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ORIGINAL CONTRIBUTION

Main nutrient patterns are associated with prospective weight change in adults from 10 European countries

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Abstract

Purpose Various food patterns have been associated with weight change in adults, but it is unknown which combinations of nutrients may account for such observations. We investigated associations between main nutrient patterns and prospective weight change in adults.

Methods This study includes 235,880 participants, 25–70 years old, recruited between 1992 and 2000 in 10 European countries. Intakes of 23 nutrients were estimated from country-specific validated dietary questionnaires using the harmonized EPIC Nutrient DataBase. Four nutrient patterns, explaining 67 % of the total variance of nutrient intakes, were previously identified from principal component analysis. Body weight was measured at recruitment and self-reported 5 years later. The relationship between nutrient patterns and annual weight change was examined separately for men and women using linear mixed models with random effect according to center controlling for confounders.

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Results Mean weight gain was 460 g/year (SD 950) and 420 g/year (SD 940) for men and women, respectively. The annual differences in weight gain per one SD increase in the pattern scores were as follows: principal component (PC) 1, characterized by nutrients from plant food sources, was inversely associated with weight gain in men (−22 g/year; 95 % CI −33 to −10) and women (−18 g/year; 95 % CI −26 to −11). In contrast, PC4, characterized by protein, vitamin B2, phosphorus, and calcium, was associated with a weight gain of +41 g/year (95 % CI +2 to +80) and +88 g/year (95 % CI +36 to +140) in men and women, respectively. Associations with PC2, a pattern driven by many micro-nutrients, and with PC3, a pattern driven by vitamin D, were less consistent and/or non-significant.
Conclusions We identified two main nutrient patterns that are associated with moderate but significant long-term differences in weight gain in adults.

Keywords Dietary patterns · Nutrients · Weight gain · Obesity · Energy balance · Public health

Introduction

The ongoing epidemic of obesity and of related diseases throughout the world's population is a major public health concern [1, 2]. Because efforts to treat obesity are confronted with enormous challenges, the primary prevention of weight gain appears as the most efficient strategy.

A variety of factors contributes to an imbalance between energy intake and energy expenditure leading to weight gain and obesity in the long term. Among the diet-related factors that convincingly contribute to weight gain are low intakes of dietary fiber and high intakes of energy-dense foods [3]. However, evidence for other diet-related factors is less strong. Particular uncertainty exists on how the overall nutrient composition of habitual diets affects long-term weight change in free-living populations. Different nutrients are known to influence different pathways of energy balance. For example, dietary fiber may directly modulate appetite or may also have metabolic effects on fat breakdown and storage [4], while ingested fat is very efficiently stored in fat cells and is characterized by a high palatability facilitating energy over-consumption [5]. Depending on the combined intake of these and other nutrients, either synergistic or antagonistic overall effects on weight control may exist [6]. A dietary pattern approach examining the joint effects of dietary components on weight change is therefore very relevant. A few prospective observational studies evaluated the association between food patterns and body

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weight change in adults, suggesting that healthier food patterns are associated with less weight gain [7–12]. A recent cross-sectional study reported that major nutrient patterns were associated with general obesity in men, but not in women [13]. However, no studies have been published to date that examined associations between dietary patterns at the nutrient level and prospective weight change. Thus, it is largely unknown which combinations of nutrient intakes may be relevant for longer-term weight control. Such knowledge could provide insights into biologic pathways and could strengthen evidence available from food patterns. Furthermore, nutrition front-of-package labeling, shelf-labeling, and nutrition information on restaurant menus are increasingly used by consumers to make healthier food choices [14]. It is thus also important to provide evidence on which combinations of nutrients best prevent weight gain.

In the European Prospective Investigation into Cancer and Nutrition (EPIC) study, a large prospective cohort study across 23 centers in 10 European countries, four main nutrient patterns were identified previously using principal component analysis (PCA) on the basis of dietary questionnaire data [15]. These four nutrient patterns, capturing 67 % of individual variation in nutrient intake, were successfully validated relative to standardized 24-h dietary recalls [15].

The objective of the present study was to investigate associations between these main nutrient patterns and prospective weight change in adults participating in the PANACEA (Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of Home and Obesity) project; PANACEA is the sub-cohort of EPIC where repeated assessments of weight are available, making it possible to study weight changes.

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. The cohort of 521,448 men and women recruited from 1992 to 2000 (age range 25–70 year) 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 centers from Italy and Spain (blood donors). The rationale for EPIC, study design, and methods has been described in detail elsewhere [16, 17].

