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The association of education with long-term weight change in the EPIC-PANACEA cohort

S Rohrmann[1,2], A Steinbrecher[2], J Linseisen[2,3], S Hermann[2], A May[4,5], J Luan[6], U Ekelund[6], K Overvad[7,8], A Tjønneland[9], J Halkjær[9], G Fagherazzi[10], M-C Boutron-Ruault[10], F Clavel-Chapelon[10], C Agnoli[11], R Tumino[12], G Masala[13], A Mattiello[14], F Ricceri[15], N Travier[16], P Amiano[17,18], E Ardanaz[18,19], M-D Chirlaque[18,20], M-J Sanchez[18,21], L Rodríguez[22], LM Nilsson[23], I Johansson[24], B Hedblad[25], M Rosvall[25], E Lund[26], T Braaten[26], A Naska[27,28], P Orfanos[27,28], A Trichopoulou[27,28], S van den Berg[5], HB Bueno-de-Mesquita[5,29], MM Bergmann[30], A Steffen[30], R Kaaks[2], B Teucher[2], NJ Wareham[6], K-T Khaw[31], FL Crowe[32], A-K Illner[33], N Slimani[33], V Gallo[34,35], T Mouw[34], T Norat[34] and PHM Peeters[4]

BACKGROUND/OBJECTIVES: Cross-sectionally, educational attainment is strongly associated with the prevalence of obesity, but this association is less clear for weight change during adult life. The objective of this study is to examine the association between educational attainment and weight change during adult life in the European Prospective Investigation into Cancer and Nutrition (EPIC).
SUBJECTS/METHODS: EPIC is a cohort study with 361 467 participants and up to 10 years of follow-up. Educational attainment was categorized according to the highest obtained school level (primary school or less, vocational secondary training, other secondary education and university). Multivariate mixed-effects linear regression models were used to study education in relation to weight at age 20 years (self-reported), to annual change in weight between age 20 years and measured weight at recruitment, and to annual change in weight during follow-up time.
RESULTS: Higher educational attainment was associated with on average a lower body mass index (BMI) at age 20 years and a lower increase in weight up to recruitment (highest vs lowest educational attainment in men: −60 g per year (95% confidence interval (CI) −80; −40), women −110 g per year (95% CI −130; −80)). Although during follow-up after recruitment an increase in body weight was observed in all educational levels, gain was lowest in men and women with a university degree (high vs low education −120 g per year (95% CI −150; −90) and −70 g per year (95% CI −90; −60), respectively).
CONCLUSIONS: Existing differences in BMI between higher and lower educated individuals at early adulthood became more pronounced during lifetime, which possibly impacts on obesity-related chronic disease risk in persons with lower educational attainment.

