

Nut intake and 5-year changes in body weight and obesity risk in adults: results from the EPIC-PANACEA study

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Electronic supplementary material

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For information on how to submit an application for gaining access to EPIC data and/or biospecimens, please follow the instructions at <http://epic.iarc.fr/access/index.php>.

1 **Abstract**

2 *Purpose* There is inconsistent evidence regarding the relationship between higher intake of
3 nuts, being an energy-dense food, and weight gain. We investigated the relationship between nut
4 intake and changes in weight over 5 years.

5 *Methods* This study includes 373,293 men and women, 25-70 years old, recruited between
6 1992 and 2000 from 10 European countries in the European Prospective Investigation into Cancer and
7 Nutrition (EPIC) study. Habitual intake of nuts including peanuts, together defined as nut intake, was
8 estimated from country-specific validated dietary questionnaires. Body weight was measured at
9 recruitment and self-reported 5 years later. The association between nut intake and body weight
10 change was estimated using multilevel mixed linear regression models with center/country as random
11 effect and nut intake and relevant confounders as fixed effects. The relative risk (RR) of becoming
12 overweight or obese after 5 years was investigated using multivariate Poisson regressions stratified
13 according to baseline body mass index (BMI).

14 *Results* On average, study participants gained 2.1 kg (SD 5.0 kg) over 5 years. Compared to
15 non-consumers, subjects in the highest quartile of nut intake had less weight gain over 5 years (-0.07
16 kg; 95% CI, -0.12- -0.02) (P -trend=0.025) and had 5% lower risk of becoming overweight (RR, 0.95;
17 95% CI, 0.92-0.98) or obese (RR, 0.95; 95% CI, 0.90-0.99) (both P -trend <0.008).

18 *Conclusions* Higher intake of nuts is associated with reduced weight gain and a lower risk of
19 becoming overweight or obese.

20 **Keywords** Nut intake, weight gain, obesity, energy balance, adults, Europe

21 **Introduction**

22 Observational studies and clinical trials, including the recent PREDIMED trial [1], have provided
23 evidence that high nut consumption has beneficial effects on the occurrence of chronic diseases such
24 as cardiovascular disease and type 2 diabetes [2–5], and a possible role in cancer prevention [5–8].

25 Nuts can provide 160–200 kcal per serving (30 g) and thus have energy-density similar to
26 foods such as crackers, chocolate candies, and cookies. Therefore, concerns persist that high nut intake
27 may lead to weight gain and increased long-term risk of obesity [9]. Whether frequent nut
28 consumption promotes weight gain is not yet conclusive. Weight gain may not occur if nuts are
29 incorporated into an isocaloric diet in which they are substitute for other foods such as red meat or
30 processed meat or refined carbohydrates, as opposed to being added to an existing diet [10].

31 Randomized nut-feeding trials showed that compared with control diets, isocaloric diets
32 enriched with nuts did not increase body weight, body mass index (BMI), or waist circumference [11,
33 12]. However, these trials were limited by small numbers of volunteers, consuming a controlled diet
34 over relatively short periods, with one notable exception, where median follow-up time was 4.8 years
35 [12], and were not primarily designed to evaluate body weight changes. In addition, such trials are
36 expensive to conduct across populations and may not test real-life settings.

37 There are little existing data from prospective observational studies [13–17], and these are
38 limited because they were based on homogeneous populations and with one exception [14], did not
39 account for overall dietary patterns. Dietary patterns may confound findings associated with nut intake
40 because individuals who eat higher quantities of nuts usually also have a better overall diet quality
41 [18], and other favourable lifestyle habits such as higher physical activity levels. Thus, it is important
42 to account for dietary quality and other lifestyle behaviours in prospective observational settings.

43 We propose to address these knowledge gaps utilizing data of the EPIC-PANACEA study;
44 PANACEA (Physical Activity, Nutrition, Alcohol, Cessation of smoking, Eating out of home in
45 relation to Anthropometry) is the sub-cohort of the EPIC (European Prospective Investigation into
46 Cancer and nutrition) study, where repeated assessments of weight are available making it possible to
47 study weight changes.

48 The main objective of the present study was to investigate the relationship between nut intake and
49 subsequent changes in weight after an average of 5 years of follow-up accounting for dietary patterns
50 and other lifestyle factors that may co-vary with nut intake. A secondary objective was to estimate
51 risks of becoming overweight or obese associated with higher nut intake.

