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Macronutrient composition of the diet and long-term changes in weight and waist circumference in the EPIC–Italy cohort

Claudia Agnoli [a], Sabina Sieri [a,*], Fulvio Ricceri [b,c], Alessandra Macciotta [b], Giovanna Masala [d], Benedetta Bendinelli [d], Salvatore Panico [e], Amalia Mattiello [e], Rosario Tumino [f], Graziella Frasca [f], Vittorio Krogh [a]

[a] *Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*
[b] *Department of Clinical and Biological Sciences, University of Turin, Italy*
[c] *Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco, Turin, Italy*
[d] *Cancer Risk Factors and Lifestyle Epidemiology Unit, Institute for Cancer Research, Prevention and Clinical Network (ISPRO), Florence, Italy*
[e] *Department of Clinical and Experimental Medicine, Federico II University of Naples, Italy*
[f] *Cancer Registry, Provincial Health Unit (ASP) Ragusa, Italy*

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Abstract *Background and aims:* The overall macronutrient composition of diet, rather than just calorie intake, may influence long-term changes of anthropometry. We investigated relationships between dietary macronutrient composition and long-term changes in weight and waist circumference in participants of the EPIC–Italy – the Italian section of the European Prospective Investigation into Cancer and Nutrition – study.

Methods and results: A total of 32,119 participants provided anthropometric measures at recruitment and 12 years later (mean). Diet at recruitment was assessed using validated semi-quantitative food frequency questionnaires. Weight and waist changes associated with replacing 10% of energy from one macronutrient with 10% of energy from another macronutrient were assessed by multivariable linear regression.

Increased energy from total protein at the expense of any other macronutrient was significantly associated with increased weight and waist circumference. Increased starch at the expense of sugar and total protein was associated with significantly decreased weight and waist circumference; when starch replaced total fat, weight significantly decreased. Increased sugar at the expense of starch and total fat was significantly associated with increased weight and waist circumference; but increase at the expense of total protein was significantly associated with decreased weight and waist circumference.

Conclusion: Our results suggest that increasing protein at the expense of fat or carbohydrates, and reducing starch by increasing other macronutrients, might be associated with increased weight and waist gain.

Abbreviations: β, beta; BMI, body mass index; CARDIA, Coronary Artery Risk Development in Young Adults; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; FAO, Food and Agriculture Organization; FFQ, food frequency questionnaire; IARC, International Agency for Research on Cancer; PREDIMED, Prevención con Dieta Mediterránea (Prevention with Mediterranean Diet); SEASONS, Seasonal Variation of Blood Cholesterol Study.

* Corresponding author. Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133, Milan, Italy. Fax: +39 02 23903516.
E-mail address: sabina.sieri@istitutotumori.mi.it (S. Sieri).

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Introduction

Over the last four decades, the worldwide prevalence of obesity has nearly tripled. In 2016, over 1.9 billion adults were overweight and over 650 million of these were obese [1]. In Italy, in 2015, more than one third (35.3%) of adults were overweight and 9.8% were obese [2]. The National Health and Nutrition Examination Survey estimated that the prevalence of abdominal obesity (both sexes) in the US increased from 46.4% to 54.2% between 1999 and 2012 [3]. General and abdominal obesity are both associated with increased mortality and increased risk of several diseases [4–6].

Overweight/obesity develops when energy intake chronically exceeds energy expenditure [7]. Food and Agriculture Organization (FAO) data indicate that the energy intake of Europeans increased steadily in the 40 years to 2000 [8], while declines in physical activity, documented in the US and England, contribute to decreased energy expenditure [9,10]. Nevertheless, some people are more susceptible to weight gain than others, and the overall macronutrient composition of the diet may play a role in obesity [11]. In fact, most (but not all) prospective studies on the effect of macronutrient intake on change in weight [12–25] and waist girth [13,14,16,17] in healthy people indicate that higher protein intake is associated with an increase in these anthropometric indices. By contrast, intervention studies usually find that a high-protein diet is effective in achieving – and to some extent maintaining – weight loss [26]. However, observational studies are typically conducted on healthy individuals, while intervention studies are usually short-term and conducted on obese/overweight persons or those with, for example, metabolic disorders. Thus, the effects of protein on body weight have not yet been elucidated: while some experts recommend to follow a high-protein diet to become slimmer, many scientists believe that manipulating diet composition is not an effective tool to lose weight, but we simply need to reduce total calorie intake [27].

The aims of this study were to investigate relationships between the macronutrient composition of the diet and long-term changes in weight and waist circumference. The study was carried out on persons enrolled in EPIC–Italy – the Italian section of the European Prospective Investigation into Cancer and Nutrition, a multicentre cohort study investigating the roles of metabolic, dietary, lifestyle, and environmental factors on the development of chronic diseases including cancer.

Methods

Study population

In 1993–1998, 47,749 healthy volunteers enrolled in EPIC–Italy from five centres: Varese and Turin (Northern Italy), Florence (Central Italy), and Naples and Ragusa (Southern Italy). Details of recruitment and study design are presented elsewhere [28]. The overall EPIC project was approved by the ethics committee of the International Agency for Research on Cancer (IARC), Lyon, France, and in Italy by the ethics committee of the Local Health Authority of Florence. All participants gave informed consent to use of their data for research.

