Dietary fat intake and subsequent weight change in adults: results from the European Prospective Investigation into Cancer and Nutrition cohorts

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ABSTRACT

Background: It is unclear from the inconsistent epidemiologic evidence whether dietary fat intake is associated with future weight change.

Objective: The objective was to assess the association between the amount and type of dietary fat and subsequent weight change (follow-up weight minus baseline weight divided by duration of follow-up).

Design: We analyzed data from 89,432 men and women from 6 cohorts of the EPIC (European Prospective Investigation into Cancer and Nutrition) study. Using country-specific food-frequency questionnaires, we examined the association between baseline fat intake (amount and type of total, saturated, polyunsaturated, and monounsaturated fats) and annual weight change by using the residual, nutrient density, and energy-partition methods. We used random-effects meta-analyses to obtain pooled estimates across centers.

Results: Mean total fat intake as a percentage of energy intake ranged between 31.5% and 36.5% across the 6 cohorts (58% women; mean ± SD age: 53.2 ± 8.6 y). The mean (±SD) annual weight change was 109 ± 817 g/y in men and 119 ± 823 g/y in women. In pooled analyses adjusted for anthropometric, dietary, and lifestyle factors and follow-up period, no significant association was observed between fat intake (amount or type) and weight change. The difference in mean annual weight change was 0.90 g/y (95% CI: −0.54, 2.34 g/y) for men and −1.30 g/y (95% CI: −3.70, 1.11 g/y) for women per 1 g/d energy-adjusted fat intake (residual method).

Conclusions: We found no significant association between the amount or type of dietary fat and subsequent weight change in this large prospective study. These findings do not support the use of low-fat diets to prevent weight gain.


INTRODUCTION

There is an ongoing intense scientific debate about whether the fat content of the diet per se predicts obesity and weight gain. Scientific opinion ranges from the view that it has an important role to the opposite view, ie, that it has no significant role (1–3), with some scientists describing efforts to reduce fat intake as a distraction from tackling obesity. In general, diets with a greater percentage of energy from fat result in a higher total energy intake, given that fat is the most energy-dense macronutrient in the diet (1, 4); however, there is a lack of clarity as to whether the fat content of the diet, with or without adjustment for total energy intake, influences weight gain. Contrary to expectations, evidence from long-term randomized trials and epidemiologic studies linking fat intake to weight gain or obesity is weak (2, 5, 6) and inconsistent (7–13). Part of the inconsistency arises from measurement error in assessment of the exposure (diet) and the outcome (anthropometric assessment). Furthermore, even if there were a relation, it is unclear whether it is the total amount of fat consumed, ie, the fat density, or the quality/type of the fat consumed that might make the most difference to weight gain. A recent analysis from the Nurses’ Health Study among 41,518 women reported that, whereas there was a weak positive association between total fat intake and weight gain over 8 y, there was a stronger association with the percentage of energy from animal fat, saturated fat, and trans fat (14). There is evidence of differential oxidation versus storage of saturated (SFA), mono-unsaturated (MUFA), and polyunsaturated (PUFA) fatty acids in...
humans (15), which lends support to the hypothesis that different types of fatty acids may contribute differentially to weight gain (16).

Identification of any modifiable risk factors for obesity and weight gain is important to help tackle this serious worldwide public health problem. The role of dietary fat intake may be important in influencing weight gain, but remains controversial and unresolved. We have studied the association between dietary fat intake and change in weight prospectively in the European Prospective Investigation into Cancer and Nutrition (EPIC) study cohorts participating in the Diet, Genes and Obesity (DiOGenes) project.

SUBJECTS AND METHODS

Study population

We used data from 6 cohorts within 5 countries participating in the EPIC study: Denmark (Copenhagen and Aarhus with identical methods and hence considered one cohort; DK-Cop/Aa), Germany (Potsdam; Ger-Pot), Italy (Florence; IT-Flo), the Netherlands [Doetinchem (NL-Doe) and Amsterdam/Maastricht (NL-AmMa)]; 2 separate cohorts because of differences in data collection methods], and the United Kingdom (Norfolk; UK-Nor). These cohorts are population based and included men and women (17).