52

53 **Methods**

54 *Study population.*

55 The EPIC study is an ongoing prospective cohort study across 23 centers in 10 European countries:
56 Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, and the United
57 Kingdom (UK). The cohort of 521,448 men and women recruited from 1992 to 2000 (age range: 25 to
58 70 years) was enrolled from the general population with exceptions for France (national health
59 insurance scheme members), Utrecht and Florence (breast cancer screening participants), Oxford
60 (health conscious, mainly vegetarian, volunteers), and some centres from Italy and Spain (blood
61 donors). The rationale for EPIC, study design, and methods have been described in detail elsewhere
62 [19, 20]. The EPIC study was approved by the Ethical Review Board of the IARC and the Institutional
63 Review Board of each participating EPIC centers.

64 For the present study, we excluded pregnant women, participants with missing dietary or
65 lifestyle information, missing data on weight and height or with implausible anthropometric values at
66 baseline (n=23,713). We further excluded 122,154 individuals with missing weight at follow-up and
67 2,288 individuals with outlying anthropometry at follow-up: weight change < -5 or > 5 kg/year and
68 BMI at follow-up < 16 kg/m². More details on follow-up exclusions are given in **Figure S1** (Online
69 Resource) and have been previously detailed [21, 22]. The final analyses included 103,303 men and
70 269,990 women with complete and plausible body weight data.

71

72 *Anthropometric measures and weight change.*

73 Two body weight measures were available for each participant: at baseline and after a median follow-
74 up time of 5 years (min.: 2 years for Heidelberg (Germany); max.: 11 years for Varese (Italy)). At
75 baseline, body weight and height were measured in most centres using comparable, standardized

76 procedures with the exception of those taken in France, Norway and the health conscious group of the
77 Oxford centre in which subjects self-reported their weight. As for the follow-up weight assessments,
78 all values were self-reported, except in Norfolk (UK) and Doetinchem (The Netherlands) where
79 weight was measured [21, 22]. The accuracy of self-reported anthropometric measures – at baseline
80 and at follow-up – was improved with the use of prediction equations derived from subjects with both
81 measured and self-reported weight at baseline [23]. Our main outcome was weight change in kg per 5
82 years, calculated as weight at follow-up – weight at baseline divided by the follow-up time in years
83 and multiplied by 5 years.

84

85 *Dietary assessment.*

86 Habitual food consumption during the previous 12 months was assessed at baseline for each individual
87 with center-specific methods; in most cases food-frequency questionnaires (FFQs) [20]. These
88 questionnaires were developed and validated in each country/center to capture country-specific dietary
89 habits. In most centers FFQs were self-administered, with the exception of Greece, Ragusa (Italy),
90 Naples (Italy) and Spain where face-to-face interviews were performed. Extensive quantitative FFQs
91 were used in northern Italy, the Netherlands, Germany and Greece. Questionnaires structured by meals
92 were used in Spain, France and Ragusa (Italy). Semi-quantitative FFQs were used in Denmark,
93 Norway, Naples (Italy) and Umea (Sweden). In the UK, both a semi-quantitative FFQ and a 7-day
94 record were used, whereas a method combining a FFQ with a 7-day record on lunch and dinner was
95 used in Malmö (Sweden) [20]. Details of the questionnaire items regarding nut intake for each center
96 or country, have been described previously [8]. In brief, the respective questionnaire food item(s) in
97 France, Germany, Greece, Ragusa (Italy), the Netherlands, Spain, and the UK asked non-specifically
98 for intake of any kind of nuts incl. peanuts; in Denmark and Norway specifically for peanuts, and in
99 Umea (Sweden) specifically for “peanuts, salted”; in northern Italy specifically for “walnuts,
100 hazelnuts, almonds, and peanuts”, and in Naples (Italy) for “walnuts”; in Spain for an exhaustive list
101 of different types of nuts incl. peanuts and seeds; in Malmö (Sweden), the FFQ included peanuts as
102 snacks, whereas other nuts had to be added to an open-ended question or recorded at lunch and dinner
103 meals; finally, in Germany, the Netherlands, and the UK separate items on peanut butter intake were

104 asked for and we included this item in our overall nut intake variable. Here we define the combined
105 intake of any of the items described above as “nut intake”; because nut intake was assessed in these
106 broad categories, a stratified analysis by specific types of nuts was not possible. Non-consumers were
107 determined from the FFQs and defined as those with an intake of nuts equal to zero.

