

The relationship between dietary magnesium intake, stroke and its major risk factors, blood pressure and cholesterol, in the EPIC-Norfolk cohort.

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Key Words: dietary magnesium, stroke, blood pressure, total cholesterol

1 **Background:** Dietary magnesium could modify the major stroke risk factors, high blood  
2 pressure (BP) and cholesterol, but has been understudied in both sexes in a single population.  
3 This study aimed to investigate if dietary magnesium intake was associated with BP, total  
4 cholesterol (TC) and incident stroke risk in an adult population.

5 **Methods:** We conducted cross-sectional analyses in a case-cohort study of 4,443, men and  
6 women aged 40-75 representative of 25,639 participants years of the EPIC (European  
7 Prospective Investigation into Cancer)-Norfolk cohort. The cohort included 928 stroke cases  
8 (42,556.5 person years). Dietary data from 7d food diaries were analysed using multivariate  
9 regression to assess associations between quintiles or data-derived categories of dietary  
10 magnesium intake and BP, TC and stroke risk, adjusted for relevant confounders.

11 **Results:** We observed differences of -7 mmHg systolic BP (P trend  $\leq 0.01$ ) and -3.8 mmHg  
12 diastolic BP (P trend 0.01) between extreme intakes of magnesium in men, a significant inverse  
13 association with TC was observed (P trend 0.02 men and 0.04 women). Compared to the  
14 bottom 10%, the top 30% of magnesium intake was associated with a 41% relative reduction  
15 in stroke risk (HR 0.59 95% CI 0.38-0.93) in men.

16 **Conclusions:** Lower dietary magnesium intake was associated with higher BP and stroke  
17 risk, which may have implications for primary prevention.

## 18 1.0 INTRODUCTION

19 Stroke accounts for more than 5.5 million deaths annually and by 2020 predictions estimate  
20 that the global burden of stroke will account for 61 million disability-adjusted life years (1).

21 Elevated BP<sup>1</sup> is a significant modifiable risk factor for stroke with an approximate fourfold  
22 increase in stroke risk in hypertensive individuals compared with the normotensive population  
23 (2). Although established evidence indicates that elevated BP, hypertension and circulating  
24 cholesterol can be modified by dietary intake including: salt, alcohol, saturated fat and  
25 cholesterol (2) other dietary components, including magnesium, which is abundantly available  
26 in nuts, green leafy vegetables and whole grains, have been less extensively studied.

27 Magnesium has a number of metabolic roles in the body and may influence BP and blood lipids  
28 through different mechanisms (3, 4). Magnesium may serve as a natural calcium channel  
29 blocker, exhibit beneficial effects on platelet coagulation, have a potential role in vasodilation  
30 and has been associated with reduced coronary artery calcification (4, 5). Other proposed  
31 mechanisms include increased peroxidation of lipoproteins with subsequent acceleration of  
32 atherosclerotic plaque formation and low magnesium may facilitate an increase in  
33 inflammation which is associated with negative changes in lipid profile (3, 4). Higher  
34 magnesium intake has been associated with lower risk of Type II diabetes (6), metabolic  
35 syndrome (7) and cardiovascular disease (CVD) (8).

36 Two recent meta-analyses have investigated the effects of dietary magnesium on stroke risk  
37 and CVD risk respectively (8, 9) showing inconsistent findings. The reason for these

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<sup>1</sup> Abbreviations

7DD – seven day diet diary, BMI – body mass index, BP – blood pressure, CVD – cardiovascular disease, DBP – diastolic blood pressure, DINER - Data Into Nutrients for Epidemiological Research, EPIC-Norfolk – European Prospective Investigation into Cancer-Norfolk, FFQ – food frequency questionnaire, HDL – high density lipoprotein, HLQ – Health and Lifestyle Questionnaire, LDL – low density lipoprotein, MI – myocardial infarction, SBP – systolic blood press, TC – total cholesterol, WHR – waist-hip ratio

38 inconsistencies may be due to estimation of magnesium intakes from less precise methods of  
39 recording diet such as Food Frequency Questionnaires (FFQ) and 24 hour recalls. However, it  
40 has been increasingly suggested that the detailed 7DD represents dietary intakes more precisely  
41 (10).

42 Therefore, the purpose of this study was to determine whether dietary magnesium intake,  
43 estimated using a 7DD, was associated with BP, lipid profile and stroke risk in an adult general  
44 population of 4,443 (representative of larger cohort 25,639) men and women.

## 45 **2.0 SUBJECTS AND METHODS**

### 46 **2.1 Study population**

47 The present study population is comprised of a randomly selected representative sample  
48 (n=4,000) of the EPIC-Norfolk cohort (n~25,639), which will herein be referred to as EPIC-  
49 Norfolk sub-cohort. EPIC-Norfolk has previously been described in detail and the  
50 characteristics of the sample was comparable with other representative UK populations with  
51 the exception of a lower proportion of current smokers (10). Ethical approval for the study was  
52 obtained from the Norwich Ethics Committee, and participants provided informed consent.

53 Briefly this sub-cohort (n=4,920) is comprised of a representative random sample of 4,000 men  
54 and women with complete data for food diaries from the EPIC-Norfolk cohort (n=25,369) and  
55 1,102 stroke cases (n=182 part of 4,000 random sample previously mentioned) giving a total  
56 of 4,920. Participants were resident in the Norfolk area at recruitment between 1993 and 1997  
57 and recruited through participating General Practices (n=35) (10). Participants were excluded  
58 from analyses if they had reported prevalent stroke at baseline or had missing values for any  
59 variables included in the multivariate model (n=477). Participants with missing values for  
60 smoking status, aspirin medication use for >3months, and magnesium from supplements

61 (including medication) were recoded and classified as 'current smoking' (n=37) and 'no'  
62 aspirin (n=813) and 'no' supplements (n=2) to reduce the risk of bias due to under-reporting.  
63 Therefore 4,443 participants remained for analysis in this study.