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); those likely to mis-report energy intake according to Goldberg [18] (n = 85,356 under-reporters and 22,513 over-reporters); and individuals with cancer at any site other than non-melanoma skin cancer, diabetes, or cardiovascular disease at baseline (n = 30,054). Finally, we excluded 121,866 individuals with missing weight at follow-up and 2066 individuals with implausible anthropometry at follow-up: weight loss of more than −5 kg/year or weight gain of more than 5 kg/year and BMI at follow-up <16 kg/m^2. More details on follow-up exclusions have been previously given [19, 20]. The final analyses included 65,297 men and 170,583 women with complete and plausible dietary and body weight data.

Anthropometric measures and weight change

Two body weight measures were available for each participant with one measure collected at baseline and the other after 5 year on average (min.: 2 year for Heidelberg; max.: 11 year for Varese). At baseline, body weight and height were measured in most centers using similar, standardized procedures with the exception of those taken in France, Norway, and the health conscious group of the Oxford center in which subjects self-reported. As for the follow-up weights, all values were self-reported, except in Norfolk (United Kingdom) and Doetinchem (The Netherlands) where weight was measured [19, 20]. 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 [21].

Our main outcome was weight change in g/year, calculated as weight at follow-up minus weight at baseline divided by years of follow-up, in order to account for the differences in time between the first and second weight assessment across centers.

Dietary assessment

Habitual food consumption during the previous 12 months was assessed at baseline for each individual with center-specific methods, in most cases dietary questionnaires [17]. These questionnaires were developed and validated in each country/center to capture country-specific dietary habits [22]. From these questionnaires, intakes of energy and nutrients were estimated using the harmonized EPIC Nutrient Database [23].

Table 1 Principal components (PC) loading matrix (correlations) and explained variances for the first four nutrient patterns identified by PCA in participants of the EPIC study

Nutrients	PC1	PC2	PC3	PC4
Total protein	−0.10	0.41	0.08	**0.55**
SFA	**−0.48**	0.05	−0.32	−0.18
MUFA	−0.06	−0.12	−0.24	−0.12
PUFA	0.09	0.25	0.26	−0.37
Cholesterol	**−0.57**	0.30	−0.17	0.25
Starch	−0.05	−0.35	0.22	−0.15
Sugars	0.30	0.14	0.02	0.15
Dietary fiber	**0.57**	0.33	0.26	−0.04
Thiamine	0.32	0.43	0.32	0.22
Riboflavin	0.06	**0.60**	−0.12	**0.51**
Vitamin B_6	0.37	**0.51**	0.25	0.36
Folate	**0.59**	**0.59**	0.03	0.16
Vitamin B_{12}	**−0.57**	**0.54**	−0.20	0.39
Vitamin C	**0.66**	0.42	−0.02	0.11
Beta-carotene	**0.60**	**0.66**	−0.12	−0.27
Retinol	**−0.73**	**0.48**	−0.26	−0.26
Vitamin E	0.41	0.28	0.10	−0.35
Vitamin D	**−0.55**	0.41	**0.70**	−0.06
Calcium	0.14	0.35	−0.16	**0.45**
Phosphorus	0.11	**0.49**	0.06	**0.48**
Iron	0.34	0.34	0.01	0.17
Potassium	0.42	**0.59**	0.21	0.36
Magnesium	0.30	**0.47**	0.15	0.23
Explained variance (%)	29	22	9	7
Cumulative explained variance (%)	29	51	60	67

EPIC-wide PCA on 23 log-transformed nutrients adjusted for energy intake using nutrient densities

Nutrients with loadings >0.45 and less than −0.45 (in bold) are being characteristic for the four patterns

Pearson correlations between each of the 4 PC were <0.04

PCA principal component analysis, *SFA* saturated fatty acids, *MUFA* monounsaturated fatty acids, *PUFA* polyunsaturated fatty acids, *EPIC* European Prospective Investigation into Cancer and Nutrition

Nutrient patterns

We used the same set of already-available nutrient patterns in the EPIC study as identified, validated, and interpreted previously [15]. Briefly, main nutrient patterns were derived with PCA on the covariance matrix of individual intakes of all the 23 nutrients available in the EPIC Nutrient Database [23]. Nutrient intake data, as estimated from dietary questionnaires, from all EPIC centers (i.e., EPIC-wide analysis) and both sexes were combined. This approach captured a good proportion of the variance explained in each EPIC center and lead to very similar patterns in men and women when PCA was conducted by sex [15]. Independence of scale of the variances and co-variances was achieved by taking the natural log of the input variables. Nutrient densities—calculated as nutrient intake (amount/day) divided by alcohol-free energy (kcal/day)—were used as input variables in order to capture variability of nutrient intakes independently from variation in energy intake. We retained the first four principal components (PC) or "patterns" taking into account the interpretability of the patterns, the percentage of total variance explained, and the scree-plot of eigenvalues against the number of PC [15]. The loading coefficients, which are comparable to correlation coefficients between the nutrient pattern scores and the individual nutrients, of the four retained patterns are shown in Table 1. Nutrients with positive loadings were positively associated with a nutrient pattern while negative loadings indicate inverse associations. For interpretation, we arbitrarily chose nutrients with loadings >0.45 or less than −0.45 as being characteristic for each pattern (in bold in Table 1).

