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ORIGINAL CONTRIBUTION

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

Heinz Freisling[1] · Hwayoung Noh[1] · Nadia Slimani[2] · Véronique Chajès[2] · Anne M. May[3] · Petra H. Peeters[3,4] · Elisabete Weiderpass[5,6,7,8] · Amanda J. Cross[4] · Guri Skeie[5] · Mazda Jenab[2] · Francesca R. Mancini[9,10] · Marie-Christine Boutron-Ruault[9,10] · Guy Fagherazzi[9,10] · Verena A. Katzke[11] · Tilman Kühn[11] · Annika Steffen[12] · Heiner Boeing[12] · Anne Tjønneland[13] · Cecilie Kyrø[13] · Camilla P. Hansen[14] · Kim Overvad[14] · Eric J. Duell[15] · Daniel Redondo-Sánchez[16,17] · Pilar Amiano[17,18] · Carmen Navarro[17,19,20] · Aurelio Barricarte[17,21,22] · Aurora Perez-Cornago[23] · Konstantinos K. Tsilidis[4,24] · Dagfinn Aune[4,25] · Heather Ward[4] · Antonia Trichopoulou[26,27] · Androniki Naska[26,27] · Philippos Orfanos[26,27] · Giovanna Masala[28] · Claudia Agnoli[29] · Franco Berrino[29] · Rosario Tumino[30] · Carlotta Sacerdote[31] · Amalia Mattiello[32] · H. Bas Bueno-de-Mesquita[4,33,34] · Ulrika Ericson[35] · Emily Sonestedt[35] · Anna Winkvist[36] · Tonje Braaten[5] · Isabelle Romieu[2] · Joan Sabaté[37]

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Abstract
Purpose There is inconsistent evidence regarding the relationship between higher intake of nuts, being an energy-dense food, and weight gain. We investigated the relationship between nut intake and changes in weight over 5 years.
Methods This study includes 373,293 men and women, 25–70 years old, recruited between 1992 and 2000 from 10 European countries in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Habitual intake of nuts including peanuts, together defined as nut intake, was estimated from country-specific validated dietary questionnaires. Body weight was measured at recruitment and self-reported 5 years later. The association between nut intake and body weight change was estimated using multilevel mixed linear regression models with center/country as random effect and nut intake and relevant confounders as fixed effects. The relative risk (RR) of becoming overweight or obese after 5 years was

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✉ Heinz Freisling
freislingh@iarc.fr

1 Nutritional Methodology and Biostatistics Group, Section of Nutrition and Metabolism, International Agency for Research on Cancer (IARC-WHO), 150, Cours Albert Thomas, 69372 Lyon Cedex 08, France

2 Nutritional Epidemiology Group, Section of Nutrition and Metabolism, International Agency for Research On Cancer (IARC-WHO), Lyon, France

3 Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands

4 Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

5 Department of Community Medicine, Faculty of Health Sciences, University of Tromsø, The Arctic University of Norway, Tromsø, Norway

6 Department of Research, Cancer Registry of Norway, Oslo, Norway

7 Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

8 Genetic Epidemiology Group, Folkhälsan Research Center, Helsinki, Finland

9 Inserm U1018, Gustave Roussy Institute, CESP, Villejuif, France

10 University Paris-Saclay, University Paris-Sud, Villejuif, France

11 Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

12 Department of Epidemiology, German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany

13 Danish Cancer Society Research Center, Copenhagen, Denmark

14 Department of Public Health, Section for Epidemiology, Aarhus University, Aarhus, Denmark

15 Unit of Nutrition and Cancer, IDIBELL, Catalan Institute of Oncology, Barcelona, Spain

16 Escuela Andaluza de Salud Pública, Instituto de Investigación Biosanitaria ibs.GRANADA, Hospitales Universitarios de Granada/Universidad de Granada, Granada, Spain

investigated using multivariate Poisson regressions stratified according to baseline body mass index (BMI).
Results On average, study participants gained 2.1 kg (SD 5.0 kg) over 5 years. Compared to non-consumers, subjects in the highest quartile of nut intake had less weight gain over 5 years (−0.07 kg; 95% CI −0.12 to −0.02) (*P* trend = 0.025) and had 5% lower risk of becoming overweight (RR 0.95; 95% CI 0.92–0.98) or obese (RR 0.95; 95% CI 0.90–0.99) (both *P* trend <0.008).
Conclusions Higher intake of nuts is associated with reduced weight gain and a lower risk of becoming overweight or obese.

