implications for health and disease. Physiol Rev 2015;95(1):1–46.
[34] Baumgartner RN, Waters DL, Gallagher D, Morley JE, Garry PJ. Predictors of skeletal muscle mass in elderly men and women. Mech Ageing Dev 1999;107(2):123–36.
[35] National Institutes of Health Office of Dietary Supplements. Magnesium fact sheet for health professionals. 2016.
[36] Rayssiguier Y, Mazur A, Durlach J. Advances in magnesium research : nutrition and health. Eastleigh: John Libbey; 2001.
[37] Rock E, Astier C, Lab C, Vignon X, Gueux E, Motta C, et al. Dietary magnesium deficiency in rats enhances free radical production in skeletal muscle. J Nutr 1995;125(5):1205–10.
[38] Aleman H, Esparza J, Ramirez FA, Astiazaran H, Payette H. Longitudinal evidence on the association between interleukin-6 and C-reactive protein with the loss of total appendicular skeletal muscle in free-living older men and women. Age Ageing 2011;40(4):469–75.
[39] Schaap LA, Pluijm SM, Deeg DJ, Harris TB, Kritchevsky SB, Newman AB, et al. Higher inflammatory marker levels in older persons: associations with 5-year change in muscle mass and muscle strength. J Gerontol A Biol Sci Med Sci 2009;64(11):1183–9.
[40] Cesari M, Penninx BW, Pahor M, Lauretani F, Corsi AM, Rhys Williams G, et al. Inflammatory markers and physical performance in older persons: the InCHIANTI study. J Gerontol A Biol Sci Med Sci 2004;59(3):242–8.
[41] Dibaba DT, Xun P, He K. Dietary magnesium intake is inversely associated with serum C-reactive protein levels: meta-analysis and systematic review. Eur J Clin Nutr 2014;68(4):510–6.
[42] Cawthon PM, Peters KW, Shardell MD, McLean RR, Dam TT, Kenny AM, et al. Cutpoints for low appendicular lean mass that identify older adults with clinically significant weakness. J Gerontol A Biol Sci Med Sci 2014;69(5):567–75.
[43] Lentjes MA, Bhaniani A, Mulligan AA, Khaw KT, Welch AA. Developing a database of vitamin and mineral supplements (ViMiS) for the Norfolk arm of the European Prospective Investigation into Cancer (EPIC-Norfolk). Public Health Nutr 2011;14(3):459–71.
[44] Ryschon TW, Rosenstein DL, Rubinow DR, Niemela JE, Elin RJ, Balaban RS. Relationship between skeletal muscle intracellular ionized magnesium and measurements of blood magnesium. J Lab Clin Med 1996;127(2):207–13.
[45] Rosanoff A, Dai Q, Shapses SA. Essential nutrient interactions: does low or suboptimal magnesium status interact with vitamin D and/or calcium status? Adv Nutr 2016;7(1):25–43.
[46] Cooper C, Fielding R, Visser M, van Loon LJ, Rolland Y, Orwoll E, et al. Tools in the assessment of sarcopenia. Calcif Tissue Int 2013;93(3):201–10.