

**Dietary magnesium and potassium intakes and circulating magnesium are associated with heel bone ultrasound attenuation and osteoporotic fracture risk in the EPIC-Norfolk cohort study.**

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Abbreviations: BMD (Bone Mineral Density); BUA (Broadband Ultrasound Attenuation); CUBA (Contact Ultrasound Bone Analyser); DINER (Data Into Nutrients for Epidemiological Research); DXA (Dual X-ray Absorptiometry); EPIC (European Prospective Investigation into Cancer); FFQ (Food-Frequency Questionnaire); HLQ (Health and Lifestyle Questionnaire); HRT (Hormone Replacement Therapy); RNI (Reference Nutrient Intake).

## 1 **ABSTRACT**

2 **Background:** In our ageing population, maintenance of bone health is critical to reduce the  
3 risk of osteoporosis and potentially debilitating consequences of fractures in older individuals.  
4 Amongst modifiable lifestyle and dietary factors, dietary magnesium and potassium intake are  
5 postulated to influence bone quality and osteoporosis, principally via calcium-dependent  
6 alteration of bone structure and turnover.

7 **Objective:** To investigate the influence of dietary magnesium and potassium intakes, and  
8 circulating magnesium, on bone density status and fracture risk in a UK adult population.

9 **Design:** A random subset of 4000 individuals from the EPIC-Norfolk cohort of 25,639 men  
10 and women with baseline data was used for bone density cross-sectional analyses, and  
11 combined with fracture cases (n=1502) for fracture case-cohort longitudinal analyses (mean  
12 follow-up 13.4 years). Relevant biological, lifestyle, and dietary covariates were used in  
13 multivariate regression analyses to determine associations between dietary magnesium and  
14 potassium intakes and calcaneal broadband ultrasound attenuation (BUA), and in Prentice-  
15 weighted Cox regression to determine associated risk of fracture. Separate analyses,  
16 excluding dietary covariates, investigated associations of BUA and fractures with serum  
17 magnesium concentration.

18 **Results:** Significant positive trends in calcaneal BUA for women (n=1360), but not men  
19 (n=968), were apparent across increasing quintiles of Mg+K z-score intake (p=0.03), or  
20 potassium intake alone (p=0.04). Reduced hip fracture risk in both men (n=1958) and women  
21 (n=2755) was evident for individuals in specific Mg+K z-score intake quintiles *versus* the  
22 lowest. Significant trends in fracture risk in men across serum magnesium concentration  
23 groups were apparent for spine fractures (p=0.02), and total hip, spine, and wrist fractures  
24 (p=0.02). None of these individual significant associations remained after adjusting for  
25 multiple-testing.

26 **Conclusions:** These findings enhance the limited literature studying the association of  
27 magnesium and potassium with bone density and demonstrate that further investigation is  
28 warranted into the mechanisms involved and the potential protective role against osteoporosis.

## 29 INTRODUCTION

30 A multitude of factors are known to influence bone health, including modifiable factors such  
31 as diet, physical activity, and smoking, but also age, sex, and genetics (1). Osteoporosis,  
32 characterised by bone loss due to deterioration of bone microarchitecture and consequent  
33 increased risk of fracture, is significantly associated with age and thus represents a major  
34 public health concern for our ageing population (2). Calcium and vitamin D have traditionally  
35 been the primary nutritional candidates for osteoporosis prevention and maintenance of bone  
36 health (3), but more recently magnesium intake has also been linked with bone mass, and  
37 magnesium deficiency with osteoporosis (4-8). Magnesium is a major component of bone,  
38 with 67% of total body magnesium found there (9). Animal studies have suggested a number  
39 of mechanisms for involvement of magnesium in bone metabolism including: nitric oxide  
40 dependent effects on osteoblast activity and osteoclast number (10); influence of magnesium  
41 on hydroxyapatite crystal formation and consequent bone stiffness (11); regulation of calcium  
42 homeostasis through parathyroid hormone, 1,25-dihydroxyvitamin D, and magnesium-  
43 dependent calcium channels (9); and altered inflammatory cytokine release (12). Similarly,  
44 recent epidemiological studies have associated lower dietary potassium intake with poorer  
45 bone density (5, 6, 8, 13). Increasing potassium intake increases urinary retention, reducing  
46 loss of calcium and thus creating a more positive calcium balance and inhibiting bone  
47 resorption; urinary loss of phosphorus also decreases, which inhibits renal synthesis of 1,25-  
48 dihydroxyvitamin D and cuts intestinal absorption of calcium, stopping the positive calcium  
49 balance persisting (14). Occurrence of this stabilisation has recently been disputed, although  
50 potassium source differences may be the cause of the discrepancy between studies (15).

51

52 When considering the dietary association of magnesium and potassium with bone health it is  
53 most appropriate to study these minerals concurrently as they are frequently consumed

54 together from intact or moderately altered plant or animal tissues (16). Metabolism of  
55 magnesium and potassium are linked as magnesium is required for effective  $\text{Na}^+/\text{K}^+$ -ATPase  
56 pump function (17), magnesium and potassium have additive effects in preventing increase in  
57 the endogenous sodium potassium pump inhibitor (16), and both have direct and indirect  
58 effects on calcium homeostasis (9, 18). Previous studies of the association of dietary  
59 magnesium and potassium with bone health have had limited generalisability due to their  
60 focus on discrete population groups, such as narrow age-range groups of relatively old (5, 19)  
61 or young individuals (20), restrictions to pre- (8, 20) or post-menopausal women only (13),  
62 and non-UK residents (5, 7, 20). Indeed, the most recent and comprehensive study, with a  
63 large cohort size and longitudinal analysis of fracture risk, was also limited to women only (7).  
64 The current study therefore aimed to explore potential associations of dietary magnesium and  
65 potassium intakes and circulating magnesium with bone density status and risk of incident  
66 osteoporotic fractures in a general population of men and women in the UK, using a measure  
67 of broadband ultrasound attenuation of the calcaneus and records of incident fractures of the  
68 hip, spine, and wrist.

## 69 **SUBJECTS AND METHODS**

70 The EPIC-Norfolk cohort analysed in this study is part of the European Prospective  
71 Investigation into Cancer (EPIC), a global collaboration involving ten countries developed  
72 primarily to examine association between diet and cancer, with additional health outcomes  
73 also examined in EPIC-Norfolk. This cohort has been described in detail previously (21), but  
74 in brief the Norfolk cohort consisted of 25,639 men and women aged 40-79 years old living in  
75 the general community who participated in a baseline health-check between 1993 and 1997. A  
76 second health-check was attended by 15,786 participants, aged 42-82 years between 1997 and  
77 2000, when quantitative ultrasound measurements of the calcaneus (heel bone) were  
78 performed according to standardised protocols using a CUBA (contact ultrasound bone  
79 analyser) device (McCue Ultrasonics, Winchester, United Kingdom). Quantitative ultrasound  
80 represents a cheaper, more rapid, and easier method of assessing bone density status in  
81 general practice compared to the gold-standard of Dual X-ray absorptiometry (DXA), and has  
82 been shown capable of predicting fracture risk (22). Measurements of broadband ultrasound  
83 attenuation (BUA; dB/MHz) from each foot were taken at least in duplicate and the mean of  
84 both feet was recorded, as described previously (22).

85  
86 The dataset analysed here includes 4000 randomly selected participants with baseline health-  
87 check data, plus a group of 1502 participants with fractures, representing all hip, spine, and  
88 wrist fracture cases in the cohort up to 31st March 2009. Some overlap exists between the  
89 random subcohort and the fracture cases and thus the fracture case-cohort contains 5319  
90 unique individuals (4713 participants had complete data for diet and fracture analyses; 3469  
91 for serum and fracture analyses). Ultrasound data was available for 2341 individuals (2328  
92 participants had complete data for diet and ultrasound analyses; 1726 for serum and  
93 ultrasound analyses).

94

95 The Norfolk District Health Authority Ethics Committee approved all procedures involving  
96 human subjects and written informed consent was provided by all participants according to  
97 the Declaration of Helsinki.

98

99 Height and weight were measured according to standard protocols (21) at both health checks,  
100 conducted either at a clinic or the participant's GP surgery. Height was determined to the  
101 nearest millimetre using a free-standing stadiometer. Weight was recorded to the nearest 0.2  
102 kilograms with the participant wearing light clothing and no shoes. BMI was calculated from  
103 these measurements ( $\text{kg/m}^2$ ).

104

105 Participants also completed a self-administered health and lifestyle questionnaire (HLQ) at  
106 both health checks. This included smoking status categorised as *current*, *former* or *never*;  
107 family history of osteoporosis categorised as *yes* or *no*; menopausal status (women only)  
108 categorised as *pre-menopausal*, *peri-menopausal (<1 year)*, *peri-menopausal (1-5 years)*, or  
109 *post-menopausal*; and HRT status (women only) categorised as *current*, *former*, or *never*  
110 users. A short physical activity questionnaire was used to assess typical physical activity over  
111 the previous 12 months. Physical activity levels were then categorised into *inactive*,  
112 *moderately inactive*, *moderately active*, and *active* categories by a method validated against  
113 heart-rate monitoring data (21, 23).

