

Effect of dietary fatty acid intake on prospective weight change in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition

Katharina Nimptsch^{1,2}, Gabriele Berg-Beckhoff³ and Jakob Linseisen^{1,4,*}

¹Division of Cancer Epidemiology, German Cancer Research Center, Im Neuenheimer Feld 280, Heidelberg, Germany; ²Department of Nutrition, Harvard School of Public Health, 665 Huntington Avenue, Boston, MA, USA; ³Department of Epidemiology and International Public Health, Faculty of Public Health, University of Bielefeld, Bielefeld, Germany; ⁴Helmholtz Zentrum München (HMGU), Institute of Epidemiology, Ingolstädter Landstr. 1, D-85764 Neuherberg, Germany

Submitted 16 February 2009; Accepted 26 November 2009; First published online 15 January 2010

Abstract

Objective: To evaluate the association between fatty acid (α -linolenic acid (ALA), EPA, DHA, palmitic, stearic, oleic, linoleic and arachidonic acids) intake and prospective weight change in the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition.

Design: Prospective cohort study with mean follow-up time of 6.5 years. In a total of 9182 men and 10867 women aged 35 to 64 years, from body weight measurement at recruitment and calibrated body weight during follow-up, weight change was expressed as mean annual weight change relative to baseline weight (%/year) and categorised into four groups (weight loss, $<-2.5\%/5$ years; stable weight, between -2.5 and $+2.5\%/5$ years; small weight gain, ≥ 2.5 to $<7.5\%/5$ years; large weight gain, $\geq 7.5\%/5$ years). Energy-adjusted dietary fatty acid intake data were estimated from the FFQ completed at baseline. Multivariate linear regression models as well as multinomial logistic regression analyses (carbohydrate replacement models) were conducted.

Results: Stearic acid intake was linearly associated with weight gain ($P < 0.01$) in men and women. Linear associations also existed for ALA and arachidonic acid intake, significantly so in women. In multinomial models, women in the highest tertile of ALA and stearic acid intake showed increased OR (95% CI) for small weight gain (1.16 (0.94, 1.38) and 1.24 (1.08, 1.43), respectively), and large weight gain (1.39 (1.03, 1.88) and 1.56 (1.27, 1.90), respectively), whereas OR were non-significantly increased in men. Dietary intake of ALA was inversely associated with large (0.80 (0.65, 0.99)) weight gain in women only.

Conclusions: These results suggest differential effects of single dietary fatty acids on prospective weight gain in adults.

Keywords

Prospective weight change
Incident overweight and obesity
Fatty acid intake
Prospective cohort study

The prevalence of overweight and obesity has increased remarkably during the past 20 years in Germany and worldwide^(1,2). Two-thirds of all obese adults have developed obesity during adulthood⁽³⁾. Since the proportion of overweight people is lowest at the age of 18–19 years⁽⁴⁾, maintenance of the body weight after adolescent growth should be the primary aim of obesity prevention in adults⁽⁵⁾.

In principle, weight change occurs when there is an imbalance between energy intake and energy expenditure over a longer time period. Psychosocial or genetic factors favouring excess energy intake and reduced energy expenditure can contribute to a positive energy balance eventually leading to weight gain⁽⁶⁾. Established determinants of weight change are alcohol consumption,

smoking habits, sociodemographic factors, physical activity, mental stress, voluntary weight loss or dieting behaviour⁽⁷⁾. The role of diet in weight change is complex and still many aspects remain to be elucidated. Fat is the most energy-dense macronutrient providing 38 kJ/g (9 kcal/g) and high-fat foods are characterised by enhanced flavour and palatability, while having a less satiating effect per kilojoule than low-fat foods rich in protein or complex carbohydrates; thus, a diet with a high proportion of fat is prone to lead to overconsumption of energy⁽⁸⁾. Although long-chain fatty acids differ only slightly with respect to the energy content, they can vary in their effect on energy balance. Both energy expenditure and satiety, which influence the magnitude of excess

*Corresponding author: Email j.linseisen@helmholtz-muenchen.de

energy intake, have been shown to be affected by the diet's fatty acid composition⁽⁹⁾. The mechanisms by which the fatty acids may impact on energy expenditure include their effect on postprandial thermogenesis⁽¹⁰⁾, fat oxidation rate^(11,12) and the sympathetic activity⁽¹³⁾. So far, observational studies in human subjects have investigated whether different types of fatty acids (i.e. PUFA *v.* MUFA *v.* SFA) differ in their effect on body weight^(8,14) or weight change⁽¹⁵⁾. However, data from experimental studies suggest that the effects of individual fatty acids are not necessarily uniform⁽¹⁶⁾. Therefore, in the present study, the hypothesis that individual fatty acids have differential effects on long-term weight change was tested within a prospective cohort study, the Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg). On the basis of the results of such observational studies, properly designed metabolic/intervention studies should follow.

Participants and methods

Study population and data collection

The EPIC-Heidelberg comprises 11 928 men (aged 40–64 years) and 13 612 women (aged 35–64 years), recruited between 1994 and 1998 (66 626 volunteers were contacted, overall participation rate was 38.3%). Habitual dietary intake during the 12 months preceding the recruitment was assessed by a validated self-administered 158-item semi-quantitative FFQ including additional questions with regard to the type of fat for cooking and fat content of milk and milk products⁽¹⁷⁾. Food coding and calculation of the individual intake of fatty acids and other nutrients were carried out using the German Food Code (version II.3)⁽¹⁸⁾. Information on lifestyle factors such as educational attainment, smoking habits and physical activity was assessed by self-administered questionnaires and a personal computer-guided interview at baseline. During the participant's visit in the study centre, body weight was measured on digital scales (Soehnle, type 7720/23, Murrhardt, Germany), and height was measured using a flexible anthropometer by educated interviewers. In the follow-up questionnaires, which are mailed to the participants at regular intervals, participants were asked to report their current body weight. The participation rates during the follow-ups were above 90% at all times. The study was approved by the local ethics committee and all participants gave their informed consent.