[1]Department of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine, University of Zurich, Zurich, Switzerland; [2]Division of Cancer Epidemiology, German Cancer Research Centre, Heidelberg, Germany; [3]Institute of Epidemiology, German Research Centre for Environmental Health (HMGU), Neuherberg, Germany; [4]Julius Centre for Health Sciences and Primary Care, University Medical Centre Utrecht, Utrecht, The Netherlands; [5]National Institute for Public Health and the Environment (RIVM), Bilthoven, The Netherlands; [6]Medical Research Council, Epidemiology Unit, Institute of Metabolic Science, Cambridge, UK; [7]Department of Cardiology, Aalborg Hospital, Aarhus University Hospital, Aalborg, Denmark; [8]Department of Clinical Epidemiology, Aarhus University Hospital, Aalborg, Denmark; [9]Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark; [10]Inserm ERI20 and Paris South University, Institut Gustave-Roussy, Villejuif, France; [11]Nutritional Epidemiology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy; [12]Cancer Registry and Histopathology Unit, 'Civile MP Arezzo' Hospital, Ragusa, Italy; [13]Molecular and Nutritional Epidemiology Unit, Cancer Research and Prevention Institute – ISPO, Florence, Italy; [14]Department of Clinical and Experimental Medicine, Federico II University, Naples, Italy; [15]Human Genetics Foundation and Department of Genetics, Biology and Biochemistry, University of Turin, Turin, Italy; [16]Unit of Nutrition, Environment and Cancer, Cancer Epidemiology Research Programme, Catalan Institute of Oncology (ICO), Barcelona, Spain; [17]Public Health Division of Gipuzkoa, IIS Institute Investigation BioDonostia, Basque Country, Spain; [18]Consortium for Biomedical Research in Epidemiology and Public Health (CIBER Epidemiología y Salud Pública-CIBERESP), Spain; [19]Navarre Public Health Institute, Pamplona, Spain; [20]Department of Epidemiology, Murcia Regional Health Authority, Murcia, Spain; [21]Andalusian School of Public Health, Granada, Spain; [22]Public Health and Participation Directorate, Health and Health Care Services Council, Asturias, Spain; [23]Department of Public Health and Clinical Medicine, Umeå University, Umeå, Sweden; [24]Department of Odontology, Umeå University, Umeå, Sweden; [25]Department of Clinical Sciences in Malmö, Lund University, Skane University Hospital, Malmö, Sweden; [26]Institute of Community Medicine, University of Tromsø, Tromsø, Norway; [27]WHO Collaborating Center for Food and Nutrition Policies, Department of Hygiene, Epidemiology and Medical Statistics, University of Athens Medical School, Athens, Greece; [28]Hellenic Health Foundation, Athens, Greece; [29]Department of Gastroenterology and Hepatology, University Medical Centre Utrecht (UMCU), Utrecht, The Netherlands; [30]German Institute of Human Nutrition Potsdam-Rehbrücke, Nuthetal, Germany; [31]Department of Public Health and Primary Care, University of Cambridge, Cambridge, UK; [32]Cancer Epidemiology Unit, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, UK; [33]International Agency for Research on Cancer, Lyon, France; [34]Department of Epidemiology and Biostatistics, Imperial College School of Public Health, London, UK and [35]Department of Social and Environmental Health Research, London School of Hygiene and Tropical Medicine, London, UK. Correspondence: Dr S Rohrmann, Department of Cancer Epidemiology and Prevention, Institute of Social and Preventive Medicine, University of Zurich, Hirschengraben 84, Zurich 8001, Switzerland.
E-mail: sabine.rohrmann@ifspm.uzh.ch

INTRODUCTION

The increasing prevalence of obesity in western and non-western countries[1] is a major health problem, leading to diseases including cardiovascular diseases and cancer.[2] Several cross-sectional studies in industrialized countries have shown that men and women with better education are leaner than less educated individuals,[3,4] but the association with weight development over time appears to be less clear.[5] Few studies have examined whether the associations between education and body mass index (BMI) in adults already existed during their adolescence or whether such a difference in weight between high and low educated persons developed during adult life.

Thus, we used the opportunity that is provided by data from participants of the European Prospective Investigation into Cancer and Nutrition (EPIC) to examine the difference in weight at the age of 20 years and in the development of weight since that age until recruitment and during follow-up time between categories of educational attainment.

MATERIALS AND METHODS

Study design

The EPIC study is an ongoing multi-center prospective cohort study consisting of 23 centers in 10 countries (Denmark (Dk), France, Germany (Ge), Greece, Italy (It), The Netherlands (Ntl), Norway, Spain (Sp), Sweden (Sw) and the United Kingdom (UK)). From 1992 to 2000, more than 500 000 individuals (in majority 35 to 70 years of age) were recruited from the population living in a defined geographical region. The cohort of France is based on female members of a health insurance plan for school employees; parts of the Italian and Spanish cohorts included members of local blood donors associations; the cohorts from Utrecht (Ntl) and Florence (It) recruited participants of breast cancer screening programs; and the Oxford (UK) cohort consisted of vegetarians, vegans and other health-conscious individuals. In France, Norway, Utrecht (Nth) and Naples (It), only women were recruited. Eligible individuals were invited by mail or in person to participate. Those agreeing to participate signed an informed consent and were questioned about their usual diet and lifestyle. The lifestyle questionnaire incorporated questions on education, occupation, medical history, tobacco smoking, physical activity and reproductive history. In most centers, usual diet was measured by country-specific, self-administered questionnaires, though some used interviewers.[6]

Study population

Of the total cohort of 519 931 apparently healthy participants, those with missing dietary data ($n = 6611$), with extreme energy intake to energy expenditure ratio ($n = 10\,209$), with no information on lifestyle data ($n = 64$), with no weight data ($n = 4079$), with extreme or implausible anthropometry information at baseline ($n = 376$), and women pregnant at baseline ($n = 623$) were excluded. Furthermore, we excluded participants with no assessment of follow-up weight ($n = 121\,853$; this included the cohorts of Turin and Ragusa (both It) and parts of cohorts from Norway and Naples (It)); extreme or implausible anthropometry at follow-up ($n = 2066$), or missing information on highest school level attained ($n = 12\,583$). Thus, the final study population comprised 100 925 men and 260 542 women.