## 64 **2.2 Anthropometric Measures**

65 At baseline participants attended a health check, which took place either at a clinic or the  
66 participant's GP surgery, where a number of anthropometric measurements were taken by  
67 trained staff according to standardised protocols (10). This included height to the nearest mm,  
68 using a free-standing stadiometer. Weight was recorded to the nearest 0.2kg with participants  
69 wearing light clothing and no shoes. From this measurement BMI was calculated. Waist and  
70 hip measurements were also recorded to the nearest mm (10).

## 71 **2.3 Clinical and Biological Measures**

72 BP was taken after participants had been seated for 3 mins. Two readings were taken using  
73 Accutorr Sphygmomanometer (Datascop, UK) with the participants arm in the horizontal  
74 position in line with the mid sternum (10). At the clinic visit, a non-fasting venous blood (42ml)  
75 sample was taken from which biochemical analysis for serum cholesterol was conducted (10).

76 Stroke cases were defined as ICD-9 430-448 or ICD-10 60-69. Fatal and non-fatal stroke  
77 incidence was established using death certificate data and linkage with hospital records, using  
78 ICD-10 60-69 this method of stroke ascertainment has been shown to have high sensitivity and  
79 specificity (11). The current study is based on follow-up to 31<sup>st</sup> March 2008. Numbers of stroke  
80 are given in the tables.

## 81 **2.4 Lifestyle Factors**

82 Information was obtained from participants on a number of lifestyle variables via a Health and  
83 Lifestyle Questionnaire (HLQ). This included smoking status which was categorised as

84 current, if participants answered “yes” to the question “Do you smoke cigarettes now?”, never  
85 if they answered “no” to the question “Have you ever smoked as much as one cigarette a day  
86 for as long as a year”. All other participants with valid data were classified as former smokers  
87 (missing data were treated as ‘current’). Physical activity was assessed by the use of a short  
88 physical activity questionnaire which assessed typical activity over the previous 12 months.  
89 Physical activity status took account of both work and leisure related activities and participants  
90 were ranked into one of four categories (inactive, moderately inactive, moderately active and  
91 active) (10). The repeatability and validity of these was confirmed against heart-rate  
92 monitoring (12).

93 Education level was determined from the HLQ and was defined at the highest qualification  
94 obtained at that time. Participants were ranked into one of four categories: ‘degree or  
95 equivalent’, ‘A-level or equivalent’, ‘O-level or equivalent’, and less than O-level or  
96 equivalent’.

## 97 **2.5 Previous Medical History**

98 The presence of a number of existing underlying medical conditions was ascertained using the  
99 HLQ. Conditions of interest included; stroke, cancer, myocardial infarction and diabetes  
100 amongst others. In conjunction with this, participants were requested to detail any medication  
101 that they were currently taking.

## 102 **2.6 Dietary Assessment Method**

103 Participants were requested to record all food and drink items consumed within the 7 day period  
104 in a food record diary. Included in each food diary were colour photographs of 17 foods, each  
105 with three incremental portion sizes. Participants were requested to indicate which photograph  
106 best represented their portion size for each of the items. They were also asked to record the

107 weight of food items or use household measures to describe the portion size. The use of dietary  
108 supplements was also recorded within the diary, and data was input into a specifically designed  
109 program ViMiS (vitamin and mineral supplements) (13). The 7-day diary was chosen after  
110 validation studies showed its reproducibility and relative validity and indicated that the diet  
111 diaries provide a more accurate representation of dietary intakes, over FFQs (10, 14). These  
112 studies indicate that FFQs overestimate dietary intakes of a number of food groups including  
113 fruit and vegetables, milk and cheese which influence the magnesium intake estimates.

114 A specific program, DINER (Data Into Nutrients for Epidemiological Research), was  
115 developed for entry of dietary information from the 7-day food diaries (15). DINER allows the  
116 detailed information provided in diet diaries to be translated into structured data files for  
117 nutritional analysis. The program is more flexible than other software which enables the detail  
118 of the diary, including cooking method, type of fat used and commercial brand names of  
119 products, to be retained (16). Due to the classification structure used to code food items DINER  
120 is also able to adapt to changes in food items available on the consumer market (15). The input  
121 of items from the food diaries requires a high level of detail, which reduces the risk of bias  
122 between coders, and analysis of consistency has echoed this (15). Nutritionists, trained to use  
123 the DINERMO program, checked the entered data after which nutrient quantities were  
124 calculated and checked for a final time (17).

125 The ratio of calcium to magnesium intake was calculated by dividing dietary calcium intake  
126 by dietary magnesium intake.

## 127 **2.7 Statistical Methods**

128 All statistical analyses were conducted using the statistical software Stata; version 11  
129 (StataCorp. College Station Tx, 2009). Continuous data are presented as mean with standard  
130 error and categorical data as number and percentage. A two-sided P-value of  $\leq 0.05$  was



131 considered statistically significant. Independent samples *t test* was used to assess differences in  
132 baseline characteristics between men and women.

133 To account for sex differences associated with a number of variables of interest including BMI  
134 and WHR sex specific analyses were conducted.