At follow-up, mean 12 years after recruitment, lifestyle and anthropometric information was obtained from questionnaires. Mailed questionnaires were used in Turin and Florence; telephone interviews in Ragusa and Naples; and a combination of both in Varese. For logistic reasons, follow-up started first in Florence (2004), and last in Turin (2008), and was completed in 2013.

A total of 44,503 participants were apparently eligible for follow-up, after excluding those lost to the study, who had died or moved out of the area, or – in Varese and Florence – who had been diagnosed with cancer at a previous follow-up. However, on attempting re-contact, 10,575 additional persons had died, moved away, or refused to participate. Thus, 33,478 persons were contacted and provided update information.

For this study, we also excluded those who did not complete the baseline food frequency questionnaire (FFQ) or lifestyle questionnaires (n = 320); those with implausible self-reported weight at follow-up, and those with a ratio of total energy intake (determined from baseline FFQ) to basal metabolic rate at either extreme of the distribution (cut-offs first and last half percentiles), leaving 32,262 persons. Finally, we excluded those with missing information on weight change (either because baseline or follow-up weight was missing) or confounder variables (n = 143). Thus, 32,119 persons (9662 men, 22,457 women) were included in the present analysis.

Anthropometric measurements and changes over time

At baseline, weight (kg), height (m), and waist circumference (cm) were measured in light clothes, without shoes, by trained personnel. At follow-up, anthropometric and lifestyle information was obtained through questionnaires; participants were instructed to weigh themselves in light clothes and without shoes. Self-reported weight was obtained, and changes in weight were analysed in all 32,119 participants. Waist circumference was obtained, and changes in waist circumference were analysed, only for the 22,919 participants from Varese, Turin, and Florence who replied to mailed questionnaires. Along with the questionnaire, participants received a paper measuring tape; they were instructed to measure waist circumference at the narrowest part of the trunk as observed from the front, or at the level of the umbilicus, if no difference was observed in the trunk girth. Follow-up body mass index (BMI, kg/m^2) was assessed from weight at follow-up and baseline height.

Because of the large variation in time between recruitment and follow-up, 5-year weight change was assessed as the difference between weight at follow-up and weight at baseline, divided by the time (years)

between baseline and follow-up multiplied by five. Five-year change in waist circumference was estimated similarly.

Dietary variables

The consumption frequency of food items was investigated by validated [29] semi-quantitative FFQs designed to capture local eating behaviour: one each for Varese–Turin–Florence, for Ragusa, and for Naples. The questionnaires contained questions on 188, 217, and 140 food items, respectively, and investigated diet over the 12 preceding months. The food items were linked, using specific software [30], to Italian Food Composition Tables [31] to obtain estimates of daily intakes of energy and 37 macro- and micronutrients.

Other covariates

Data on reproductive and medical history, alcohol consumption, smoking, physical activity, education, and other socioeconomic variables were collected at baseline using a standardized lifestyle questionnaire.

Statistical methods

Baseline characteristics of participants, according to tertiles of percentages of energy from available carbohydrate, protein, and fat, were assessed as means and standard deviations (continuous variables) or frequencies (categorical variables).

Relations between percentages of energy obtained from macronutrients and 5-year weight change were assessed using multivariable linear regression models. A minimally adjusted model was used, with centre, age, sex, and total energy intake as covariates. A fully adjusted model was also used, in which time from baseline to follow-up (years, continuous), baseline BMI (<25 kg/m^2, 25–<30 kg/m^2, ≥ 30 kg/m^2), education (≤ 8 years, >8 years), menopausal status in women (perimenopausal, premenopausal, and postmenopausal), previous diagnosis of diabetes (yes/no), hyperlipidaemia (yes/no), duodenal ulcer (yes/no), myocardial infarction (yes/no), stroke (yes/no), and physical activity (active, moderately active, moderately inactive, inactive) were additional covariates.

Substitution models [32] were used to estimate the effects of substituting 10% of the energy from one macronutrient with 10% of the energy from another on weight change. Our substitution models are parameterized by excluding proportion of energy intake from one of five macronutrients (i.e. protein, fat, starch, sugar, alcohol) into each regression model. For example, for an isoenergetic replacement of 10% of energy from starch by 10% of energy from protein, the percentages of energy from protein, sugar, and fat, as well as total energy intake (kcal) and percentage of energy from alcohol sources were further included as independent variables. Since total energy intake was added to the models, the beta (β) coefficients in these models can be interpreted as the estimated change in 5-year weight per 10% increase in energy from one nutrient at the expense of another, keeping total energy intake and other macronutrients constant. Substitution models were run considering total protein, total fat, sugar, and starch and also dividing total protein and total fat into animal protein, vegetable protein, animal fat, and vegetable fat. Multivariable linear regression models, as described above, were also used to probe associations between replacing 10% of energy from one macronutrient with 10% from another, and 5-year change in waist circumference. These analyses differed from those on weight change in that the fully adjusted models were adjusted for waist circumference at baseline (continuous) instead of baseline BMI; we also ran a model that further adjusted for baseline BMI. We repeated the analyses on weight and waist change after excluding those who said that they were dieting at recruitment (27,378 persons analysed for weight change; 18,899 analysed for waist change).