114

115 Dietary intake of each participant was assessed by using a 7 day food diary (24), with each  
116 participant recording all food and drink consumed within a 7 day period, as well as the  
117 portion sizes. This method has previously been validated, proving more accurate in estimating  
118 dietary nutrient intake than food-frequency questionnaires (FFQ) (21, 25). Detail of the

119 DINER (Data Into Nutrients for Epidemiological Research) software used to record and  
120 translate the dietary information provided by the 7-day food diaries into nutrient quantities is  
121 reported elsewhere (26). All data entries were checked by nutritionists trained in use of the  
122 system (27).

123

124 Serum magnesium concentration was determined using blood sampled by peripheral  
125 venepuncture during the baseline health check. Samples were stored in liquid nitrogen at -  
126 196°C until analysed by Quotient Bioresearch, Fordham, UK, using an Olympus AU640  
127 Chemistry Immuno Analyser to perform a xylidyl blue based colorimetric assay.

128

129 Fracture incidence data were collected by questionnaire at baseline and follow-up health  
130 checks. In addition the East Norfolk Health Authority database (ENCORE), which records all  
131 hospital contact Norfolk residents have in England and Wales, was available to EPIC  
132 researchers for data linkage (28). This enabled the incidence of osteoporotic fractures  
133 occurring in the cohort, up to the end of March 2009, to be determined by retrieving data  
134 using the NHS numbers of EPIC participants and the International Classification of Diseases  
135 (ICD) 9 and 10 diagnostic codes for osteoporotic fractures by site (hip, spine, and wrist).

136

### 137 *Statistical analyses*

138 Statistical analyses were performed using STATA statistical software (version 12; Stata Corp.,  
139 College Station, Tx). All analyses were stratified by sex since significant differences in age-  
140 related changes in bone between men and women have previously been reported for this  
141 population, with a much greater magnitude of deterioration evident in women (22).  
142 Hypotheses and covariates included in regression models were well defined *a priori* using  
143 evidence from previous research and thus p-values  $\leq 0.05$  were considered to be statistically



144 significant in individual analyses. The individual hypotheses tested in this study have been  
145 grouped into families of tests (**Supplemental Table 1**), allowing the significance of  
146 individual p values to be determined in comparison to a Bonferroni-generated family-wise  
147 critical p value.

148  
149 Due to the high degree of collinearity between magnesium and potassium dietary intakes  
150 (Pearson  $r=0.84$  and  $r=0.82$  in men and women, both  $p<0.001$ ) and thus the potential for  
151 statistical issues, and any independent effects to be diminished, a summation of magnesium  
152 and potassium intake was used as the main exposure; however, since the amounts of each  
153 mineral consumed varies widely, both minerals were standardised before summation,  
154 resulting in a Mg+K z-score intake variable (5).

155  
156 Univariate linear regression was used to estimate the association of selected biological,  
157 lifestyle and dietary factors with sex-specific quintiles of dietary magnesium, potassium, or  
158 Mg+K z-score intake. Multivariable regression with ANCOVA was used to investigate  
159 differences in calcaneal BUA across sex-specific quintiles of dietary magnesium, potassium,  
160 or Mg+K z-score intake. An adjusted model was tested, correcting for the potential effects of  
161 biological (age, BMI, family history of osteoporosis, menopausal status, HRT status,  
162 corticosteroid use), lifestyle (smoking status, and physical activity) and dietary factors  
163 (calcium intake (29, 30), total energy intake (31), and calcium and vitamin D supplement use,  
164 previously shown to influence bone ultrasound measurements in this population (22, 32).

165 Participants were excluded from analyses if they had missing values for any variables  
166 included in the multivariate model ( $n=1672$ , 41.8%). In a similar way, differences in calcaneal  
167 BUA across sex-specific groups of serum magnesium concentration were investigated using  
168 the same covariates, but excluding dietary factors in the adjusted model. Published guidance

169 suggests 0.7-1.0 mmol/L should be used as a normal reference range (33). Concentration  
170 groups were categorised as <0.7 mmol/L (group 1, deficient), 0.7-0.8 mmol/L (group 2), 0.8-  
171 0.9 mmol/L (group 3), 0.9-1.0 mmol/L (group 4), and >1.0 mmol/L (group 5, excess).

172

173 Prentice-weighted Cox regression was used to investigate associations between incidence of  
174 fractures and sex-specific quintiles of dietary magnesium, potassium, or Mg+K z-score intake.

175 An unadjusted model without covariates was tested followed by a model adjusting for the  
176 aforementioned variables. The full case-cohort dataset described above, including the random

177 subset and all fracture cases, was used for these analyses. Participants were excluded from

178 analyses if they had missing values for any variables included in the adjusted model. For

179 analysis of specific-site fracture risk (hip, spine, or wrist) other fracture data were excluded

180 from the analysis unless contained in the subcohort, in order to retain a distinct control group.

181 Total risk of hip spine or wrist fracture was calculated as the risk of an individual having one

182 of these types of fracture. This total does not include multiple fractures and therefore the

183 specific-site fracture incidences described may not sum to the total. The association between

184 incidence of fractures and sex-specific groups of serum magnesium concentration was

185 investigated, using the same covariates, but excluding dietary factors in the adjusted model.

## 186 RESULTS

### 187 *Descriptive statistics*

188 Selected characteristics are summarised in **Table 1**, for men and women, as mean values  $\pm$  SD,  
189 or frequency and percentage for categorical variables. There were 968 men and 1360 women  
190 in the ultrasound cohort population with information for all selected variables; in the fracture  
191 case-cohort there were data for 1958 men and 2755 women. The mean age was  $63.0 \pm 9.3$  for  
192 men and  $61.7 \pm 9.2$  for women in the ultrasound cohort; in the fracture case-cohort mean age  
193 at baseline was  $59.7 \pm 9.6$  for men and  $59.8 \pm 9.5$  for women. Mean BMI was  $26.9 \pm 3.4$   
194  $\text{kg/m}^2$  for men and  $26.5 \pm 4.4 \text{ kg/m}^2$  for women in the ultrasound cohort; in the fracture case-  
195 cohort mean BMI at baseline was  $26.5 \pm 3.3 \text{ kg/m}^2$  for men and  $26.2 \pm 4.3 \text{ kg/m}^2$  for women.  
196 Mean total daily energy intake was  $2263 \pm 478 \text{ kcal}$  for men and  $1732 \pm 374 \text{ kcal}$  for women  
197 in the ultrasound cohort; in the fracture case-cohort mean intake at baseline was  $2239 \pm 514$   
198  $\text{kcal}$  for men and  $1683 \pm 385 \text{ kcal}$  for women. Mean magnesium intake was  $329 \pm 92 \text{ mg/day}$   
199 for men and  $277 \pm 72 \text{ mg/day}$  for women in the ultrasound cohort; in the fracture case-cohort  
200 mean intake at baseline was  $321 \pm 92 \text{ mg/day}$  for men and  $265 \pm 73 \text{ mg/day}$  for women; these  
201 values are slightly higher than the UK Reference Nutrient Intake (RNI) of 300 mg and 270  
202 mg (34), respectively. Mean calcium intake was  $925 \pm 282 \text{ mg/day}$  for men and  $782 \pm 247$   
203  $\text{mg/day}$  for women in the ultrasound cohort; in the fracture case-cohort mean intake at  
204 baseline was  $914 \pm 296 \text{ mg/day}$  for men and  $762 \pm 253 \text{ mg/day}$  for women; these values are  
205 also higher than the UK RNI of 700 mg for all adults over 19 years old (34). Calcium  
206 supplements were used by 1.5% of men and 7.2% of women in the ultrasound cohort, and by  
207 1.3% of men and 5.6% of women in the fracture case-cohort. Mean potassium intake was  
208  $3525 \pm 803 \text{ mg/day}$  for men and  $3070 \pm 662 \text{ mg/day}$  for women in the ultrasound cohort; in  
209 the fracture case-cohort mean intake at baseline was  $3445 \pm 815 \text{ mg/day}$  for men and  $2969 \pm$   
210  $690 \text{ mg/day}$  for women. Potassium intake for women in this cohort is therefore lower than the

211 UK RNI of 3500 mg for all adults over 18 years old (34). Mean serum magnesium  
212 concentration was  $0.81 \pm 0.12$  mmol/L for men (n=1006) and  $0.79 \pm 0.13$  mmol/L for women  
213 (n=720). Vitamin D supplements were used by 23.6% of men and 34.6% of women in the  
214 ultrasound cohort, and by 22.0% of men and 31.8% of women in the fracture case-cohort.  
215  
216 Current smokers represented 7.9% of men and 9.8% of women in the ultrasound cohort and  
217 the proportion of never smokers was higher for women than men (58.6% vs. 36.6%); in the  
218 fracture case-cohort current smokers and never smokers represented 12.2% and 32.6% of men,  
219 and 12.5% and 55.2% of women, respectively. There was a broad spread of physical activity  
220 levels across the four categories (inactive, moderately inactive, moderately active, or active)  
221 for both men and women, although there was a higher proportion of women classified as  
222 inactive or moderately inactive than men (59.1 vs. 52.8% ultrasound cohort; 64.8 vs. 55.5%  
223 fracture case-cohort). Family history of osteoporosis in the ultrasound cohort was 3.2% in  
224 men and 6.1% in women; in the fracture case-cohort it was 3.0% in men and 5.6% in women.  
225 The majority (72.1% ultrasound cohort; 64.1% fracture case-cohort) of women were post-  
226 menopausal and 37.5% in ultrasound cohort and 28.9% in the fracture case-cohort were  
227 current or former users of hormone replacement therapy (HRT). Current or former users of  
228 corticosteroids for 3 months or more accounted for 4.4% of men and 5.2% of women in the  
229 ultrasound cohort; in the fracture case-cohort it was 2.6% of men and 3.5% of women.