Calibration of self-reported body weight at follow-up

To correct for biases in the self-reported weight, to data from the three follow-up rounds, a calibration method was applied, as described by Spencer *et al.*⁽¹⁹⁾, using data from the subsample of volunteers who participated in the

24 h dietary recalls conducted by trained interviewers at baseline (n 2121). During the recalls, participants gave self-reported information on their body weight at baseline. In a simple regression analysis, measured weight was modelled as a function of age and self-reported weight, stratified by sex and standard BMI categories (<25, 25–29.9, \geq 30 kg/m²). The obtained equations were used to calibrate the self-reported weight data of the follow-up, assuming a consistency in bias in the self-reported values at baseline and follow-up. Comparison of reported and calibrated follow-up weight revealed that, on average, men tended to underestimate their follow-up weight less than women: the mean difference between calibrated and reported weight was 0.72 (SD 0.59), 0.67 (SD 0.60), 0.65 kg (SD 0.60) in men and 1.07 (SD 0.70), 1.03 (SD 0.70), 0.98 kg (SD 0.68) in women, in the first (1998–2000), second (2001–2004) and third (2004–2007) follow-up, respectively.

Statistical analyses

Follow-up time was defined as the time between baseline interview and last follow-up contact. Weight change was calculated as the difference between calibrated self-reported body weight at the last completed follow-up and measured body weight at baseline. For the analysis, annual weight change was expressed as a percentage of baseline body weight to take into account that absolute weight change is strongly dependent on baseline weight. Four categories of weight change in the percentage of baseline weight were defined as follows: stable body weight (weight change between -2.5 and $+2.5\%$ /5 years); weight loss (weight change $<-2.5\%$ /5 years); small weight gain (weight change of ≥ 2.5 to $<7.5\%$ /5 years) and large weight gain (weight change $\geq 7.5\%$ /5 years). Change in smoking status between baseline and last follow-up was accounted for as follows: smokers at baseline and last follow-up ('habitual smokers'), non-smokers at both assessment periods ('habitual non-smokers'), smokers at baseline, reporting non-smoking at follow-up ('quitters') and non-smokers at baseline and reporting smoking at follow-up ('new smokers'). Physical activity was classified into four categories (inactive, moderately inactive, moderately active and active), combining both occupational and recreational activities⁽²⁰⁾.

All nutrient values were energy-adjusted by the residual method as described by Willett and Stampfer⁽²¹⁾. The association between fatty acid intake (palmitic, stearic, oleic, linoleic, arachidonic, α -linolenic acid (ALA), EPA and DHA) and prospective weight change was investigated using linear and multinomial logistic regression models. In multiple linear regression analyses, a 5-year weight change was modelled as a continuous dependent variable. Nutrient intakes were entered as continuous independent variables into the model. Participants who lost more than 2.5% of their baseline weight (weight losers) during 5 years of follow-up were excluded from

this analysis to focus on weight gain. In a subanalysis, only participants with normal weight (BMI between 18.5 and 25 kg/m²) at baseline were included.

For the multinomial logistic regression, generalised logits were modelled for the three weight change categories *v.* stable weight. OR and 95% CI were calculated by tertiles of fatty acid intake with the lowest tertile being the reference category. Risk estimates for small and large gain are given in the Results section (results for weight loss are not shown). A test for trend across increasing tertiles of fatty acid intake was performed by entering median intake values of the fatty acid tertiles as a continuous variable in the multivariate models. In the multinomial logistic regression analysis, weight change is treated as a categorical outcome variable. Participants with stable weight are considered the outcome reference corresponding to non-diseased participants in classical binary logistic regression models. The OR can be interpreted as the relative risk to fall into a certain weight change category according to tertiles of dietary fatty acid intake with the lowest tertile being the reference.

Isoenergetic nutrient residual models were created by entering the energy-adjusted intakes of all fatty acids of interest (as continuous variable or tertile categories for the linear and multinomial logistic regression, respectively) simultaneously together with the intake of other SFA, other MUFA, other PUFA, protein and alcohol, as well as total energy intake. The coefficients derived from these models represent the effect of substituting energy from carbohydrates by energy from a specific fatty acid⁽²²⁾. As intake of EPA and DHA was highly correlated ($r > 0.97$), their intake was entered into the model as the sum of both. All models were adjusted for weight and height at baseline, age, physical activity, education, change in smoking status and length of follow-up. In women, multivariate models were additionally adjusted for menopausal status at baseline (premenopausal, perimenopausal, postmenopausal, surgical menopausal and missing information). The analyses were repeated with a model representing the effect of substituting energy from MUFA by energy from specific fatty acids (adjusted for intakes of other PUFA, other SFA, carbohydrates, protein, alcohol and total energy). In contrast to the carbohydrate replacement model in the MUFA replacement model, the proportion of energy from fat is held constant.

In a final approach, incident overweight and obesity, respectively, were treated as outcomes in a binary logistic regression. Participants were defined as incident overweight or obese if they had a BMI < 25 or < 30 kg/m², respectively, at baseline and a BMI of ≥ 25 or ≥ 30 kg/m², respectively, at last follow-up. For this analysis, participants who were overweight or obese, respectively, at baseline were excluded. Adjustment was identical to the multinomial logistic regression analyses.

All statistical analyses were performed by the SAS statistical software package version 9.1 (SAS Institute, Cary, NC, USA, 2002). Analyses were performed separately for

men and women. Statistical tests were two-sided, and significance level was set at $P < 0.05$.