Individual PC scores for each study participant were then computed from each of the four retained patterns as the sum of products of the observed variables [nutrient intakes (amount/day)] multiplied by weights proportional to the nutrient's loading on the pattern [15].

Assessment of other covariates

Data on physical activity (inactive, moderately inactive, moderately active, and active), smoking (never, former, and current), and education (primary school, technical school, secondary school, and university degree) were collected at baseline through questionnaires [17]. Information on smoking status was also collected during 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). Participants with missing values for physical activity (8 %), education (5 %), and change in smoking status (12 %) were classified as a separate category.

Statistical analyses

The association between each of the four nutrient patterns and annual body weight change (g/year) was estimated using multilevel mixed linear regression models with center as random effect and the nutrient patterns on a continuous scale. Random effects on both intercept and slope according to center were modeled when indicated by likelihood ratio tests. We decided a priori to run all models separately for men and women. Model assumptions and fit were checked visually by plotting the residuals against each of the categorical predictors. The linearity of the associations was checked by adding splines of each continuous predictor to

the models. We fitted three multivariable-adjusted models (M1–M3) controlling for an increasing number of potential confounders (see footnotes of Table 3) as fixed effects.

We performed sensitivity analyses by excluding participants with missing values for physical activity ($n = 9144$) or those who started or quit smoking during follow-up ($n = 23{,}296$).

We further explored a priori effect modification by age, BMI at baseline, change of smoking status, physical activity, level of education, and follow-up time by including interaction terms between each variable and the individual patterns in the models. P values for the interaction term were calculated by using F tests, and group-specific coefficients were presented when statistically significant interactions were detected.

In order to evaluate heterogeneity across centers, we performed center-specific analyses using generalized linear models and combined the results using random-effect meta-analysis (I^2).

Differences were considered statistically significant at $P < 0.05$. All statistical analyses were performed with STATA 11.2 (College Station TX).

Results

Nutrient patterns

The nutrient patterns used in the current study have been described previously [15]. Briefly, principal component (PC) 1 showed high loadings of nutrients from plant food sources such as vitamin C, beta-carotene, folate or dietary fiber, and low loadings of nutrients typical for animal foods such as saturated fatty acids, cholesterol, or retinol. PC2 was characterized by many vitamins and minerals; PC3 by vitamin D and to a lesser degree by thiamine; and PC4 by total protein, riboflavin, phosphorus, and calcium (Table 1).

Characteristics of study population

The main characteristics of men and women at baseline by quintiles of the four nutrient patterns are shown in Table 2. The mean weight gain was 460 g/year (SD 950 g/year) and 420 g/year (SD 940 g/year) in men and women, respectively. In both men and women, higher scores on PC1 and PC2 were associated with having a higher educational level and not being a current smoker; the opposite was true for higher scores on PC3 and PC4.

Associations between nutrient patterns and prospective weight change

The adjusted increase or decrease in annual weight gain (g/year) for 1 SD increase in PC scores in men and women is shown in Table 3. PC1 was inversely associated with weight gain in both men and women (both $P < 0.001$), although the observed effects were small: 1 SD increase in PC1 corresponded to gaining ~5 % less weight than the population average. In contrast, for 1 SD increase in PC4, annual weight gain was 9 and 20 % higher than the mean weight gain in men ($P = 0.03$) and women ($P = 0.001$), respectively. Weak effects in opposite directions for men and women were observed for PC2, with an inverse association in men and a positive association in women (both $P = 0.003$). With regard to PC3, no significant association with weight change was observed in men ($P = 0.57$), while a moderately increased weight gain was observed in women ($P < 0.001$) (Table 3).

Categorical analyses of each of the four nutrient patterns using their quintiles confirmed the findings using patterns on a continuous scale, except for PC2, where no association with weight gain was evident (P trend men: 0.08; P trend women: 0.71) (Table 4).