230

### 231 *Associations between dietary magnesium and potassium intake and bone density*

232 Mean calcaneal BUA values stratified by quintiles of dietary magnesium, potassium, or  
233 Mg+K z-score intake, are shown in **Figure 1** stratified by sex. Data are presented for the fully  
234 adjusted model. In men, no linear trends in fully adjusted BUA were apparent across quintiles  
235 of magnesium, potassium or Mg+K z-score intake. In women significant linear trends were

236 apparent across quintiles of potassium and Mg+K z-score intake, but not magnesium intake  
237 alone, for fully adjusted BUA ( $p=0.04$ ,  $p=0.03$  and  $p=0.15$ , respectively). Individual  
238 significant differences in fully adjusted BUA were also identified for women between quintile  
239 5 and quintile 1 for Mg+K z-score intake ( $74.6 \pm 16.1$  dB/MHz,  $n=272$  vs.  $70.8 \pm 16.3$   
240 dB/MHz,  $n=272$ ; a 5.3% difference;  $p=0.02$ ), but not potassium ( $74.0 \pm 16.2$  dB/MHz,  $n=272$   
241 vs.  $71.0 \pm 16.3$  dB/MHz,  $n=272$ ; a 4.2% difference;  $p=0.05$ ) or magnesium alone ( $73.9 \pm 15.8$   
242 dB/MHz,  $n=272$  vs.  $71.6 \pm 16.2$  dB/MHz,  $n=272$ ; a 3.3% difference;  $p=0.11$ ) (see Figure 1).  
243 No p values were below the Bonferroni-adjusted family-wise critical value (Supplementary  
244 Table 1).

245

#### 246 *Associations between serum magnesium groups and bone density*

247 Analysis of bone density measures according to serum magnesium concentration groups,  
248 adjusting for all covariates previously described, with the exception of dietary factors, showed  
249 no significant differences in BUA in either men or women (see Figure 1 and Supplemental  
250 Table 1). Furthermore, no correlation was apparent between dietary magnesium intake and  
251 serum magnesium concentration for either men ( $r=0.01$ ,  $p=0.87$ ,  $n=717$ ) or women ( $r=-0.04$ ,  
252  $p=0.25$ ,  $n=1006$ ).

253

#### 254 *Associations between dietary magnesium and potassium intake and fracture risk*

255 Between baseline and follow-up, the percentage of men with one or more hip, spine, or wrist  
256 fractures was 23.4% lower in quintile 5 versus quintile 1 for magnesium intake quintiles,  
257 18.1% for potassium quintiles, and 10.2% for Mg+K z-score quintiles. In women these  
258 figures were 35.9%, 32.1% and 30.8%. Risk of hip fracture in men was significantly lower in  
259 Mg+K z-score quintiles 2 and 5 than quintile 1 in the fully adjusted model ( $p=0.03$  and  
260  $p=0.02$ ) (Figure 2 and Supplemental Table 2). The lowest risk of hip fracture in men was

261 evident in Mg+K z-score quintile 5 (0.35 (95% CI: 0.14, 0.85)). In women, a significantly  
262 reduced risk of hip fracture was evident in Mg+K z-score quintile 4 *versus* quintile 1 in the  
263 fully adjusted model (0.59 (95% CI: 0.36, 0.97),  $p=0.04$ ). A reduced risk of spinal fracture in  
264 women was evident for dietary magnesium quintile 3 *versus* quintile 1 (0.49 (95% CI: 0.25,  
265 0.97),  $p=0.04$ ) (Figure 2 and **Supplemental Table 3**), but not Mg+K z-score or potassium  
266 quintiles (Figure 2, Supplementary Table 2 and **Supplemental Table 4**). No p values were  
267 below the Bonferroni-adjusted family-wise critical value (Supplementary Table 1).

268  
269 Analysis of risk of fracture according to concentration groups of serum magnesium showed a  
270 number of significant associations (Figure 2 and **Supplemental Table 5**). In men there were  
271 significant trends in fracture risk across serum concentration groups for spine fractures  
272 ( $p=0.02$ ), and total hip, spine, and wrist fractures ( $p=0.02$ ), but not for hip ( $p=0.06$ ) or wrist  
273 fractures alone ( $p=0.38$ ). Hip fracture risk was significantly lower in groups 2 ( $p=0.03$ ) and 3  
274 ( $p<0.01$ ) than group 1 in the fully adjusted model, with the lowest risk in group 3 (0.34 (95%  
275 CI: 0.17, 0.70)). Spinal fracture risk was significantly lower (0.20 (95% CI: 0.05, 0.75),  
276  $p=0.02$ ) in group 4 than group 1; total risk of hip, spine, and wrist fractures was significantly  
277 lower in groups 2 ( $p=0.03$ ), 3 ( $p=0.03$ ), and 4 ( $p<0.01$ ) than group 1, with the lowest risk in  
278 group 4 (0.41 (95% CI: 0.22, 0.77)). In women there were no significant trends for fracture  
279 risk across groups of magnesium serum concentration, nor between specific groups compared  
280 to group 1. No p values were below the Bonferroni-adjusted family-wise critical value  
281 (Supplementary Table 1).

282

## 282 **DISCUSSION**

283 This study has shown significant associations between combined dietary magnesium and  
284 potassium intake and a quantitative measure of bone density, with significantly higher  
285 calcaneal BUA evident in women in the highest *versus* lowest Mg+K z-score intake quintiles  
286 of these micronutrients, after adjustment for important biological, lifestyle and other dietary  
287 covariates. Furthermore, risk of hip fracture in both women and men was significantly  
288 reduced in specific higher Mg+K intake quintiles compared to the lowest. We believe this  
289 study is also the first to show lower total risk of hip, spine, or wrist fracture for men with a  
290 clinically normal serum magnesium concentration compared to those classed as deficient.  
291 However, while each of the described associations was significant individually, no significant  
292 associations were evident after adjusting for multiple-testing.

293  
294 The mechanisms by which magnesium and potassium may influence bone metabolism are not  
295 fully understood, although a number of theories have been proposed. Insufficient magnesium  
296 results in an increased rate of hydroxyapatite formation, resulting in larger crystals and thus  
297 lower bone mass and brittle bones which may be unable to support normal loads. Magnesium  
298 also has an effect on osteoblast activity and osteoclast number through a nitric oxide  
299 dependent mechanism (10), and both magnesium and potassium affect bone metabolism  
300 through altered calcium homeostasis via influences on calcium transport and urinary retention  
301 (9, 10, 14). A number of other studies investigating associations between magnesium and  
302 potassium and bone health, either individually or in combination, have demonstrated some  
303 degree of improvement with higher intake (4-7, 13, 19, 20), and thus the results presented  
304 here largely corroborate these findings. However, a recent USA study (7) of post-menopausal  
305 women found no difference in relative risk of hip and total fractures across quintiles of  
306 magnesium intake. Conversely, high magnesium intake ( $\geq 422.5$  mg/day) was associated with

307 increased falls and wrist or lower-arm fractures (7). By contrast, our analyses show significant  
308 reduction in hip fracture risk with moderately high (206-442 mg/day; quintile 4) combined  
309 magnesium and potassium intakes, and no significant increases in risk of wrist fracture in  
310 either men or women in fully adjusted models, although it is acknowledged that the 95%  
311 confidence intervals for wrist fracture risk are wide. Differences between the population  
312 groups in the two studies with respect to genetics, demographic lifestyle, the range of  
313 magnesium intakes, and dietary analysis methods (Orchard *et al* (7) used FFQs) may explain  
314 the discrepancy (27, 35). Also the Orchard study (7) did not present their results adjusted for  
315 potassium and energy, although they stated that potassium did not modify the associations  
316 between magnesium and fracture risk.

317

318 The magnitude of the differences seen here is similar to data published by other authors. For  
319 example, fully adjusted BUA was 5.3% greater (+3.8 dB/MHz) in Mg+K z-score quintile 5  
320 *versus* quintile 1 for women. This compares to 3.5% and 3.8% increases in lumbar spine  
321 BMD for premenopausal women quartile 4 *versus* quartile 1 of dietary magnesium and  
322 potassium intakes, respectively (8). Also similar are results from Ryder *et al* (19) and Orchard  
323 *et al* (7) showing whole body BMD was 4.0% greater and 3.0% greater, respectively, for  
324 women in magnesium quintile 5 *versus* quintile 1. Tucker *et al* (5) show larger differences in  
325 BMD across quartiles of combined magnesium and potassium: quartile 4 *versus* quartile 1 for  
326 women had 12.8% greater lumbar spine BMD, although the relatively old age and limited  
327 number in this group (562 women, 69-97 years old) could explain the greater differences seen.  
328 In terms of the implications of the magnitude of change seen in the current study, previous  
329 published data for this cohort showed a 5 dB/MHz greater BUA was associated with HRT use,  
330 and that a 20 dB/MHz decline in BUA approximately doubled fracture risk (36), thus  
331 demonstrating the relevance of our observations.