Results

Participants who were lost to follow-up or did not report their body weight in at least one of the follow-up rounds (n 176) and participants who were predisposed to weight change because of prevalent or incident cancer, myocardial infarction, stroke or inflammatory bowel disease (n 4904) were excluded, as well as the top and bottom percentile of weight change (in percentage of baseline weight, n 411). Finally, 20 049 participants (9182 men and 10 867 women) were included in the analysis.

Characteristics of the study population including dietary intake of the fatty acids of interest are presented in Table 1. Male participants were older and had a higher BMI than female participants. The proportion of normal weight participants at baseline was 55.3% in women, but only 32.0% in men. On average, women gained, in a 5-year interval of follow-up, 1.6% of baseline weight compared with 0.8% in men. The proportion of participants with a baseline BMI < 25 kg/m² who became overweight during follow-up (incident overweight) was 19.9% and 12.4% in men and women, respectively. Around 5% of all men and women, who had a BMI < 30 kg/m² at baseline, were obese at their last follow-up (incident obese). Mean follow-up time was 6.5 years for both men and women.

Table 2 shows the distribution of the weight change categories. Stable weight participants form the largest group with a proportion of 50.7% and 42.7% in men and women, respectively. About 18% of male and female participants had a 5-year weight loss of more than 2.5%. More women (39.8%) than men (31.1%) were characterised by a 5-year weight gain. The proportion of men and women who gained weight during follow-up decreased with increasing baseline age. Age at baseline and the percentage of weight change were significantly inversely correlated in men and women ($P < 0.0001$).

The results of the linear regression analyses modelling the influence of fatty acid intake on prospective weight gain in men and women are presented in Table 3. Stearic acid intake was significantly positively associated with weight gain, yielding a weight gain $> 3\%$ in men and women per 10 g increment ($> 4\%$ in normal weight participants at baseline). For a better illustration, a participant with a baseline body weight of 100 kg would gain an additional 3 kg over 5 years by increasing stearic acid intake by 10 g/d (at the expense of an equal proportion of energy from carbohydrates); a participant with 70 kg would increase body weight by approximately 2 kg. In addition, the dietary intake of the *n*-6 PUFA linoleic acid (only significant in women) and arachidonic acid was significantly associated with prospective weight gain, more pronounced in normal weight participants at

Table 1 Characteristics of male and female study participants (EPIC-Heidelberg)

	Men		Women		P value
	Mean or %	SD	Mean or %	SD	
<i>n</i>	9182		10867		
Age at baseline (years)	51.4	7.1	48.4	8.5	<0.001*
Baseline body weight (kg)	83.3	12.0	67.7	12.2	<0.001*
Baseline BMI (kg/m ²)	26.8	3.6	25.2	4.5	
Underweight (BMI < 18.5 kg/m ² , %)	0.1		1.4		
Normal weight (18.5 ≤ BMI < 25 kg/m ² , %)	32.0		55.3		
Overweight (25 ≤ BMI < 30 kg/m ² , %)	51.1		29.3		
Obese (BMI ≥ 30 kg/m ² , %)	16.8		14.0		<0.001†
Follow-up body weight‡ (kg)	84.1	12.1	68.9	12.5	<0.001*
Follow-up BMI (kg/m ²)	27.1	3.7	25.7	4.7	<0.001*
Five-year weight change (kg/5 years)	0.6	3.9	1.0	3.6	<0.001*
Five-year weight change (%/5 years)	0.8	4.5	1.6	5.1	<0.001*
Incident overweight (%)	19.9		12.4		<0.001†
Incident obesity (%)	5.0		4.7		<0.001†
Length of follow-up (years)	6.5	2.2	6.5	2.1	<0.83*
Nutrient intake					
Total energy (kcal/d)§	9204	3263	7237	2449	<0.001
Carbohydrates (g/d)	236.1	91.4	193.6	72.4	<0.001
Protein (g/d)	78.5	28.3	62.4	20.9	<0.001
Alcohol (g/d)	25.8	27.2	11.0	14.2	<0.001
Total fat (g/d)	84.6	37.7	69.8	28.7	<0.001
(% Energy)	34.4	6.0	36.1	5.6	<0.001
SFA (g/d)	35.1	16.8	29.6	13.3	
(% Energy)	14.2	3.0	15.2	3.0	<0.001
Palmitic acid (g/d)	17.0	7.9	14.2	6.1	<0.001
Stearic acid (g/d)	7.6	4.2	6.1	3.2	<0.001
MUFA (g/d)	29.9	14.0	24.1	10.3	
(% Energy)	12.1	2.4	12.4	2.2	<0.001
Oleic acid (g/d)	26.2	12.4	21.0	9.1	<0.001
PUFA (g/d)	14.0	6.3	11.5	4.9	
(% Energy)	5.7	1.6	6.1	1.6	<0.001
<i>n</i> -6 PUFA					
Linoleic acid (g/d)	11.9	5.5	9.9	4.3	<0.001
Arachidonic acid (mg/d)	201.5	105.9	143.5	81.1	<0.001
<i>n</i> -3 PUFA					
ALA (g/d)	1.4	0.6	1.2	0.5	<0.001
EPA (mg/d)	102.6	128.8	69.7	106.3	<0.001
DHA (mg/d)	201.3	185.6	146.9	152.5	<0.001
Physically active ¶	27.0		24.1		<0.001†
With university degree	38.6		25.3		<0.001†
Habitual non-smokers	71.4		75.9		
Habitual smokers	19.3		16.5		<0.001†
Premenopausal			47.8		
Perimenopausal			11.4		
Postmenopausal			38.8		

EPIC-Heidelberg, Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition; ALA, α -linolenic acid.

**t*-test. Data are presented as mean and standard deviation, or percentage.

†Chi-square test.

‡Calibrated.

§1 kcal = 4.184 kJ.

||Wilcoxon rank-sum test.