135 Multiple regression analysis with multivariate adjustment was employed to assess differences  
136 in SBP, DBP and total cholesterol TC with sex specific quintiles of dietary magnesium intake.

### 137 Statistical Models

138 Model 1 comprised of age, BMI, smoking, physical activity (PA) levels, education (all  
139 outcomes); use of antihypertensive medications (BP only); baseline reported myocardial  
140 infarction (MI) or diabetes, family history of stroke or MI, and use of statin medication (TC  
141 only) (2, 18, 19). Model 2, additionally adjusted for dietary factors, including total energy  
142 intake in order to demonstrate the effect of magnesium intake independent of total caloric  
143 intake, as well as previous incident myocardial infarction (MI) or diabetes at baseline, family  
144 history of stroke and MI (BP model only). Alcohol intake, dietary potassium and sodium were  
145 included due to their associations with BP (2) and total fat (TC model only). The use of calcium  
146 supplements and the ratio of calcium to magnesium intake were included; these two ions  
147 antagonise each other, may compete during intestinal absorption and the Ca:Mg ratio may be  
148 important for total mortality and coronary heart disease (20).

149 For stroke risk, model 1 comprised age, BMI, smoking, PA, education and alcohol intake.  
150 Model 2 additionally adjusted for serum TC, baseline reported MI or diabetes and family  
151 history of stroke or MI. Model 3 included the addition of SBP and DBP, use of aspirin  
152 medication >3 months, use of antihypertensive medication, the ratio of dietary Ca:Mg and the  
153 use of calcium and magnesium supplements.

154 A modified Prentice-weighted Cox regression analysis, for case-cohort studies, was used to  
155 calculate hazard ratios with 95% CIs for the risk of incident of stroke in association with dietary  
156 magnesium intake (21). This modified method accounts for the potential overlap of participants  
157 with incident stroke and also randomly present in the representative sub-cohort. Analyses were  
158 conducted by sex-stratified data derived categories of magnesium intake with the lowest 10%  
159 of intakes (<214mg/d and <180mg/d for men and women), forming the reference category, and  
160 subsequent 30% groups of magnesium intake. This approach was taken as we hypothesised  
161 that the lowest risk of incident stroke would be in those with the highest dietary magnesium  
162 intakes.

163 Sensitivity analysis was conducted excluding those taking antihypertensive and statin  
164 medication respectively.

165 Total energy was not included as a covariate in cox regression analysis. This was for a number  
166 of reasons, including that in the cox regression we adjusted for classical risk factors for stroke  
167 and have previously adjusted for total energy in early BP analyses, which indicated that dietary  
168 magnesium intake has an effect on BP independently of total energy, specifically for men, and  
169 BP was included in cox regression analyses. Additionally with the inclusion of total energy  
170 there is potential for collinearity, as a number of covariates included in the model such as BMI,  
171 alcohol intake and physical activity are highly correlated with total energy intake. There is also  
172 the potential for over adjustment, and for these reasons we chose not to include total energy in  
173 the cox regression models.

### 174 3.0 RESULTS

175 In the 4,443 participants included in these analyses 45.0% were male, with an age range of 39-  
176 78 years. Mean BP was 140/85 (SD 18.5/11.5) and 136/82 (SD 19.5/11.4) mmHg for males  
177 and females respectively (**Table 1**). There was a total of 928 incident strokes during follow-up  
178 (mean 9.58 years; total person years 42,556.5) between 1993 and 2008.

179 Men had significantly higher SBP, DBP and BMI and women had significantly higher TC  
180 levels (P for all <0.001), and BMI (P=0.01), but not family history of stroke or MI (P=0.35 and  
181 0.17 respectively), and antihypertensive or lipid lowering medication use (P=0.89 and 0.34  
182 respectively). This illustrates the need to conduct sex-stratified analyses.

183 Both men and women with the lowest 10% of dietary magnesium intake, compared with the  
184 remaining 90% of intakes, tended to be older (64 vs. 61 years, and 63 vs. 60 years for men and  
185 women respectively), had a higher percentage of current smokers (18.6% vs. 10.9% and 21.1%  
186 vs. 12.0% for men and women respectively), inactive people (42.7% vs. 31.0% and 47.4% vs.  
187 31.2% for men and women respectively) and people taking antihypertensive medication  
188 (25.6% vs. 20.3% and 30.2% vs. 20.2% for men and women respectively). There was no  
189 substantial difference in BMI, use of statin or aspirin and MI or diabetes at baseline between  
190 lowest 10% of magnesium and remaining intakes. Across quintiles of dietary magnesium  
191 intake a significantly higher intake of fruit, vegetables and bread and cereals was seen in men  
192 and women (P<0.001 for all).

193 In men but not women, there were inverse associations between dietary magnesium intake and  
194 SBP and DBP that remained significant after analysis that accounted for age, dietary sodium  
195 intake and use of aspirin or antihypertensive medication (**Table 2**). There were differences of  
196 -7 mmHg and -3.8 mmHg between Quintile-1 and Quintile-5 in SBP and DBP (P≤0.01 and

197 P=0.01 respectively). In women there were no significant associations between dietary  
198 magnesium intake and SBP or DBP (Table 2).

199 Significant inverse associations between dietary magnesium intakes and TC were identified for  
200 both genders (P=0.02 in men and P=0.04 in women) after adjustment for anthropometric and  
201 lifestyle factors (Table 2). However, these associations were attenuated with the addition of  
202 dietary factors; alcohol intake, total fat intake, ratio of Ca:Mg, total energy and calcium  
203 supplement intake to the multivariate model but remained significant (P=0.02 in men and  
204 P=0.04 in women) (Table 2).