332  
333 Our findings showed no correlation between dietary magnesium intake and serum magnesium  
334 concentration for either men or women. Although supplementation studies with magnesium  
335 have demonstrated that serum is a suitable biomarker for diet, other studies like ours found no  
336 relationship between dietary and serum magnesium; this is likely a reflection of the tight  
337 homeostatic control of this cation in the circulation (37-39). However, while serum  
338 magnesium concentration was not associated with calcaneal BUA, nor risk of hip, spine, or  
339 wrist fracture in women, a number of significant associations with fracture risk were evident  
340 in men, with those in the healthy normal clinical range, 0.7-1.0 mmol/L (33), showing  
341 significantly reduced risk compared to those with sub-optimal concentrations.

342

#### 343 *Strengths and Limitations*

344 In the UK, dietary intake of magnesium is mainly provided by fruit and vegetables, cereals,  
345 and beverages; potassium is provided by dietary fruit and vegetables, meat, potato, and  
346 savoury snacks (40). Accurate estimation of dietary nutrient intake is critical to the findings of  
347 this type of study. The methodology used here of quantitative 7-day food diaries has been  
348 validated previously and is expected to have provided more precise dietary intake figures  
349 compared to FFQs or 24-hour recall methods (27). Indeed previous UK EPIC analyses have  
350 shown correlations between potassium intake estimated from food diary data and 24 hour  
351 potassium excretion were significantly greater than for FFQ or 24-hour recall (41). It is  
352 reasonable to assume that this validity would also translate to magnesium. The strong  
353 collinearity between dietary intake of magnesium and potassium, a likely consequence of  
354 magnesium rich food typically also being rich in potassium, makes it difficult to differentiate  
355 individual effects of these nutrients on bone density. Other studies have considered this to  
356 varying degrees, but an appropriate compromise is achieved by presenting data using

357 standardised magnesium and potassium intakes which have been combined and re-  
358 standardised (5), thus the inclusion of this data analysis is a strength of this work. Previous  
359 use of this methodology was confined to analyses of BMD measures alone (5), making our  
360 additional longitudinal analysis of fracture risk valuable. Hospital admission data was used to  
361 determine fracture incidence and it is acknowledged this may underestimate incidence,  
362 particularly for spine fractures, and could differ between sexes. We used a subset of the EPIC-  
363 Norfolk dietary data and, in order to reduce the potential for bias, included randomly selected  
364 participants from the cohort. Magnesium and potassium dietary data were derived from food  
365 intake only, and therefore may underestimate total nutrient intakes, although supplements  
366 consumed by this cohort provide a relatively small contribution to mineral intakes (42); we  
367 included calcium and vitamin D supplement use in our models nevertheless. We acknowledge  
368 that mineral contributions of drinking and bottled water may be imprecise due to varying  
369 concentrations not detailed sufficiently in food composition tables. Although this  
370 observational study cannot show causality in effects, this report is, to our knowledge, the first  
371 to provide analysis of bone quality and fracture risk by magnesium serum concentration  
372 groups in addition to dietary intake in a general population of both men and women.

373

## 374 **Conclusions**

375 This study has positively associated dietary magnesium and potassium intake with a  
376 quantitative ultrasound measure of bone density status and reduced fracture risk in a mixed  
377 UK population group of men and pre- and post-menopausal women. These results thus  
378 support policies to promote a good quality diet with sufficient magnesium and potassium  
379 intake. Clinically normal serum magnesium concentration, compared to suboptimal  
380 concentration, has also been shown to be associated with reduced risk of incident fracture in  
381 men. Further study will be required to determine how generalisable the results of these

382 analyses are, and to fully understand the relationship between intake of these micronutrients,  
383 bone health, and osteoporosis.

384

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387 The authors' contributions to the manuscript were as follows: AAW developed the research

388 question together with RPGH who performed the data analyses and drafted the manuscript.

389 AAW organised data collection in conjunction with RNL who implemented the record

390 linkage. MAHL prepared dietary and supplemental data for statistical analysis. K-TK is

391 principal investigator of the EPIC-Norfolk Study. All authors were involved in interpreting

392 the data, contributed to the writing of the manuscript, and read and approved the final

393 manuscript. AAW had primary responsibility for the final content. None of the authors had a

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395

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## TABLES AND FIGURES

**Table 1** – Selected characteristics of the EPIC-Norfolk cohort population stratified by sex for the ultrasound cohort group (n=2328) and the fracture case-cohort group (n=4713).

Selected Characteristics	Ultrasound cohort <sup>1</sup>		<i>P</i> <sup>3</sup>	Fracture case-cohort <sup>2</sup>		<i>P</i>
	Men	Women		Men	Women	
	n=968	n=1360		n=1958	n=2755	
Age (years)	63.0 ± 9.3 <sup>4</sup>	61.7 ± 9.2	<0.001	59.7 ± 9.6	59.8 ± 9.5	0.809
BMI (kg/m <sup>2</sup> )	26.9 ± 3.4	26.5 ± 4.4	0.039	26.5 ± 3.3	26.2 ± 4.3	0.004
Magnesium intake (mg/day)	329 ± 92	277 ± 72	<0.001	321 ± 92	265 ± 73	<0.001
Potassium intake (mg/day)	3525 ± 803	3070 ± 662	<0.001	3445 ± 815	2969 ± 690	<0.001
Calcium intake (mg/day)	925 ± 282	782 ± 247	<0.001	914 ± 296	762 ± 253	<0.001
Calcium supplement use	14 (1.5)	98 (7.2)	<0.001	25 (1.3)	155 (5.6)	<0.001
Vitamin D supplement use	228 (23.6)	471 (34.6)	<0.001	430 (22.0)	875 (31.8)	<0.001
Total energy intake (kcal/day)	2263 ± 478	1732 ± 374	<0.001	2239 ± 514	1683 ± 385	<0.001
Serum [Mg] (mmol/L)	0.81 ± 0.12 <sup>5</sup>	0.79 ± 0.13 <sup>6</sup>	0.003	0.81 ± 0.12 <sup>7</sup>	0.79 ± 0.13 <sup>8</sup>	0.001
BUA (dB/MHz)	89.6 ± 17.4	72.1 ± 16.5	<0.001	--	--	
Smoking			<0.001			<0.001
Current	76 (7.9)	133 (9.8)		238 (12.2)	343 (12.5)	
Former	538 (55.6)	430 (31.6)		1082 (55.3)	890 (32.3)	
Never	354 (36.6)	797 (58.6)		638 (32.6)	1522 (55.2)	
Physical activity			<0.001			<0.001
Inactive	275 (28.4)	342 (25.1)		614 (31.4)	908 (33.0)	
Moderately inactive	236 (24.4)	462 (34.0)		472 (24.1)	877 (31.8)	
Moderately active	248 (25.6)	333 (24.5)		436 (22.3)	577 (20.9)	
Active	209 (21.6)	223 (16.4)		436 (22.3)	393 (14.3)	

Family history of osteoporosis			<i>0.001</i>		<i>&lt;0.001</i>
No	937 (96.8)	1277 (93.9)		1900 (97.0)	2601 (94.4)
Yes	31 (3.2)	83 (6.1)		58 (3.0)	154 (5.6)
Corticosteroid use			<i>0.391</i>		<i>0.243</i>
Current or former (>3 months)	43 (4.4)	71 (5.2)		50 (2.6)	97 (3.5)
Never (<3 months)	925 (95.6)	1289 (94.8)		1908 (97.5)	2658 (96.5)
Menopausal status					
Pre-menopausal	--	86 (6.3)		--	414 (15.0)
Peri-menopausal (<1 y)	--	47 (3.5)		--	127 (4.6)
Peri-menopausal (1-5 y)	--	246 (18.1)		--	448 (16.3)
Post-menopausal	--	981 (72.1)		--	1766 (64.1)
HRT					
Current	--	288 (21.2)		--	472 (17.1)
Former	--	222 (16.3)		--	324 (11.8)
Never	--	850 (62.5)		--	1959 (71.1)

<sup>1</sup>Ultrasound group characteristics at 2<sup>nd</sup> health-check (time of ultrasound).

<sup>2</sup>Fracture group characteristics at 1<sup>st</sup> health-check or time of consent.

<sup>3</sup>P values are for differences between men and women for each applicable variable, according to t-test for continuous or chi-square for categorical variables.

<sup>4</sup>Values are mean ± SD or frequency (percentage).

<sup>5</sup>n=720. <sup>6</sup>n=1006. <sup>7</sup>n=1460. <sup>8</sup>n=2009

**Figure 1** – Fully adjusted<sup>1</sup> calcaneal Broadband Ultrasound Attenuation (BUA) of the EPIC-Norfolk cohort population (968 men and 1360 women) stratified by sex and quintiles of Magnesium<sup>2</sup> or Potassium<sup>3</sup> dietary intake, z-score quintiles of dietary Magnesium+Potassium<sup>4</sup> intake, or serum Magnesium concentration groups<sup>5</sup> (720 men and 1006 women).