¶Combined occupational, cycling and sports activities.

baseline. Each 100 mg increment of arachidonic acid intake resulted in a 5-year weight gain of 0.62% and 0.42% in men and women with normal weight at baseline, respectively. None of the other fatty acids were significantly associated with weight gain in the linear regression models. Total SFA, MUFA or PUFA intake was not associated with weight gain (data not shown). Parameter estimates obtained from the repetition of the analyses using MUFA replacement models were quite similar to those obtained from the carbohydrate replacement models (data not shown).

Results of the multinomial logistic regression analysis for male and female participants are presented in Tables 4 and 5, respectively. As seen in the linear regression models, the risk estimates of the multinomial logistic regression indicate a positive association between stearic acid intake and weight gain, although not all were statistically significant. With regard to the dietary intake of oleic acid, an inverse association was observed in male (Table 4) and female (Table 5) participants who were normal weight at baseline. In both men and women, the dietary intake of linoleic acid (*n*-6) was positively

Table 2 Distribution of categories of incident weight change by age groups in male and female participants of the EPIC-Heidelberg cohort

Five-year weight change* category	<45 years		45–<55 years		55–65 years		Total	
	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%	<i>n</i>
Men (<i>n</i> 9182)								
Weight loss (<−2.5%/5 years)	15.2	309	16.7	629	21.7	733	18.2	1671
Stable weight (±2.5%/5 years)	44.2	896	51.4	1942	53.7	1815	50.7	4653
Small gain (+2.5% to +7.5%/5 years)	31.9	647	25.2	953	20.3	685	24.9	2285
Large gain (>7.5%/5 years)	8.6	175	6.7	252	4.3	146	6.2	573
Women (<i>n</i> 10 867)								
Weight loss (<−2.5%/5 years)	15.9	667	17.8	648	19.7	597	17.6	1912
Stable weight (±2.5%/5 years)	39.4	1653	42.3	1536	47.6	1447	42.7	4636
Small gain (+2.5% to +7.5%/5 years)	31.0	1301	29.3	1064	25.5	774	28.9	3139
Large gain (>7.5%/5 years)	13.7	575	10.6	385	7.2	220	10.9	1180

EPIC-Heidelberg, Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition.

*Difference of latest follow-up weight minus baseline weight, divided by baseline weight and years of follow-up, and multiplied by five.

Table 3 Association between energy-adjusted dietary fatty acid intake and prospective weight gain in male and female participants of the EPIC-Heidelberg cohort* as assessed by multivariate linear regression models

	All subjects			Normal weight subjects at baseline†		
	β‡	SE	<i>P</i> value	β‡	SE	<i>P</i> value
Men						
	<i>n</i> 7511			<i>n</i> 2550		
SFA						
Palmitic acid (10 g/d)§	−1.64	1.40	0.24	−2.53	2.51	0.31
Stearic acid (10 g/d)	3.16	1.09	0.004	4.24	1.96	0.03
MUFA						
Oleic acid (10 g/d)	−0.02	0.24	0.95	−0.22	0.40	0.57
PUFA						
<i>n</i> -6						
Linoleic acid (10 g/d)	0.31	0.20	0.12	0.59	0.34	0.08
Arachidonic acid (100 mg/d)	0.23	0.13	0.08	0.62	0.24	0.01
<i>n</i> -3						
ALA (1 g/d)	0.08	0.26	0.74	−0.07	0.45	0.88
DHA + EPA (100 mg/d)¶	0.06	0.05	0.22	0.06	0.08	0.45
Women						
	<i>n</i> 8955			<i>n</i> 5090		
SFA						
Palmitic acid (10 g/d)	−2.59	1.55	0.09	−2.70	2.05	0.19
Stearic acid (10 g/d)	3.61	1.14	0.002	4.07	1.49	0.01
MUFA						
Oleic acid (10 g/d)	−0.25	0.24	0.29	−0.28	0.30	0.35
PUFA						
<i>n</i> -6						
Linoleic acid (10 g/d)	0.62	0.19	0.00	0.71	0.25	0.00
Arachidonic acid (100 mg/d)	0.28	0.14	0.04	0.42	0.18	0.02
<i>n</i> -3						
ALA (1 g/d)	−0.03	0.26	0.91	−0.19	0.34	0.57
DHA + EPA¶ (100 mg/d)	−0.06	0.05	0.23	−0.01	0.06	0.83

EPIC-Heidelberg, Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition; ALA, α -linolenic acid.

*Subjects with weight loss (<−2.5%/5 years, *n* 1671 in men, *n* 1912 in women) excluded.

†Baseline BMI between 18.5 and 25 kg/m².

‡Adjusted for other PUFA, MUFA and SFA intakes (g/d), protein, alcohol intake (g/d), total energy intake (kcal/d (1 kcal = 4.184 kJ)), baseline weight (kg) and height (cm), age at baseline (years), physical activity, education, smoking (never, habitual, new, quit), follow-up-time (years); in women additionally adjusted for menopausal status at baseline (premenopausal, perimenopausal, postmenopausal, surgical menopausal, missing).

§All nutrients energy-adjusted by the residual method.