205 Sensitivity analysis excluding those on antihypertensive medication (n=1583 men and 1927  
206 women) or statin medication (n=1973 men and 2400 women) provided similar results.

207 Stroke risk showed a non-significant inverse trend across quintiles of dietary magnesium  
208 intakes in men and women after adjustment (**Table 3**). In further analyses examining  
209 magnesium intake by categories there was a significant trend across categories in men. In those  
210 in the highest 30<sup>th</sup> percentile of dietary magnesium intake (**Table 4**), in men, but not in women  
211 (Table 4), there was a 41% relative reduction of stroke risk (HR 0.59 95% CI 0.38-0.93  
212 (P=0.04)) compared to the lowest 10% of magnesium intakes. Although stroke risk was also  
213 lower in women this was not significant.

214 Sensitivity analyses excluding those taking antihypertensive medication attenuated the  
215 association of stroke risk in men to be non-significant and strengthened the association in  
216 women to be significant and separately excluding those taking statin medication attenuated the  
217 association in men to be non-significant.

## 218 4.0 DISCUSSION

219 The main findings of this case-cohort study of British adults suggest that, after adjustment for  
220 several important confounding factors including age, smoking status, history of CVD,  
221 medication use, total energy intake and other dietary variables, there was a strongly significant  
222 association ( $P \leq 0.01$ ) between dietary magnesium intake and SBP and DBP in men, but not in  
223 women. There was also an association with TC in both men and women ( $P = 0.001$  and  $P \leq 0.01$   
224 respectively) which was attenuated but remained significant after adjustment for other dietary  
225 factors ( $P = 0.02$  and  $P = 0.04$  for men and women respectively). Furthermore in relation to stroke  
226 risk specifically, we identified a significant decrease in risk (HR 0.59 95% CI 0.38-0.93  
227  $P = 0.04$ ) in men with dietary magnesium intakes  $\geq 354$  mg/d (the highest 30%) compared to  
228 those with intakes  $\leq 214$  mg (the lowest 10%).

229 Compared with our findings, previous studies have shown ~~Previously~~ a significant inverse  
230 association between dietary magnesium intake and SBP and DBP in men has also been reported  
231 (22) with differences of -6.4 mmHg and -3.1 mmHg for SBP and DBP respectively between  
232 those with the highest and lowest intakes in 615 older Japanese men (age 63-82 years) using  
233 24hr recall. Using 7d food diary data, a more robust measure of dietary intakes, in a  
234 representative general population of middle and older age we identified slightly greater  
235 differences in BP between extreme quintiles of magnesium intakes with a difference of -7  
236 mmHg ( $P < 0.001$ ) and -3.8 mmHg ( $P < 0.001$ ) for SBP and DBP respectively. We identified  
237 between quintiles differences were 250 mg/d for men, and 198 mg/d for women, the equivalent  
238 to approximately 2 slices of wholemeal bread with peanut butter and 9 Brazil nuts, therefore  
239 achievable through dietary intakes (23). We also noted a tendency towards lower fruit,  
240 vegetable and bread and cereal intake in those with the lowest dietary magnesium intakes and  
241 may be relevant for identifying individuals whom may benefit from increased intake.

242 In women a potential benefit from increased consumption of magnesium has previously been  
243 reported (24-26). Witteman et al (22) and Song et al (23) showed a reduction in relative risk  
244 RR 0.77 95%CI: 12%-33% and RR 0.93, 95% CI 0.86-1.02 respectively for developing  
245 hypertension in prospective studies using FFQs. ~~Also~~ a meta-analysis of RCTs using oral  
246 magnesium supplements also reported a dose dependent effect of supplementation on blood  
247 pressure (27). This is in contrast to the current study where we did not find any significant  
248 trends between magnesium intake and BP in women. This discrepancy may be due to  
249 differences in the models used. For example Witteman et al (1989) (24) did not adjust for  
250 lifestyle factors including physical activity levels and smoking status which are known to  
251 influence BP. We further explored why we might have identified differences between genders.  
252 It may be due to the fact that older age, higher BMI, and higher level of physical inactivity  
253 were more prevalent in women with low magnesium intakes which may in part explain why a  
254 significant effect was shown in men not women. As highlighted in the results section  
255 differences were identified between those with the lowest 10% of intakes and those with higher  
256 intakes, however, we took these factors into account during our analyses. It is also of note that  
257 differences identified were largely the same for both men and women, although there was a  
258 higher percentage of women, with the lowest 10% magnesium intakes, using antihypertensive  
259 medication which may influence the findings due to modifying effect of medication on future  
260 risk. In addition there was a narrower range of magnesium intakes for women (644mg/d)  
261 compared with men (744mg/d) which may attenuate the results. It may also be that the cohort  
262 was insufficiently powered to detect an affect in women.

263 A number of intervention trials, using oral magnesium supplements, have reported significant  
264 reductions in BP ranging from 2.0 – 12.0 and 2.7 – 8.0 mmHg for SBP and DBP respectively  
265 (28-32). Although, the supplement doses were comparable with dietary intake, ranging  
266 between 200 mg/d to 600 mg/d, the formulations used were inconsistent.