Several sensitivity analyses were conducted. The risk of developing overweight/obesity (BMI≥ 25 kg/m^2) in those who were normal weight (BMI<25 kg/m^2) at baseline, and the risk of developing abdominal obesity (waist>102 cm for men and >88 cm for women) in those with waist circumference below these cut-offs at baseline, were estimated using logistic regression models. Minimally and fully adjusted models were run, using the same covariates as for linear regression (except baseline BMI in the models on overweight/obesity risk and baseline waist circumference in the models on abdominal obesity risk).

Another sensitivity analysis repeated the analysis classifying fat into saturated, monounsaturated, and polyunsaturated (instead of vegetable and animal fat). Finally, we explored whether adherence to the Italian Mediterranean Index [33] modified associations by adding, to the model, product terms for energy from one macronutrient (continuous, 10% increase) and Italian Mediterranean Index (two categories of adherence, below and above the median, i.e. score 0–4/5-11), and performing the Wald test. All statistical tests were two-sided. Differences were considered significant at $P < 0.05$. The analyses were performed with Stata 14.2 (College Station, TX, USA).

Results

Baseline characteristics of study participants

After a mean 11.97 years, mean 5-year weight increase in the entire follow-up population was 0.67 kg; mean 5-year waist increase was 3.37 cm. The mean percentages of total energy obtained from carbohydrate, protein, and fat were 48.8%, 16.2%, and 34.2%, respectively.

Baseline characteristics of participants, according to tertiles of each macronutrient, are shown in Table 1. Compared with participants in the first tertile of energy from carbohydrate, those in the third tertile had lower BMI, higher energy and fibre intake, were less educated, smoked less, were less physically active, and had lower alcohol intake. They were also less likely to have been diagnosed with

Table 1 Baseline characteristics of study participants according to percentage of energy from carbohydrate, protein, and fat.