Keywords Nut intake · Weight gain · Obesity · Energy balance · Adults · Europe

Introduction

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

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

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

There are little existing data from prospective observational studies [13–17], and these are limited because they were based on homogeneous populations and with one exception [14], did not account for overall dietary patterns. Dietary patterns may confound findings associated with nut intake because individuals who eat higher quantities of nuts

[17] CIBER de Epidemiología y Salud Pública (CIBERESP), Madrid, Spain

[18] Public Health Division of Gipuzkoa, BioDonostia Research Institute, San Sebastian, Spain

[19] Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain

[20] Department of Health and Social Sciences, Universidad de Murcia, Murcia, Spain

[21] Navarra Public Health Institute, Pamplona, Spain

[22] Navarra Institute for Health Research (IdiSNA) Pamplona, Pamplona, Spain

[23] Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford, Oxford, UK

[24] Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece

[25] Bjørknes University College, Oslo, Norway

[26] Hellenic Health Foundation, Athens, Greece

[27] WHO Collaborating Center for Nutrition and Health, Unit of Nutritional Epidemiology and Nutrition in Public Health, Department of Hygiene, Epidemiology and Medical Statistics, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece

[28] Cancer Risk Factors and Life-Style Epidemiology Unit, Cancer Research and Prevention Institute, ISPO, Florence, Italy

[29] Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy

[30] Cancer Registry and Histopathology Unit, "Civic-M.P.Arezzo" Hospital, ASP Ragusa, Ragusa, Italy

[31] Unit of Cancer Epidemiology, Città della Salute e della Scienza University-Hospital and Center for Cancer Prevention (CPO), Turin, Italy

[32] Dipartimento di Medicina Clinica E Chirurgia, Federico II University, Naples, Italy

[33] Department for Determinants of Chronic Diseases, National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands

[34] Department of Social and Preventive Medicine, Faculty of Medicine, University of Malaya, Kuala Lumpur, Malaysia

[35] Department of Clinical Sciences Malmö, Lund University, Malmö, Sweden

[36] Department of Internal Medicine and Clinical Nutrition, The Sahlgrenska Academy, University of Gothenburg, Gothenburg, Sweden

[37] Center for Nutrition, Healthy Lifestyle and Disease Prevention, School of Public Health, Loma Linda University, Loma Linda, USA

usually also have a better overall diet quality [18], and other favourable lifestyle habits such as higher physical activity levels. Thus, it is important to account for dietary quality and other lifestyle behaviours in prospective observational settings.

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

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

Methods

Study population

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

For the present study, we excluded pregnant women, participants with missing dietary or lifestyle information, missing data on weight and height or with implausible anthropometric values at baseline (n = 23,713). We further excluded 122,154 individuals with missing weight at follow-up and 2288 individuals with outlying anthropometry at follow-up: weight change <−5 or >5 kg/year and BMI at follow-up <16 kg/m^2. More details on follow-up exclusions are given in Figure S1 (Online Resource) and have been previously detailed [21, 22]. The final analyses included 103,303 men and 269,990 women with complete and plausible body weight data.

Anthropometric measures and weight change

Two body weight measures were available for each participant: at baseline and after a median follow-up time of 5 years [min.: 2 years for Heidelberg (Germany); max.: 11 years for Varese (Italy)]. At baseline, body weight and height were measured in most centres using comparable, standardized procedures with the exception of those taken in France, Norway and the health conscious group of the Oxford centre in which subjects self-reported their weight. As for the follow-up weight assessments, all values were self-reported, except in Norfolk (UK) and Doetinchem (The Netherlands) where weight was measured [21, 22]. The accuracy of self-reported anthropometric measures—at baseline and at follow-up—was improved with the use of prediction equations derived from subjects with both measured and self-reported weight at baseline [23]. Our main outcome was weight change in kg per 5 years, calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years.