Data assessment

Anthropometric measures. Weight and height measures at baseline examination were taken by trained personnel,[7] except for participants from France, Norway and part of the Oxford (UK) cohort, where self-reports were obtained. For part of the Oxford (UK) cohort, linear regression models were used to predict sex- and age-specific values derived from participants with both measured and self-reported body measures.[8,9] Measurements were performed on participants in light underwear (most Italian centers (Florence, Varese and Naples), Spain, Germany and Denmark), in light clothing after removal of shoes, heavier sweaters or indoor jackets and emptying heavy objects from pockets (Greece, Bilthoven (Ntl), Malmö (Sw) and the general population of the UK), or normally dressed but without shoes (France, Umea (Sw) and Utrecht (Ntl)). Measures taken on participants in light clothing or normally dressed were subsequently corrected by subtracting 1.0–1.5 kg, respectively.

At follow-up, weight was self-reported in most centers except for Cambridge (UK) and Doetinchem (Ntl), where weight was measured in light underwear. As the average follow-up times were different across the study centers (ranging from 1.1 years in France to 9.4 years in Varese (It)), we computed for each participant the annual weight change (kg per year), that is, weight at follow-up minus weight at baseline divided by follow-up time (in years).

Weight at age 20 was assessed by questionnaire in the following centers: Varese (It), Naples (It), Cambridge (UK), Oxford (UK), Greece, Potsdam (Ge), Malmö (Sw), Aarhus (Dk), Copenhagen (Dk) and Norway ($n = 166\,567$). Detail on participants at different points in time with anthropometric measurements is given in Figure 1.

BMI at baseline was calculated as weight (in kg) at baseline divided by height (in m) at baseline squared. BMI at follow-up was accordingly computed using follow-up weight but baseline height. BMI at age 20 years was calculated from retrospectively self-reported weight at the age of 20 years and measured body height at baseline. Annual weight change since age 20 years was computed as weight at baseline minus weight at age of 20 years divided by the time until recruitment into the study (in years).

Educational attainment. Information on highest level of education was assessed by country-specific questionnaires during recruitment. Educational attainment was categorized on the basis of the highest attained school level: primary school or less; vocational secondary education; other secondary education; and university degree.

Covariates. Age of participants was assessed at time of recruitment and categorized as <50, 50–60 and $\geqslant 60$ years. Follow-up time for each participant was time elapsed between date of recruitment and date of the follow-up assessments. Information on smoking habits was assessed at baseline subsequently categorized as never, former, current or missing. Level of physical activity was categorized as inactive, moderately inactive, moderately active, active and missing.[10] Total energy intake and amount of daily consumed alcohol (covering the period of 12 month before recruitment) were assessed by validated country-specific dietary assessment instruments. Alcohol consumption was summarized as non-consumers, 1–6, 7–18, 19–30, 31–60 and >60 g per day (for men: 61–96

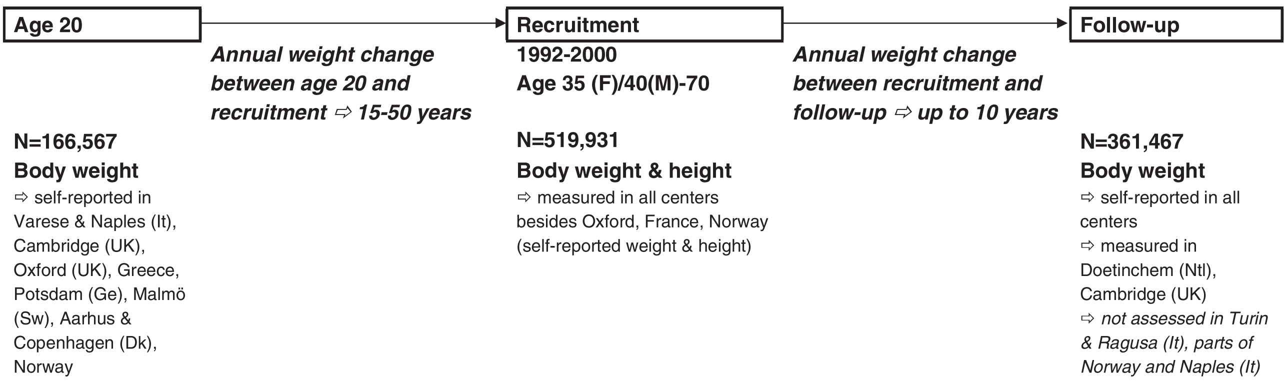

Figure 1. Overview of the assessment of anthropometric measurements by time point and cohort in EPIC.

and >96 g per day). Information on the presence of chronic diseases (heart disease, stroke, diabetes mellitus and cancer) before or at recruitment was assessed by questionnaire.