267 Limited studies have previously investigated associations between dietary magnesium intake  
268 and TC or subfractions and two previous studies found no association with TC unlike our study  
269 which found that TC was  $\approx 4\%$  lower in Quintile-5 compared with Quintile-1 (33-36). However,  
270 a higher magnesium intake has been related to beneficial increases in high density lipoprotein  
271 (HDL) concentrations (33, 35).

272 Although several studies have previously investigated stroke risk and dietary magnesium  
273 intakes, to our knowledge none have included populations of both men and women  
274 simultaneously or included risk factors as well as stroke risk (26, 33-35, 37-42). Previous  
275 studies in large populations of American, Taiwanese and Northern European cohorts, which  
276 have mainly used food frequency questionnaires (FFQ), have reported no associations (26, 33,  
277 34, 38, 40-42). However, several studies found significant associations in men (35), women  
278 (43), and men and women (40). Additionally, a meta-analysis by Larsson et al (2012) (9), in  
279 241,378 people, reported an inverse association between dietary magnesium intake, recorded  
280 by FFQ, and risk of stroke. A more recent meta-analysis, of CVD, but not stroke specifically,  
281 by Del Gobbo et al (8) in 313,041 participants, concluded that there was no significant  
282 association between dietary magnesium intake and CVD. However, a significant inverse  
283 association was identified in relation to circulating magnesium and CVD incidence potentially  
284 indicating mechanisms that could also affect stroke risk. In addition Guasch-Ferré et al (44)  
285 recently reported that an increase in magnesium intake was associated with a decrease in both  
286 CVD mortality and total mortality in individuals at high CVD risk. Our results indicated a non-  
287 significant trend across quintiles of dietary magnesium intake and stroke risk in men and  
288 women (Table 3). However, when we compared men with the lowest 10% of magnesium intake  
289 with the remainder of the cohort, we identified a significant inverse trend ( $P=0.04$ ) across  
290 groups in men only (Table 4). This finding would suggest that it is the very lowest magnesium

291 intakes that may infer the greatest risk of stroke incidence, and the current findings suggest an  
292 association between lower dietary magnesium intake and higher stroke risk.

#### 293 **4.1 Strengths and Limitations**

294 The strengths of the present analyses include; the size of the cohort, the representativeness of  
295 the UK general population and prospective design for the stroke analyses, which reduces the  
296 susceptibility of the study to selection bias. The study design also reduces the likelihood of  
297 measurement error, due to the recording of dietary intake at baseline prior to the onset of stroke.  
298 Additionally robust and systematic adjustment for a number of potential confounding factors  
299 allowed for the identification of dietary associations independent of known risk factors. It is  
300 possible that factors not included in the model may also influence associations such as  
301 medication use; proton pump inhibitors, and diuretics. The use of quantitative 7-day food  
302 diaries is likely to have provided a more accurate representation of micronutrient intakes,  
303 including magnesium intake, compared with FFQ and 24-hr recall methods (45). To our  
304 knowledge our study is the only one to use dietary intake values from 7-day diaries as opposed  
305 to estimates from FFQs. Seven day food diaries have been shown to more accurately represent  
306 dietary intakes of a number of food groups that contribute to magnesium intake, including fruit  
307 and vegetables, and micronutrient intakes including potassium, carotene and vitamin C in  
308 validation studies (14, 45, 46). Despite this, dietary intakes do not account for variation in  
309 bioavailability and absorption of magnesium, potentially the use of a biomarker would  
310 strengthen the findings (47) and we were also unable to take into account possible contributions  
311 of magnesium from drinking water (48). Furthermore in the same population we were able to  
312 examine the complex relationship between magnesium intake, BP and cholesterol and stroke  
313 risk taking into account potential relevant risk specific confounders.



314 Selection bias may be possible although the whole EPIC-Norfolk cohort was representative of  
315 the UK population, with comparable cohort characteristics, and the sub-cohort for these  
316 analyses was representative of the EPIC-Norfolk cohort. Furthermore, truncation of the sample  
317 distribution due to potential healthy responder bias would likely only attenuate the observed  
318 associations and therefore associations may actually be stronger than are presented. It should  
319 also be noted that, as with other cross-sectional and observational longitudinal studies, it is not  
320 possible to infer causation from these findings. However, the prospective relationship observed  
321 with dietary magnesium intake and stroke risk reduces the likelihood of reverse causality.  
322 Furthermore the associations were in agreement with the existing literature. Residual  
323 confounding is possible but, the likelihood is reduced due to previous validation of dietary  
324 methods and results of the EPIC-Norfolk cohort (46, 49).

## 325 **4.2 Summary**

326 To our knowledge this is the first study to investigate the association of dietary magnesium  
327 with BP, TC and stroke risk in a UK general population of both genders. The results suggest  
328 that increased dietary magnesium could positively impact on BP and stroke risk in men and  
329 total cholesterol levels in both genders. Our findings suggest that men with the lowest  
330 magnesium intakes are at the greatest risk of stroke, lower magnesium intake was also  
331 associated with higher blood pressure. Therefore a higher dietary magnesium intake may be  
332 beneficial for prevention of stroke in men and warrants further investigation.

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335 Author Contributions

336 Contribution of each author: The research question was formulated by AAW, PKM and LKMB  
337 who also analysed the data and wrote the manuscript. KTK and NJW are Principal Investigators  
338 of the EPIC-Norfolk. The data collection was organised by AAW, RNL. RNL performed the  
339 record linkage. MAHL obtained data from both food and supplement sources using the 7-day  
340 diet diaries. All authors contributed to the manuscript and commented on the final version. No  
341 authors declare a conflict of interest.