From the 146,543 initial participants across 6 cohorts, our final study population consisted of 89,432 eligible participants (52,307; 58% women), after exclusions. An a priori decision was made to exclude participants in the top 1% or bottom 1% of the ratio of total energy intake/predicted energy expenditure (n = 1803), women who were pregnant at either baseline or follow-up (n = 133), those with missing data on diet at baseline (n = 113), those with missing anthropometric measures (baseline or follow-up) or follow-up time (n = 2022), those with baseline chronic disease (prevalent diabetes, cancer, or cardiovascular disease; n = 8512), those with extreme anthropometric data [height < 130 cm, body mass index (BMI; in kg/m²) < 16, waist circumference < 40 or > 160 cm, and weight change > 5 kg/y or waist circumference change > 7 cm/y; n = 331], or those with no follow-up data available (n = 44,197). The mean duration of follow-up ranged from 3.7 to 10.0 y, and the mean age ranged from 42.5 to 58.1 y in the 6 cohorts.

Dietary assessment

Detailed dietary information at baseline was collected with a country-specific food-frequency questionnaire (FFQ) that asked about habitual intake of medium-sized serving of foods over the past year (17). Food intake (in g/d) was derived by multiplying the frequency of intake with portion sizes. Energy intake was calculated by using national food-composition tables (17). Estimated daily fat intakes were calculated by multiplying the fat content of each food of the specific portion size by the frequency of consumption as stated on the FFQ by using country-specific food tables. In a random sample constituting ~8% of each EPIC cohort, dietary intake was also assessed with a highly standardized 24-h recall by using EPIC-SOFT (18, 19). Data from this method were used to improve the comparability of dietary data collected with different national FFQs and to reduce measurement error (20, 21). Calibrated dietary intake variables were derived from a linear calibration model that regressed dietary intake variables from the 24-h recall on the FFQ dietary values (22).

Both observed and calibrated dietary fat intake data consisted of fat intake (in g/d) for total fat and types of fat, including SFAs, PUFAs, and MUFAs. We also used data for other macronutrients (carbohydrate and protein) and alcohol and fiber intake (in g/d) and for total energy intake (in kcal/d). We also derived the nutrient density of fat intake as a percentage of the total energy intake (energy from fat intake/total energy intake × 100).

Assessment of anthropometric measures and weight change

At baseline, weight, height, and waist circumference were measured according to a prespecified protocol by trained staff in all 6 cohorts, with participants wearing no shoes and either light indoor clothing (UK-Nor, NL-Doe, and NL-AmMa) or underwear (IT-Flo, Ger-Pot, and DK-Cop/Aa). At follow-up, anthropometric measurements were performed according to an identical protocol as during baseline examination by staff in UK-Nor and NL-Doe or were self-reported by the participants in a follow-up questionnaire in the other cohorts. Weight was only assessed once at baseline and once at follow-up. BMI was calculated by dividing weight (kg) by the square of height (m²). We used observed anthropometric measures without applying any correction factors to give an accurate reflection of the available weight data across Europe. In a comparison study in the EPIC-Norfolk (UK-Nor) cohort, the correlation between measured and self-reported weight was 0.95, and 96.5% of the difference between measured and self-reported weight was within 2 SDs either side of the mean (unpublished data).

The outcome in the current analysis was annual change in body weight (g/y). This was calculated for each participant by subtracting the baseline weight from follow-up weight and dividing the difference (in g) by the duration of follow-up in years.

Statistical analysis

First we examined the distribution of dietary fat intake (exposure) and of annual weight change (outcome) across the 6 cohorts in men and women separately. Next, we explored the association between total dietary fat intake and annual weight change using 3 different modeling approaches (23). In the residual method, the residuals from the regression of total fat intake on total energy intake are obtained and then rescaled by adding the expected fat intake for a person with mean total energy intake. This energy-adjusted fat intake was the main exposure, and total energy intake was included as a covariate. Thus, effects on annual weight change were estimated per 1-g/d increase in “energy-adjusted fat.” This approach attempts to overcome the potential underreporting of dietary fat intake (24) and was used as our primary modeling approach. In the nutrient density method, the nutrient density from fat (ie, % of total energy intake from dietary fat) was the main exposure, and total energy intake was included as a covariate. Thus, effects on annual weight change were estimated per 1% increase in fat (as a % of total energy intake). The nutrient density approach is useful because it represents the dietary public health recommendations, which are expressed in terms of percentage of...
energy from fat. We also repeated our analyses using a third approach, to check for consistency in the results. In the energy partition method, we included absolute fat intake (in g/d) and included other macronutrients (absolute carbohydrate, protein, and alcohol intakes) but omitted total energy intake as a co-
variate in the model (23).