	Tertiles of energy from carbohydrate			Tertiles of percentage of energy from protein			Tertiles of percentage of energy from fat		
	I (12.9 −45.9)	II (45.9 −52.1)	III (52.1 −88.4)	I (8.0 −5.3)	II (15.3 −17.0)	III (17.0 −29.3)	I (4.6 −31.7)	II (31.7 −36.4)	III (36.4 −63.2)
N	10,707	10,706	10,706	10,707	10,706	10,706	10,707	10,706	10,706
Mean age, years	50.7 (SD 7.5)	50.1 (SD 7.7)	50.3 (SD 7.9)	49.9 (SD 7.9)	50.2 (SD 7.7)	51.0 (SD 7.5)	51.1 (SD 7.7)	50.1 (SD 7.7)	49.9 (SD 7.6)
Time from baseline to follow-up, years	11.9 (SD 2.3	11.9 (SD 2.3)	12.1 (SD 2.5)	12.2 (SD 2.5)	12.0 (SD 2.3)	11.7 (SD 2.2)	11.9 (SD 2.4)	12.0 (SD 2.3)	12.1 (SD 2.3)
Baseline BMI, kg/m^2	26.1 (SD 4.0)	25.7 (SD 3.9)	25.6 (SD 4.0	25.3 (SD 3.8)	25.7 (SD 3.9)	26.3 (SD 4.2)	25.6 (SD 3.7)	25.7 (SD 3.9)	26.0 (SD 4.2)
Total energy intake, kcal/day	2250 (SD 682)	2372 (SD 683)	2408 (SD 669)	2491 (SD 709)	2381 (SD 651)	2158 (SD 639)	2424 (SD 672)	2367 (SD 679)	2239 (SD 680)
Fibre intake, g/day	20.7 (SD 8.1)	24.5 (SD 9.5)	28.4 (SD 12.5)	27.6 (SD 12.2)	25.1 (SD 10.3)	21.0 (SD 7.8)	26.5 (SD 12.1)	24.6 (SD 10.2)	22.6 (SD 9.1)
Glycaemic index	52.9 (SD 2.9)	53.4 (SD 2.7)	54.2 (SD 2.7)	53.7 (SD 2.9)	53.6 (SD 2.7)	53.1 (SD 2.9)	54.3 (SD 2.7)	53.5 (SD 2.6)	52.7 (SD 2.8)
Males [a]	3268 (30.5)	3258 (30.4)	3136 (29.3)	4120 (38.5)	3217 (30.0)	2325 (21.7)	4322 (40.4)	3258 (30.4)	2082 (19.4)
Centre [a]									
Turin	2901 (27.1)	2036 (19.0)	1320 (12.3)	2143 (20.0)	2000 (18.7)	2114 (19.7)	1784 (16.7)	2055 (19.2)	2418 (22.6)
Varese	2848 (26.6)	2563 (23.9)	1796 (16.8)	2107 (19.7)	2329 (21.7)	2771 (25.9)	1754 (16.4)	2523 (23.6)	2930 (27.4)
Florence	3461 (32.3)	3519 (32.9)	3546 (33.1)	3299 (30.8)	3303 (30.9)	3924 (36.6)	3904 (36.4)	3416 (31.9)	3206 (29.9)
Naples	650 (6.1)	1232 (11.5)	1936 (18.1)	982 (9.2)	1577 (14.7)	1259 (11.8)	1737 (16.2)	1254 (11.7)	827 (7.7)
Ragusa	847 (7.9)	1356 (12.7)	2108 (19.7)	2176 (20.3)	1497 (14.0)	638 (6.0)	1528 (14.3)	1458 (13.6)	1325 (12.4)
Education: ≤8 years[a]	4827 (45.1)	4919 (46.0)	5218 (48.7)	4780 (44.6)	4903 (45.8)	5281 (49.3)	5278 (49.3)	4874 (45.5)	4812 (45.0)
Smoking status [a]									
Current smoker	2839 (26.5)	2639 (24.7)	2785 (26.0)	2911 (27.2)	2777 (25.9)	2575 (24.0)	2955 (27.6)	2732 (25.5)	2576 (26.1)
Ex-smoker	3127 (29.2)	3026 (28.2)	2793 (26.1)	3241 (30.3)	2922 (27.3)	2783 (26.0)	3196 (29.9)	2930 (27.4)	2820 (26.3)
Never smoker	4741 (44.3)	5041 (47.1)	5128 (47.9)	4555 (42.5)	5007 (46.8)	5348 (50.0)	4556 (42.5)	5044 (47.1)	5310 (49.6)
Physical activity [a]									
Inactive	2663 (24.9)	2942 (27.5)	3739 (34.9)	2774 (25.9)	3317 (31.0)	3253 (30.4)	3451 (32.2)	3002 (28.0)	2891 (27.0)
Moderately inactive	4447 (41.5)	4151 (38.8)	3714 (34.7)	3917 (36.6)	3991 (37.3)	4404 (41.1)	3725 (34.8)	4186 (39.1)	4401 (41.1)
Moderately active	1961 (18.3)	1990 (18.6)	1752 (16.4)	2021 (18.9)	1931 (18.0)	1751 (16.4)	1835 (17.2)	1943 (18.2)	1925 (18.0)
Active	1636 (15.3)	1623 (15.1)	1501 (14.0)	1995 (18.6)	1467 (13.7)	1298 (12.1)	1696 (15.8)	1575 (14.7)	1489 (13.9)
Postmenopausal women[b,a]	3520 (47.3)	3355 (45.1)	3548 (46.9)	2852 (43.3)	3391 (45.3)	4180 (49.9)	3203 (50.2)	3377 (45.3)	3843 (44.6)
Alcohol intake [a]									
≤0.1 g/day	1127 (10.5)	1599 (14.9)	2440 (22.8)	1323 (12.4)	1673 (15.6)	2170 (20.3)	1497 (14.0)	1619 (15.1)	2050 (19.2)
>0.1−12 g/day	4500 (42.0)	5415 (50.6)	6189 (57.8)	4505 (42.1)	5419 (50.6)	6180 (57.7)	4195 (39.2)	5408 (50.5)	6501 (60.7)
>12−24 g/day	2009 (18.8)	1923 (18.0)	1310 (12.2)	1956 (18.3)	1862 (17.4)	1424 (13.3)	1959 (18.3)	1918 (17.9)	1365 (12.7)
>24 g/day	3071 (28.7)	1769 (16.5)	767 (7.2)	2923 (27.3)	1752 (16.4)	932 (8.7)	3056 (28.5)	1761 (16.5)	790 (7.4)
Diabetes	281 (2.6)	198 (1.9)	149 (1.4)	112 (1.1)	163 (1.5)	353 (3.3)	154 (1.4)	217 (2.0)	257 (2.4)
Hyperlipidaemia	2550 (23.8)	2563 (23.9)	2676 (25)	2596 (24.2)	2544 (23.8)	2649 (23.8)	2961 (27.7)	2562 (23.9)	2266 (21.2)
Duodenal ulcer	821 (7.7)	802 (7.5)	767 (7.2)	776 (7.3)	798 (7.5)	816 (7.6)	831 (7.7)	801 (7.5)	758 (7.1)
Myocardial infarction	59 (0.6)	47 (0.4)	50 (0.5)	50 (0.5)	51 (0.5)	55 (0.5)	68 (0.6)	46 (0.4)	42 (0.4)
Stroke	28 (0.3)	29 (0.3)	19 (0.2)	18 (0.2)	27 (0.3)	31 (0.3)	20 (0.2)	29 (0.3)	27 (0.3)

[a] Data are numbers of participants (percentages of tertile).
[b] Data are numbers of postmenopausal women (percentages of tertile).

diabetes. Ragusa and Naples participants had higher carbohydrate intake than those at other centres.

Compared with participants in the first tertile of energy from protein, third tertile participants had higher BMI, lower energy and fibre intake, were more likely to be female, were less educated, smoked less, were less physically active, had lower alcohol intake, and more likely to have been diagnosed with diabetes. Women were more likely to be postmenopausal. Varese and Florence participants had higher protein intake than those at other centres.

Compared with participants in the first tertile of energy from fat, third tertile participants had higher BMI, lower energy and fibre intake, were more likely to be female, were more educated, smoked less, had lower alcohol intake. They were also more likely to have been diagnosed with diabetes but less likely to have hyperlipidaemia and the women were less likely to be postmenopausal. Varese and Turin participants had higher fat intake than those at other centres.

However, all the associations found come from univariate cross-sectional analyses, thus the possibility of mutual confounding cannot be ruled out.