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## Tables

**Table 1.** Baseline characteristics by sex in 4443 men and women, aged 40-75 years in EPIC-Norfolk cohort (1993-1997)

	<b>Men</b>	<b>Women</b>	<b>P-value<sup>1</sup></b>
	<b>n=2000</b>	<b>n=2443</b>	
Age (years)	61.1 ( $\pm$ 9.53)	60.4 ( $\pm$ 9.71)	0.02
BMI (kg/m <sup>2</sup> )	26.5 ( $\pm$ 3.18)	26.2 ( $\pm$ 4.24)	<0.01
Family History Stroke (%)	465 (23.3%)	601 (24.6%)	0.29
Family History MI (%)	720 (36.0%)	934 (38.2%)	0.13
Family History DM (%)	222 (11.1%)	305 (12.5%)	0.16
<b>Blood Pressure mmHg</b>			
SBP	140 ( $\pm$ 18.5)	136 ( $\pm$ 19.5)	<0.001
DBP	85.3 ( $\pm$ 11.5)	81.8 ( $\pm$ 11.4)	<0.001
PP	54.2 ( $\pm$ 11.2)	54.0 ( $\pm$ 11.4)	0.66
Antihypertensive Use (%)	417 (20.9%)	516 (21.1%)	0.83

Aspirin Use (%)	271 (13.6%)	197 (8.06%)	<0.001
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### **Blood Lipids mmol/L**

Total Cholesterol	6.07 ( $\pm$ 1.10)	6.36 ( $\pm$ 1.22)	<0.001
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### **Smoking (%)**

Current	234 (11.7%)	314 (12.9%)	<0.001
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Former	1114 (55.7%)	774 (31.7%)	
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Never	652 (32.6%)	1355 (55.5%)	
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### **Physical Activity (%)**

Inactive	644 (32.2%)	800 (32.8%)	<0.001
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Moderately Inactive	476 (23.8%)	790 (32.3%)	
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Moderately Active	440 (22.0%)	514 (21.0%)	
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Active	440 (22.0%)	339 (13.9%)	
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### **Education Level (%)**

0 – No Qualifications	667 (33.4%)	1086 (44.5%)	<0.001
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1 – O-Level or Equivalent	165 (8.3%)	249 (10.2%)	
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2 – A-Level or Equivalent      887 (44.4%)    822 (33.7%)

3 – Degree or Equivalent      281 (14.1%)    286 (11.7%)

### **Dietary Factors**

Total Energy (kcal/d)      2218 (±505)    1685 (±384)    <0.001

Magnesium (mg/d)      318 (±92.0)    265 (±73.2)    <0.001

Ca:Mg Ratio      2.93      2.93      0.96

Potassium (mg/d)      3423 (±819)    2962 (±683)    <0.001

Alcohol (g/d)      15.9 (±20.8)    7.70 (±11.7)    <0.001

Sodium (mg/d)      3150 (±864)    2405 (±660)    <0.001

Calcium Supplement Use (%) 34 (1.70%)    160 (6.55%)    <0.001

Magnesium supplement use 22 (1.10%)    53 (2.17%)    <0.01

(%)

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<sup>1</sup>P-value difference between males and females.

Values are mean and standard deviations where continuous and number and percentage where categorical.

**Table 2.** Association of quintiles of dietary magnesium intake (range and mean quintile intake) and blood pressure and total cholesterol (means and SE) in 4443 men and women, aged 40-75 years in EPIC-Norfolk cohort (1993-1997).

Men		Dietary Magnesium Intake					P for trend
		Q1	Q2	Q3	Q4	Q5	
		85-242 mg	243-284 mg	285-328 mg	329-385 mg	386-829	
		206 mg	266 mg	307 mg	355 mg	456 mg	
		n=400	n=400	n=400	n=400	n=400	
SBP	Unadjusted	143 ( $\pm$ 0.98)	140 ( $\pm$ 0.97)	140 ( $\pm$ 0.88)	139 ( $\pm$ 0.90)	136 ( $\pm$ 0.87)	<0.001
	Model 1 <sup>1</sup>	140 ( $\pm$ 0.87)	139 ( $\pm$ 0.86)	140 ( $\pm$ 0.86)	140 ( $\pm$ 0.86)	139 ( $\pm$ 0.87)	0.64
	Model 2 <sup>2</sup>	143 ( $\pm$ 1.16)	140 ( $\pm$ 0.90)* <sup>3</sup>	140 ( $\pm$ 0.85)*	138 ( $\pm$ 0.89)**	136 ( $\pm$ 1.18)***	0.002
DBP	Unadjusted	86.1 ( $\pm$ 0.58)	85.9 ( $\pm$ 0.60)	85.4 ( $\pm$ 0.57)	85.2 ( $\pm$ 0.56)	84.1 ( $\pm$ 0.56)	0.008
	Model 1	85.4 ( $\pm$ 0.57)	85.4 ( $\pm$ 0.56)	85.3 ( $\pm$ 0.56)	85.5 ( $\pm$ 0.56)	85.0 ( $\pm$ 0.57)	0.68
	Model 2	87.15 ( $\pm$ 0.76)	86.1 ( $\pm$ 0.59)	85.1 ( $\pm$ 0.55)*	84.9 ( $\pm$ 0.58)*	83.4 ( $\pm$ 0.77)**	0.01