¶Entered as sum because of high correlation ($r > 0.97$).

associated with small and large weight gain. Arachidonic acid intake was positively associated with weight gain in women only (Table 5). Dietary intake of the *n*-3 PUFA ALA was significantly inversely associated with large weight gain in women (Table 5), but not in men (Table 4). The results for EPA and DHA were conflicting; although a positive association was seen in men (Table 4), women in

the second tertile of dietary intake had a significantly reduced risk of small weight gain (Table 5). When tertiles of the total intake of SFA, MUFA and PUFA were analysed, only the high intake of PUFA was significantly positively associated with small and large weight gain in men and women (data not shown). Re-evaluation of the analyses with the MUFA replacement model did not alter the

Table 4 Odds ratios and 95% confidence intervals for the association between energy-adjusted dietary fatty acid intake (in tertiles) and small and large weight gain (*v.* stable weight) in male participants of the EPIC-Heidelberg cohort as assessed by multinomial logistic regression models

	All (n 7511)				Normal weight subjects at baseline* (n 2550)			
	Small weight gain (n 2285)		Large weight gain (n 573)		Small weight gain (n 806)		Large weight gain (n 251)	
Men	OR	95% CI†	OR	95% CI†	OR	95% CI†	OR	95% CI†
SFA								
Palmitic acid (g/d)‡								
<12.8	1.00		1.00		1.00		1.00	
12.8–15.1	1.17	0.94, 1.47	1.33	0.89, 1.97	0.95	0.64, 1.40	1.14	0.62, 2.13
>15.1	1.27	0.91, 1.75	1.40	0.79, 2.48	1.01	0.58, 1.78	1.11	0.46, 2.70
<i>P</i> _{trend}	0.18		0.32		1.00		0.91	
Stearic acid (g/d)								
<5.5	1.00		1.00		1.00		1.00	
5.5–6.6	0.85	0.70, 1.02	0.92	0.66, 1.28	0.99	0.72, 1.35	1.23	0.74, 2.03
>6.6	1.06	0.83, 1.35	1.25	0.82, 1.91	1.21	0.80, 1.82	1.85	0.98, 3.48
<i>P</i> _{trend}	0.47		0.19		0.29		0.04	
MUFA								
Oleic acid (g/d)								
<20.00	1.00		1.00		1.00		1.00	
20.0–23.2	0.98	0.83, 1.16	1.12	0.83, 1.51	0.89	0.67, 1.18	0.87	0.56, 1.38
>23.2	0.89	0.71, 1.11	0.93	0.63, 1.37	0.82	0.57, 1.17	0.56	0.31, 1.00
<i>P</i> _{trend}	0.32		0.66		0.29		0.04	
PUFA								
<i>n</i> -6								
Linoleic acid (g/d)								
<8.6	1.00		1.00		1.00		1.00	
8.6–10.9	1.11	0.97, 1.28	1.09	0.85, 1.40	1.03	0.81, 1.30	1.23	0.83, 1.82
>10.9	1.18	1.00, 1.39	1.27	0.94, 1.70	1.19	0.90, 1.58	1.64	1.04, 2.61
<i>P</i> _{trend}	0.08		0.11		0.22		0.03	
Arachidonic acid (g/d)								
<0.14	1.00		1.00		1.00		1.00	
0.14–0.19	1.01	0.87, 1.17	0.82	0.62, 1.07	1.09	0.84, 1.40	0.91	0.60, 1.36
>0.19	0.97	0.80, 1.17	0.81	0.58, 1.14	1.00	0.71, 1.39	0.85	0.49, 1.46
<i>P</i> _{trend}	0.64		0.27		0.95		0.58	
<i>n</i> -3								
ALA (g/d)								
<1.04	1.00		1.00		1.00		1.00	
1.04–1.23	0.95	0.82, 1.10	0.95	0.73, 1.24	1.11	0.85, 1.44	0.88	0.57, 1.35
>1.23	0.97	0.81, 1.16	1.12	0.83, 1.53	1.07	0.78, 1.46	0.86	0.52, 1.43
<i>P</i> _{trend}	0.82		0.36		0.79		0.62	
EPA + DHA (g/d)§								
<0.16	1.00		1.00		1.00		1.00	
0.16–0.28	1.06	0.92, 1.21	1.23	0.97, 1.57	1.17	0.93, 1.47	1.25	0.86, 1.82
>0.28	1.17	0.99, 1.37	1.43	1.07, 1.90	1.03	0.78, 1.36	1.34	0.85, 2.12
<i>P</i> _{trend}	0.05		0.02		0.92		0.22	

EPIC-Heidelberg, Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition; ALA, α -linolenic acid.*Baseline BMI between 18.5 and 25 kg/m².

†Adjusted for other PUFA, MUFA, SFA intakes, protein, alcohol intake, total energy intake, baseline weight (kg) and height (cm), age at baseline (years), physical activity, education, smoking (never, habitual, new, quit), follow-up time (years) and menopausal status in women.

‡All nutrients energy-adjusted by the residual method.

§Entered as sum because of high correlation ($r > 0.97$).Bold values are estimates significant at $P < 0.05$.

risk estimates substantially (data not shown). The OR obtained differed from those from the carbohydrate replacement models by the second decimal only. In terms of weight loss (data not shown), in the case of arachidonic acid, positive associations with weight gain were reflected by the tendency of inverse associations with weight loss (OR for weight loss, comparing highest *v.* lowest tertile, was 0.80 (95% CI 0.64, 0.99) in men and 0.85 (95% CI 0.69, 1.04) in women). Dietary intake of ALA, palmitic, stearic and acids was not associated with weight loss.

The associations between fatty acid intake and incident overweight and obesity, respectively, are shown in Fig. 1. As in the multinomial logistic regression, stearic acid was positively associated with weight gain. Compared with participants in the lowest tertile, men in the highest tertile of stearic acid intake had a significantly increased OR of becoming overweight, while women in the same tertile had a significantly increased OR of becoming incident obese. The *n*-6 PUFA of linoleic and arachidonic acids were positively associated with incident overweight and obesity, especially in women. With regard to ALA, non-significant

Table 5 Odds ratios and 95% confidence intervals for the association between energy-adjusted dietary fatty acid intake (in tertiles) and small and large weight gain (*v.* stable weight) in female participants of the EPIC-Heidelberg cohort as assessed by multinomial logistic regression models