Additional analyses

Results for all four patterns were similar after excluding participants who started or quit smoking during follow-up ($n = 23{,}296$) or participants with missing information on physical activity ($n = 9144$) (not shown). All results were also similar when we investigated relative (percent) rather than absolute weight changes (not shown). In stratified analysis (Table 5), the observed small inverse association of PC1 with weight gain in men and women was more pronounced in participants who quit smoking during follow-up (men: $P_{\text{interaction}} < 0.001$; women: $P_{\text{interaction}} = 0.005$) than in the other categories. Strengths of effects of PC4 with weight gain were twice as much in both men and women aged >50 year at baseline ($P_{\text{interaction}} = 0.005$) compared to their younger counterparts. We observed an inverse association between a 1 SD increase in PC4 and weight gain (−175 g/year) ($P = 0.003$) in obese men with a baseline BMI > 30 kg/m^2 compared to men with a BMI < 30 kg/m^2 ($P_{\text{interaction}} < 0.001$). Tests for effect modification by levels of physical activity, by levels of education, and by follow-up time were either non-significant or stratified results were similar in magnitude as overall results (not shown).

In men, there was little evidence for heterogeneity across centers for all four nutrient patterns (all $I^2 < 32$ %, all $P > 0.13$). In women, moderate-to-high heterogeneity was observed with I^2-values between 47 and 89 % (all $P < 0.02$) (Online Resource 1).

Discussion

We found that different nutrient patterns were independently associated with weight gain in adults after a mean

Table 2 Main characteristics of the study population according to the lowest and highest quintile of the four nutrient patterns by gender ($n = 235{,}880$)

	PC1				PC2				PC3				PC4			
	Q1		Q5		Q1		Q5		Q1		Q5		Q1		Q5	
Men																
Age (year)[a]	53.4	9.0	51.8	11.8	50.0	9.8	56.3	8.7	52.2	9.8	52.2	9.9	51.0	10.7	53.2	8.7
University degree (%)[b]	25		28		21		34		25		25		32		22	
BMI at baseline (kg/m^2)[a]	26.1	3.4	26.7	3.6	26.2	3.5	26.3	3.3	26.7	3.5	26.3	3.5	25.6	3.4	26.9	3.5
Physically inactive and moderately inactive (%)[b,d]	48		52		47		47		46		50		47		48	
Current smokers (%)[b,c]	29		10		25		19		19		23		17		30	
Quitting smoking during follow-up (%)[b]	8		2		6		6		5		6		5		7	
Follow-up time (year)[a]	5.9	2.2	5.9	2.5	5.7	2.7	5.3	1.7	6.3	2.6	5.0	2.2	6.1	2.4	4.7	1.8
Plausible energy reporters (%)[b]	71		60		72		59		71		65		71		64	
Total energy intake (kcal/day)[a]	2600	450	2500	460	2700	470	2500	430	2700	480	2600	440	2600	460	2600	450
Energy density (kcal/g)[a]	1.6	0.3	1.3	0.2	1.6	0.3	1.3	0.2	1.5	0.3	1.5	0.3	1.7	0.3	1.3	0.3
Protein (E %)[a]	16.2	2.7	15.5	2.7	15.5	2.8	17.8	2.7	15.9	2.5	16.6	3.1	14.2	2.1	18.2	2.8
Carbohydrates (E %)[a]	40.9	6.3	42.2	8.5	44.1	7.1	40.3	7.0	40.3	7.0	43.2	7.6	43.2	6.9	41.2	7.4
Fat (E %)[a]	36.6	5.4	36.4	8.2	34.8	6.1	34.3	6.3	37.4	6.7	33.9	5.9	38.3	6.0	32.1	5.7
Alcohol (E %)[a]	6.4	6.2	5.9	6.3	5.5	5.8	7.6	6.9	6.4	6.4	6.3	6.3	4.3	4.4	8.5	7.7
Fiber (g/1000 kcal)[a]	8.8	2.2	12.5	3.3	9.6	2.7	11.3	2.9	9.5	2.5	10.8	3.2	10.5	2.8	10.0	3.0
Women																
Age (year)[a]	51.2	8.3	51.2	10.8	49.4	9.7	53.1	8.4	51.8	8.3	49.8	9.6	49.8	9.7	51.8	9.4
University degree (%)[b]	18		29		20		26		27		21		25		22	
BMI at baseline (kg/m^2)[a]	24.4	3.9	24.5	4.2	24.9	4.4	24.3	3.7	24.2	4.0	24.4	3.9	24.0	4.0	25.1	4.1
Physically inactive and moderately inactive (%)[b,d]	45		61		64		49		60		44		46		60	
Current smokers (%)[b,c]	23		8		17		14		12		16		14		16	
Quitting smoking during follow-up (%)[b]	6		2		4		3		3		5		4		4	
Follow-up time (year)[a]	5.7	2.3	5.1	2.2	5.7	2.9	4.8	1.7	5.2	2.8	5.2	1.7	5.6	2.3	4.7	2.0
Plausible energy reporters (%)[b]	68		63		69		65		72		61		70		60	
Total energy intake (kcal/d)[a]	2100	340	2000	330	2100	360	2000	320	2100	350	2000	320	2100	350	2000	330
Energy density (kcal/g)[a]	1.5	0.3	1.2	0.2	1.6	0.3	1.2	0.2	1.4	0.3	1.3	0.3	1.5	0.3	1.2	0.2
Protein (E %)[a]	17.5	2.9	16.3	2.9	15.9	2.8	18.6	2.8	17.1	2.7	17.7	3.1	15.0	2.4	19.3	2.9
Carbohydrates (E %)[a]	41.9	6.2	46.3	7.8	46.7	6.7	42.3	7.0	42.0	6.9	46.4	6.5	44.8	6.5	44.5	7.5
Fat (E %)[a]	37.5	5.2	34.7	7.7	35.1	6.1	35.4	6.1	37.8	6.2	33.5	5.6	38.0	5.9	32.5	6.0
Alcohol (E %)[a]	3.2	4.3	2.6	3.8	2.3	3.5	3.7	4.7	3.1	4.1	2.4	3.5	2.2	3.0	3.7	5.0
Fiber (g/1000 kcal)[a]	9.5	2.3	13.8	3.3	10.2	2.8	12.5	3.0	10.3	2.5	12.7	3.3	11.8	2.9	11.5	3.4