108 In order to account for healthy diet, which may confound nut intake, we used the modified
109 relative Mediterranean Diet Score (mrMDS) [24]. This score included the nutritional components that
110 characterize the Mediterranean diet: i.e. higher intake of vegetables, legumes, fruit and nuts, cereals,
111 fish and seafood, plant oils, and moderate alcohol consumption; and lower intakes of meat/products,
112 and dairy products. Each mrMDS component (apart from alcohol) was measured in grams per 1000
113 kcal (to express intake as energy density) and higher scores (range: 0-18) characterizing a
114 Mediterranean diet [24]. In order to avoid over-adjustment, we used the mrMDS after subtracting the
115 “fruit and nuts” component.

116

117 *Assessment of other covariates.*

118 Data on objectively validated physical activity [25], smoking status, and education were collected at
119 baseline through questionnaires [20]. Information on smoking status was also collected at follow-up at
120 the same time as anthropometric data collection. Thus, we could account for smoking status
121 modification during follow-up (stable current smoker, stable former smoker, stable never smoker, quit
122 smoking, started smoking).

123

124 *Statistical analyses.*

125 Habitual nut intake as estimated from the dietary questionnaires was analysed both on a continuous
126 scale per 15 g/day increment, which corresponds to the mean intake of nut consumers in the highest
127 cohort category of intake, and by categories with all non-consumers (~25%) placed in the first
128 (reference) category and the consumers divided by quartiles into the remaining four categories of
129 intake (categories 2 to 5), similar as in Jenab et al. [8]. As a secondary analysis, we also modelled
130 frequency of nut intake using the following categories: “never/almost never”, “0.5-2 times/month”,
131 “0.5-≤1 times/week”, “more than 1 times/week”, which is similar to Bes-Rastrollo et al.[14].

132 Frequency data for the centers Cambridge (UK) (n=14,535) and Malmö (Sweden) (n=21,566) were
133 not available because open-ended dietary methodologies were used.

134 The association between nut intake and body weight change (kg/5 years) was estimated using
135 multilevel mixed linear regression models with center as random effect and nut intake and relevant
136 confounders as fixed effects. Models with three different sets of adjustment were fit (see footnotes of
137 Table 2 for complete list). Participants with missing values for physical activity (1.5%), education
138 (2.1%), and smoking status at follow-up (0.4% after replacing missing values at follow-up [10.5%] by
139 smoking status at baseline) were classified as a separate category and included in the models. Model
140 assumptions and fit were checked visually by plotting the residuals against each of the categorical
141 covariates. The linearity of the associations for each continuous covariate was evaluated by three-knot
142 restricted cubic spline models at Harrell's default percentiles (i.e. 10th, 50th, and 90th) in combination
143 with a Wald-type test [26]. Because baseline BMI and follow-up time in years (both *P* non-linear <
144 0.001) showed a non-linear relationship with weight change, splines with 3 knots for these two
145 variables were included as covariates.

146 In order to evaluate heterogeneity across countries/centers, we performed country/center-
147 specific analyses using generalized linear models and pooled results by random-effect meta-analysis
148 and calculated *I* squared and respective *P* values for heterogeneity [27].

149 We performed a range of sensitivity analyses such as excluding participants with chronic
150 diseases at baseline or missing values in covariates, excluding countries where nut intake included
151 peanuts only or adjusting for main food groups instead of the mrMDS (**Table S1**, Online Resource).

152 We tested *a priori* for effect modification by age (categorised as younger than median age <51
153 and ≥ 51 years), sex, BMI categories at baseline (<25, 25-≤30, >30kg/m²), and change of smoking
154 status (never, current, start smoking, quitter, former) by including interaction terms between each
155 variable and nut intake (continuous per 15 g/d) in the models. *P* values for the interaction term were
156 calculated by using *F* tests.

157 We used a modified Poisson regression approach [28] to estimate the relative risks (RR) and
158 95% confidence intervals (CI) of becoming overweight or obese according to nut intake (in categories
159 of absolute intakes and frequency of intake). Analyses were stratified by initial BMI categories (<25:

160 normal weight, $25 \leq \text{BMI} < 30$: overweight and $\geq 30 \text{ kg/m}^2$: obese). RRs were adjusted as in our model 3
161 described above. The BMI after 5 years was calculated from the 5 year follow-up weight and baseline
162 height.

163 Differences were considered statistically significant at $P < 0.05$. All statistical analyses were
164 performed with STATA 12.1 (College Station TX).