	All (<i>n</i> 8955)				Normal weight subjects at baseline* (<i>n</i> 5090)			
	Small weight gain (<i>n</i> 3139)		Large weight gain (<i>n</i> 1180)		Small weight gain (<i>n</i> 1689)		Large weight gain (<i>n</i> 581)	
Women	OR	95% CI†	OR	95% CI†	OR	95% CI†	OR	95% CI†
SFA								
Palmitic acid (g/d)‡								
<12.8	1.00		1.00		1.00		1.00	
12.8–15.1	1.00	0.82, 1.21	1.07	0.81, 1.42	1.06	0.82, 1.38	1.17	0.79, 1.72
>15.1	0.93	0.70, 1.24	1.01	0.67, 1.52	1.29	0.88, 1.89	1.23	0.69, 2.17
<i>P</i> _{trend}	0.56		0.99		0.18		0.52	
Stearic acid (g/d)								
<5.5	1.00		1.00		1.00		1.00	
5.5–6.6	1.07	0.92, 1.26	1.26	0.99, 1.59	1.07	0.86, 1.32	1.26	0.91, 1.74
>6.6	1.16	0.94, 1.43	1.39	1.03, 1.88	1.08	0.82, 1.42	1.50	1.00, 2.26
<i>P</i> _{trend}	0.15		0.03		0.63		0.04	
MUFA								
Oleic acid (g/d)								
<20.5	1.00		1.00		1.00		1.00	
20.5–23.8	0.91	0.79, 1.05	0.95	0.77, 1.17	0.86	0.71, 1.03	0.93	0.70, 1.24
>23.8	0.86	0.71, 1.02	0.89	0.69, 1.16	0.76	0.60, 0.96	0.78	0.55, 1.10
<i>P</i> _{trend}	0.10		0.37		0.02		0.14	
PUFA								
<i>n</i> -6								
Linoleic acid (g/d)								
<8.9	1.00		1.00		1.00		1.00	
8.9–11.2	1.06	0.94, 1.20	1.10	0.92, 1.32	1.16	0.99, 1.36	1.12	0.88, 1.43
>11.2	1.24	1.08, 1.43	1.56	1.27, 1.90	1.36	1.13, 1.64	1.65	1.25, 2.18
<i>P</i> _{trend}	0.00		<0.00		0.00		0.00	
Arachidonic acid (g/d)								
<0.12	1.00		1.00		1.00		1.00	
0.12–0.17	1.16	1.02, 1.33	1.10	0.90, 1.35	1.23	1.04, 1.47	0.92	0.70, 1.21
>0.17	1.30	1.10, 1.54	1.23	0.96, 1.58	1.40	1.11, 1.76	1.15	0.81, 1.62
<i>P</i> _{trend}	0.01		0.16		0.01		0.50	
<i>n</i> -3								
ALA (g/d)								
<1.1	1.00		1.00		1.00		1.00	
1.1–1.3	0.88	0.78, 1.00	0.85	0.71, 1.02	0.90	0.77, 1.07	0.88	0.68, 1.13
>1.3	0.88	0.76, 1.02	0.80	0.65, 0.99	0.86	0.71, 1.04	0.82	0.62, 1.10
<i>P</i> _{trend}	0.11		0.05		0.14		0.20	
EPA + DHA (g/d)§								
<0.15	1.00		1.00		1.00		1.00	
0.15–0.25	0.81	0.72, 0.92	0.87	0.72, 1.03	0.82	0.70, 0.97	0.83	0.65, 1.06
>0.25	0.90	0.78, 1.05	0.94	0.76, 1.16	0.89	0.73, 1.08	0.97	0.72, 1.30
<i>P</i> _{trend}	0.40		0.73		0.36		0.93	

EPIC-Heidelberg, Heidelberg cohort of the European Prospective Investigation into Cancer and Nutrition; ALA, α -linolenic acid.

*Baseline BMI between 18.5 and 25 kg/m².

†Adjusted for other PUFA, MUFA, SFA intakes, protein, alcohol intake, total energy intake, baseline weight (kg) and height (cm), age at baseline (years), physical activity, education, smoking (never, habitual, new, quit), follow-up time (years) and menopausal status in women.

‡All nutrients energy-adjusted by the residual method.

§Entered as sum because of high correlation ($r > 0.97$).

Bold values are estimates significant at $P < 0.05$.

inverse associations between incident overweight and obesity were observed in both men and women.

Discussion

In the present study, the effects of dietary fatty acid intakes on long-term weight change were investigated in a prospective setting. Weight-promoting effects were observed for stearic, linoleic and arachidonic acids in men and women, whereas ALA showed inverse associations with weight gain in women. Oleic acid intake was

inversely associated with prospective weight gain in the multinomial logistic regression, especially after restriction to participants who were normal weight at baseline. No clear associations were observed for palmitic acid and the sum of EPA and DHA.

Several biological mechanisms may help in explaining the differential effects of fatty acids on weight development in adults, as observed in the present study. Fatty acids differ slightly with respect to their energy content. The order of fatty acids according to their energy content is linolenic acid (38.7 kJ/g) < linoleic (39.0 kJ/g) < palmitic acid (39.2 kJ/g) < oleic (39.4 kJ/g) < stearic acid