[a] Continuous variable. All values are mean ± SD. $P < 0.001$ (ANOVA)

[b] Categorical variable. $P < 0.001$ (Chi-square test)

[c] At second weight assessment

[d] Inactive and moderately inactive participants combined

Table 3 Adjusted decrease or increase in weight gain (g/y) for 1 SD-unit increase in nutrient pattern scores, PC1–4, by gender ($n = 235{,}880$)

Nutrient pattern	Men ($n = 65{,}297$)		Women ($n = 170{,}583$)	
	g/year (95 % CI)	*P* value	g/year (95 % CI)	*P* value
PC1				
Model 1	−17 (−29 to −5)	0.004	−16 (−23 to −8)	<0.001
Model 2	−26 (−36 to −16)	<0.001	−26 (−33 to −18)	<0.001
Model 3	−22 (−33 to −10)	<0.001	−18 (−26 to −11)	<0.001
PC2				
Model 1	−57 (−79 to −36)	<0.001	25 (−0.1 to 49)	0.051
Model 2	−39 (−63 to −16)	<0.001	30 (3 to 56)	0.030
Model 3	−28 (−49 to −7)	0.009	35 (9 to 60)	0.003
PC3				
Model 1	10 (−33 to 53)	0.647	58 (24 to 93)	0.001
Model 2	6 (−35 to 47)	0.556	68 (32 to 104)	<0.001
Model 3	12 (−29 to 53)	0.572	64 (29 to 98)	<0.001
PC4				
Model 1	−8 (−48 to 31)	0.680	66 (18 to 114)	0.007
Model 2	49 (13 to 85)	0.031	75 (25 to 124)	0.003
Model 3	41 (2 to 80)	0.027	88 (36 to 140)	0.001

We performed mixed linear models with center as random effect on the intercept, and where indicated by likelihood ratio tests, also on the slope

P interaction between sex and nutrient patterns were for PC1: $P < 0.001$, PC2: $P < 0.001$, PC3: $P = 0.95$, and PC4: $P = 0.016$

Model 1 was adjusted for age at recruitment and mutually for each PC score

Model 2 was adjusted as in M1 plus for BMI at baseline

Model 3 was adjusted as in M2 plus for physical activity, education, change in smoking status, energy intake, time in years between the two body weight assessments, time in years-squared, time in years with knots at percentiles 25 and 75, and BMI with knots at 25 and 30 kg/m^2

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follow-up of 5 years. The magnitude of these observed effects was small to moderate; for example, the accumulated decrease or increase in weight gain over 5 years ranged from −100 g for a 1 SD increase in PC1 (nutrients from plant foods) to +400 g for a 1 SD increase in PC4 (characterized by total protein, riboflavin, phosphorus, and calcium). Considering that the observed changes in weight were unrelated to any sort of weight loss or dietary interventions and that obesity is a multi-factorial condition, much larger effects were not expected.

In sub-group analyses, the inverse association between PC1 and weight gain was more pronounced in participants who quit smoking during follow-up. Important to note is also the strengthened positive effect of the relationship between PC4 and weight gain in men and women >50 year at baseline, where for example in men, the 5 year extra weight gain was about 900 g for a 1 SD increase in PC4 scores (i.e., ~50 % higher gain than the average weight gain).

To the best of our knowledge, this is the first prospective study relating dietary patterns at the nutrient level to weight change. In terms of foods contributing to these nutrient patterns, our 1st pattern (PC1) was similar to a "prudent" pattern characterized by a diet rich in plant foods such as fruits, vegetables, legumes, and low in (processed) meats, eggs, and milk (Online Resource 2). Our results of PC1 are therefore consistent with the prospective cohort studies that have assessed dietary patterns at the food level in relation to long-term weight change [7–12] and provide evidence for nutrients accounting for the effects of a prudent dietary pattern.