Dietary assessment

Habitual food consumption during the previous 12 months was assessed at baseline for each individual with center-specific methods; in most cases food-frequency questionnaires (FFQs) [20]. These questionnaires were developed and validated in each country/center to capture country-specific dietary habits. In most centers FFQs were self-administered, with the exception of Greece, Ragusa (Italy), Naples (Italy) and Spain where face-to-face interviews were performed. Extensive quantitative FFQs were used in northern Italy, the Netherlands, Germany and Greece. Questionnaires structured by meals were used in Spain, France and Ragusa (Italy). Semi-quantitative FFQs were used in Denmark, Norway, Naples (Italy) and Umea (Sweden). In the UK, both a semi-quantitative FFQ and a 7-day record were used, whereas a method combining a FFQ with a 7-day record on lunch and dinner was used in Malmö (Sweden) [20]. Details of the questionnaire items regarding nut intake for each center or country, have been described previously [8]. In brief, the respective questionnaire food item(s) in France, Germany, Greece, Ragusa (Italy), the Netherlands, Spain, and the UK asked non-specifically for intake of any kind of nuts incl. peanuts; in Denmark and Norway specifically for peanuts, and in Umea (Sweden) specifically for "peanuts, salted"; in northern Italy specifically for "walnuts, hazelnuts, almonds, and peanuts", and in Naples (Italy) for "walnuts"; in Spain for an exhaustive list of different types of nuts incl. peanuts and seeds; in Malmö (Sweden), the FFQ included peanuts as snacks, whereas other nuts had to be added to an open-ended question or recorded at lunch and dinner meals; finally, in Germany, the Netherlands, and the UK separate items on peanut butter intake were asked for and we included this item in our overall nut intake variable. Because nut intake was assessed in these broad categories, a stratified analysis by specific types of nuts was not possible. Here, we define the combined intake of any of the items described above as "nut intake". Non-consumers were determined from the FFQs and defined as those with an intake of nuts equal to zero.

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

Assessment of other covariates

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

Statistical analyses

Habitual nut intake as estimated from the dietary questionnaires was analysed both on a continuous scale per 15 g/day increment, which corresponds to the mean intake of nut consumers in the highest cohort category of intake, and by categories with all non-consumers (~25%) placed in the first (reference) category and the consumers divided by quartiles into the remaining four categories of intake (categories 2–5), similar as in Jenab et al. [8]. As a secondary analysis, we also modelled frequency of nut intake using the following categories: "never/almost never", "0.5–2 times/month", "0.5–≤1 times/week", "more than 1 times/week", which is similar to Bes-Rastrollo et al. [14]. Frequency data for the centers Cambridge (UK) (n = 14,535) and Malmö (Sweden) (n = 21,566) were not available because open-ended dietary methodologies were used.

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

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

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

We tested a priori for effect modification by age (categorised as younger than median age <51 and ≥51 years), sex, BMI categories at baseline (<25, 25–30, >30 kg/m^2), and change of smoking status (never, current, start smoking, quitter, former) by including interaction terms between each variable and nut intake (continuous per 15 g/day) in the models. P values for the interaction term were calculated using F tests.

We used a modified Poisson regression approach [28] to estimate the relative risks (RR) and 95% confidence intervals (CI) of becoming overweight or obese according to nut intake (in categories of absolute intakes and frequency of intake). Analyses were stratified by initial BMI categories (<25: normal weight, 25≤ BMI <30: overweight and ≥30 kg/m^2: obese). RRs were adjusted as in our model 3 described above. The BMI after 5 years was calculated from the 5 year follow-up weight and baseline height.

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

Results

The main characteristics of the study population at baseline by categories of nut intake are shown in Table 1. Higher