Statistical methods

Baseline descriptives of the study population are given for four categories of educational attainment for men and women separately. For continuous variables, mean and s.d., and for categorical variables percentages are given.

Associations between educational level and BMI at 20 years, annual weight change between age of 20 years and study recruitment, and annual change in weight between study recruitment and end of follow-up were examined in the total EPIC cohort and for each country. Sex-specific multilevel mixed-effects linear regression with random effect on intercept and on slope was used to model the association between level of education and annual weight change; thus, considering clustering of data within countries and within centers. The lowest educational level was considered the reference. The analyses by countries were done depending on the number of study centers per country. For countries with only one center (The Netherlands (men) and Greece), adjusted linear models were run. For countries with more than one study center (Italy, Spain, The Netherlands (women), Sweden, Denmark, Germany, France and Norway), adjusted mixed linear models with random intercept at center level were used. In the analysis on weight change between age 20 years and age at recruitment, we adjusted for follow-up time (in years, continuous); in the analysis on changes in weight, we adjusted for age at recruitment (in years, continuous), follow-up time (in years, continuous), baseline BMI (in kg, continuous), physical activity level (categorical), smoking status at baseline (categorical), total energy intake (in kcal, continuous) and alcohol intake at recruitment (categorical). Analyses were re-run after excluding participants with any chronic disease at baseline (heart disease, stroke, diabetes mellitus and/or cancer). Effect modification by age group (<50, 50–60⩾60 years), smoking status (at baseline), and self-reported versus measured data were evaluated by estimating stratum-specific regression coefficients. All results were computed using STATA 10 (StataCorp, College Station, TX, USA).

RESULTS

Participants with the lowest educational level were older at baseline than participants with highest education (Table 1). Men with highest educational attainment were most likely to be a never smoker, whereas in women, those with the highest educational attainment were most likely to be a former smoker as compared with women with the lowest educational attainment.

The prevalence of overweight or obesity was low at age 20 years: generally less than 20% in men and less than 10% in women (data not shown). Individuals with a university degree had a significantly lower BMI at age 20 years than those with the lowest education, irrespective of sex. Men with university degree had 0.55 kg/m^2 lower BMI (95% confidence interval (CI) 0.42–0.67); for women, this difference was 0.67 kg/m^2 (95% CI 0.46–0.87) (Table 2). Although men of all educational levels on average gained weight between age 20 years and recruitment, those with the highest education gained 60 g per year (95% CI 40–80) less than men with the lowest education. Similarly, women of all educational levels on average gained weight, but the difference was even wider with 110 g per year (95% CI 80–130) between highest and least educated participants. The associations were similar in participants younger or older at baseline (data not shown).

Mean follow-up time was 5.3 (s.d. ± 2.4) years, which was similar between education groups (data not shown). Between recruitment and follow-up, men in the highest education category gained 120 g per year (95% CI 90–150) less weight during follow-up than men in the lowest educational level (Table 3). This relation was similar when we only adjusted for follow-up time, age at baseline and baseline BMI. Excluding men with reported chronic disease at baseline did not alter the results. The relation was the same in smokers and non–smokers, and in young and elderly participants (data not shown). Also, we observed similar results in centers in which weight was measured at follow-up and in the centers with self-reported weight (Table 3). Country-specific analyses showed that the associations between weight gain and educational attainment (highest vs lowest) were strongest in Doetinchem (Ntl), and weakest in Umea (Sw) and the general population cohort in Oxford (UK) (Figure 2).

Highest educated women gained 70 g per year (95% CI 60–90) less weight between recruitment and follow-up when compared with the least educated (Table 3). Excluding women with chronic diseases at baseline did not yield materially different results; the same was true when analyses were restricted to centers with measured weight. Results by smoking status and by age groups

Table 1. Baseline characteristics of study participants by level of education in EPIC-PANACEA