\*  $p \leq 0.05$  versus quintile 1, according to ANCOVA (not significant after multiple testing adjustment).

<sup>1</sup>Adjusted for: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, corticosteroid use, calcium intake and supplement use (excluding serum Mg model), vitamin D supplement use (excluding serum Mg model), and total energy intake (excluding serum Mg model). Values are presented as mean  $\pm$  SD.

<sup>2</sup>**Mg intake (mean  $\pm$  SD; mg/day) by Mg quintiles (Q).** *Men:* mean, 329  $\pm$  32; Q1, 218  $\pm$  31; Q2, 277  $\pm$  12; Q3, 319  $\pm$  13; Q4, 366  $\pm$  16; Q5, 466  $\pm$  73. *Women:* mean, 277  $\pm$  72; Q1, 189  $\pm$  26; Q2, 237  $\pm$  10; Q3, 270  $\pm$  10; Q4, 307  $\pm$  12; Q5, 383  $\pm$  58.

<sup>3</sup>**K intake (mean  $\pm$  SD; mg/day) by K quintiles.** *Men:* mean, 3525  $\pm$  803; Q1, 2505  $\pm$  344; Q2, 3099  $\pm$  125; Q3, 3478  $\pm$  101; Q4, 3854  $\pm$  122; Q5, 4697  $\pm$  603. *Women:* mean, 3070  $\pm$  662; Q1, 2196  $\pm$  287; Q2, 2721  $\pm$  99; Q3, 3038  $\pm$  90; Q4, 3367  $\pm$  106; Q5, 4030  $\pm$  429.

<sup>4</sup>**Mg intake (mean  $\pm$  SD; mg/day) by Mg+K z-score quintiles.** *Men:* mean 329  $\pm$  92; Q1, 221  $\pm$  35; Q2, 279  $\pm$  22; Q3, 321  $\pm$  29; Q4, 364  $\pm$  29; Q5, 460  $\pm$  78. *Women:* mean 277  $\pm$  72; Q1, 192  $\pm$  29; Q2, 238  $\pm$  19; Q3, 271  $\pm$  21; Q4, 306  $\pm$  24; Q5, 378  $\pm$  61. **K intake (mean  $\pm$  SD; mg/day) by Mg+K z-score quintiles.** *Men:* mean 3525  $\pm$  803; Q1, 2539  $\pm$  375; Q2, 3117  $\pm$  218; Q3, 3489  $\pm$  229; Q4, 3857  $\pm$  270; Q5, 4630  $\pm$  668. *Women:* mean 3070  $\pm$  662; Q1, 2217  $\pm$  309; Q2, 2753  $\pm$  177; Q3, 3047  $\pm$  205; Q4, 3351  $\pm$  230; Q5, 3983  $\pm$  479.

<sup>5</sup>**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).

**Figure 2** – Risk<sup>1</sup> of hip, spine, and wrist fractures in the EPIC-Norfolk cohort population (1958 men and 2755 women) at follow-up *versus* baseline stratified by sex and quintile of Magnesium<sup>2</sup> or Potassium<sup>3</sup> dietary intake, z-score quintiles of dietary Magnesium+Potassium<sup>4</sup> intake, or serum Magnesium concentration groups<sup>5</sup> (1460 men and 2009 women). (Prentice-weighted Cox proportional hazard ratio and 95% CI of quintiles or groups, quintile or group 1 as reference).

\*  $p \leq 0.05$  *versus* quintile 1, according to ANCOVA; \*\*  $p \leq 0.01$  (not significant after multiple testing adjustment). Insufficient data was available in the highest serum Mg concentration group for some hazard ratio calculations.

<sup>1</sup>Adjusted for: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, corticosteroid use, calcium intake and supplement use (excluding serum Mg model), vitamin D supplement use (excluding serum Mg model), and total energy intake (excluding serum Mg model). Values are presented as mean  $\pm$  SD.

<sup>2</sup>**Mg intake (mean  $\pm$  SD; mg/day) by Mg quintiles (Q).** *Men:* mean, 321  $\pm$  93; Q1, 209  $\pm$  31; Q2, 268  $\pm$  12; Q3, 312  $\pm$  13; Q4, 358  $\pm$  15; Q5, 460  $\pm$  75. *Women:* Mean, 265  $\pm$  73; Q1, 175  $\pm$  25; Q2, 223  $\pm$  10; Q3, 257  $\pm$  9; Q4, 294  $\pm$  13; Q5, 373  $\pm$  59.

<sup>3</sup>**K intake (mean  $\pm$  SD; mg/day) by K quintiles.** *Men:* mean, 3449  $\pm$  821; Q1, 2390  $\pm$  356; Q2, 3019  $\pm$  119; Q3, 3405  $\pm$  111; Q4, 3797  $\pm$  126; Q5, 4635  $\pm$  607. *Women:* mean, 2964  $\pm$  689; Q1, 2065  $\pm$  285; Q2, 2595  $\pm$  102; Q3, 2921  $\pm$  92; Q4, 3268  $\pm$  113; Q5, 3974  $\pm$  448.

<sup>4</sup>**Mg intake (mean  $\pm$  SD; mg/day) by Mg+K z-score quintiles.** *Men:* mean 321  $\pm$  93; Q1, 212  $\pm$  35; Q2, 271  $\pm$  23; Q3, 314  $\pm$  28; Q4, 357  $\pm$  28; Q5, 454  $\pm$  80. *Women:* mean 265  $\pm$  73; Q1, 178  $\pm$  29; Q2, 225  $\pm$  19; Q3, 257  $\pm$  20; Q4, 294  $\pm$  24; Q5, 368  $\pm$  63. **K intake (mean  $\pm$  SD; mg/day) by Mg+K z-score quintiles.** *Men:* mean 3449  $\pm$  821; Q1, 2422  $\pm$  386; Q2, 3040  $\pm$  212; Q3, 3419  $\pm$  245; Q4, 3788  $\pm$  263; Q5, 4577  $\pm$  663. *Women:* mean 2964  $\pm$  687; Q1, 2087  $\pm$  307; Q2, 2618  $\pm$  183; Q3, 2925  $\pm$  189; Q4, 3257  $\pm$  223; Q5, 3935  $\pm$  490.

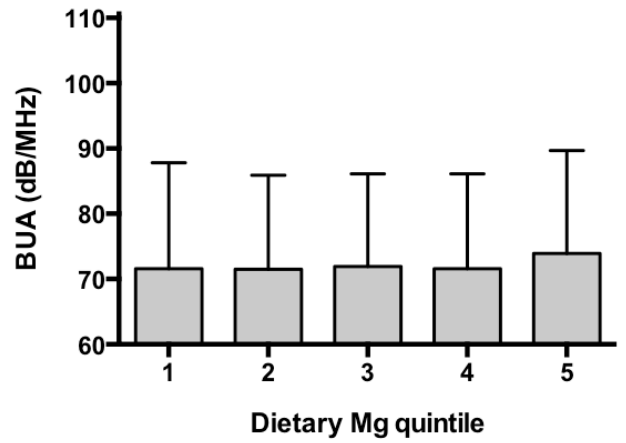
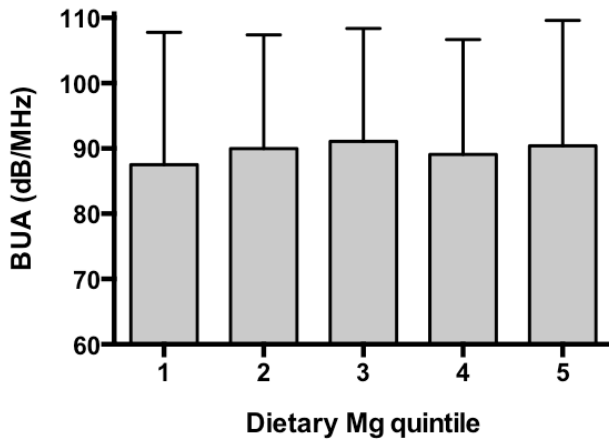
<sup>5</sup>**Serum Mg concentration groups:** <0.7 mmol/L (group 1), 0.7-0.8 mmol/L (group 2), 0.8-0.9

mmol/L (group 3), 0.9-1.0 mmol/L (group 4), and >1.0 mmol/L (group 5).