We are not aware of a dietary pattern—neither level at food nor nutrient level—described in the literature that was similar to our PC4. The main food sources contributing to the nutrient intakes of PC4—dairy (particularly milk), read meat and poultry, and fish and shellfish (Online Resource 2)—have been investigated individually in a number of cohort studies and randomized controlled trials (RCT), but with no clear conclusion with regard to weight change [24–27], with the exception of red or processed meat intake, which promote unhealthy weight gain and obesity [19, 28]. However, it is very likely that the combined intake of multiple dietary factors act synergistically [6]. It is also known that individuals vary considerably in their ability to maintain energy balance in response to the very same dietary component [3]. Therefore, the net "synergistic" effect of a dietary pattern may well be that a greater proportion of individuals of a population are susceptible to at least one dietary component of a given pattern [6]. At the nutrient level, we are suspecting the high protein intake (~19 E % in the highest quintile of PC4—Table 2) combined with a low intake of dietary fiber (~11 g/day) being responsible for the positive associations with weight gain. Despite the convincing evidence from RCT and physiological studies that a high protein intake is beneficial for weight loss and control in the short-term, longer-term and/or large-scale observational studies have reported the opposite [29–31]. The effects of dietary nutrient mixtures on appetite and weight control are poorly understood. However, it is known that control systems are least effective at low levels of physical activity [3]. We hypothesize that the lower physical activity levels in older adults, as observed in our study population, may be a plausible reason why adults >50 years with a high adherence to PC4 are more susceptible to weight gain than their younger counterparts. Despite our attempts to improve the accuracy of self-reported body weight at follow-up with the use of a prediction equation [21], the most likely explanation for the observed interactions with baseline BMI, particularly in women, is a higher likelihood of bias in self-reported follow-up weight in overweight/obese

Table 4 Adjusted decrease or increase in weight gain (g/year) by quintiles of nutrient patterns scores (SD-units), PC1–4, by gender ($n = 235{,}880$)

	Quintile 1 (reference)	Q3 g/year (95 % CI)	Q5 g/year (95 % CI)	*P* trend
PC1				
Men	0	−42 (−68 to −17)	−50 (−83 to −16)	0.022
Women	0	−30 (−49 to −12)	−56 (−77 to −35)	<0.001
PC2				
Men	0	−22 (−55 to 12)	−46 (−99 to 6)	0.08
Women	0	−40 (−67 to −13)	11(−32 to 54)	0.706
PC3				
Men	0	−36 (−89 to 17)	−12 (−77 to 52)	0.594
Women	0	52 (19 to 84)	72 (24 to 120)	0.004
PC4				
Men	0	2 (−40 to 45)	70 (24 to 115)	0.001
Women	0	20 (−12 to 52)	106 (70 to 142)	<0.001

We performed mixed linear models with center as random effect on the intercept, and where indicated by likelihood ratio tests, also on the slope

Adjustments were made for age, BMI at recruitment, physical activity, education, change in smoking status, energy intake, time in years between the two body weight assessments, time in years-squared, time in years with knots at percentiles 25 and 75, and BMI with knots at 25 and 30 kg/m^2 , and mutually for each PC score

P trend was tested by using a contrast in the coefficients corresponding to the levels of categorical predictors

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individuals [32]. The inverse association with weight gain observed in obese men with high adherence to PC4 could also be a chance finding because of the lack of consistency.

A recent cross-sectional study among Iranian adults reported associations between two main nutrient patterns and body mass index in men, but not in women [13]. Although their derived nutrient patterns were different to ours, probably because of a larger set of available nutrients (38 compounds) to derive patterns, differences in study designs and dietary assessment methods, and in underlying dietary habits, their findings support the hypothesis that nutrient patterns can be linked to obesity. Ultimately, if the combined intake of nutrients were related to obesity, or other chronic diseases, similar nutrient patterns should emerge as the culprit.

The physiological cause of weight gain is the consumption of more energy from foods and drinks than is expended. However, the maintenance of energy balance involves many physiological control mechanisms such as satiety responses or appetite control, which are linked to dietary and other cues [3]. Potential mechanisms by which PC1 is inversely associated with weight gain may be linked to the combination of high intake of dietary fiber, low intake of saturated fatty acids, and the low energy density. Although it is possible that dietary fiber is more a marker of low-energy-dense foods, there is considerable evidence that fiber favorably affects satiety, satiation, and appetite control [3]. These mechanisms—independent of energy density—are supported by our observation that a high adherence to PC4 was equally low in energy density (1.2 kcal/g) as PC1, while they have opposite associations with weight gain. Although there are also several plausible mechanisms linking dietary fat to positive energy balance and obesity such as the efficiency of storage in fat cells, the palatability and ease of passive over-consumption [3], we observed a higher fat intake in the 5th quintile of PC1 as compared to the 5th quintile of PC4. While carbohydrate intake was similar between these two patterns, alcohol intake was higher for subjects with high adherence to PC4. At the food level, most pronounced differences between subjects with high adherence to PC1 as compared to PC4 were much higher intakes of fruits and vegetables combined with much lower intakes of milk, and red and processed meats (Online Resource 2).