Linear regression models were constructed, initially testing for statistical interactions between the dietary fat exposure and 1) cohort, 2) age, 3) duration of follow-up, 4) BMI, and 5) smoking behavior (defined in 4 categories by using smoking information from baseline and follow-up, as nonsmokers, stable smokers, starting smokers, and stopping smokers), to define our analytic strategy. A model was fit by using data from all cohorts (but separately in men and women), with the relevant interaction term included (eg, age × dietary fat exposure). The P value for the interaction terms was calculated by using an F test. The residual method (our primary approach) was used to assess interactions.

We investigated the effect of total fat intake on annual weight change, accounting for potential confounders, using the following modeling strategy. In model 1 we adjusted for baseline age, baseline weight, baseline height, total energy intake, and duration of follow-up (all continuous variables). Model 2 adjusted additionally for smoking status at baseline and follow-up, education (highest level achieved from self-reported categories of none/primary school, secondary school, technical/professional qualification, or university degree), and physical activity. In each center standardized questions elicited information on the type and duration of occupational and nonoccupational activities (17, 25), and the reproducibility and relative validity of these questions in ranking individuals was established (26). A physical activity index of total physical activity was created, in which participants were cross-classified on the basis of sex-specific quartiles of leisure-time activity and on categories of occupational work, and coded as inactive, moderately inactive, moderately active, and active. This index was validated and enabled the ranking of participants according to their energy expenditure estimated by self-report, by comparison with objectively measured energy expenditure assessed by heart rate monitoring with individual calibration (27). Additionally, among women, model 2 also included menopausal status and hormone use at baseline (yes/no categories from questionnaire). In model 3 we additionally adjusted model 2 for alcohol intake (continuous variable). Finally, in model 4 we also included protein intake, thus estimating the effect of substituting 1% of energy from fat for 1% of energy from carbohydrate, with the amount of total energy fixed in an isocaloric model including total energy intake. In the nutrient density model, we included alcohol intake and protein intake, both as a percentage of total energy intake, whereas, in the residual model, we included energy-adjusted alcohol intake and energy-adjusted protein intake. In the energy partition method, because all macronutrients are included simultaneously in the model, substitution of carbohydrate for fat was not performed; thus, only models 1, 2, and 3 (see above) were fit, but without total energy intake. Using our primary approach, the residual method, we also assessed the effects of different types of fat (SFA, PUFAs, and MUFA) and the ratio of PUFAs to SFAs (P:S) and of MUFA to SFAs (M:S) on annual weight change. Other covariates included in the analysis were the same as those included in model 4 (defined above).

Estimates (and 95% CIs) of the effect of the exposure were calculated within each cohort and sex group and displayed in forest plots. A combined estimate (and 95% CI) across cohorts was calculated by using a random-effects meta-analysis approach (28). F2, the percentage of variability between cohorts due to heterogeneity, and a P value (based on Cochran’s Q test for heterogeneity) were also reported (29).

We performed a series of sensitivity analyses in which we used BMI instead of weight and height at baseline, included or omitted waist circumference, repeated the analyses using nonalcohol total energy intake, omitted alcohol intake from the models, and included or omitted fiber intake and repeated the analyses using uncalibrated dietary exposure data. We applied a correction for differences in body weight across cohorts by subtracting 1 kg when the participants were measured wearing light clothing and by applying a regression equation to predict weight from self-report (30). We also repeated the analysis excluding participants who were either overweight (BMI: 25–30) or obese (BMI ≥ 30) at baseline. Finally, to investigate the potential role of morbidity during follow-up, we excluded participants with incident chronic diseases (cancer, cardiovascular disease, and diabetes) from the analyses.

To investigate the potential effect of intentional dieting on weight change, we performed a subsample analysis among participants in the EPIC-Norfolk cohort, where such information was ascertained with a health and lifestyle questionnaire at baseline. Thus, data were available for self-report of being on a low-fat diet, weight-losing diet, or having modified the diet because of overweight or obesity.

Finally, we also investigated the effect of total fat intake on annual change in waist circumference (cm/y) using the residual method. Annual weight change was included as a covariate in the model, along with all other covariates included in model 4. The analyses were performed by using STATA software (version 10; StataCorp, College Station, TX).