	Men				*Women*			
	Primary school or less	*Vocational secondary training*	*Other secondary education*	*University*	*Primary school or less*	*Vocational secondary training*	*Other secondary education*	*University*
	Mean (± s.d.)	*Mean (± s.d.)*	*Mean (± s.d.)*	*Mean (± s.d.)*	*Mean (± s.d.)*	*Mean (± s.d.)*	*Mean (± s.d.)*	*Mean (± s.d.)*
N	35 518	24 564	12 204	28 639	75 292	55 044	66 839	63 367
Age at recruitment	55.6 (± 8.4)	52 0 (± 9.1)	48.2 (± 11.1)	51 1 (± 9.5)	54 0 (± 8.8)	51.0 (± 8.9)	50.5 (± 8.9)	48.9 (± 9.2)
BMI at baseline (kg/m^2)	27.6 (± 3.7)	26.5 (± 3.4)	25.9 (± 3.5)	25.8 (± 3.3)	27.1 (± 4.8)	25.0 (± 4.1)	23.7 (± 3.6)	23.3 (± 3.5)
Smoking status at baseline (%)								
Never	27.9	30.7	38.2	40.1	64.4	47.7	58.6	56.6
Former	37.1	38.6	33.0	36.5	15.1	27.4	22.5	26.1
Smoker	34.0	30.1	27.8	22.6	19.1	23.7	15.4	14.6
Unknown	1.0	0.7	1.0	0.9	1.4	1.2	3.5	2.7
Physical activity at baseline (%)								
Active	19.9	14.1	15.7	16.4	34.5	13.1	15.4	13.8
Moderately active	25.4	26.9	28.1	35.8	30.5	28.7	32.8	35.1
Moderately inactive	24.5	23.4	18.1	23.8	15.2	19.1	24.5	27.9
Inactive	26.0	27.0	17.0	18.5	10.6	18.8	11.4	14.3
Missing	4.3	8.6	21.0	5.7	9.2	20.4	15.9	9.0

Abbreviations: BMI, body mass index; EPIC-PANACEA, European Prospective Investigation into Cancer-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of home And obesity.

Table 2. Association of BMI at age 20 years and annual weight change between age 20 and baseline with educational level by sex in EPIC-PANACEA

	Primary school or less	Vocational secondary training	Other secondary education	University
		Estimate (95% CI)	*Estimate (95% CI)*	*Estimate (95% CI)*
Men	N = 16 151	N = 13 936	N = 5 161	N = 17 831
BMI at age 20 years[a]	Reference	− 0.33 (− 0.40 to − 0.26)	− 0.47 (− 0.58 to − 0.36)	− 0.55 (− 0.08 to − 0.04)
Annual weight change between age 20 years and baseline[b]	Reference	− 0.03 (− 0.05 to 0.00)	− 0.01 (− 0.03 to 0.02)	− 0.06 (− 0.08 to − 0.04)
Women	N = 30 684	N = 37 678	N = 19 480	N = 25 646
BMI at age 20 years[a]	Reference	− 0.56 (− 0.64 to − 0.48)	− 0.63 (− 0.77 to − 0.49)	− 0.67 (− 0.87 to − 0.46)
Annual weight change between age 20 years and baseline[b]	Reference	− 0.04 (− 0.06 to − 0.03)	− 0.08 (− 0.10 to − 0.06)	− 0.11 (− 0.13 to − 0.08)

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC-PANACEA, European Prospective Investigation into Cancer-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of home And obesity. [a]Difference with reference category in kg/m^2. [b]Difference with reference category in kg per year.

Table 3. Associations of change in body weight between baseline and follow-up with level of education, EPIC-PANACEA