165

166 **Results**

167 The main characteristics of the study population at baseline by categories of nut intake are shown in
168 **Table 1**. Higher intake of nuts was associated with younger age, a lower BMI, a higher educational
169 level, never smoking, and being more physically active. Participants in the highest category of nut
170 intake also had higher intakes of vegetables, fruit, cereals/cereal products, non-alcoholic and alcoholic
171 beverages, but also of sugar/confectionary, and cakes/biscuits; they also had a slightly higher mrMED
172 score. In contrast, they had lower intakes of meat/products, dairy, fish, and potatoes. On average, study
173 participants gained 2.1 kg of weight between baseline and the 2nd weight assessment with considerable
174 variation between subjects (SD 5.0 kg).

175 Body weight changes (kg) over 5 years according to baseline nut intake are shown in **Table 2**.
176 After adjustment for potential confounders, each 15g/day increase in nut intake was associated with
177 less weight gain (-0.04 kg/5-years , 95% CI, -0.071 - -0.012). The observed effects were small and
178 corresponded to $\sim 2.5\%$ -reduction in body weight increase. Associations remained virtually unchanged
179 after further adjustment for Mediterranean diet using the mrMDS (Model 3, Table 2). Estimated
180 results were consistent across countries/centers with low heterogeneity (I -squared=21%, P
181 heterogeneity = 0.22) (**Figure S2**, Online Resource). Analyses by categories of nut intake confirmed
182 the findings using intake on a continuous scale, where participants in the highest category of nut intake
183 gained 0.07 kg/5-years less weight as compared to non-consumers (P trend = 0.025) (Table 2).
184 Furthermore, when we analyzed frequency of nut intake without accounting for amounts of intake,
185 strengths of associations increased, where subjects consuming nuts more than once per week gained
186 0.1 kg/5-years less weight as compared to non-consumers (P trend < 0.001) (Table 2).

187 Our main findings were also robust to a range of sensitivity analyses (**Table S1**, Online
188 Resource). For example, excluding participants who started or quit smoking during follow-up (Model
189 S4), with missing values in any of the covariates (Model S8), , or in non-smokers only (to exclude
190 residual confounding in smokers) (Model S16) resulted in virtually similar effect estimates. Similarly,
191 excluding participants from Denmark, Norway, and Umea (Sweden), where the country/center-
192 specific FFQ only included peanuts, did not alter the estimates (Model S9). In contrast, when we
193 excluded France (Model S11), where the FFQ item on nuts was asked only in relation to “aperitif”
194 before lunch or dinner, which in France is typically consumed with an alcoholic beverage, effect
195 estimates per 15g/day nut intake doubled from -0.042 (95% CI, -0.071 - -0.012) to -0.083 kg/5-years
196 (95% CI, -0.114 - -0.051). Another important finding in our sensitivity analysis was that adjustment
197 for main food groups as indicated in Table 1, instead of the mrMDS, resulted in similar effect
198 estimates (Model S12), but only when intake of meat/products was excluded. Inclusion of intake of
199 meat/products completely attenuated associations between intake of nuts and peanuts (15g/day) and 5-
200 y weight change (0.004 kg/5-y; 95% CI, -0.027 - 0.034) (Model S13).

201 No effect modification was found with regard to baseline age (P interaction = 0.54), sex (P
202 interaction = 0.62), baseline weight status (P interaction = 0.18) or change in smoking status (P
203 interaction = 0.95).

204 Adjusted relative risks (95% CI) of becoming overweight or obese after 5 years according to
205 categories of nut intake and initial BMI are presented in **Table 3**. At baseline, 197,291 subjects were
206 normal weight, 127,445 were overweight and 48,557 were obese. After 5 years, 31,215 (15.8%)
207 normal weight subjects became overweight or obese and 14,913 (13.2%) overweight subjects became
208 obese. Compared to non-consumers of nuts, normal weight subjects at baseline in the highest category
209 of nut intake had a 5% (95% CI, 2%-8%) lower risk of becoming overweight or obese. Similarly,
210 overweight subjects at baseline had a 5% (95% CI, 1%-10%) lower risk of becoming obese.
211 Frequency of nut intake was also associated with 5% (95% CI, 1%-10%) lower risk of becoming
212 overweight or obese in subjects that were normal weight at baseline. However, no association was
213 observed for risk of becoming obese in subjects that were already overweight at baseline (P trend =
214 0.39).