RESULTS

Baseline characteristics and weight change

The mean (±SD) age of the combined study population was 53.8 ± 8.2 y among men and 52.7 ± 8.8 y among women, with the 2 Dutch cohorts being the youngest (Table 1). Mean waist circumference ranged from 90.5 to 95.3 cm among men and from 76.9 to 85.5 cm among women across the cohorts. The mean duration of follow-up was shortest in the United Kingdom (3.7 y), and longest (10 y) in the Netherlands (Amsterdam/ Maastricht cohort). The greatest annual change in weight was in Doetinchem (433 g/y in men and 447 g/y in women), whereas the greatest prevalence of obesity (BMI > 30) was observed in Germany at both baseline and follow-up, in both men and women. Physical inactivity levels were greatest in the United Kingdom and Germany, in both men and women, and additionally in Italy in women.

The levels of dietary fat intake and other macronutrients in each cohort are shown in Table 2. Mean total and SFA intakes (as a % of total energy intake) were highest in the Netherlands and Germany, the mean MUFA intake and M:S ratio were highest in Italian men and women, and the mean P:S ratio was highest in the United Kingdom. The mean protein intake (% total energy) was
## TABLE 1
Characteristics of men and women at baseline and follow-up in each of the 6 cohorts and overall: the Diet, Genes and Obesity (DiOGenes) project

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
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<tbody>
<tr>
<td></td>
<td>IT-Flo (n = 2041)</td>
<td>IT-Flo (n = 7256)</td>
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<tr>
<td></td>
<td>UK-Nor (n = 5594)</td>
<td>UK-Nor (n = 7214)</td>
</tr>
<tr>
<td></td>
<td>NL-AmMa (n = 2996)</td>
<td>NL-AmMa (n = 3915)</td>
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<td></td>
<td>NL-Doee (n = 2009)</td>
<td>NL-Doee (n = 2191)</td>
</tr>
<tr>
<td></td>
<td>Ger-Pot (n = 6214)</td>
<td>Ger-Pot (n = 10,093)</td>
</tr>
<tr>
<td></td>
<td>DK-Cop/Aa (n = 18,271)</td>
<td>DK-Cop/Aa (n = 21,638)</td>
</tr>
<tr>
<td></td>
<td>All (n = 37,125)</td>
<td>All (n = 52,307)</td>
</tr>
<tr>
<td>Age at baseline (y)</td>
<td>51.0 ± 7.2</td>
<td>51.6 ± 7.7</td>
</tr>
<tr>
<td>Duration of follow-up (y)</td>
<td>9.4 ± 1.1</td>
<td>9.4 ± 1.1</td>
</tr>
<tr>
<td>Waist circumference at baseline (cm)</td>
<td>90.5 ± 8.9</td>
<td>76.9 ± 9.5</td>
</tr>
<tr>
<td>Weight (at baseline) (kg)</td>
<td>78.1 ± 10.8</td>
<td>64.0 ± 10.3</td>
</tr>
<tr>
<td>BMI (at baseline) (kg/m²)</td>
<td>26.1 ± 3.2</td>
<td>25.0 ± 3.9</td>
</tr>
<tr>
<td>Obese (BMI &gt;30 kg/m²) at baseline (%)</td>
<td>11.3</td>
<td>10.2</td>
</tr>
<tr>
<td>Obese (BMI &gt;30 kg/m²) at follow-up (%)</td>
<td>14.0</td>
<td>14.0</td>
</tr>
<tr>
<td>Physical activity at baseline (%)</td>
<td>Inactive 13.1</td>
<td>28.1</td>
</tr>
<tr>
<td></td>
<td>Moderately active 24.7</td>
<td>27.4</td>
</tr>
<tr>
<td></td>
<td>Active 27.4</td>
<td>17.8</td>
</tr>
</tbody>
</table>

1 DK-Cop/Aa, Denmark (Copenhagen and Aarhus) cohort; Ger-Pot, Germany (Potsdam) cohort; IT-Flo, Italy (Florence) cohort; NL-Doee, the Netherlands (Doetinchem) cohort; NL-AmMa, Amsterdam/Maastricht cohort; UK-Nor, United Kingdom (Norfolk) cohort.