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

	Non-consumers (*n* = 97,852)	>0–0.8 g/day (*n* = 85,470)	>0.8–2.8 g/day (*n* = 55,335)	>2.8–6.0 g/day (*n* = 65,815)	>6.0 g/day (*n* = 68,821)
Nut intake (g/day), median (IQR)	0.0	0.5 (0.2–07)	1.7 (1.5–2.3)	4.1 (3.3–4.9)	12.4 (8.1–18.8)
Follow-up time (years)	4.6 ± 1.7	7.0 ± 2.7	5.0 ± 2.2	5.0 ± 2.2	4.7 ± 2.0
Weight change (kg/5 years)[a]	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 (years)	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 (%)[b]	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/day)	1980 ± 594	2015 ± 598	2061 ± 573	2071 ± 576	2297 ± 626
Vegetables (g/day)	208 ± 136	185 ± 139	231 ± 147	236 ± 152	255 ± 167
Fruits (g/day)	233 ± 184	218 ± 169	236 ± 171	235 ± 171	252 ± 185
Legumes (g/day)	19 ± 31	8 ± 14	14 ± 20	15 ± 21	20 ± 25
Meat/products (g/day)	106 ± 59	99 ± 56	99 ± 59	96 ± 58	100 ± 65
Dairy (g/day)	332 ± 232	329 ± 249	337 ± 231	308 ± 214	325 ± 226
Fish (g/day)	50 ± 42	29 ± 25	32 ± 27	40 ± 38	36 ± 36
Egg/egg products (g/day)	21 ± 19	15 ± 15	18 ± 16	19 ± 17	20 ± 18
Potatoes (g/day)	94 ± 70	102 ± 87	88 ± 65	84 ± 58	85 ± 58
Cereals/cereal products (g/day)	198 ± 99	224 ± 112	210 ± 103	212 ± 95	225 ± 103
Sugar/confectionary (g/day)	38 ± 48	44 ± 55	44 ± 46	40 ± 41	42 ± 39
Cakes/biscuits (g/day)	37 ± 42	41 ± 43	41 ± 42	42 ± 40	45 ± 43
Added fat (g/day)	27 ± 18	30 ± 18	27 ± 18	26 ± 17	28 ± 19
Nonalcoholic beverages (g/day)	983 ± 792	1086 ± 804	1225 ± 731	1100 ± 719	1136 ± 735
Alcoholic beverages (g/day)	145 ± 265	182 ± 293	172 ± 262	165 ± 253	192 ± 270
mrMED score units/day	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

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)

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)

[a] Calculated as weight at follow-up minus weight at baseline divided by the follow-up time in years and multiplied by 5 years

[b] Type 2 diabetes, cardiovascular disease, cancer

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/day	Model 1 *beta* (95% CI)	Model 2 *beta* (95% CI)	Model 3 *beta* (95% CI)
Beta per 15 g/day	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)
Categories of absolute nut intake					
Non-consumer (g/day)	97,852 (26)	0.0	Reference	Reference	Reference
>0–0.8	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	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	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	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)
P trend (linear)			0.001	0.006	0.025
Frequency of nut intake[a]					
Never/almost never	87,520 (26)	–	Reference	Reference	Reference
0.5–2 times/month	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/week	72,760 (21)	–	−0.077 (−0.128, −0.026)	−0.065 (−0.117, −0.014)	−0.058 (−0.110, −0.006)
>1 times/week	83,691 (25)	–	−0.124 (−0.177, −0.071)	−0.115 (−0.169, −0.061)	−0.102 (−0.156, −0.047)
P 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)

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

intake of nuts was associated with younger age, a lower BMI, a higher educational level, never smoking, and being more physically active. Participants in the highest category of nut intake also had higher intakes of vegetables, fruit, cereals/cereal products, non-alcoholic and alcoholic beverages, but also of sugar/confectionary, and cakes/biscuits; they also had a slightly higher mrMED score. In contrast, they had lower intakes of meat/products, dairy, fish, and potatoes. On average, study participants gained 2.1 kg of weight between baseline and the 2nd weight assessment with considerable variation between subjects (SD 5.0 kg).

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

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

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

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

Discussion

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

In a post hoc analysis, we found that habitual high intake of meat and processed meat appears to attenuate associations. We believe that the observed effects of nut intake on body weight change are at least partly mediated via a reduced intake of meat/products shown to be positively associated with weight gain [22, 29]. This has been hypothesized earlier as being one of the potential pathways of weight stabilizing effects of nuts [10] and