Associations between macronutrients and weight change

Table 2 shows associations of 10% increase in energy from one macronutrient (at the expense of another) with 5-year weight change. A 10% higher proportion of total protein at the expense of starch, sugar, and total fat was significantly associated with weight increase, with β coefficients of 0.87, 0.71, and 0.82 for replacement of starch, sugar, and total fat, respectively (fully adjusted model). Results were similar for animal protein and vegetable protein when considered separately. Substitution of animal protein by vegetable protein and vice versa were not significantly associated with weight change. Increase in starch at the expense of sugar, total fat, and total protein was significantly associated with weight decrease (β = −0.16, −0.05, and −0.82 for sugar, total fat, and total protein, respectively). Increase in sugar was associated with weight increase when it replaced starch and total fat (β = 0.16 and 0.11 for starch and total fat, respectively), and with weight decrease when it replaced total protein (β = −0.66). Increase in total and vegetable fat was associated with weight decrease when they replaced sugar or total protein, and with weight increase when they replaced starch (weight increase was not significant for vegetable fat). Animal fat was associated with weight increase when it replaced starch and with weight decrease when it replaced total protein Substitution of animal fat by vegetable fat and vice-versa were not significantly associated with weight change.

When participants who said they were dieting were excluded, results changed as follows. Increases in vegetable protein at the expense of total fat, starch and sugar were no longer significantly associated with reductions in weight; replacing animal protein with vegetable protein was now significantly associated with decreased weight. Increases in starch at the expense of total fat and vice versa were no longer associated with significant weight change;

Table 2 Mean 5-year weight change (in kg) in relation to 10% increase in energy from one macronutrient at the expense of 10% energy from another macronutrient. Significant β values shown in bold.

	β[a] (95% CI)	β[b] (95% CI)	β[c] (95% CI)
Increase in total protein at the expense of:			
Starch	**0.66 (0.51, 0.81)**	**0.87 (0.72, 1.02)**	**0.63 (0.46, 0.79)**
Sugar	**0.48 (0.34, 0.62)**	**0.71 (0.57, 0.85)**	**0.51 (0.35, 0.66)**
Total fat	**0.66 (0.49, 0.84)**	**0.82 (0.64, 0.99)**	**0.63 (0.44, 0.82)**
Increase in animal protein at the expense of:			
Starch	**0.61 (0.44, 0.79)**	**0.88 (0.71, 1.05)**	**0.54 (0.36, 0.73)**
Sugar	**0.47 (0.33, 0.62)**	**0.71 (0.56, 0.85)**	**0.50 (0.34, 0.65)**
Total fat	**0.66 (0.48, 0.84)**	**0.82 (0.64, 1.00)**	**0.63 (0.43, 0.83)**
Vegetable protein	0.22 (−0.29, 0.73)	−0.13 (−0.63, 0.38)	0.51 (−0.02, 1.04)
Increase in vegetable protein at the expense of:			
Starch	0.22 (−0.38, 0.81)	**0.81 (0.22, 1.40)**	−0.13 (−0.74, 0.49)
Sugar	0.11 (−0.42, 0.65)	**0.69 (0.15, 1.22)**	−0.15 (−0.71, 0.41)
Total fat	0.28 (−0.27, 0.83)	**0.79 (0.25, 1.33)**	−0.03 (−0.60, 0.53)
Animal protein	−0.31 (−0.82, 0.20)	0.06 (−0.45, 0.56)	**−0.59 (−1.12, −0.07)**
Increase in starch at the expense of:			
Sugar	**−0.17 (−0.23, −0.11)**	**−0.16 (−0.21, −0.10)**	**−0.12 (−0.17, −0.06)**
Total fat	0.00 (−0.05, 0.06)	**−0.05 (−0.10, 0.00)**	0.00 (−0.05, 0.06)
Total protein	**−0.62 (−0.76, −0.48)**	**−0.82 (−0.96, -0.68)**	**−0.60 (−0.75, -0.44)**
Increase in sugar at the expense of:			
Starch	**0.17 (0.11, 0.22)**	**0.16 (0.10, 0.21)**	**0.11 (0.06, 0.17)**
Total fat	**0.17 (0.10, 0.25)**	**0.11 (0.03, 0.18)**	**0.12 (0.04, 0.20)**
Total protein	**−0.45 (−0.59, −0.32)**	**−0.66 (−0.79, −0.53)**	**−0.48 (−0.62, −0.34)**
Increase in total fat at the expense of:			
Starch	−0.01 (−0.06, 0.05)	**0.05 (0.00, 0.11)**	0.00 (−0.06, 0.03)
Sugar	**−0.19 (−0.27, −0.11)**	**−0.11 (−0.19, −0.03)**	**−0.13 (−0.21, −0.04)**
Total protein	**−0.67 (−0.84, −0.49)**	**−0.82 (−0.99, −0.64)**	**−0.64 (−0.83, −0.45)**
Increase in animal fat at the expense of:			
Starch	0.03 (−0.04, 0.10)	**0.07 (0.00, 0.14)**	**0.09 (0.02, 0.16)**
Sugar	**−0.14 (−0.24, −0.04)**	−0.09 (−0.19, 0.01)	−0.01 (−0.11, 0.10)
Total protein	**−0.58 (−0.79, −0.37)**	**−0.77 (−0.99, −0.56)**	**−0.40 (−0.62, −0.17)**

(*continued on next page*)

Table 2 (*continued*)