215 **Discussion**

216 Gradual age-related body weight increase during adulthood is a well observed phenomenon in many
217 non-obese populations — in our study, about 0.4 kg per year. Using baseline and follow-up data from
218 a large European multi-center cohort study, EPIC-PANACEA, we found that long-term weight gain
219 was significantly less in individuals consuming higher levels of nuts. These inverse associations were
220 modest for absolute intake of nuts, but were more pronounced for the frequency of consumption –
221 possibly reflecting different dietary habits or difficulties in reporting portion size accurately – where
222 >1 serving of nuts per week was associated with a 10% lower body weight increase. Importantly, our
223 findings are not likely to be confounded by a better overall diet quality, which is often observed in
224 high consumers of nuts, because we adjusted for dietary patterns and other lifestyle factors notably
225 physical activity and smoking.

226 In a post hoc analysis, we found that habitual high intake of meat and processed meat appears
227 to attenuate associations. We believe that the observed effects of nut intake on body weight change are
228 at least partly mediated via a reduced intake of meat/products shown to be positively associated with
229 weight gain [22, 29]. This has been hypothesized earlier as being one of the potential pathways of
230 weight stabilizing effects of nuts [10] and confirmed in our sensitivity analysis (Table S1, Online
231 Resource).

232 Our findings are in line with the few other prospective observational studies [13–17]. Women
233 in the Nurses' Health Study II (NHS II), who reported eating nuts ≥ 2 times/wk, experienced 0.5 kg
234 less weight gain (95% CI, -0.8- -0.2) after a mean 8 years of follow-up compared with those who
235 rarely ate nuts [14]. Similar results were observed in the Seguimiento Universidad de Navarra (SUN)
236 study, a prospective cohort in Spain, where weight change in men and women was assessed after a
237 median of 28 months [13] and after 6 years [16]. In the Nurses' Health Study (NHS), no differences in
238 weight gain over 16 years of follow-up across categories of nut consumption were observed [15]. A
239 pooled analysis of the NHS, the NHS II, and the Health Professionals Follow-up Study, where the
240 relationship of dietary changes over 4-year periods was related to changes in body weight, found that
241 per serving increase in nut intake, study participants gained 0.57 lb (~0.3 kg) less weight per 4-year
242 period [17]. The observed differences in effect sizes across these studies can most likely be explained

243 by a combination of factors including differences in length of weight follow-up, confounder
244 adjustment, accuracy of dietary assessment instruments used, but also differences in terms of
245 frequency and amount of consumed nuts, underlying dietary habits and other lifestyle factors that are
246 specific to a population. Interestingly, the only randomized controlled nut-feeding trial (PREDIMED)
247 that had a comparably long follow-up as in our study reported very similar results with regard to
248 adjusted difference in 5 year changes in bodyweight in the nut group as compared with the control
249 group (-0.08 kg) though not statistically significant (95% CI, $-0.50-0.35$ kg) and only in the context
250 of a Mediterranean diet [12]. We specifically accounted for Mediterranean dietary patterns in our
251 analysis in order to evaluate associations of nut intake with weight change in the context of other diets.
252 Romaguera et al. showed previously in the same study population that high adherence to a
253 Mediterranean diet was associated with a 5-year weight change of -0.16 kg (95% CI, $-0.24- -0.07$ kg)
254 and were 10% (95% CI, 4%-18%) less likely to develop overweight or obesity compared to
255 individuals with a low adherence [30].

256 Several mechanistic hypotheses have been proposed that could explain the association
257 between nut consumption and lessened weight gain, despite a potentially higher total energy intake in
258 nut consumers [10, 31]. These include increased satiety/supressed hunger due to the high dietary fibre
259 and plant protein content of nuts; the high content of unsaturated fat, which together with the high
260 protein content can lead to an increase in resting energy expenditure and diet-induced thermogenesis,
261 both of which can reduce body weight and weight gain; and incomplete mastication of nuts may cause
262 a low level of fat absorption that could result in the loss of available energy [10, 31]. In addition,
263 individuals who consume nuts regularly tend to consume less red and processed meat [10]. As already
264 mentioned above, such a replacement is likely to be beneficial for the prevention of weight gain
265 because red and processed meat intake have been associated with weight gain, risk of obesity and
266 higher BMI [17, 22, 29].