	Primary school or less	Vocational secondary training	Other secondary education	University
		Estimate (95% CI)[a]	*Estimate (95% CI)*[a]	*Estimate (95% CI)*[a]
Men	N = 35 518	N = 24 564	N = 12 204	N = 28 639
Model 1	Reference	− 0.05 (− 0.07 to − 0.03)	− 0.07 (− 0.10 to − 0.04)	− 0.13 (− 0.16 to − 0.10)
Model 2	Reference	− 0.05 (− 0.07 to − 0.03)	− 0.07 (− 0.10 to − 0.04)	− 0.12 (− 0.15 to − 0.09)
All prevalent chronic diseases excluded	Reference	− 0.05 (− 0.08 to − 0.03)	− 0.07 (− 0.10 to − 0.04)	− 0.13 (− 0.17 to − 0.09)
Prevalent cancers excluded	Reference	− 0.05 (− 0.07 to − 0.03)	− 0.07 (− 0.10 to − 0.04)	− 0.12 (− 0.16 to − 0.09)
Measured data	Reference	− 0.05 (− 0.11 to 0.00)	− 0.08 (− 0.16 to − 0.01)	− 0.10 (− 0.17 to − 0.03)
Self-reported data	Reference	− 0.05 (− 0.07 to − 0.03)	− 0.06 (− 0.10 to − 0.03)	− 0.12 (− 0.16 to − 0.08)
Women	N = 75 292	N = 55 044	N = 66 839	N = 63 367
Model 1	Reference	− 0.02 (− 0.04 to − 0.01)	− 0.05 (− 0.06 to − 0.03)	− 0.08 (− 0.10 to − 0.06)
Model 2	Reference	− 0.02 (− 0.04 to − 0.01)	− 0.04 (− 0.06 to − 0.03)	− 0.07 (− 0.09 to − 0.06)
All prevalent chronic diseases excluded	Reference	− 0.02 (− 0.04 to − 0.01)	− 0.04 (− 0.06 to − 0.03)	− 0.07 (− 0.09 to − 0.06)
Prevalent cancers excluded	Reference	− 0.02 (− 0.03 to − 0.01)	− 0.04 (− 0.05 to − 0.03)	− 0.07 (− 0.09 to − 0.06)
Measured data	Reference	− 0.03 (− 0.08 to 0.02)	− 0.11 (− 0.18 to − 0.04)	− 0.09 (− 0.16 to − 0.02)
Self-reported data	Reference	− 0.02 (− 0.04 to − 0.01)	− 0.04 (− 0.06 to − 0.03)	− 0.07 (− 0.09 to − 0.06)

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC-PANACEA, European Prospective Investigation into Cancer-Physical Activity, Nutrition, Alcohol, Cessation of Smoking, Eating out of home And obesity. Model 1 = adjusted for age at baseline, BMI at baseline, follow-up period (years); Model 2 = additionally adjusted for physical activity, alcohol consumption, smoking and energy intake at baseline (used for all following results). [a]Difference with reference category in kg per year.

were quite similar to the overall results (data not shown). In all but three study centers (France, Doetinchem (Nth), Umea (Sw)), the difference in weight gain between highest and lowest level of education was statistically significant (Figure 2). The strongest associations between education and weight changes were observed in the Italian centers.

DISCUSSION

In this European cohort, we observed differences in BMI between individuals with the highest and lowest level of education that already existed at the age of 20 years. The increase in weight thereafter also differed by educational level, with men and women with university degree gaining less weight than less-educated individuals.

We previously showed that participants with the lowest education had significantly higher BMI and waist circumference at recruitment into the EPIC cohort than individuals with a university degree.[11] We have now extended our analysis showing that the difference is already present at age 20 years and persists into older age. Both men and women with highest educational attainment had a lower BMI at age 20 years compared with participants of the lowest education level. The difference between these two extreme groups was 0.6 kg/m^2 in men and 0.7 kg/m^2 in women. This difference is considerably smaller than the difference that we observed for BMI assessed at recruitment into the study, that is, 15–50 years later (1.3 kg/m^2 in men; 2.1 kg/m^2 in women[11]). The prevalence of obesity increased considerably in recent years and it has been shown in the MONICA (MONItoring CArdiovascular disease) project that the difference in BMI between less and better educated participants increased over time,[4] which is consistent with our findings that the difference between age 20 years and recruitment increased in our cohort.

Education may influence obesity-related behaviors such as diet and physical activity, finally having an impact on energy balance. If these obesity-related health behaviors do not change, the imbalance accumulates over time, leading to an accelerated weight gain, and thus, high mid-adulthood BMI in participants of low educational status. Comparing the results of BMI at age 20 years and BMI at baseline examination, it has to be taken into account that BMI at baseline was measured in almost all centers, whereas BMI at age 20 years was retrospectively self-reported by the participants. A US study has shown that recalled adolescent body weight at age 70 + years old correlated quite well with body weight measured during adolescence, although obese women tended to underestimate and lean men to overestimate past body