	β[a] (95% CI)	β[b] (95% CI)	β[c] (95% CI)
Vegetable fat	0.07 (−0.02, 0.15)	0.03 (−0.05, 0.11)	**0.18 (0.09, 0.26)**
Increase in vegetable fat at the expense of:			
Starch	−0.04 (−0.10, 0.03)	0.04 (−0.03, 0.10)	**−0.09 (−0.16, −0.02)**
Sugar	**−0.21 (−0.29, −0.12)**	**−0.13 (−0.21, −0.04)**	**−0.19 (−0.27, −0.10)**
Total protein	**−0.64 (−0.82, −0.46)**	**−0.81 (−0.98, −0.63)**	**−0.57 (−0.76, −0.38)**
Animal fat	−0.07 (−0.15, 0.01)	−0.03 (−0.12, 0.05)	**−0.18 (−0.27, −0.09)**

[a] Adjusted for centre, age, sex, and total energy intake.
[b] Further adjusted for time from baseline to follow-up, BMI at baseline, education, physical activity, diabetes, hyperlipidaemia, myocardial infarction, stroke, duodenal ulcer, and menopausal status (in women).
[c] Further excluding participants who were dieting at baseline (n = 27,378 participants included).

increases in vegetable fat at the expense of starch and animal fat were now associated with weight reduction, while replacing vegetable fat with animal fat significantly increased weight.

Associations between macronutrients and waist change

Table 3 shows 5-year changes in waist circumference in relation to 10% energy increases from one macronutrient at the expense of another. Results were similar to those found for weight change, with the exceptions that: increasing vegetable protein at the expense of starch, sugar, and total fat was not associated with change in waist girth; increases in starch at the expense of fat and vice versa were not associated with waist change; substitution of animal fat by vegetable fat was associated with decreased waist girth; and substitution of vegetable fat by animal fat was associated with increased waist girth. Models adjusted and not for baseline BMI afforded similar results.

Excluding participants who were dieting at baseline changed results as follows. Increase in vegetable protein at the expense of animal protein decreased waist girth; increase in animal fat at expense of starch was now associated with waist increase, while increase in vegetable fat was now associated with waist reduction.

Sensitivity analyses

Results of sensitivity analyses are presented in the Supplementary material.

Discussion

In this prospective study, a 10% increase in energy from protein at the expense of energy from fat, starch, or sugar

Table 3 Mean 5-year change in waist circumference (in cm) in relation to 10% increase in energy from one macronutrient at the expense of 10% energy from another macronutrient. Significant β values shown in bold.

	β[a] (95% CI)	β[b] (95% CI)	β[c] (95% CI)	β[d] (95% CI)
Increase in total protein at the expense of:				
Starch	**0.98 (0.76, 1.20)**	**1.22 (1.00 −1.44)**	**1.11 (0.89, 1.33)**	**0.83 (0.58, 1.08)**
Sugar	**0.77 (0.56, 0.98)**	**1.03 (0.82, 1.24)**	**0.94 (0.74, 1.15)**	**0.70 (0.47, 0.93)**
Total fat	**1.02 (0.76, 1.28)**	**1.19 (0.93, 1.45)**	**1.13 (0.87, 1.39)**	**0.89 (0.60, 1.18)**
Increase in animal protein at the expense of:				
Starch	**0.92 (0.65, 1.20)**	**1.23 (0.95, 1.50)**	**1.07 (0.80, 1.35)**	**0.61 (0.31, 0.91)**
Sugar	**0.76 (0.55, 0.98)**	**1.04 (0.82, 1.25)**	**0.94 (0.73, 1.16)**	**0.68 (0.43, 0.91)**
Total fat	**1.02 (0.75, 1.30)**	**1.21 (0.94, 1.49)**	**1.14 (0.87, 1.41)**	**0.87 (0.57, 1.17)**
Vegetable protein	**1.17 (0.25, 2.08)**	0.91 (0.00, 1.82)	**1.28 (0.38, 2.18)**	**2.36 (1.37 −3.35)**
Increase in vegetable protein at the expense of:				
Starch	0.36 (−0.72, 1.44)	1.02 (−0.05, 2.10)	0.58 (−0.48, 1.64)	−1.00 (−2.17, 0.17)
Sugar	0.16 (−0.82, 1.14)	0.79 (−0.19, 1.77)	0.39 (−0.58, 1.36)	−1.06 (−2.12, 0.00)
Total fat	0.39 (−0.61, 1.39)	0.95 (−0.04, 1.95)	0.57 (−0.42, 1.55)	−0.88 (−1.96, 0.20)
Animal protein	−0.54 (−1.47, 0.39)	−0.14 (−1.07, 0.79)	−0.47 (−1.39, 0.45)	**−1.68 (−2.68, −0.67)**
Increase in starch at the expense of:				
Sugar	**−0.19 (−0.28, −0.11)**	**−0.18 (−0.26, −0.09)**	**−0.15 (−0.24, −0.07)**	**−0.12 (−0.21, −0.02)**
Total fat	0.03 (−0.05, 0.11)	−0.03 (−0.11, 0.05)	0.01 (−0.06, 0.09)	0.06 (−0.03, 0.14)
Total protein	**−0.88 (−1.09, −0.68)**	**−1.10 (−1.31, −0.89)**	**−1.00 (−1.21, −0.80)**	**−0.75 (−0.98, −0.51)**
Increase in sugar at the expense of:				
Starch	**0.20 (0.11, 0.28)**	**0.18 (0.10, 0.27)**	**0.16 (0.07, 0.24)**	**0.12 (0.03, 0.21)**
Total fat	**0.23 (0.11, 0.35)**	**0.15 (0.04, 0.27)**	**0.17 (0.06, 0.29)**	**0.18 (0.05, 0.30)**
Total protein	**−0.69 (−0.89, −0.50)**	**−0.93 (−1.12, −0.73)**	**−0.85 (−1.04, −0.66)**	**−0.63 (−0.85, −0.41)**
Increase in total fat at the expense of:				
Starch	−0.03 (−0.12, 0.06)	0.04 (−0.05, 0.12)	−0.01 (−0.09, 0.07)	−0.06 (−0.15, 0.04)
Sugar	**−0.23 (−0.36, −0.11)**	**−0.15 (−0.27, −0.03)**	**−0.17 (−0.29, −0.05)**	**−0.18 (−0.31, −0.05)**
Total protein	**−0.97 (−1.22, −0.70)**	**−1.13 (−1.39, −0.87)**	**−1.07 (−1.32, −0.81)**	**−0.84 (−1.13, −0.56)**
Increase in animal fat at the expense of:				
Starch	0.05 (−0.06, 0.16)	**0.12 (0.01, 0.23)**	0.09 (−0.02, 0.20)	**0.12 (0.00, 0.24)**