267 Our study has limitations. First, only self-reported weight at follow-up was available in most
268 centers. To mitigate this potential source of bias, we used a prediction equation to improve self-
269 reported weight estimates [23]. Furthermore, in the EPIC-Norfolk study, a sub-cohort of EPIC, a high
270 correlation between self-reported and measured weight data has been shown ($r=0.97$ in men and

271 $r=0.98$ in women), which means that ranking of participants according to self-reported weight was
272 adequate [32]. Second, we were not able to accurately measure changes in body composition (e.g.,
273 using dual-energy x-ray absorptiometry, DXA); therefore we had to assume that observed weight
274 changes are largely due to changes in body fat mass and not in lean body mass. Third, we were not
275 able to account for potential changes in diet during follow-up; yet, magnitudes of changes in weight
276 appear to be more pronounced and more robust if changes in diet can be accounted for [33].
277 Nevertheless, mean dietary changes at the population level are often small; for example, in the NHS,
278 the mean 4-year change in nut intake corresponded to a 5% increase of the baseline intake [17].
279 Fourth, we were not able to stratify our analysis by specific types of nuts because nut intake was
280 assessed in broad categories of nut intake across the EPIC centers/countries. Finally, measurement
281 error is a limitation inherent to all epidemiological studies using self-reported dietary data. We
282 attempted to minimize this bias by adjusting for total energy intake and for plausibility of dietary
283 energy reporting; the latter has been recently shown in the EPIC-Potsdam sub-study to improve
284 expected associations between intakes of energy-dense foods and BMI [34].

285 Strengths of our study include its prospective design with a reasonably long follow-up, the
286 very large sample size, which provided sufficient power to also detect smaller associations, despite the
287 large variability of weight change, and to perform a number of sensitivity analyses. In order to
288 improve dietary intake assessment of nuts, like for many other food groups, it is important to continue
289 the search for and validation of biomarkers of nut intake in the future and metabolomics approaches
290 may offer new opportunities in this regard [35]. Future research may also assess the mediating role of
291 plasma fatty acid changes in the association between nuts and weight change.

292 We conclude that in this prospective study of middle-aged adults from 10 European countries
293 representing populations with heterogeneous diets, higher nut intake is associated with slightly less
294 weight gain after 5 years of follow-up. Higher nut consumers also demonstrated a lower risk of
295 becoming overweight or obese. Our findings are thus in line with short-term randomized nut-feeding
296 trials and support dietary recommendations to increase nut consumption to reduce chronic disease risk
297 and mortality.

Ethical standards The study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments and obtained ethical approval from participating centres and IARC ethics committees. Informed consent was given by all study participants.

Conflicts of interest The authors declare that they have no conflict of interest.

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Table 1 Main characteristics of the study population according to categories^a of nut intake (n = 373,293)