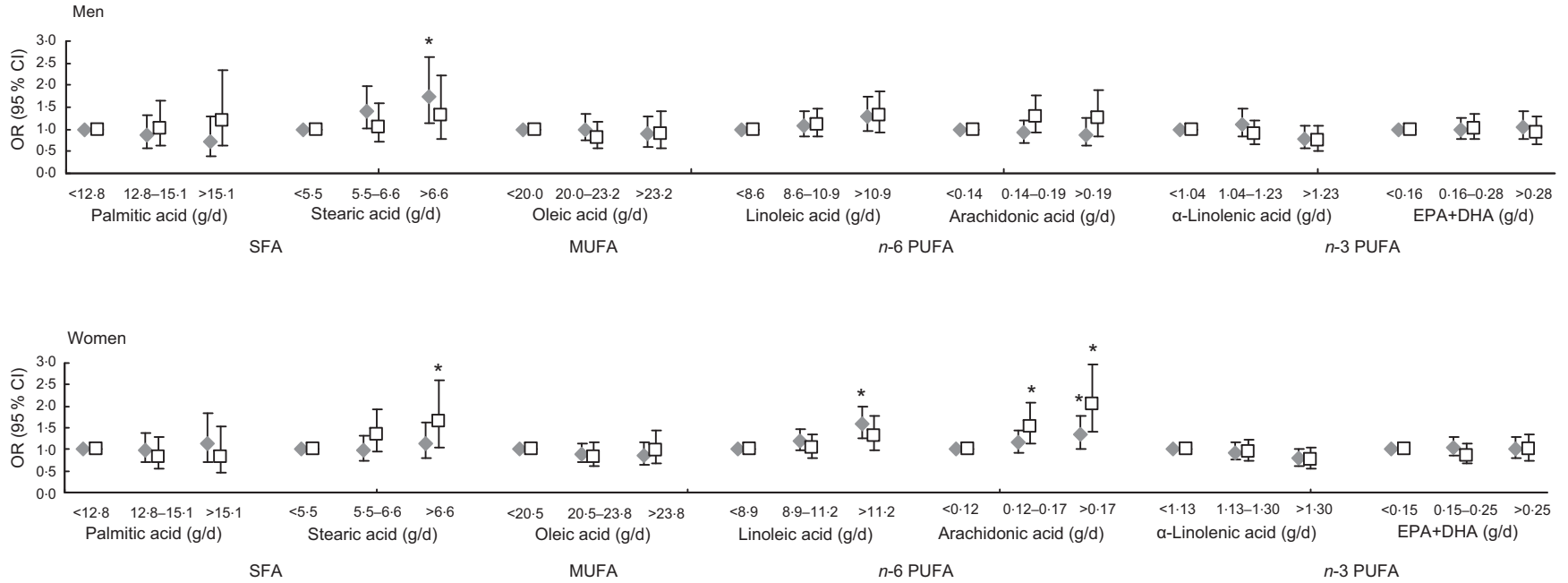


Fig. 1 Multivariate adjusted OR (bars indicate 95% CI) for the association between fatty acid intake and incident overweight (◆) or obesity (□), respectively. * $P_{\text{trend}} < 0.01$

(40.0 kJ/g) < arachidonic acid (40.5 kJ/g)⁽²³⁾. However, the metabolisable energy depends on the intestinal absorption, which is lower for stearic acid than for other fatty acids such as palmitic, oleic or linoleic acid^(24,25). Considering that some fatty acids are consumed in very small amounts, differences in energy content and bio-availability cannot be the only explanation for the observed effects. Furthermore, in the present study, dietary fatty acid intake was adjusted for energy intake, so that differences in energy content are rather unlikely to explain the observed results. A diet with a high proportion of PUFA has been shown to induce a higher thermogenic effect in man than a diet high in SFA⁽¹⁰⁾. The oxidation rates of fatty acids depend on the chain length and the degree of saturation. In man, the order of oxidation rates from highest to lowest was observed as follows: ALA > linoleic acid > oleic acid > palmitoleic acid > stearic acid⁽¹²⁾. Accordingly, a diet high in saturated fats (such as stearic acid) with a low oxidation rate might be more prone to lead to weight gain than a diet rich in polyunsaturated fats (such as ALA) with a higher oxidation rate. In a study on rats, animals on a diet high in beef tallow (saturated fat) accumulated more body fat than animals on a diet high in safflower oil (polyunsaturated fat), which was related to a decrease in sympathetic activity in the beef tallow diet⁽¹³⁾. In addition to effects directly related to the efficiency of energy storage, certain fatty acids, (i.e. *n*-3 and *n*-6 PUFA) have been shown to act as transcription factors influencing the expression of genes important in fat metabolism. Especially, *n*-3 fatty acids (ALA, EPA and DHA) promote the expression of genes involved in fat oxidation and thermogenesis, yielding decreased body fat deposition and improved glucose clearance⁽¹⁶⁾. Fatty acids may also exert different effects on postprandial appetite. In an experimental study on normal weight men, food intake was lowest after intestinal infusion of linoleic acid than that of oleic or stearic acid⁽²⁶⁾. In contrast, in a study in which test meals with different fatty acid compositions were given to overweight men, no differences regarding subsequent energy intake were observed⁽²⁷⁾.

In the present study, dietary intake of stearic acid was positively associated with weight gain, especially in the linear regression approach. This finding seems plausible in the context of the low oxidation rate (i.e. fat is more prone to be stored in fat tissue) and relatively high energy content of stearic acid⁽¹²⁾. However, no association was found for palmitic acid, which has an oxidation rate only slightly above stearic acid and provides minimally lower energy content. Neither prospective nor cross-sectional analyses have been conducted in order to explicitly investigate the effect of habitual intake of these two SFA on BMI or weight gain.

Oleic acid, contributing 90% to total MUFA intake, was inversely associated with prospective weight gain in the multinomial logistic regression restricted to participants

who were normal weight at baseline. There are no directly comparable studies investigating oleic acid intake and weight change prospectively. In a prospective cohort study from Spain (SUN study), baseline consumption of olive oil (70% oleic acid) was associated with a lower likelihood of weight gain, although not statistically significant⁽²⁸⁾. The comparability of Bes-Rastrollo *et al.*'s⁽²⁸⁾ study to the present study might be impaired due to differing dietary habits in Spain and Germany, especially in terms of olive oil consumption, which determine high intake of oleic acid.

The *n*-6 PUFA linoleic and arachidonic acids showed weight-promoting effects in the linear regression as well as in the multinomial logistic regression models. In the Nurses' Health Study, linoleic acid intake was positively correlated with BMI⁽¹⁵⁾. To our knowledge, the effect of dietary arachidonic acid intake on prospective weight change has not been investigated in an epidemiological study so far. However, in the EPIC-Potsdam study, dietary intake of meat, the major food source of arachidonic acid, was associated with increased risk of a large, 2-year weight gain in women⁽²⁹⁾.