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**Women**


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		<b>48-204 mg</b>	<b>205-240 mg</b>	<b>241-274 mg</b>	<b>275-319 mg</b>	<b>320-692 mg</b>	<b>P for trend</b>
		<b>176 mg</b>	<b>223 mg</b>	<b>258 mg</b>	<b>295 mg</b>	<b>374 mg</b>	
		<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=488</b>	
SBP	Unadjusted	140 ( $\pm 0.90$ )	135 ( $\pm 0.85$ )	137 ( $\pm 0.93$ )	135 ( $\pm 0.89$ )	133 ( $\pm 0.81$ )	<0.001
	Model 1	136 ( $\pm 0.79$ )	135 ( $\pm 0.77$ )	137 ( $\pm 0.77$ )	136 ( $\pm 0.77$ )	135 ( $\pm 0.78$ )	0.85
	Model 2	137 ( $\pm 1.07$ )	135 ( $\pm 0.82$ )	137 ( $\pm 0.77$ )	135 ( $\pm 0.81$ )	135 ( $\pm 1.09$ )	0.45
DBP	Unadjusted	83.5 ( $\pm 0.51$ )	81.5 ( $\pm 0.50$ )	82.4 ( $\pm 0.55$ )	80.9 ( $\pm 0.53$ )	80.7 ( $\pm 0.48$ )	<0.001
	Model 1	82.0 ( $\pm 0.49$ )	81.3 ( $\pm 0.48$ )	82.6 ( $\pm 0.48$ )	81.4 ( $\pm 0.48$ )	81.7 ( $\pm 0.49$ )	0.71
	Model 2	82.5 ( $\pm 0.67$ )	81.6 ( $\pm 0.51$ )	82.5 ( $\pm 0.48$ )	81.1 ( $\pm 0.51$ )	81.2 ( $\pm 0.68$ )	0.26

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**Men**


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<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Q5</b>
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		<b>85-242 mg</b>	<b>243-284 mg</b>	<b>285-328 mg</b>	<b>329-385 mg</b>	<b>386-829</b>	<b>P for trend</b>
		<b>206 mg</b>	<b>266 mg</b>	<b>307 mg</b>	<b>355 mg</b>	<b>456 mg</b>	
		<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	
Total	Unadjusted	6.21 ( $\pm$ 0.06)	6.16 ( $\pm$ 0.06)	6.02 ( $\pm$ 0.05)	6.05 ( $\pm$ 0.06)	5.91 ( $\pm$ 0.05)	<0.001
Cholesterol							
	Model 1 <sup>4</sup>	6.17 ( $\pm$ 0.06)	6.16 ( $\pm$ 0.06)	6.03 ( $\pm$ 0.05)	6.06 ( $\pm$ 0.05)	5.93 ( $\pm$ 0.06)**	0.001
	Model 2 <sup>5</sup>	6.18 ( $\pm$ 0.07)	6.16 ( $\pm$ 0.06)	6.03 ( $\pm$ 0.05)	6.06 ( $\pm$ 0.06)	5.94 ( $\pm$ 0.07)*	0.02
<b>Women</b>							
		<b>48-204 mg</b>	<b>205-240 mg</b>	<b>241-274 mg</b>	<b>275-319 mg</b>	<b>320-692 mg</b>	<b>P for trend</b>
		<b>176 mg</b>	<b>223 mg</b>	<b>258 mg</b>	<b>295 mg</b>	<b>374 mg</b>	
		<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=488</b>	
Total	Unadjusted	6.67 ( $\pm$ 0.06)	6.35 ( $\pm$ 0.05)	6.28 ( $\pm$ 0.05)	6.32 ( $\pm$ 0.05)	6.16 ( $\pm$ 0.05)	<0.001
Cholesterol							

Model 1 <sup>3</sup>	6.51 (±0.05)	6.33 (±0.05)*	6.31 (±0.05)*	6.36 (±0.05)*	6.26 (±0.05)**	0.005
Model 2 <sup>4</sup>	6.52 (±0.06)	6.34 (±0.05)*	6.31 (±0.05)*	6.35 (±0.05)	6.25 (±0.06)*	0.04

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<sup>1</sup>Model 1: age, BMI, smoking status, physical activity, education level, antihypertensive medication use

<sup>2</sup>Model 2: model 1 + baseline MI or diabetes, family history stroke, family history MI, alcohol intake, dietary sodium, potassium, ratio Ca:Mg, total energy and calcium supplement use (including contribution from medication)

<sup>3</sup>Model 1: age, BMI, smoking status, physical activity, education level, baseline MI or diabetes, family history stroke, family history MI, statin medication use

<sup>4</sup>Model 2: model 1 + alcohol, dietary total fat intake, ratio Ca:Mg, total energy and calcium supplement use (including contribution from medication).

<sup>5</sup>P value for significance compared with Q1: \* = P value ≤ 0.05, \*\* = P value ≤ 0.005, \*\*\* = P value ≤ 0.001

**Table 3.** Quintiles of dietary magnesium intake (range and mean quintile intake) at baseline (1993-1997) and stroke risk (HR and 95%CI), follow-up March 2008, in 4443 men and women, aged 40-75 in EPIC-Norfolk cohort.