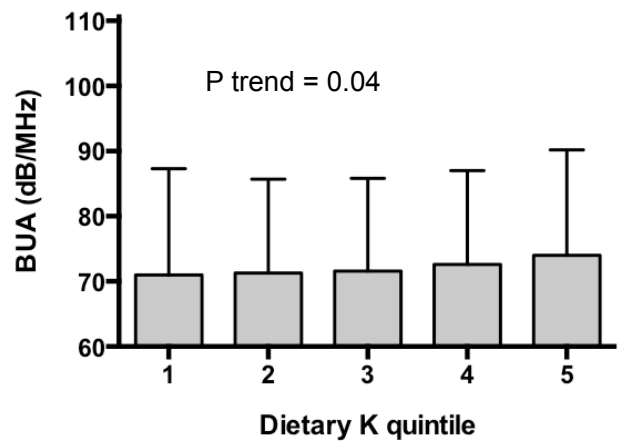
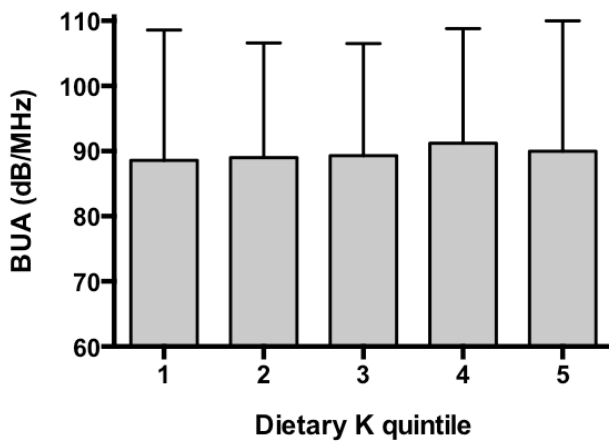
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Women

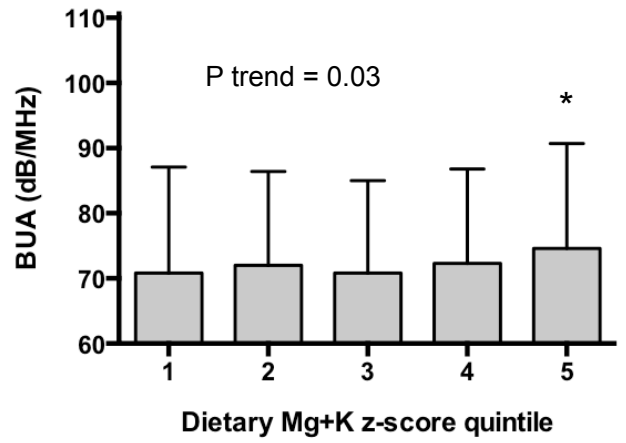
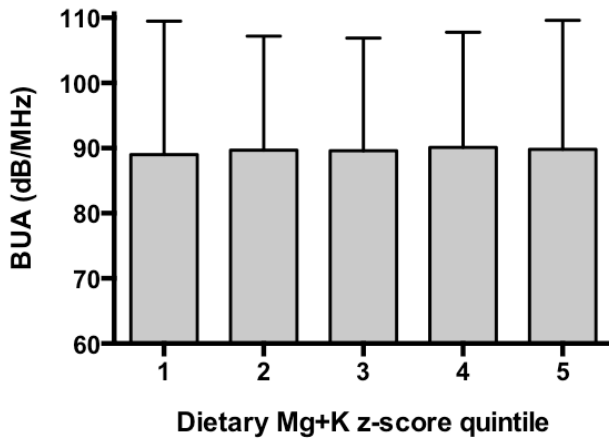
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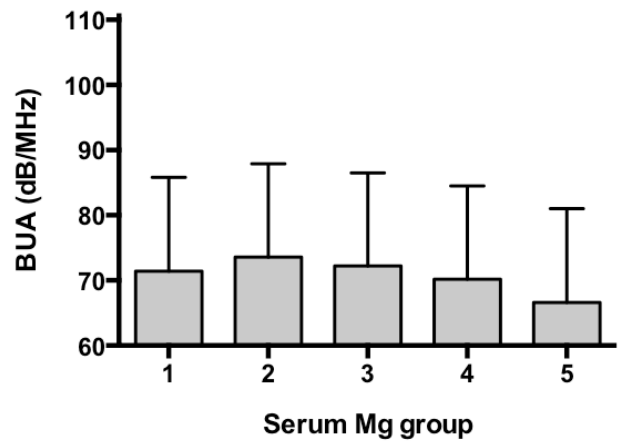
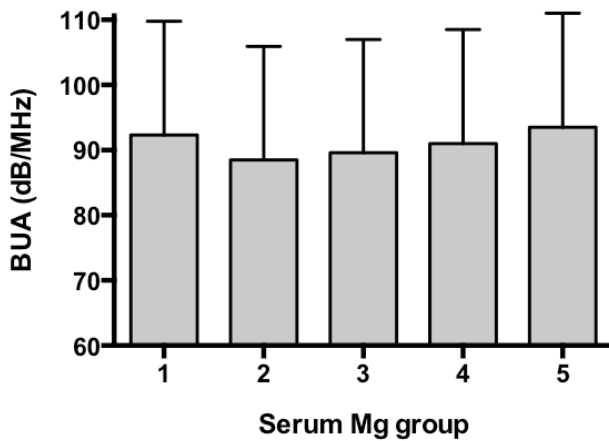
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Mg+K



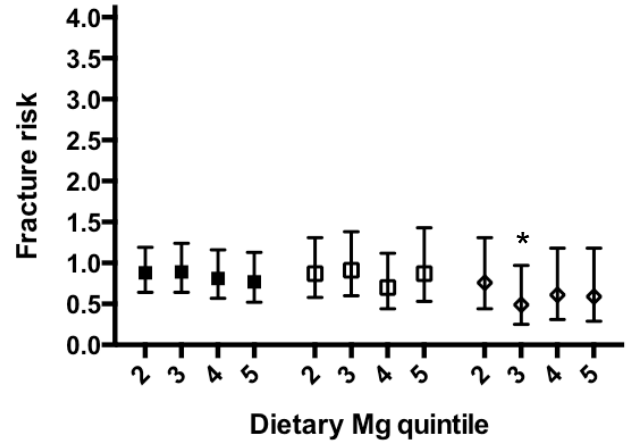
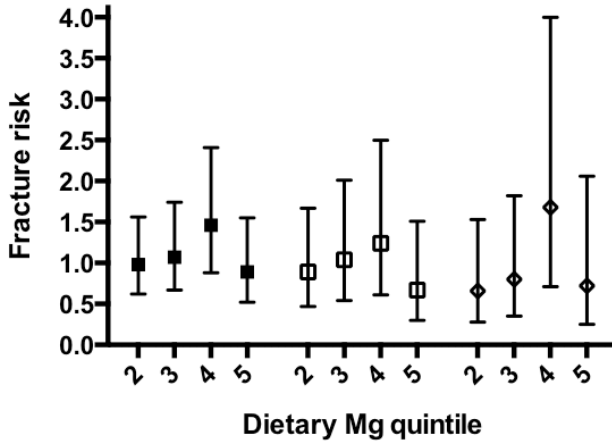
[Mg]



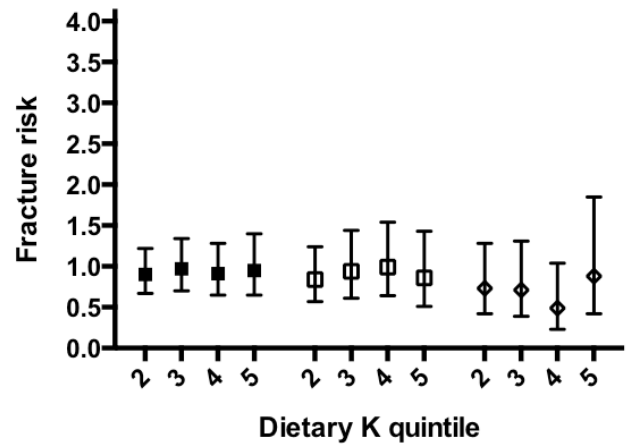
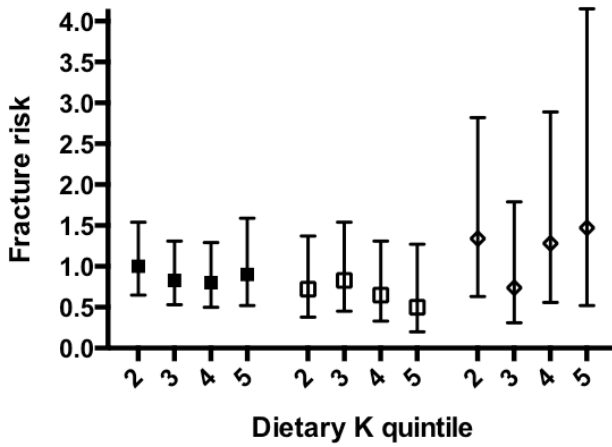
Men

Women

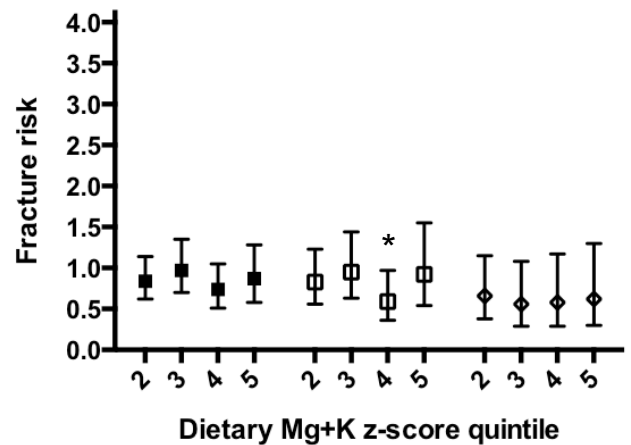
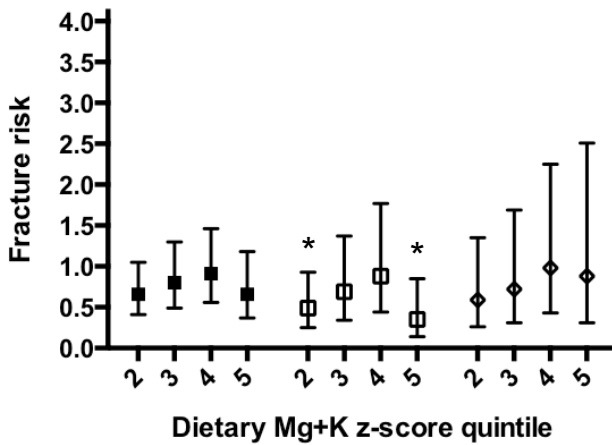
Mg