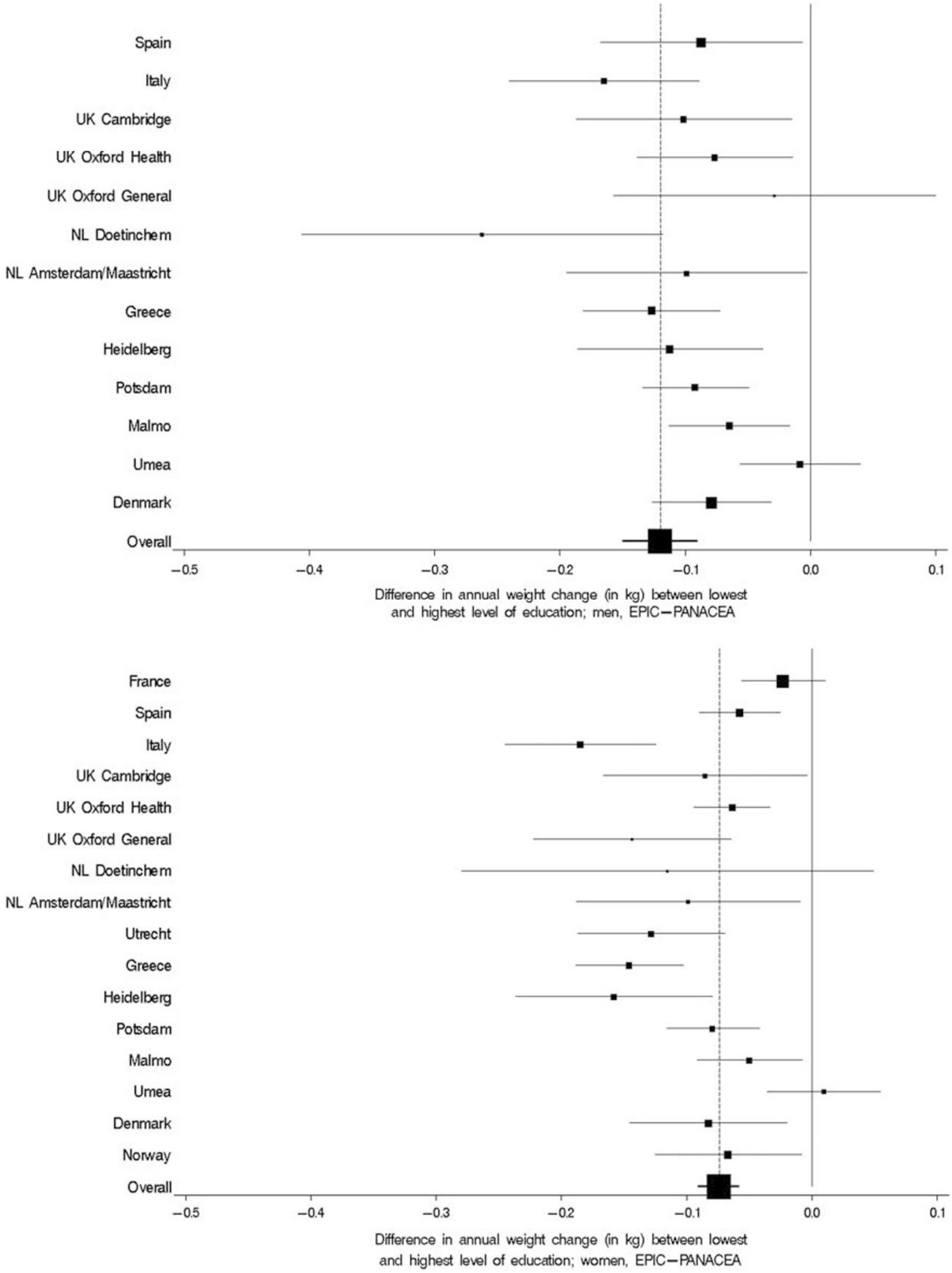

Figure 2. Difference (mean and 95% CI) in annual weight change (in kg) during follow-up between highest and lowest educational level in men (top) and women (bottom); EPIC participants interviewed between 1992 and 2000. The dotted vertical line indicates the overall mean difference between highest and lowest educational level.

weight.[12] Another study showed a high reproducibility of recalling past body weight.[13] However, we cannot exclude differential recall of past body weight by education such that individuals with higher education are more aware of an association between obesity and chronic diseases and, therefore, tend to underreport body weight at age 20 years. This, however, has not been examined in previous studies, but it has recently been observed in the EPIC-Cambridge cohort that underreporting of (current, not past) body weight was more common among women with higher education and higher social class.[14] Recall of past body weight may differ by age or time-span passed, but differences in body weight gain between educational levels were similar for younger and older participants. Additionally, although BMI at baseline was available for the full cohort (see Figure 1) BMI at age 20 years was assessed only in some EPIC centers. On average, the difference in weight gain between highest and lowest educational level was 60 g per year in men and 110 g per year in women between age 20 years and recruitment into the cohort. This amounts to less than 1 kg mean difference in weight gain in men and slightly more than 1 kg in women over a period of 10 years. These average differences translate to notably higher percentages of overweight and obese subjects at the time of recruitment in the less educated group as compared with the best educated group.[11] Taking also into account that the gap in BMI already exists young adulthood, we conclude that education is an important risk factor for the development of overweight and obesity throughout the first decades of adult life.