	Non-consumers (n = 97,852)	>0-0.8 g/d (n = 85,470)	>0.8-2.8 g/d (n = 55,335)	>2.8-6.0 g/d (n = 65,815)	>6.0 g/d (n = 68,821)
Nut intake, g/d, median [IQR]	0.0	0.5 [0.2-0.7]	1.7 [1.5-2.3]	4.1 [3.3-4.9]	12.4 [8.1-18.8]
Follow-up time, y	4.6 ± 1.7	7.0 ± 2.7	5.0 ± 2.2	5.0 ± 2.2	4.7 ± 2.0
Weight change, kg/5y ^b	1.7 ± 5.3	2.1 ± 4.4	2.2 ± 5.0	2.2 ± 4.9	2.3 ± 5.1
Women %	73.7	66.0	72.9	77.7	72.7
Age, y	53.8 ± 8.3	51.5 ± 9.8	52.3 ± 9.6	50.7 ± 9.1	49.9 ± 9.7
BMI at inclusion, kg/m ²	25.8 ± 4.4	25.7 ± 4.2	25.0 ± 4.1	24.9 ± 4.1	24.8 ± 4.0
BMI categories, %					
<25 kg/m ²	47.8	48.1	55.6	58.1	58.7
25-<30 kg/m ²	36.3	37.7	33.0	31.1	30.5
30-≤35 kg/m ²	12.5	11.2	9.1	8.6	8.7
>35 kg/m ²	3.4	3.0	2.3	2.2	2.1
University degree or higher, %	17.4	22.1	28.4	28.5	31.3
Missing	1.5	0.6	1.5	1.6	1.5
Physically inactive, %	25.1	20.7	19.5	16.9	17.2
Missing	1.4	0.4	1.5	1.7	2.6
Smoking status at follow-up, %					
Never	49.9	40.0	46.4	45.2	43.9
Former	27.8	27.3	28.6	28.1	29.6
Current	19.1	15.4	14.0	14.7	16.2
Missing	3.3	17.3	11.0	12.0	10.3
Previous illness, % ^c	9.3	6.8	8.3	7.0	7.1
Missing	12.7	5.8	10.1	7.1	4.9
Dietary intake					
Total energy intake, kcal/d	1,980 ± 594	2,015 ± 598	2,061 ± 573	2,071 ± 576	2,297 ± 626
Vegetables, g/d	208 ± 136	185 ± 139	231 ± 147	236 ± 152	255 ± 167
Fruits, g/d	233 ± 184	218 ± 169	236 ± 171	235 ± 171	252 ± 185
Legumes, g/d	19 ± 31	8 ± 14	14 ± 20	15 ± 21	20 ± 25
Meat/products, g/d	106 ± 59	99 ± 56	99 ± 59	96 ± 58	100 ± 65
Dairy, g/d	332 ± 232	329 ± 249	337 ± 231	308 ± 214	325 ± 226
Fish, g/d	50 ± 42	29 ± 25	32 ± 27	40 ± 38	36 ± 36
Egg/egg products, g/d	21 ± 19	15 ± 15	18 ± 16	19 ± 17	20 ± 18
Potatoes, g/d	94 ± 70	102 ± 87	88 ± 65	84 ± 58	85 ± 58
Cereals/cereal products, g/d	198 ± 99	224 ± 112	210 ± 103	212 ± 95	225 ± 103
Sugar/confectionary, g/d	38 ± 48	44 ± 55	44 ± 46	40 ± 41	42 ± 39
Cakes/biscuits, g/d	37 ± 42	41 ± 43	41 ± 42	42 ± 40	45 ± 43
Added fat, g/d	27 ± 18	30 ± 18	27 ± 18	26 ± 17	28 ± 19
Nonalcoholic beverages, g/d	983 ± 792	1,086 ± 804	1,225 ± 731	1,100 ± 719	1,136 ± 735
Alcoholic beverages, g/d	145 ± 265	182 ± 293	172 ± 262	165 ± 253	192 ± 270
mrMED score units/d	8.7 ± 3.0	8.4 ± 3.1	9.0 ± 3.0	9.2 ± 2.9	9.4 ± 3.0

Data are expressed as arithmetic mean ± SD if not stated otherwise.

^a First category corresponds to non-consumers of nut intake based on food-frequency questionnaires; categories 2-5 are quartiles of consumers; note that proportion of subjects in categories 2-5 is unequal because observations with the same value were categorised in the same band ('xtile' command in Stata).

^b Calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years.

^c Type 2 diabetes, cardiovascular disease, cancer.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); IQR, interquartile range; mrMED, modified relative Mediterranean diet score (range: 0-18; higher scores characterizing a Mediterranean diet).

Table 2 Difference in body weight gain (kg) over 5 years according to baseline nut intake in 373,293 men and women

	N (%)	Median nut intake [IQR] g/d	Model 1 <i>beta</i> (95% CI)	Model 2 <i>beta</i> (95% CI)	Model 3 <i>beta</i> (95% CI)
<i>Beta</i> per 15g/d	373,293 (100)	0.9 [0.0-4.3]	-0.046 (-0.075, -0.018)	-0.046 (-0.075, -0.017)	-0.042 (-0.071, -0.012)
----- <i>Categories of absolute nut intake</i> -----					
Non-consumer	97,852 (26)	0.0	Reference	Reference	Reference
>0-0.8 g/d	85,470 (23)	0.5 [0.2-07]	-0.039 (-0.095, 0.018)	-0.038 (-0.094, 0.019)	-0.035 (-0.092, 0.021)
>0.8-2.8 g/d	55,335 (15)	1.7 [1.5-2.3]	-0.04 (-0.096, 0.015)	-0.022 (-0.077, 0.034)	-0.014 (-0.070, 0.041)
>2.8-6.0 g/d	65,815 (18)	4.1 [3.3-4.9]	-0.059 (-0.112, -0.007)	-0.047 (-0.099, 0.006)	-0.037 (-0.089, 0.016)
>6.0 g/d	68,821 (18)	12.4 [8.1-18.8]	-0.089 (-0.142, -0.036)	-0.082 (-0.135, -0.028)	-0.069 (-0.123, -0.015)
<i>P</i> trend (linear)			0.001	0.006	0.025
----- <i>Frequency of nut intake</i> ^a -----					
Never/almost never	87,520 (26)	-	Reference	Reference	Reference
0.5-2 times/mo	93,221 (28)	-	-0.03 (-0.083, 0.023)	-0.022 (-0.075, 0.03)	-0.018 (-0.071, 0.034)
0.5-≤1 times/wk	72,760 (21)	-	-0.077 (-0.128, -0.026)	-0.065 (-0.117, -0.014)	-0.058 (-0.110, -0.006)
>1 times/wk	83,691 (25)	-	-0.124 (-0.177, -0.071)	-0.115 (-0.169, -0.061)	-0.102 (-0.156, -0.047)
<i>P</i> trend (linear)			<0.001	<0.001	<0.001