2 Mean ± SD (all such values).
Dietary fat, protein, carbohydrate, and alcohol intakes in men and women at baseline in each of the 6 cohorts and overall: the Diet, Genes and Obesity (DiOGenes) project\(^1\)

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th></th>
<th>Women</th>
<th></th>
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</thead>
<tbody>
<tr>
<td></td>
<td>IT-Flo (n = 2041)</td>
<td>UK-Nor (n = 5594)</td>
<td>NL-AmMa (n = 2996)</td>
<td>NL-Doe (n = 2000)</td>
</tr>
<tr>
<td>Total fat (% of total energy)</td>
<td>31.5 ± 5.0(^2)</td>
<td>34.0 ± 5.6</td>
<td>35.9 ± 5.3</td>
<td>36.5 ± 4.8</td>
</tr>
<tr>
<td>Saturated fat (% of total energy)</td>
<td>10.9 ± 2.3</td>
<td>13.1 ± 3.2</td>
<td>14.8 ± 2.6</td>
<td>15.2 ± 2.3</td>
</tr>
<tr>
<td>Polyunsaturated fat (% of total energy)</td>
<td>3.5 ± 0.7</td>
<td>6.9 ± 2.1</td>
<td>7.1 ± 1.8</td>
<td>7.2 ± 1.7</td>
</tr>
<tr>
<td>Monounsaturated fat (% of total energy)</td>
<td>15.5 ± 2.9</td>
<td>11.4 ± 2.1</td>
<td>12.3 ± 2.2</td>
<td>12.4 ± 2.0</td>
</tr>
<tr>
<td>P:S</td>
<td>0.33 ± 0.08</td>
<td>0.56 ± 0.23</td>
<td>0.49 ± 0.15</td>
<td>0.49 ± 0.13</td>
</tr>
<tr>
<td>M:S</td>
<td>1.46 ± 0.31</td>
<td>0.90 ± 0.16</td>
<td>0.84 ± 0.14</td>
<td>0.82 ± 0.12</td>
</tr>
<tr>
<td>Protein (% of total energy)</td>
<td>15.8 ± 2.0</td>
<td>16.5 ± 2.8</td>
<td>14.7 ± 2.0</td>
<td>15.1 ± 1.9</td>
</tr>
<tr>
<td>Carbohydrate (% of total energy)</td>
<td>46.3 ± 6.5</td>
<td>45.1 ± 6.7</td>
<td>44.0 ± 6.3</td>
<td>43.8 ± 5.7</td>
</tr>
<tr>
<td>Alcohol (g/d)(^3)</td>
<td>21.3</td>
<td>7.7</td>
<td>12.9</td>
<td>11.7</td>
</tr>
</tbody>
</table>

\(^1\) DK-CopAa, Denmark (Copenhagen and Aarhus) cohort; Ger-Pot, Germany (Potsdam) cohort; IT-Flo, Italy (Florence) cohort; NL-Doe, the Netherlands (Doetinchem) cohort; NL-AmMa, Amsterdam/ Maastricht cohort; UK-Nor, United Kingdom (Norfolk) cohort; P:S, ratio of polyunsaturated to saturated fat; M:S, ratio of monounsaturated to saturated fat.

\(^2\) Mean ± SD (all such values).

\(^3\) Because of a skewed distribution, values are reported as medians (interquartile ranges).
highest in Denmark and United Kingdom, whereas the mean carbohydrate intake (% total energy) was lowest in Denmark.

**Association between total fat intake and annual weight change**

With the use of the residual method, we found no statistical interaction of fat intake with age (<60 or ≥60 y; \( P = 0.68 \) in men and \( P = 0.12 \) in women) or smoking behavior in men (\( P = 0.13 \)). There were, however, significant interactions between fat intake and cohort (\( P = 0.039 \) in men and \( P < 0.001 \) in women), duration of follow-up (\( P = 0.031 \) in men and \( P < 0.001 \) in women), BMI (\( P = 0.0026 \) in men and \( P = 0.008 \) in women), and smoking behavior in women (\( P < 0.001 \)).

The interactions with BMI and smoking were not consistent across cohorts and the sexes, so, to avoid separating the data into too many different strata, we chose to present results separately for men and women within each cohort (but not stratified further) and used a random-effects meta-analysis to estimate a combined effect across cohorts.

**Residual method**

There was an overall null association between dietary fat intake and annual weight change in both men and women (Figure 1A). There was significant heterogeneity between cohorts in women, but not in men, with a negative association in UK women (\( -8.3; 95\% \text{ CI:} -14.9, -1.7 \text{ g/y} \)) in model 3 and \(-11.2 (95\% \text{ CI:} -17.9, -4.4 \text{ g/y} \)) in model 4 for a 1-g higher energy-adjusted fat intake, but a null or positive association in other cohorts. Further adjustment for the P:S ratio or M:S ratio did not alter our findings.