Table 3 (*continued*)

	β^a (95% CI)	β^b (95% CI)	β^c (95% CI)	β^d (95% CI)
Sugar	−0.13 (−0.28, 0.02)	−0.04 (−0.20, 0.11)	−0.05 (−0.20, 0.11)	0.05 (−0.11, 0.22)
Total protein	**−0.75 (−1.07, −0.43)**	**−0.90 (−1.22, −0.58)**	**−0.80 (−1.11, −0.49)**	**−0.36 (−0.71, −0.01)**
Vegetable fat	**0.15 (0.02, 0.27)**	**0.15 (0.03, 0.28)**	**0.18 (0.06, 0.30)**	**0.34 (0.20, 0.47)**
Increase in vegetable fat at the expense of:				
Starch	−0.09 (−0.20, 0.01)	−0.03 (−0.13, 0.07)	−0.09 (−0.19, 0.01)	**−0.21 (−0.32, −0.10)**
Sugar	**−0.27 (−0.40, −0.14)**	**−0.19 (−0.32, −0.06)**	**−0.22 (−0.35, −0.10)**	**−0.28 (−0.42, −0.14)**
Total protein	**−0.90 (−1.17, −0.63)**	**−1.06 (−1.32, −0.79)**	**−0.99 (−1.25, −0.72)**	**−0.70 (−0.99, −0.41)**
Animal fat	**−0.14 (−0.26, −0.01)**	**−0.14 (−0.26, −0.01)**	**−0.18 (−0.29, −0.04)**	**−0.33 (−0.46, −0.19)**

[a] Adjusted for centre, age, sex, and total energy intake.
[b] Further adjusted for time from baseline to follow-up, waist circumference at baseline, education, physical activity, diabetes, hyperlipidaemia, myocardial infarction, stroke, duodenal ulcer, and menopausal status (women).
[c] Further adjusted for BMI at baseline.
[d] Further excluding participants who were dieting at baseline (n = 18,899 participants included).

was significantly associated with 5-year gains in weight and waist circumference. By contrast, a 10% energy increase from starch at the expense of energy from protein or sugar, was associated with lower weight and waist girth. Furthermore, increased energy from sugar, at the expense of total fat or starch, was also associated with increased weight and waist girth, but decreased weight and waist girth when sugar replaced total protein. Similar associations were found between variations in proportions of energy obtained from these macronutrients and risks of overweight/obesity and abdominal obesity.

These findings are consistent with those of many observational studies with fairly long follow-up [12,17,19,21,23,25]. Thus, in the entire EPIC cohort, a 5% increase in (energy from) protein, at the expense of fat or carbohydrate, was associated with 5-year weight gain, and a 5% increase in fat at the expense of protein was associated with weight reduction [25]. Compared with diets in which up to 14% of energy came from protein, diets with >22% of energy from protein were associated with a 23–24% greater risk of overweight/obesity in participants normal at baseline [25]. In a study on EPIC cohorts from five countries [17], intake of total and animal (but not vegetable) protein was associated with later weight gain. In a secondary analysis of PREDIMED data [19] significantly increased risk of weight gain was associated with increased total protein intake at the expense of carbohydrate, but not at the expense of fat. In the US CARDIA (Coronary Artery Risk Development in Young Adults) study [21] – a population-based cohort study on changes in cardiovascular disease risk factors in 2909 healthy adults – intakes of protein, carbohydrate and total fat were directly, inversely, and not associated, respectively, with weight gain after 10 years.

Some observational studies [13,17,19,20,22,24] report contrasting findings. Studies conducted in New England [24] and Denmark [20] found that no macronutrient was significantly related to weight change. Ankarfeldt et al. [13] assessed whether dietary protein and anthropometric measures interacted with changes in body weight and waist circumference: baseline protein intake was not associated with changes in weight or waist circumference; and those in the highest tertile of baseline BMI had significantly lower waist circumference when protein replaced carbohydrate, although not when protein replaced fat. Finally, in a 1-year study, the proportions of energy from carbohydrate and fat were unrelated to BMI [22].

As regards intervention studies, a 2014 meta-analysis [26] found that low-carbohydrate/high-protein diet was associated with significant weight and fat mass reduction, which persisted for 12 or more months. The discrepancy between interventional and observational studies may be because most intervention studies recruited persons with chronic diseases or disease risk factors (e.g. obesity or overweight); while observational studies were conducted on healthy persons. Furthermore, follow-up in intervention studies is shorter than in observational studies, and long-term results of intervention studies are lacking. We stress the long follow-up in our study (mean 12 years).