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)
Categories of absolute nut intake						
Non-consumer (g/day)	46,784 (24)	7082 (23)	Reference	31,495 (28)	3637 (25)	Reference
>0–0.8	41,148 (21)	8374 (27)	0.97 (0.94, 1.00)	28,283 (25)	4353 (29)	0.96 (0.92, 1.00)
>0.8–2.8	30,786 (16)	4360 (14)	0.94 (0.91, 0.97)	16,244 (14)	2110 (14)	0.98 (0.93, 1.03)
>2.8–6.0	38,206 (19)	5629 (18)	0.95 (0.93, 0.98)	18,337 (16)	2432 (16)	0.93 (0.89, 0.98)
>6.0	40,367 (20)	5770 (18)	0.95 (0.92, 0.98)	18,771 (17)	2381 (16)	0.95 (0.90, 0.99)
P trend (linear)			0.002			0.018
Frequency of nut intake[a]						
Never/almost never	40,688 (23)	6678 (24)	Reference	27,825 (28)	3776 (28)	Reference
0.5–2 times/month	50,523 (28)	8100 (29)	0.98 (0.95, 1.01)	28,250 (28)	3802 (28)	0.98 (0.94, 1.03)
0.5–1 times/week	39,836 (22)	6644 (23)	0.96 (0.94, 0.99)	21,443 (21)	3121 (23)	0.94 (0.90, 0.98)
>1 times/week	48,416 (27)	6822 (24)	0.95 (0.92, 0.98)	22,859 (23)	2924 (21)	0.99 (0.95, 1.04)
P 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

confirmed in our sensitivity analysis (Table S1, Online Resource).

Our findings are in line with the few other prospective observational studies [13–17]. Women in the Nurses' Health Study II (NHS II), who reported eating nuts ≥2 times/week, experienced 0.5 kg less weight gain (95% CI −0.8 to −0.2) after a mean 8 years of follow-up compared with those who rarely ate nuts [14]. Similar results were observed in the Seguimiento Universidad de Navarra (SUN) study, a prospective cohort in Spain, where weight change in men and women was assessed after a median of 28 months [13] and after 6 years [16]. In the Nurses' Health Study (NHS), no differences in weight gain over 16 years of follow-up across categories of nut consumption were observed [15]. A pooled analysis of the NHS, the NHS II, and the Health Professionals Follow-up Study, where the relationship of dietary changes over 4-year periods was related to changes in body weight, found that per serving increase in nut intake, study participants gained 0.57 lb (~0.3 kg) less weight per 4-year period [17]. The observed differences in effect sizes across these studies can most likely be explained by a combination of factors including differences in length of weight follow-up, confounder adjustment, accuracy of dietary assessment instruments used, but also differences in terms of frequency and amount of consumed nuts, underlying dietary habits and other lifestyle factors that are specific to a population. Interestingly, the only randomized controlled nut-feeding trial (PREDIMED) that had a comparably long follow-up as in our study reported very similar results with regard to adjusted difference in 5 year changes in bodyweight in the nut group as compared with the control group (−0.08 kg) though not statistically significant (95% CI −0.50–0.35 kg) and only in the context of a Mediterranean diet [12]. We specifically accounted for Mediterranean dietary patterns in our analysis to evaluate associations of nut intake with weight change in the context of other diets. Romaguera et al. showed previously in the same study population that high adherence to a Mediterranean diet was associated with a 5-year weight change of −0.16 kg (95% CI −0.24 to −0.07 kg) and were 10% (95% CI 4–18%) less likely to develop overweight or obesity compared to individuals with a low adherence [30].

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

Our study has limitations. First, only self-reported weight at follow-up was available in most centers. To mitigate this potential source of bias, we used a prediction equation to improve self-reported weight estimates [23]. Furthermore, in the EPIC-Norfolk study, a sub-cohort of EPIC, a high correlation between self-reported and measured weight data has been shown (r = 0.97 in men and r = 0.98 in women), which means that ranking of participants according to self-reported weight was adequate [32]. Second, we were not able to accurately measure changes in body composition (e.g. using dual-energy X-ray absorptiometry, DXA); therefore we had to assume that observed weight changes are largely due to changes in body fat mass and not in lean body mass. Third, we were not able to account for potential changes in diet during follow-up; yet, magnitudes of changes in weight appear to be more pronounced and more robust if changes in diet can be accounted for [33]. Nevertheless, mean dietary changes at the population level are often small; for example, in the NHS, the mean 4-year change in nut intake corresponded to a 5% increase of the baseline intake [17]. Fourth, we were not able to stratify our analysis by specific types of nuts because nut intake was assessed in broad categories of nut intake across the EPIC centers/countries. Finally, measurement error is a limitation inherent to all epidemiological studies using self-reported dietary data. We attempted to minimize this bias by adjusting for total energy intake and for plausibility of dietary energy reporting; the latter has been recently shown in the EPIC-Potsdam sub-study to improve expected associations between intakes of energy-dense foods and BMI [34].

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

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

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Compliance with ethical standards

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.

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

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