**Nutrient density method**

Among men, there was a very small increase in annual weight change (pooled estimate: 3.8 g/y; 95% CI: 0.9, 6.8 g/y) for a 1% higher fat as a percentage of total energy intake in model 3 (Figure 1B). However, this association was not statistically significant once substitution of fat for carbohydrate was included (model 4). There was an inverse association between fat intake and annual weight change in several cohorts among women, but the magnitude was small (Figure 1B).

**Energy partition method**

The results derived by using the energy partition method were consistent with those derived by using the other 2 methods, with no evidence of an association in men and a very small inverse association in women (Figure 1C).

**Sensitivity analyses**

None of the sensitivity analyses (see Subjects and Methods) made any difference to the overall magnitude or direction of findings. Exclusion of those who were overweight or obese at baseline also did not alter the findings.

**Association between different types of fat, P:S ratio, and M:S ratio and annual weight change**

There was a minor (low magnitude) overall inverse association between SFA intake and annual weight change in women, but a null association in men (Table 3). Among both men and women, there was a null association for MUFA and PUFA intakes after adjustment for other types of fat. An increase in the P:S ratio was associated with an increase in annual weight change in women, but not in men; the association between the M:S ratio and annual weight change was not statistically significant after adjustment for the P:S ratio in men or women (Table 3).

**Effect of intentional dieting: analysis in the UK cohort**

Among 12,793 UK participants, women reported greater intentional dieting than men. The prevalence at baseline of self-report of a low-fat diet was 47% in women (35% in men), of a weight-losing diet was 13.4% in women (5% in men), and of having modified their diet because of overweight or obesity was 30% in women (17% in men). As expected, participants who were overweight or obese reported greater intentional dieting than did normal-weight-weight participants: eg, the prevalences of a weight-losing diet were 0%, 5%, 12%, and 19% across BMI categories <18.5, 18.5–24.9, 25–29.9, and ≥30, respectively. In exploratory analysis in UK women only, we compared the association between fat intake and weight change among all women with those in women on a diet or not. With the nutrient density approach (in which the inverse association was most extreme in UK women; Figure 1B), in model 4, the effect of a 1% higher fat intake was \(-16.9 \text{ g/y} (95\% \text{ CI:} -36.8, 3.0 \text{ g/y} \)) in the 3564 UK women on some sort of diet and was \(-1.8 \text{ g/y} (95\% \text{ CI:} -23.3, 19.7 \text{ g/y} \)) in the 2612 UK women not on any sort of diet, and \(-24.8 \text{ g/y} (95\% \text{ CI:} -38.9, -10.6 \text{ g/y} \)) overall. This suggested that the extreme negative result seen overall in women was largely being driven by intentional dieting.

**Association between total fat intake and annual waist circumference change**

A 1-g higher total fat intake was associated with an increase of \(<0.001 \text{ cm/y} \) in annual waist circumference in men and a decrease of 0.001 cm/y in women, with neither change being statistically significant.

**DISCUSSION**

In this large prospective study among European populations, we found a null effect of dietary fat intake on subsequent weight change. This was the case whether we examined total fat intake or different types of fat and included a wide range of fat intake among the study participants in the different cohorts. The findings were broadly consistent with a variety of statistical modeling approaches in analyses adjusted for a comprehensive set of potential confounders. Our findings lend support to the scientific view that promoting low-fat diets may not offer the optimal approach for tackling the obesity epidemic and might potentially divert attention from the recommended goals of reducing the dietary total energy content or promoting greater physical activity as set out in the current US national dietary guidelines (31).