Some caution is warranted with the interpretation of our findings for the following reasons. 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 [21]. Furthermore, in the EPIC Norfolk study, a subcohort 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 good [33]. In the two centers with measured weight at follow-up (Doetinchem and Norfolk), observed associations were in the same direction as overall with only a few exceptions (Online Resource 1) adding confidence to our findings.

Second, we were not able to account for potential changes in diet during follow-up. However, previous studies have demonstrated a reasonable stability of dietary patterns over time [11, 34, 35]. For example, the reliability correlation for a prudent food pattern derived by PCA from 2 FFQ 1 year apart was $r_{\text{Pearson}} = 0.7$ [34].

Third, measurement error is a limitation inherent to all epidemiological studies using self-reported dietary data. We attempted to minimize this bias by using energy-adjusted nutrient intakes and by excluding participants with implausible diet reporting. The latter has been shown to partly account for BMI-related dietary under-reporting [36]. Fourth, we were limited by the number of nutrients available in the harmonized nutrient database (i.e., 23 compounds) to derive patterns. Therefore, we could not separate sugars into for example, fructose or galactose, or protein into animal and plant proteins. Finally, as with all observational studies, residual confounding by other dietary or lifestyle factors and selection bias cannot be ruled out completely and may have influenced our results.

Table 5 Adjusted decrease or increase in weight gain (g/year) for 1 SD-unit increase in nutrient pattern scores, PC1–4, by gender and interaction variables (n = 235,880)

	PC1			PC2		
	g/year (95 % CI)	*P* value	*P* interaction	g/year (95 % CI)	*P* value	*P* interaction
Men						
Age			0.363			0.159
≤50 year	−15 (−33 to 3)	0.102		−10 (−44 to 25)	0.583	
>50 year	−17 (−35 to 2)	0.079		−31 (−65 to 4)	0.081	
BMI			0.200			0.059
<25 kg/m^2	−15 (−33 to 3)	0.102		−10 (−44 to 25)	0.583	
25–30 kg/m^2	−18 (−36 to −0.1)	0.049		−20 (−55 to 14)	0.246	
>30 kg/m^2	−37 (−63 to −12)	0.004		30 (−17 to 77)	0.206	
Change in smoking status			<0.001			0.092
Current	−7 (−31 to 17)	0.560		−42 (−82 to −2)	0.039	
Former	−10 (−31 to 11)	0.353		−16 (−54 to 23)	0.421	
Never	−15 (−33 to 3)	0.102		−10 (−44 to 25)	0.583	
Quitters	−96 (−136 to −56)	<0.001		−39 (−99 to 21)	0.205	
Starters	34 (−21 to 90)	0.227		69 (−18 to 156)	0.118	
Women						
Age			<0.001			0.006
≤50 year	−25 (−36 to −15)	<0.001		5 (−26 to 36)	0.747	
>50 year	−34 (−44 to −24)	<0.001		−17 (−49 to 14)	0.284	
BMI			<0.001			<0.001
<25 kg/m^2	−25 (−36 to −15)	<0.001		5 (−26 to 36)	0.747	
25–30 kg/m^2	3 (−11 to 17)	0.654		74 (40 to 107)	<0.001	
>30 kg/m^2	−9 (−30 to 11)	0.381		89 (50 to 127)	<0.001	
Change in smoking status			0.005			0.216
Current	−7 (−27 to 12)	0.473		26 (−9 to 62)	0.148	
Former	−29 (−44 to −14)	<0.001		21 (−12 to 55)	0.214	
Never	−25 (−36 to −15)	<0.001		5 (−26 to 36)	0.747	
Quitters	−81 (−115 to −47)	<0.001		−4 (−54 to 45)	0.865	
Starters	−10 (−52 to 33)	0.664		27 (−30 to 85)	0.351	
	PC3			PC4		
	g/year (95 % CI)	*P* value	*P* interaction	g/year (95 % CI)	*P* value	*P* interaction
Men						
Age			0.722			0.005
≤50 year	−52 (−130 to 27)	0.195		76 (1 to 152)	0.05	
>50 year	−40 (−119 to 38)	0.310		176 (96 to 256)	<0.001	
BMI			0.536			<0.001
<25 kg/m^2	−52 (−130 to 27)	0.195		76 (1 to 152)	0.05	
25–30 kg/m^2	−35 (−111 to 40)	0.359		−57 (−136 to 22)	0.157	
>30 kg/m^2	−84 (−183 to 16)	0.100		−175 (−292 to −58)	0.003	
Change in smoking status			0.057			0.062
Current	59 (−30 to 149)	0.196		155 (60 to 249)	0.001	
Former	26 (60 to 111)	0.556		39 (−47 to 126)	0.376	
Never	−52 (−130 to 27)	0.195		76 (1 to 152)	0.05	
Quitters	36 (−103 to 176)	0.612		63 (−86 to 211)	0.410	
Starters	124 (−72 to 320)	0.215		−112 (−326 102)	0.304	