Multilevel linear mixed models with random effect on the intercept and slope according to center.

Overall mean 5-year weight gain corresponded to 2.1 kg (SD 5.0) and negative beta-values indicate less weight gain (kg) over the same period.

Model 1 adjusted for age, sex, and body mass index (BMI) at baseline (3-knot restricted cubic spline); Model 2 was further adjusted for follow-up time in years (3-knot restricted cubic spline), total energy intake (kcal/day), educational level, levels of physical activity, smoking status at follow-up, and plausibility of dietary energy reporting; Model 3 was further adjusted for the modified relative Mediterranean diet score (without fruit and nut component). IQR, interquartile range.

^a Frequency data for the centers Cambridge (UK) (n=14,535) and Malmö (Sweden) (n=21,566) were not available.

Table 3 Adjusted relative risks (RR) (95% CI) of becoming overweight or obese over 5 years according to baseline nut intake and baseline body mass index (BMI) in men and women

	BMI <25 kg/m ² at baseline n=197,291			BMI ≥25 to <30 kg/m ² at baseline n=127,445		
	N (%)	N overweight or obese (%)	RR of becoming overweight or obese (95% CI)	N (%)	N obese (%)	RR of becoming obese (95% CI)
<i>Categories of absolute nut intake</i>						
Non-consumer	46,784 (24)	7,082 (23)	Reference	31,495 (28)	3,637 (25)	Reference
>0-0.8 g/d	41,148 (21)	8,374 (27)	0.97 (0.94, 1.00)	28,283 (25)	4,353 (29)	0.96 (0.92, 1.00)
>0.8-2.8 g/d	30,786 (16)	4,360 (14)	0.94 (0.91, 0.97)	16,244 (14)	2,110 (14)	0.98 (0.93, 1.03)
>2.8-6.0 g/d	38,206 (19)	5,629 (18)	0.95 (0.93, 0.98)	18,337 (16)	2,432 (16)	0.93 (0.89, 0.98)
>6.0 g/d	40,367 (20)	5,770 (18)	0.95 (0.92, 0.98)	18,771 (17)	2,381 (16)	0.95 (0.90, 0.99)
<i>P</i> trend (linear)			0.002			0.018
<i>Frequency of nut intake^a</i>						
Never/almost never	40,688 (23)	6,678 (24)	Reference	27,825 (28)	3,776 (28)	Reference
0.5-2 times/mo	50,523 (28)	8,100 (29)	0.98 (0.95, 1.01)	28,250 (28)	3,802 (28)	0.98 (0.94, 1.03)
0.5-≤1 times/wk	39,836 (22)	6,644 (23)	0.96 (0.94, 0.99)	21,443 (21)	3,121 (23)	0.94 (0.90, 0.98)
>1 times/wk	48,416 (27)	6,822 (24)	0.95 (0.92, 0.98)	22,859 (23)	2,924 (21)	0.99 (0.95, 1.04)
<i>P</i> trend (linear)			0.001			0.385

A modified Poisson regression approach (Zou 2004) was used to calculate the RR and 95% CI.

Adjusted for age, sex, country/center, BMI at baseline (3-knot restricted cubic spline), follow-up time in years (3-knot restricted cubic spline), total energy intake (kcal/day), educational level, levels of physical activity, smoking status at follow-up, and plausibility of dietary energy reporting, and for the modified relative Mediterranean diet score (without fruit and nut component).

^a Frequency data for the centers Cambridge (UK) (n=14,535) and Malmö (Sweden) (n=21,566) were not available.