In 2014, Ankarfeldt et al. [34] sought to reconcile the conflicting findings of intervention and observational studies by comparing those recruited to a clinical intervention trial (DiOGenes) with those from an observational cohort – the Danish Diet, Cancer, and Health (DCH) cohort: Trial participants were heavier, had larger waist circumference and greater fat mass than DCH participants. Better weight maintenance in the high-protein group compared with the low-protein group was observed in DCH cohort subgroups with closely similar body characteristics to those of trial participants, suggesting that the effects of protein on satiation and thermogenesis were more pronounced in those with higher BMI, and that other mechanisms may override these effects in normal/underweight persons. These inferences are supported by a study in which high- and low-protein diets were fed to lean young healthy persons: the two groups did not differ for insulin levels, appetite, or total energy expenditure [35].

Nevertheless, mechanisms underlying the protein intake-weight gain association in observational studies remain unclear. Some experimental results suggest that dietary amino acids could stimulate the activity of the hypothalamic orexin/hypocretin system, which promotes reward seeking and food intake and decrease brown adipose tissue thermogenesis (reviewed in Ref. [36]). In contrast, physiological evidence suggests that, in comparison with a low-protein diet, high protein helps weight control by increasing satiation and thermogenesis, and maintaining/increasing fat-free mass [37,38]. However, an increase in protein intake may be required to have this satiating effect, which may then attenuate over time [39].

The satiating effect of protein may vary inversely with habitual protein intake [40]; and when intake in an intervention trial is similar to habitual protein intake, the intervention has no effect on weight loss [41].

We found that high energy from starch – but not sugar – was associated with lower weight and waist circumference. This is in contrast to previous prospective observational studies [20,22,24,42] that reported no associations of total carbohydrate intakes with change in weight or waist circumference, although the CARDIA study [21] did report an inverse association between carbohydrate and weight gain after 10 years. EPIC–PANACEA (European Prospective Investigation into Cancer and Nutrition–Physical Activity, Nutrition, Alcohol, Cessation of smoking, Eating out of home And obesity) study reported no association when total carbohydrate, starch, and sugar replaced fat, but a negative association when they replaced protein [25]. These discrepancies could be due to variation in energy intake adjustment [32], other dietary factors, and covariates; and also between-study variation in macronutrient sub-group categorization (e.g. low/high glycaemic index (GI) carbohydrate versus starch/sugar). We, in fact, found that weight/waist decreased – and risks of overweight/obesity decreased – when starch replaced sugar, protein, or fat in the diet. Compared with an isoenergetic high-starch diet, a high-sugar diet could, because of its higher fructose content, lower production and levels of leptin, leading to decreased energy expenditure and weight gain [43]. Increased formation of resistant starch from starch (mainly by cooking) could also play a role [44]. Resistant starch may prevent weight gain by reducing postprandial insulin, increasing release of gut satiety peptides, increasing fat oxidation, and lowering fat storage [45].

Study strengths are prospective design, large sample size, availability of information on long-term changes in weight/waist circumference, use of validated questionnaires to capture dietary intake over a year, and availability of information on non-dietary variables, to allow control for confounding effects.

Use of self-reported weight at follow-up is a limitation since self-reporters (particularly when overweight/obese) underestimate their weight [46,47]. In fact, mean 5-year weight increase was low in our cohort, even though most were sedentary. Weight underestimation would have attenuated associations of macronutrient intakes with anthropometric changes. In the EPIC–PANACEA study, "correction equations" were applied to self-reported weights, and the results obtained were more in agreement with those of the centres with measured weights [25].

Another limitation is that macronutrient intake was obtained at a single FFQ administration, and changes in diet over the 6–20 subsequent years could not be assessed. We conducted a sensitivity analysis in which those most likely to have changed their diet (because dieting at recruitment) were excluded. After this exclusion, most macronutrient–anthropometry associations persisted. Moreover, since volunteers with higher baseline BMI had higher protein intake, our findings that higher protein at the expense of other macronutrients are associated with increased weight and waist may partially reflect a failure of these people to lose weight. We sought to take this issue into account adding baseline BMI or waist circumference in the fully adjusted regression models, and results were substantially unchanged; nevertheless, residual confounding due to suboptimal measurements might have occurred. However, it should be noted that the analysis on risk of developing overweight/obesity – which excluded persons with BMI$\geq$ 25 kg/m^2 at baseline – afforded similar results. Finally, the fact that about 24% of participants were lost to follow-up may have limited the validity of our results.

To conclude, our main findings suggest that increasing protein intake at the expense of fat or carbohydrate, and reducing starch by increasing other macronutrients, might increase weight and waist circumference. Several other long-term observational studies have produced similar findings, while other studies have not. The mechanisms by which habitual diets characterized by high protein and low starch lead to long-term weight gain deserve further investigation.

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Contributor statements

Study concept and design: VK, GM, SP, and RT. Data management and statistical analysis: CA and VK. Manuscript drafting: CA and SS. Results interpretation: VK, CA, and SS. Critical review of the manuscript: FR, AM, BB, AM, and GF. All authors approved the final manuscript.

Declaration of competing interest

The authors declare no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2020.08.007.

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