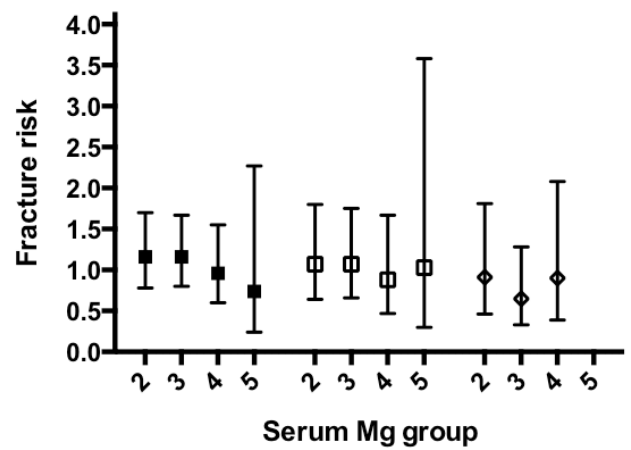
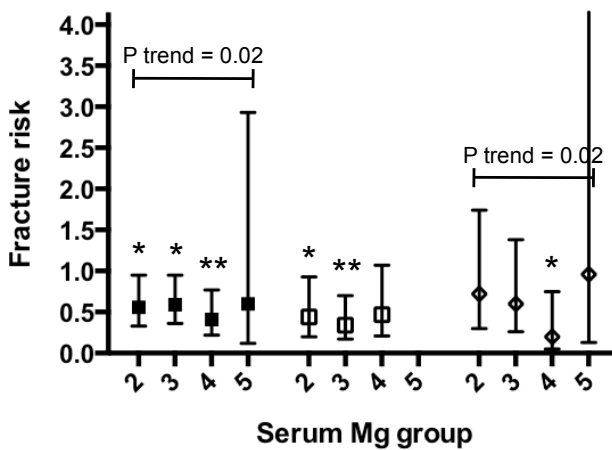
K



Mg+K



[Mg]



■ Total □ Hip ◇ Spine





ONLINE SUPPLEMENTAL MATERIAL

P values are quoted to 3 decimal places when less than 0.01, otherwise 2 decimal places are used.

**Supplemental Table 2** – Risk of hip, spine, and wrist fractures in the EPIC-Norfolk cohort population (1958 men and 2755 women) at follow-up *versus* baseline, stratified by z score quintiles of dietary Magnesium+Potassium intake (Prentice-weighted Cox proportional hazard ratio and 95% CI).

<b>Men</b>		<b>Dietary Magnesium+Potassium Intake</b>					
		<b>Quintile 1</b>	<b>Quintile 2</b>	<b>Quintile 3</b>	<b>Quintile 4</b>	<b>Quintile 5</b>	<b>P for trend</b>
Total <sup>1</sup>	<i>248/1958</i>	<i>60/392</i>	<i>46/392</i>	<i>48/391</i>	<i>54/392</i>	<i>40/391</i>	
	Full Model <sup>2</sup>	1.0 (ref)	0.66 (0.41-1.05)	0.80 (0.49-1.30)	0.91 (0.56-1.46)	0.66 (0.37-1.18)	0.56
Hip	<i>112/1843</i>	<i>37/369</i>	<i>21/369</i>	<i>21/368</i>	<i>24/369</i>	<i>9/368</i>	
	Full Model	1.0 (ref)	0.49 (0.25-0.93)*	0.69 (0.34-1.37)	0.88 (0.44-1.77)	0.35 (0.14-0.85)*	0.25
Spine	<i>78/1809</i>	<i>19/362</i>	<i>13/362</i>	<i>13/362</i>	<i>18/362</i>	<i>15/361</i>	
	Full Model	1.0 (ref)	0.59 (0.26-1.35)	0.72 (0.31-1.69)	0.98 (0.43-2.25)	0.88 (0.31-2.51)	0.76
Wrist	<i>70/1807</i>	<i>7/362</i>	<i>13/361</i>	<i>16/362</i>	<i>17/361</i>	<i>17/361</i>	
	Full Model	1.0 (ref)	1.60 (0.61-4.16)	1.79 (0.71-4.50)	1.76 (0.72-4.28)	1.49 (0.57-3.91)	0.51
<b>Women</b>							<b>P for trend</b>
Total	<i>616/2755</i>	<i>156/551</i>	<i>127/551</i>	<i>126/551</i>	<i>99/551</i>	<i>108/551</i>	
	Full Model	1.0 (ref)	0.84 (0.62-1.14)	0.97 (0.70-1.35)	0.74 (0.51-1.05)	0.87 (0.58-1.28)	0.36
Hip	<i>339/2526</i>	<i>92/506</i>	<i>73/505</i>	<i>70/505</i>	<i>44/505</i>	<i>60/505</i>	
	Full Model	1.0 (ref)	0.83 (0.56-1.23)	0.95 (0.63-1.44)	0.59 (0.36-0.97)*	0.92 (0.54-1.55)	0.42
Spine	<i>124/2335</i>	<i>38/467</i>	<i>26/467</i>	<i>19/467</i>	<i>19/467</i>	<i>22/467</i>	
	Full Model	1.0 (ref)	0.66 (0.38-1.15)	0.56 (0.29-1.08)	0.58 (0.29-1.17)	0.62 (0.30-1.30)	0.21
Wrist	<i>218/2410</i>	<i>49/482</i>	<i>43/482</i>	<i>49/482</i>	<i>42/482</i>	<i>35/482</i>	
	Full Model	1.0 (ref)	0.92 (0.58-1.46)	1.13 (0.71-1.81)	1.02 (0.61-1.70)	0.85 (0.48-1.48)	0.77

<sup>1</sup> Total risk is for an individual having a hip, spine, or wrist fracture, thus specific fracture incidences may not sum to total.

## ONLINE SUPPLEMENTAL MATERIAL

<sup>2</sup> Full model: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, corticosteroid use, calcium intake and supplement use, vitamin D supplement use, and total energy intake. \*  $p \leq 0.05$  *versus* quintile 1 (not significant after multiple testing adjustment).

ONLINE SUPPLEMENTAL MATERIAL

**Supplemental Table 3** – Risk of hip, spine, and wrist fractures in the EPIC-Norfolk cohort population (1958 men and 2755 women) at follow-up *versus* baseline, stratified by quintiles of dietary Magnesium intake (Prentice-weighted Cox proportional hazard ratio and 95% CI).

<b>Men</b>		<b>Dietary Magnesium Intake</b>					<b>P for trend</b>
		<b>Quintile 1</b>	<b>Quintile 2</b>	<b>Quintile 3</b>	<b>Quintile 4</b>	<b>Quintile 5</b>	
Total <sup>1</sup>	<i>248/1958</i>	<i>51/392</i>	<i>49/392</i>	<i>51/391</i>	<i>58/392</i>	<i>39/391</i>	
	Full Model <sup>2</sup>	1.0 (ref)	0.98 (0.62-1.56)	1.07 (0.67-1.74)	1.46 (0.88-2.41)	0.89 (0.52-1.55)	0.69
Hip	<i>112/1843</i>	<i>31/369</i>	<i>24/369</i>	<i>24/368</i>	<i>21/369</i>	<i>12/368</i>	
	Full Model	1.0 (ref)	0.89 (0.47-1.67)	1.04 (0.54-2.01)	1.24 (0.61-2.50)	0.67 (0.30-1.51)	0.73
Spine	<i>78/1809</i>	<i>17/362</i>	<i>12/362</i>	<i>14/362</i>	<i>24/362</i>	<i>11/361</i>	
	Full Model	1.0 (ref)	0.66 (0.28-1.53)	0.80 (0.35-1.82)	1.68 (0.71-4.00)	0.72 (0.25-2.06)	0.60
Wrist	<i>70/1807</i>	<i>5/362</i>	<i>14/361</i>	<i>16/362</i>	<i>18/361</i>	<i>17/361</i>	
	Full Model	1.0 (ref)	2.34 (0.78-7.06)	2.51 (0.85-7.43)	2.79 (0.94-8.26)	2.26 (0.72-7.03)	0.21
<b>Women</b>							<b>P for trend</b>
Total	<i>616/2755</i>	<i>159/551</i>	<i>124/551</i>	<i>120/551</i>	<i>111/551</i>	<i>102/551</i>	
	Full Model	1.0 (ref)	0.88 (0.64-1.19)	0.89 (0.64-1.24)	0.81 (0.57-1.16)	0.77 (0.52-1.13)	0.18
Hip	<i>339/2526</i>	<i>93/506</i>	<i>70/505</i>	<i>66/505</i>	<i>52/505</i>	<i>58/505</i>	
	Full Model	1.0 (ref)	0.87 (0.58-1.31)	0.91 (0.60-1.38)	0.70 (0.44-1.12)	0.87 (0.53-1.43)	0.37
Spine	<i>124/2335</i>	<i>39/467</i>	<i>27/467</i>	<i>16/467</i>	<i>21/467</i>	<i>21/467</i>	
	Full Model	1.0 (ref)	0.76 (0.44-1.31)	0.49 (0.25-0.97)*	0.61 (0.31-1.18)	0.59 (0.29-1.18)	0.11
Wrist	<i>218/2410</i>	<i>53/482</i>	<i>42/482</i>	<i>43/482</i>	<i>48/482</i>	<i>32/482</i>	
	Full Model	1.0 (ref)	0.84 (0.53-1.33)	0.91 (0.56-1.49)	1.00 (0.61-1.64)	0.64 (0.35-1.16)	0.34

<sup>1</sup>Total risk is for an individual having a hip, spine, or wrist fracture, thus specific fracture incidences may not sum to total.