Overall, there was a mean weight gain between recruitment and end of follow-up in all educational levels; however, the increase in weight gain was less strong among participants with a university degree, especially in men. Although the association between education and BMI is well recognized cross-sectionally, this seems to be less clear for weight gain. In Finnish adults, weight gain was higher in low socio-economic status (SES) groups than high SES groups.[15] A Swedish study reported an inverse association between weight change and SES in men but not in women,[16] and a Dutch study observed no association at all between SES and BMI change.[17] In general, among non-Black populations, an inverse association between occupation and weight gain appears to be more consistent than the association between education and weight gain.[5] Education is, in contrast to occupation and income, stable throughout adult life and reflects childhood conditions, and does not take social advancements and status later in life or the SES of the spouse, in particular for women, into account.[18] However, adjusting for marital status did not change our study results.

When we examined the association between education and weight gain during follow-up, we adjusted for several factors that are associated with weight gain and that might differ by education, that is, physical activity, energy intake, smoking status at recruitment and alcohol consumption, which did not attenuate the differences. Also, further adjustments for changes in smoking habits during follow-up, marital status, parity and menopausal status did not alter the observed differences. Most important determinants of change in body weight are energy intake and energy expenditure. As the observed differences did not change materially after adjusting for energy intake and expenditure, one might assume that less educated individuals more frequently underreport food intake or overreport physical activity than better educated. As 74% of the participants in the lowest education category in our cohort are either overweight or obese,[11] and individuals with higher BMI, more frequently and to a greater extent, underreport dietary intake,[19,20] the impact of dietary underreporting may be more meaningful among less educated people. Additionally, foods with a high energy density and an unhealthy image might more commonly be underreported.[20,21]

The strengths of our study are its size and the ability to examine the association in a variety of European populations. However, some weaknesses have to be taken into consideration. Firstly, weight at age 20 years and weight at follow-up are self-reported information in most of the cohorts. Therefore, underreporting of weight, especially among overweight and obese individuals[9,14] has to be taken into account when interpreting differences in weight changes over educational categories. However, in two centers, follow-up weight has actually been measured and the results of these two cohorts are largely in line with results from the other centers. Although most EPIC cohorts were recruited from the general population, the cohorts are not representative of a country. Therefore, our results may not be generalizable to a country's population. Only little research has been conducted on the accuracy of reporting educational status. Education is likely to be more accurately reported than measures based on more sensitive information such as income,[22] although accuracy of reported information on education status or years of schooling appears to vary between 61 and 89% in the few studies conducted on this issue. Finally, occupation or job position, an alternative for defining SES, have not consistently been assessed in the EPIC centers.

In conclusion, our results clearly show that differences in BMI between different educational levels in men and women already exist in young adulthood with best-educated individuals having a lower BMI than those with the lowest education. These differences appear to aggravate during adulthood and even in later adulthood.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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AUTHOR CONTRIBUTIONS

PHMP: principal investigator of the EPIC-PANACEA project and guarantor of the article; the EPIC study was conceptualized, designed and implemented in collaboration with the main investigators in the collaborating countries as follows: Denmark (A Tjønneland, KO), France (FC-C and M-CB-R), Germany (RK), Greece (A Trichopoulou), Italy (RT), Netherlands (HBB-d-M and PHMP), Norway (EL), Spain (M-DC, LR and M-JS), Sweden (IJ) and United Kingdom (NW and K-TK; these authors contributed to the study design, subject recruitment, and data collection and acquisition, and are responsible for the ongoing follow-up and management of the EPIC cohort); SR, J Linseisen and SH: conceived the current study; SR, A Steinbrecher and J Linseisen: responsible for the design of the study, analyses of data, interpretation of results and drafting of the manuscript, with close assistance from SH, AMM, J Luan and PHMP, and taking into account the comments and suggestions of the coauthors; contributors from the collaborating centers (UE, JH, GF, CA, GM, AM, FR, NT, PA, EA, LR, LMN, BH, MR, TB, AN, PO, SvdB, MMB, A Steffen, BT, FLC, A-KI, SN, VG, TM, TN): provided the original data, information on the respective populations, and advice on study design, analysis and interpretation of the results; and all coauthors had the opportunity to comment on the analysis and interpretation of the findings, and approved the final version of the manuscript.

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