Previous studies have shown that dietary fat increases energy intake across the range of typical consumption (4) and that the observed effect of lower weight gain among people on low-fat diets is removed when the effect of total energy intake is taken into account (32). We performed our analyses adjusting for the
FIGURE 1. (Continued)
The effect of total energy intake in 2 ways: we included total energy intake in our statistical models, and we also used energy-adjusted fat intake in the residual method (24, 33). Indeed, when we used the residual method, which adjusts the fat intake for total energy intake and thus reduces the potential effect of underreporting (24), we found a null association in both men and women and in all models. Among women, particularly with the nutrient density method and the energy partition method, we observed a small decrease in weight change in the pooled analysis, but the magnitude was low and of questionable biological meaning (mean annual weight change of between 2.1.4 and 2.6.4 g/y per 1% fat as a percentage of total energy intake, or 1 g absolute fat intake). We speculated that a relatively lower weight change might be observed because of potential underreporting of fat intake combined with an underestimation of self-reported weight among the overweight or obese individuals in the cohorts, for whom measured follow-up weight was unavailable. However, to our surprise, we observed the greatest inverse association mainly in the cohorts in which weight at both baseline and follow-up was measured at the health-check examination. When we explored this in the UK cohort (with the greatest magnitude of inverse association), it appeared to be driven by women who were intentionally dieting, as when we restricted our analysis to women not on a diet, we found a null association with weight change. This highlights the importance of considering the effect of deliberate attempts at weight loss in epidemiologic studies of free-living individuals, as also previously shown by Ballard-Barbash et al (34). The high self-reported prevalence of intentional dieting, particularly in women, in our study was comparable with other cohorts (35). It is unlikely that comorbidity during follow-up was the explanation for the reduced weight change, based on the analyses that excluded participants with incident chronic disease.

Apart from a small effect of SFAs and the P:S ratio in women, we found no other associations between the type of fat consumed and weight change. Our lack of association with the quality of dietary fat is at variance with the recent results from the Nurses’ Health Study, in which increases in percentage of energy from SFAs, trans fat, and animal fat (but not vegetable fat) were associated positively with weight change (14). One explanation for their observed association, as the authors discussed, may have been residual confounding on the basis that persons who consume diets high in SFAs and trans fats may also exhibit other unhealthy lifestyle behaviors, such as a high consumption of sugar-sweetened beverages and fast food. In a review by Moussavi et al (36), 3 of 9 studies found a positive association...
between the type of fatty acids and weight change, 3 reported a negative association, and 3 found a null association. Thus, to date, the evidence is inconclusive. Clearly, given the public health importance of the accumulating evidence base that the substitution of “unhealthy fats” (SFA and trans fats) with “healthy fats” (unsaturated fats) is beneficial for coronary risk prevention (37), we need to further examine the role of dietary fat quality on obesity and weight gain in specifically designed studies.

Our study had some limitations. Use of the FFQ for dietary assessment potentially resulted in the underreporting of fat intake (38), particularly in the overweight/obese persons (39, 40); however, the use of energy-adjusted fat intake, as we did in our residual approach, minimizes such potential (23, 24, 33). An advantage of the FFQ is that it can be used relatively cheaply and easily and hence offers a pragmatic advantage for large epidemiologic studies. However, smaller studies might be able to examine more objectively measured plasma or erythrocyte membrane fatty acid content, which offer greater precision and have lower measurement error than FFQs. We analyzed fat intake only at one time point (baseline) and did not examine any changes in fat intake, which might vary considerably with time. We had no data on trans fatty acids; hence, we could not test the hypothesis that trans fats might be positively associated with weight gain, as in the Nurses’ Health Study (14). Our endpoint, weight change, is a dynamic process, which is complex to measure with only 2 time points, as in this study (baseline and follow-up). Indeed, there may be differential weight change with varying durations of follow-up. To overcome the differences in weight change, we examined annual weight change rather than absolute weight change over the entire follow-up duration and additionally adjusted for the duration of follow-up in our analyses. Weight at follow-up was objectively measured by trained staff in only 2 of the 6 cohorts. Of the remaining 4 cohorts, follow-up weight was based on self-report, which may have led to potential underestimation, particularly among the overweight or obese, and we particularly suspect this to have been the case in the Danish cohort, in whom, overall, there was a net weight loss reported over the follow-up period. However, in a sensitivity analysis, we did apply corrections for the self-report of weight in some cohorts, but this did not appreciably change our findings of an overall null effect. Notably, we also found a similar magnitude and direction of weight change when we excluded overweight or obese individuals at baseline, thus excluding underreporting among such groups as the explanation for the null association. There might also have been correlated errors (in dietary exposures, including between various foods and with anthropometric measures), which made it difficult to distinguish the direction of bias in our results. Finally, the lack of follow-up data in 30% of the original cohort limited the generalizability of the findings in the nonparticipating group, but the results remained valid among those included.