## ONLINE SUPPLEMENTAL MATERIAL

<sup>2</sup> Full model: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, corticosteroid use, calcium intake and supplement use, vitamin D supplement use, and total energy intake. \*  $p \leq 0.05$  *versus* quintile 1 (not significant after multiple testing adjustment).

ONLINE SUPPLEMENTAL MATERIAL

**Supplemental Table 4** – Risk of hip, spine, and wrist fractures in the EPIC-Norfolk cohort population (1958 men and 2755 women) at follow-up *versus* baseline, stratified by quintiles of dietary Potassium intake (Prentice-weighted Cox proportional hazard ratio and 95% CI).

<b>Men</b>		<b>Dietary Potassium Intake</b>					
		<b>Quintile 1</b>	<b>Quintile 2</b>	<b>Quintile 3</b>	<b>Quintile 4</b>	<b>Quintile 5</b>	<b>P for trend</b>
Total <sup>1</sup>	<i>248/1958</i>	<i>55/392</i>	<i>56/392</i>	<i>48/391</i>	<i>44/392</i>	<i>45/391</i>	
	Full Model <sup>2</sup>	1.0 (ref)	1.00 (0.65-1.54)	0.83 (0.53-1.31)	0.80 (0.50-1.29)	0.91 (0.52-1.59)	0.46
Hip	<i>112/1843</i>	<i>34/369</i>	<i>24/369</i>	<i>26/368</i>	<i>18/369</i>	<i>10/368</i>	
	Full Model	1.0 (ref)	0.72 (0.38-1.37)	0.83 (0.45-1.54)	0.65 (0.33-1.31)	0.50 (0.20-1.27)	0.16
Spine	<i>78/1809</i>	<i>15/362</i>	<i>19/362</i>	<i>11/362</i>	<i>17/362</i>	<i>16/361</i>	
	Full Model	1.0 (ref)	1.34 (0.63-2.82)	0.74 (0.31-1.79)	1.28 (0.56-2.89)	1.47 (0.52-4.15)	0.57
Wrist	<i>70/1807</i>	<i>8/362</i>	<i>13/361</i>	<i>14/362</i>	<i>15/361</i>	<i>20/361</i>	
	Full Model	1.0 (ref)	1.49 (0.60-3.67)	1.39 (0.58-3.35)	1.40 (0.57-3.45)	1.66 (0.66-4.20)	0.43
<b>Women</b>							<b>P for trend</b>
Total	<i>616/2755</i>	<i>156/551</i>	<i>125/551</i>	<i>120/551</i>	<i>109/551</i>	<i>106/551</i>	
	Full Model	1.0 (ref)	0.90 (0.67-1.22)	0.97 (0.70-1.34)	0.91 (0.65-1.28)	0.95 (0.65-1.40)	0.82
Hip	<i>339/2526</i>	<i>93/506</i>	<i>68/505</i>	<i>64/505</i>	<i>62/505</i>	<i>52/505</i>	
	Full Model	1.0 (ref)	0.84 (0.57-1.24)	0.94 (0.61-1.44)	0.99 (0.64-1.54)	0.86 (0.51-1.43)	0.84
Spine	<i>124/2335</i>	<i>38/467</i>	<i>25/467</i>	<i>21/467</i>	<i>14/467</i>	<i>26/467</i>	
	Full Model	1.0 (ref)	0.73 (0.42-1.28)	0.71 (0.39-1.31)	0.49 (0.23-1.04)	0.88 (0.42-1.85)	0.45
Wrist	<i>218/2410</i>	<i>53/482</i>	<i>41/482</i>	<i>45/482</i>	<i>43/482</i>	<i>36/482</i>	
	Full Model	1.0 (ref)	0.87 (0.56-1.36)	1.00 (0.63-1.59)	0.99 (0.61-1.61)	0.84 (0.49-1.42)	0.75

<sup>1</sup>Total risk is for an individual having a hip, spine, or wrist fracture, thus specific fracture incidences may not sum to total.

## ONLINE SUPPLEMENTAL MATERIAL

<sup>2</sup> Full model: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, corticosteroid use, calcium intake and supplement use, vitamin D supplement use, and total energy intake.

ONLINE SUPPLEMENTAL MATERIAL

**Supplemental Table 5** – Risk of hip, spine, and wrist fractures in the EPIC-Norfolk cohort population (1460 men and 2009 women) at follow-up *versus* baseline, stratified by groups defined by serum Magnesium concentration (Prentice-weighted Cox proportional hazard ratio and 95% CI).

<b>Men</b>		<b>Serum Magnesium Concentration</b>					
		<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>	<b>Group 5</b>	<b>P for trend</b>
Total <sup>1</sup>	<i>183/1460</i>	<i>30/183</i>	<i>45/365</i>	<i>86/689</i>	<i>20/206</i>	<i>2/17</i>	
	Full Model <sup>2</sup>	1.0 (ref)	0.56 (0.33-0.95)*	0.59 (0.36-0.95)*	0.41 (0.22-0.77)**	0.60 (0.12-2.93)	0.02
Hip	<i>82/1374</i>	<i>16/171</i>	<i>21/346</i>	<i>31/641</i>	<i>14/201</i>	<i>0/15</i>	
	Full Model	1.0 (ref)	0.44 (0.20-0.93)*	0.34 (0.17-0.70)**	0.47 (0.21-1.07)	--	0.06
Spine	<i>56/1348</i>	<i>8/164</i>	<i>17/340</i>	<i>27/635</i>	<i>3/193</i>	<i>1/16</i>	
	Full Model	1.0 (ref)	0.72 (0.30-1.74)	0.60 (0.26-1.38)	0.20 (0.05-0.75)*	0.96 (0.13-7.30)	0.02
Wrist	<i>52/1352</i>	<i>9/165</i>	<i>9/335</i>	<i>29/642</i>	<i>4/194</i>	<i>1/16</i>	
	Full Model	1.0 (ref)	0.42 (0.16-1.11)	0.71 (0.32-1.60)	0.30 (0.09-1.01)	1.06 (0.12-9.21)	0.38
<b>Women</b>							<b>P for trend</b>
Total	<i>445/2009</i>	<i>53/285</i>	<i>131/603</i>	<i>209/881</i>	<i>47/215</i>	<i>5/25</i>	
	Full Model	1.0 (ref)	1.16 (0.78-1.70)	1.16 (0.80-1.67)	0.96 (0.60-1.55)	0.74 (0.24-2.27)	0.78
Hip	<i>249/1848</i>	<i>27/265</i>	<i>69/553</i>	<i>121/808</i>	<i>28/198</i>	<i>4/24</i>	
	Full Model	1.0 (ref)	1.07 (0.64-1.80)	1.07 (0.66-1.75)	0.88 (0.47-1.67)	1.03 (0.30-3.58)	0.76
Spine	<i>90/1704</i>	<i>14/251</i>	<i>29/513</i>	<i>34/733</i>	<i>13/187</i>	<i>0/20</i>	
	Full Model	1.0 (ref)	0.91 (0.46-1.81)	0.65 (0.33-1.28)	0.90 (0.39-2.08)	--	0.22
Wrist	<i>218/1757</i>	<i>19/254</i>	<i>48/528</i>	<i>78/767</i>	<i>11/187</i>	<i>1/21</i>	
	Full Model	1.0 (ref)	1.11 (0.63-1.94)	1.09 (0.64-1.85)	0.58 (0.27-1.26)	0.44 (0.05-3.53)	0.18

<sup>1</sup>Total risk is for an individual having a hip, spine, or wrist fracture, thus specific fracture incidences may not sum to total.



## ONLINE SUPPLEMENTAL MATERIAL

<sup>2</sup> Full model: age, BMI, smoking status, physical activity, family history of osteoporosis, menopausal and HRT status in women, and corticosteroid use. \*  
p≤0.05 *versus* quintile 1; \*\* p≤0.01 (not significant after multiple testing adjustment).