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Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study

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Abstract. Bamia C, Halkjær J, Lagiou P, Trichopoulos D, Tjønneland A, Berentzen TL, Overvad K, Clavel-Chapelon F, Boutron-Ruault M-C, Rohrmann S, Linseisen J, Steffen A, Boeing H, May AM, Peeters PH, Bas Bueno-de-Mesquita H, van den Berg SW, Dorronsoro M, Barricarte A, Rodriguez Suarez L, Navarro C, González CA, Boffetta P, Pala V, Hallmans G, Trichopoulou A (University of Athens, Athens, Greece; Institute of Cancer Epidemiology, Copenhagen, Denmark; Harvard School of Public Health, Boston, MA, USA; Bureau of Epidemiologic Research, Athens, Greece; Hellenic Health Foundation, Athens, Greece; Institute of Preventive Medicine, Copenhagen, Denmark; Institute of Public Health, Aarhus University, Aarhus, Denmark; Center for Cardiovascular Research, Aalborg, Denmark; Institut Gustave-Roussy, Paris, France; German Cancer Research Centre, Heidelberg, Germany; Institute of Epidemiology, Potsdam, Germany; German Institute of Human Nutrition Potsdam-Rehbruecke, Potsdam, Germany; University Medical Center Utrecht, Utrecht, the Netherlands; Public Health and Primary Care, London, UK; National Institute of Public Health and the Environment (RIVM), Bilthoven, the Netherlands; Public Health Department of Gipuzkoa & Ciberesp, San Sebastian, Spain; Health Institute of Navarra, Pamplona, Spain; CIBER Epidemiología y Salud Pública (CIBERESP), Spain; Health and Healthcare services council, Asturias, Spain; Murcia Regional Health Council, Murcia, Spain; Catalan Institute of Oncology, Barcelona, Spain; International Agency for Research on Cancer, Lyon, France; Fondazione IRCSS Istituto Nazionale dei Tumori, Milan, Italy; and Nutritional Research, Umea, Sweden). Weight change in later life and risk of death amongst the elderly: the European Prospective Investigation into Cancer and Nutrition-Elderly Network on Ageing and Health study.

Objective. Later life weight change and mortality amongst elders.

Design. Nested case–control study.

Setting. Six countries from the European Investigation into Cancer and nutrition – Elderly, Network on Ageing and Health.

Subjects. A total of 1712 deceased (cases) and 4942 alive (controls) were selected from 34 239 participants, ≥ 60 years at enrolment (1992–2000) who were followed-up until March 2007. Annual weight change was estimated as the weight difference from recruitment to the most distant from-date-of-death re-assessment, divided by the respective time.

Outcome measures. Mortality in relation to weight change was examined using conditional logistic regression.

Results. Weight loss >1 kg $year^{-1}$ was associated with statistically significant increased death risk (OR = 1.65; 95% CI: 1.41–1.92) compared to minimal weight change (±1 kg $year^{-1}$). Weight gain >1 kg $year^{-1}$ was also associated with increased risk of death (OR = 1.15; 95% CI: 0.98–1.37), but this was evident and statistically significant only amongst overweight/obese (OR = 1.55; 95% CI: 1.17–2.05). In analyses by time interval since weight re-assessment, the association of mortality with weight loss was stronger for the interval proximal (<1 year) to death (OR = 3.10; 95% CI: 2.03–4.72). The association of mortality with weight gain was stronger at the interval of more than 3 years and statistically significant only amongst overweight/obese (OR = 1.58; 95% CI: 1.07–2.33). Similar patterns were observed regarding death from circulatory diseases and cancer.

Conclusions. In elderly, stable body weight is a predictor of lower subsequent mortality. Weight loss is associated with increased mortality, particularly short-term, probably reflecting underlying nosology. Weight gain, especially amongst overweight/obese elders, is also associated with increased mortality, particularly longer term.

Keywords: body mass index, mortality, obesity, weight gain, weight loss.

Abbreviations: BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; ICD-10, International statistical Classification of Diseases and related health problems, Tenth Revision; IQR, interquartile range; NAH, Network on Ageing and Health; OR, odds ratio.

Introduction

The relations of mortality with weight and weight change have been explored in many studies, and there is evidence that these relations vary with age [1, 2]. There are numerous investigations which have shown that high body mass index (BMI) is associated with increased risk of death and the occurrence of several diseases [3–14]. The association of BMI with mortality, however, is less clear amongst the elderly, with several studies reporting that low BMI is associated with higher mortality [15–19]. It is possible that, amongst the elderly, frequent subclinical nosology, which increases the risk of death, is also associated with weight loss, as several studies have shown [16, 20–26]. However, most of these studies have investigated the effect of long-term change in weight, for example from adulthood to old age [16, 20, 25, 26]. Moreover, in some of these studies there was limited information on underlying morbidity that could result in both weight loss and increased mortality.