<b>Men</b>						
	<b>Q1</b>	<b>Q2</b>	<b>Q3</b>	<b>Q4</b>	<b>Q5</b>	
	<b>85-242 mg</b>	<b>243-284 mg</b>	<b>285-328 mg</b>	<b>329-385 mg</b>	<b>386-829</b>	<b>P trend</b>
	<b>206 mg</b>	<b>266 mg</b>	<b>307 mg</b>	<b>355 mg</b>	<b>456 mg</b>	
	<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	<b>n=400</b>	
Stroke Events	126 (30.6)	111 (26.9)	93 (22.6)	85 (20.6)	75 (18.3)	
Model 1 <sup>1</sup>	1.0 (reference)	0.85 (0.60-1.20)	0.70 (0.49-1.00)	0.86 (0.60-1.24)	0.80 (0.55-1.16)	0.22
Model 2 <sup>2</sup>	1.0 (reference)	0.86 (0.60-1.20)	0.68 (0.47-0.99)	0.81 (0.56-1.17)	0.74 (0.50-1.09)	0.11
Model 3 <sup>3</sup>	1.0 (reference)	0.87 (0.61-1.25)	0.73 (0.50-1.06)	0.80 (0.55-1.17)	0.81 (0.53-1.22)	0.21
<b>Women</b>						

	<b>48-204 mg</b>	<b>205-240 mg</b>	<b>241-274 mg</b>	<b>275-319 mg</b>	<b>320-692 mg</b>	
	<b>176 mg</b>	<b>223 mg</b>	<b>258 mg</b>	<b>295 mg</b>	<b>374 mg</b>	
	<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=489</b>	<b>n=488</b>	
Stroke Events	152 (30.5)	102 (20.5)	87 (17.5)	82 (16.5)	88 (17.7)	
Model 1 <sup>1</sup>	1.0 (reference)	0.74 (0.53-1.05)	0.74 (0.51-1.06)	0.84 (0.59-1.20)	0.83 (0.57-1.20)	0.39
Model 2 <sup>2</sup>	1.0 (reference)	0.71 (0.50-1.01)	0.71 (0.49-1.03)	0.82 (0.57-1.17)	0.76 (0.52-1.11)	0.23
Model 3 <sup>3</sup>	1.0 (reference)	0.72 (0.50-1.04)	0.73 (0.50-1.08)	0.86 (0.59-1.26)	0.82 (0.54-1.24)	0.45

<sup>1</sup>model 1: age, BMI, education status, physical activity, smoking status, alcohol intake

<sup>2</sup>model 2: model 1 + serum total cholesterol, baseline MI or diabetes, family history stroke, or MI

<sup>3</sup>model 3: model 2 + SBP, DBP, aspirin use >3 months, antihypertensive medication, ratio Ca:Mg and magnesium and calcium supplement use (including contribution from medication)

**Table 4.** Stroke risk (HR 95% CI) by magnesium groups (range and mean intake), bottom 10% (Group 1 reference category) and 3 groups of 30% intakes each, in 4443 men and women, aged 40-75 in EPIC-Norfolk cohort.

<b>Men</b>	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>	<b>P trend</b>
	<b>85-214 mg</b>	<b>215-285 mg</b>	<b>286-353 mg</b>	<b>354-828mg</b>	
	<b>181 mg</b>	<b>254 mg</b>	<b>318 mg</b>	<b>427 mg</b>	
	<b>n=199</b>	<b>n=605</b>	<b>n=591</b>	<b>n=605</b>	
Stroke Events	65 (32.7%)	157 (26.0%)	123 (20.8%)	104 (17.2%)	
Model 1 <sup>1</sup>	1.00	0.73 (0.50-1.07)	0.63 (0.43-0.94) <sup>*4</sup>	0.67 (0.44-1.01) <sup>*4</sup>	0.07
Model 2 <sup>2</sup>	1.00	0.72 (0.48-1.07)	0.61 (0.41-0.92) <sup>*4</sup>	0.61 (0.40-0.94) <sup>*4</sup>	0.03
Model 3 <sup>3</sup>	1.00	0.67 (0.45-1.01) <sup>*</sup>	0.60 (0.40-0.90) <sup>*4</sup>	0.59 (0.38-0.93) <sup>*4</sup>	0.04



<b>Women</b>	<b>Group 1</b>	<b>Group 2</b>	<b>Group 3</b>	<b>Group 4</b>	
	<b>48-180 mg</b>	<b>181-240 mg</b>	<b>241-294 mg</b>	<b>295-691 mg</b>	
	<b>156 mg</b>	<b>213 mg</b>	<b>267 mg</b>	<b>352 mg</b>	
	<b>n=232</b>	<b>n=745</b>	<b>n=740</b>	<b>n=726</b>	
Stroke Events	73 (31.5%)	165 (22.2%)	126 (17.0%)	115 (15.8%)	
Model 1 <sup>1</sup>	1.00	0.73 (0.49-1.08)	0.70 (0.46-1.06)	0.74 (0.48-1.12)	0.27
Model 2 <sup>2</sup>	1.00	0.67 (0.45-1.00) * <sup>4</sup>	0.65 (0.43-0.98) * <sup>4</sup>	0.66 (0.43-1.02)	0.14
Model 3 <sup>3</sup>	1.00	0.65 (0.43-0.99) * <sup>4</sup>	0.65 (0.42-1.01)	0.69 (0.44-1.09)	0.27

<sup>1</sup>model 1: age, BMI, education status, physical activity, smoking status, alcohol intake

<sup>2</sup>model 2: model 1 + serum total cholesterol, baseline MI or diabetes, family history stroke, or MI

<sup>3</sup>model 3: model 2 + SBP, DBP, aspirin use >3 months, antihypertensive medication, ratio Ca:Mg and magnesium and calcium supplement use (including contribution from medication)

<sup>4</sup>P value for significance compared with reference (Group 1): \*= P value ≤0.05