Reduced risks of small and large weight gain were observed in women with high ALA intake, significantly so for large weight gain. Although an inverse association between dietary intake of ALA and weight gain has not been observed in an epidemiological study so far, this finding seems plausible in the context of the high oxidation rate of ALA and its potential activity as a transcription factor enhancing fat oxidation rates and thermogenesis.

Here, the applied isoenergetic models represent the effect of substituting energy from carbohydrates by the same amount of energy provided by a certain fatty acid (carbohydrate replacement model). Increased intake of a certain fatty acid in such a model implies the proportion of energy provided by fat to increase. A high percentage of energy from fat has been associated with weight gain in several epidemiological studies⁽³⁰⁾. In this context, increased intake of any fatty acid in the carbohydrate replacement model would be expected to promote weight gain due to the implied higher proportion of energy from fat. However, the quite similar results obtained from the MUFA replacement models show that certain fatty acids also affect weight change when the percentage of energy from fat remains constant (i.e. substituting energy from MUFA by energy from the fatty acid of interest).

The linear and the multinomial logistic regression approaches yielded fairly consistent results. The definition of incident overweight/obesity is an alternative approach to study weight change longitudinally, with a more health-related focus. The consistent results of the analysis of incident overweight/obesity, as compared to weight gain per se, argue for a factor associated with weight gain to be most likely also related to incident overweight or obesity.

Apart from the fact that our findings require confirmation by other studies, the conclusion in terms of

dietary advice for the prevention of weight gain by controlled fatty acid intake would include a reduced consumption of meat and dairy products (low intake of arachidonic and stearic acids) and a higher consumption of plant food rich in ALA (e.g. nuts or rapeseed oil)⁽³¹⁾. Such advice would be in agreement with existing dietary guidelines for the prevention of chronic disease occurrence.

Limitations

Several limitations of the present study should be noted. First, the ability to assess absolute intake of individual dietary fatty acids by means of an FFQ is limited. Furthermore, by using dietary intake data ascertained by FFQ at baseline in this prospective analysis, we assume that dietary habits remain stable over time. This assumption, however, seems justified, as moderate-to-good long-term reproducibility of the FFQ data and fair agreement of individual classification by food groups and nutrients between baseline and follow-up were observed in a comparison of the two dietary assessments in our study population⁽³⁵⁾. The validity of fat intake assessment by the EPIC-Heidelberg FFQ has been evaluated by using twelve 24 h dietary recalls as a reference method. The resulting adjusted correlation coefficients were 0.75, 0.51 and 0.43 for PUFA, MUFA and SFA, respectively⁽¹⁷⁾. However, the validity of specific fatty acid intake has not been addressed in the present validation study. Thus, it can only be assumed that the validity of specific fatty acid data is similar to that observed in subgroups of comparable cohort studies by using weighed dietary records^(32–34) or subcutaneous fat aspirates⁽³⁴⁾ as reference methods. In a British validation study of an FFQ that included a greater detail of foods from which the majority of dietary fatty acids are obtained, correlation coefficients of energy-adjusted fatty acid intake with 7 d weighed records were 0.77 for palmitic, 0.70 for stearic, 0.20 for oleic, 0.24 for linoleic and 0.70 for arachidonic acids⁽³²⁾. Similarly, in a Japanese validation study of a 138-item FFQ with 28 d weighed records, relatively high correlations were observed for stearic and palmitic acids (0.61 and 0.63, respectively), whereas correlation coefficients for PUFA were rather low, between 0.27 (linolenic acid) and 0.38 (EPA)⁽³³⁾. Overall, it cannot be dismissed that the fatty acid intake data in the present study require cautious interpretation, also because databases on the fatty acid composition of food are limited in precision. Nevertheless, we hope that the results of this hypothesis-driven analysis stimulate further research on this question, ideally involving studies applying more precise methods of dietary fatty acid intake measurement.

Also, the validity and precision of the self-reported body weight at follow-up are limited. However, the self-reported data were calibrated by a method using BMI- and sex-specific equations derived from a 7% subsample to reduce the misclassification error.

It has been shown that the accuracy of weight⁽³⁶⁾ and diet⁽³⁷⁾ reports depends on BMI. Therefore, the results of the subanalysis restricted to participants with normal weight at baseline may be regarded as more reliable than the analysis of the total cohort. Results from the full analysis and the subanalysis were, however, fairly comparable.

Here, the applied index ranking participants in terms of their physical activity combining occupational and leisure-time physical activity has been validated using accelerometers⁽³⁸⁾ and heart rate monitoring⁽²⁰⁾ as reference instruments, showing acceptable agreement. Nevertheless, a more precise instrument to measure physical activity would have been desirable.

Conclusion

Here, the observed associations of fatty acid intake with prospective weight change lack comparable analyses from other prospective studies, and even experimental studies on human subjects focusing on specific fatty acids and their effect on weight change are scarce. Therefore, further studies on this issue are strongly warranted before detailed dietary recommendations focussing on the prevention of adult weight gain can be given.

Acknowledgements

The present study was supported by funds of the Kurt-Eberhard-Bode-Stiftung. K.N. was the recipient of a scholarship from the Deutsche Forschungsgemeinschaft, Graduiertenkolleg 793. K.N. was responsible for the statistical analysis and interpretation of the data and drafting the manuscript. G.B.B. was responsible for critical revision of the manuscript for important intellectual content. J.L. was responsible for the study concept and design, acquisition of data, critical revision of the manuscript for important intellectual content, and for obtaining the funding for the study. None of the authors had any conflicts of interest in connection with the present study.

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