We have used data from participants of the European Prospective Investigation into Cancer and Nutrition (EPIC), who were 60 years or older at enrolment and were followed-up for an average of about 10 years. We have examined the associations of weight changes and risk of death, using a nested case–control sampling approach to accommodate the variable times at which sequential weight measurements were made.

Participants and methods

European Prospective Investigation into Cancer and Nutrition is an ongoing multicentre, prospective cohort study investigating the role of biological, dietary, lifestyle, and environmental factors in cancer and other chronic diseases [27]. A total of 519 978 apparently healthy males and females, aged 25–70 years, were recruited between 1992 and 2000 in 23 centres from 10 European countries. At enrolment, all subjects completed questionnaires on diet, lifestyle, and medical history and had anthropometric measurements taken. Details of the EPIC study have been previously published [27]. The study protocol has been approved by the ethical review board of the International Agency for Research on Cancer, as well as, by the ethical committees in the participating centres. All participants signed informed consent forms before enrolment and procedures have been in line with the Helsinki declaration for human rights.

Data for 64 077 EPIC participants, who were 60 years or older at recruitment were included in the EPIC-Elderly Network on Ageing and Health (EPIC-Elderly NAH) project. EPIC-Elderly NAH aimed at investigating aspects and predictors of healthy ageing. The following countries participated in EPIC-Elderly NAH: France (one centre), Greece (one centre), Germany (two centres), Italy (two centres), Netherlands (two centres), Spain (five centres), Denmark (two centres) and Sweden (one centre).

Anthropometry

At enrolment At enrolment, measurements of waist and hip circumferences, as well as, of weight and height were undertaken according to a common protocol with slight variations amongst centres [11, 28]. To correct for the indicated differences, the participants' body weight was corrected by subtracting from the original measurements of weight 1.5 kg for subjects who were normally dressed and 1 kg for subjects in light clothing [28].

In France, measurements of weight, height, waist and hip circumferences at enrolment were undertaken for a minority of participants and only these were considered in this study.

Postenrolment During the follow-up period, reassessment of weight was undertaken through self reports in all EPIC-Elderly NAH contributing centres except for Italian and Swedish centres for which relevant data were not available. The number of reports about a person's weight during the postenrolment period varied between one and four.

Dietary, lifestyle, and medical variables

Usual dietary intakes at enrolment were assessed through compatible instruments (food frequency questionnaires and, in some centres, records of intake over seven or 14 days) that had been developed and validated in each centre [29]. Total energy intake was calculated using country-specific food composition tables [30].

A precoded questionnaire was used at enrolment to record socio-demographic data, as well as data on lifestyle and medical history. Physical activity at work was recorded for participants still working at enrolment whereas for leisure, time spent on each of several activities during the past year was assessed for every participant [31]. Based on the above information, an index was created which expresses the total physical activity expended per day for each subject [32]. In the context of medical history, participants were asked at recruitment whether they had been diagnosed by a medical doctor with myocardial infarction, cancer, stroke or diabetes mellitus.

Mortality data

Vital status, cause and date of death of EPIC participants is ascertained using record linkages with cancer and death registries (Denmark, Italy, the Netherlands, Spain and Sweden), or, by active follow-up (Germany, Greece, France). The International statistical Classification of Diseases and related health problems, Tenth Revision (ICD-10) was used to code causes of death [33]. We investigated death from all causes, from diseases of the circulatory system (codes I 00–I 99 and R 96, R 98, R 99) and from cancer (codes C 00-D 48).

The EPIC-Elderly NAH cohort

The EPIC-Elderly NAH cohort includes 64 077 EPIC participants who were 60 years or older at enrolment and without extreme values in energy intake (those with values above the top 1% and below the bottom 1% of the ratio of energy intake to estimated energy requirement were excluded). As indicated, the Umea (Sweden) cohort, as well as, the Milan and Ragusa (Italy) cohorts did not have data on re-assessment of weight during follow-up, at the time of the analysis and were, thus, excluded. From the remaining 50 269 participants who had at least one weight reassessment during the follow-up period, we considered the 41 518 who, at enrolment, had also a valid weight measurement. We further excluded 6346 individuals with a pre-enrolment diagnosis of cancer, myocardial infarction, diabetes or stroke to avoid possible confounding influences of the indicated prevalent conditions, as well as 738 participants with missing information in any of the covariates of interest. From the remaining 34 434 subjects, after a median follow-up of 9.8 years (1.2–13.6 years), 1863 (5%) had died, 32 376 (94%) were still alive, whereas the remaining 195 subjects (1%) were lost to follow-up and therefore excluded. Thus, the study base included 34 239 subjects with a total of 50 229 instances of weight re-assessment during follow-up.