Table 5 continued

	PC3			PC4		
	g/year (95 % CI)	*P* value	*P* interaction	g/year (95 % CI)	*P* value	*P* interaction
Women						
Age			0.816			0.005
≤50 year	118 (77 to 159)	<0.001		62 (−1 to 124)	0.053	
>50 year	114 (73 to 155)	<0.001		130 (66 to 193)	<0.001	
BMI			<0.001			0.458
< 25 kg/m^2	118 (77 to 159)	<0.001		62 (−1 to 124)	0.053	
25–30 kg/m^2	11 (−37 to 59)	0.662		39 (−33 to 111)	0.294	
> 30 kg/m^2	−28 (−94 to 38)	0.404		89 (−6 to 183)	0.065	
Change in smoking status			0.171			0.01
Current	111 (53 to 168)	<0.001		−16 (−97 to 64)	0.692	
Former	92 (43 to 142)	<0.001		86 (14 to 159)	0.019	
Never	118 (77 to 159)	<0.001		62 (−1 to 124)	0.053	
Quitters	84 (−11 to 178)	0.082		−96 (−220 to 33)	0.145	
Starters	−13 (−130 to 103)	0.822		20 (−143 to 183)	0.813	

We performed mixed linear models with center as random effect on the intercept, and where indicated by likelihood ratio tests, also on the slope

P interaction between sex and nutrient patterns were for PC1: $P < 0.001$, PC2: $P < 0.001$, PC3: $P = 0.95$, and PC4: $P = 0.016$

Model 1 was adjusted for age at recruitment and mutually for each PC score

Model 2 was adjusted as in M1 plus for BMI at baseline

Model 3 was adjusted as in M2 plus for physical activity, education, change in smoking status, energy intake, time in years between the two body weight assessments, time in years-squared, time in years with knots at percentiles 25 and 75, and BMI with knots at 25 and 30 kg/m^2

P interaction was tested by likelihood ratio when an interaction term was included in the model

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There was evidence for a moderate-to-high heterogeneity across study centers in women, but not in men. We looked for possible explanations of this variation in women using post hoc meta-regression analysis, where we tested heterogeneity after adjustment for the country-specific covariates in our models (i.e., mean baseline age, BMI, follow-up time, smoking, physical activity, and education). Since heterogeneity was not appreciably reduced (not shown) and we have no reason to assume different associations between nutrient patterns and weight gain, there were most likely other (unmeasured) differences between these study populations (e.g., in health consciousness), which in EPIC were not always population-based [16, 17].

The main strengths of our study include its prospective design with a reasonably long follow-up, the very large sample size, and the variability in nutrient intakes across these European countries [37], which provided sufficient power to also detect small associations, despite the large variability of weight change, and to perform sub-group analyses. With regard to nutrient patterns, an unsupervised data reduction method (i.e., PCA) was used, which does not aim at improving the explanatory power of the outcome and thus, facilitated hypothesis testing. Furthermore, the relative validity of the nutrient patterns has been positively evaluated and their food sources have been illustrated [15].

Our nutrient pattern approach was particularly useful for comparing dietary patterns across European countries considering the large heterogeneity in foods consumed. For example, PC1 loaded on a broad range of food sources across the 10 countries participating in EPIC [15]. Because different food sources contributed to the very same nutrient patterns, it reduces the likelihood that results are confounded by other dietary compounds not captured by a given pattern, which adds further strength to our findings.

Previous research has shown that various food patterns are associated with weight change [7–12]. Here we show, for the first time, which combinations of nutrients may account for such observations, thus providing insight into potential biologic pathways. Adherence to a healthy pattern characterized by nutrients from plant food sources such as vitamin C, beta-carotene, folate, or dietary fiber, was moderately, but significantly associated with less weight gain while a pattern rich in protein, riboflavin, phosphorus, and calcium promoted weight gain. These findings may also help to make food choices that prevent weight gain based on their nutrient content.

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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 centers 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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