The strengths of our study included its large size (nearly 90,000 participants), the inclusion of both men and women, the wide age range of persons included, and the use of participants from 6 cohorts across European countries with widely varying dietary fat intakes (17). Our analyses were robust to a range of assumptions and were adjusted for a comprehensive range of potential confounders, including lifestyle and important dietary and socioeconomic factors, which was an attempt to minimize the effect of confounding from clustering of healthier lifestyles that might be associated with lower intakes of dietary fat. We presented the results for each cohort separately, but also calculated a pooled estimate of effect using a random-effects model, which allowed us to take into account the between-cohort heterogeneity and allowed for different effects of the potential confounders across cohorts (28). Finally, we used several methods to assess the association between fat intake and weight gain, including the

### Table 3

<table>
<thead>
<tr>
<th>All cohorts combined</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/y</td>
<td>g/y</td>
</tr>
<tr>
<td>Saturated fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without adjustment for other types of fat</td>
<td>1.1 (−1.3, 3.5)</td>
<td>−5.0 (−9.1, −1.0)</td>
</tr>
<tr>
<td>With adjustment for other types of fat</td>
<td>−0.9 (−6.1, 4.2)</td>
<td>−8.1 (−11.1, −5.0)</td>
</tr>
<tr>
<td>Monounsaturated fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without adjustment for other types of fat</td>
<td>2.9 (−2.4, 8.1)</td>
<td>−2.7 (−9.4, 4.0)</td>
</tr>
<tr>
<td>With adjustment for other types of fat</td>
<td>4.8 (−5.5, 15.1)</td>
<td>2.0 (−7.0, 11.0)</td>
</tr>
<tr>
<td>Polysaturated fat</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without adjustment for other types of fat</td>
<td>0.5 (−2.7, 3.6)</td>
<td>6.0 (1.3, 10.6)</td>
</tr>
<tr>
<td>With adjustment for other types of fat</td>
<td>−3.4 (−10.0, 3.3)</td>
<td>5.1 (−1.6, 11.8)</td>
</tr>
<tr>
<td>P:S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without adjustment for M:S ratio</td>
<td>−1.7 (−12.8, 9.3)</td>
<td>34.3 (15.5, 53.1)</td>
</tr>
<tr>
<td>With adjustment for M:S ratio</td>
<td>−18.7 (−40.8, 32.9)</td>
<td>27.4 (36.9, 51.2)</td>
</tr>
<tr>
<td>M:S</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without adjustment for P:S ratio</td>
<td>9.6 (−11.1, 30.3)</td>
<td>24.3 (4.6, 44.2)</td>
</tr>
<tr>
<td>With adjustment for P:S ratio</td>
<td>21.3 (−13.7, 56.4)</td>
<td>8.5 (−16.7, 33.6)</td>
</tr>
</tbody>
</table>

1 Model 4 (see Subjects and Methods); adjusted for baseline age, baseline weight, baseline height, total energy intake, duration of follow-up, smoking status at baseline and follow-up, baseline physical activity index, education, menopausal status (women only), hormone use at baseline (women only), energy-adjusted alcohol intake, and energy-adjusted protein intake. Differences and CIs are pooled estimates from a random-effects meta-analysis across centers.
residual, the nutrient density, and the energy-partition methods and found broadly similar results, with mainly a null association.

In conclusion, we report a null association between the amount of dietary fat intake and annual weight change among European populations. Our findings highlight that an emphasis on dietary fat intake alone may be misplaced and that we need to consider wider dietary contexts and both sides of energy balance to include energy expenditure as well as energy intake.

The Diet, Obesity and Genes (DiOGenes) project is a pan-European study within the EU Sixth Framework Programme for Research and Technological Development (2005–2009). This integrated program was set up to target the obesity problem from a dietary perspective, seeking new insights and new routes to prevention. We thank the EPIC study investigators.

The authors’ responsibilities were as follows—NGF and SJS: had full access to all of the data in this study and take responsibility for the integrity of the data and the accuracy of the data analysis; and NJW, AT, DP, KO, HB, EJMF, and TIAS: designed the study, contributed to acquiring the data and providing funding, helped with the interpretation of the results, and gave critical comments on the manuscript. All authors contributed to the study and draft versions of the manuscript. None of the authors had any financial disclosures relevant to the current analysis or article.

REFERENCES


2. Willett WC, Leibel RL. Dietary fat is not a major determinant of body fat. Am J Med 2002;113(suppl 9B):47S–59S.