The nested case–control study

A nested case–control study design was used for the present analysis. The 1863 from the 34 239 subjects who had died as of March 2007 were defined as cases. For each case, an attempt was made to choose three control subjects, from amongst the 32 376 participants who were alive as of March 2007. Control subjects were matched with cases for study centre, gender, age at enrolment (exact year), date of recruitment (±0.5 year) and date of weight re-assessment

(±3 months). For cases with more than one weight re-assessments, the earliest date of weight re-assessment was used for the matching. From all potential control subjects for each case, the first three matches were chosen. Control subjects were matched to only one case (matching without replacement).

From the 1863 deceased cases, we could not identify matching controls for 151 (8%), whereas 1712 (92%) were successfully matched. Amongst those, 71 (4%) had only one successful match, 52 (3%) had two successful matches and the remaining 1589 (93%) had three successful matches. In total, 1712 case–control sets including 1712 cases and 4942 control subjects (6654 individuals in total) were analysed.

Statistical analysis

Median values and interquartile ranges of quantitative characteristics – or percentages for qualitative ones – by gender and case–control status, were calculated for descriptive purposes.

Weight change per year since recruitment was estimated as the difference in weight from recruitment to the date of weight re-assessment, divided by the respective time interval. Weight change was then classified into three groups: weight loss of more than 1 kg year^{-1}, weight gain of more than 1 kg year^{-1}, and minimal or no change (that is, weight change of 1 kg year^{-1} or less in either direction). We also assessed weight change, as the per cent change in weight from enrolment to the date of weight re-assessment, classified in four categories: more than five per cent loss, five to three per cent loss, less than three per cent change in either direction (stable weight), three to five per cent gain and more than five per cent gain.

Odds ratios (ORs) of death with the associated 95% confidence intervals (CIs) for those with weight loss, as well as for those with weight gain, compared to those with minimal change (reference) were estimated through conditional logistic regression. We also performed conditional logistic regression models for those case–control sets for which cause of death was attributed to diseases of the circulatory system and for those case–control sets for which cause of death was attributed to cancer. To assess whether overall results were affected by inclusion of people with underlying diseases not evident, unknown or not reported at recruitment, we repeated the analyses separately: (i) for case–control sets for which date of weight re-assessment and date of case death differed by <1 year, (ii) for case–control sets for which date of weight re-assessment and date of case death were between 1 and 3 years, and (iii) for case–control sets for which date of weight re-assessment and date of case death differed by more than 3 years. To explore potential differences in the association of weight change with risk of death according to BMI at enrolment, additional analyses were run for those who were: (i) underweight or of normal weight (BMI: <25.0 kg m^{-2}; only 52 subjects were underweight with a BMI <18.5 kg m^{-2}), (ii) overweight or obese (BMI: ≥25 kg m^{-2}) at enrolment. Similarly, analyses were repeated for never smokers, former smokers and current smokers at enrolment.

All conditional regression models were controlled for the following potential confounders assessed at enrolment: BMI (<25.0 kg m^{-2}, 25 to <30 kg m^{-2} and ≥30 kg m^{-2}; categorically), waist circumference (continuously), ethanol intake (for men: <10 g day^{-1}, 10–50 g day^{-1} and >50 g day^{-1}, for women: <5 g day^{-1}, 5–25 g day^{-1} and >25 g day^{-1}; categorically), smoking status (never, former, current; categorically), educational achievement (none, elementary, secondary, university or college; categorically), physical activity (inactive, moderately inactive, moderately active, active; ordered) and energy intake (continuously).

Analyses were run in STATA statistical software [34].

Results

In Table 1, the distribution by study centre is presented for the EPIC-Elderly NAH participants, those eligible for being cases and controls, as well as those selected in the nested case–control study. Many participants from France had to be excluded because at enrolment body weight was reported rather than measured. We also had to exclude participants from the Italian centres as well as the Umea (Sweden) centre, because data on re-assessment of body weight after enrolment were not available. As expected, the distributions of deceased and control subjects were almost identical as centre of recruitment was one of the matching variables.

Table 2 shows socio-demographic and lifestyle characteristics at enrolment for the 1712 cases and the 4942 controls by gender. There were slightly more men (52%) than women (48%) in this study. The median age at enrolment was 63.61 years for women and 63.14 years for men; age at enrolment was calculated by subtraction of date of birth from the date at enrolment and was used without any rounding. Differ-

Table 1 *EPIC-Elderly NAH participants, all, those eligible for the case–control study, and those selected in the study*

	No. (%)							
	EPIC-Elderly				Selected[b] for the nested case–control study			
Recruitment-centre	NAH cohort		Eligible[a] for study		Deceased (cases)		Alive (controls)	
France	13 104	20%	2672	8%	96	6%	284	6%
Greece	9194	14%	6370	19%	332	19%	925	19%
Italy								
Milan	1978	3%	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
Ragusa	422	1%	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
Spain								
Asturias	950	1%	827	2%	32	2%	91	2%
Granada	1236	2%	860	3%	41	2%	118	2%
Murcia	967	2%	720	2%	42	2%	115	2%
Navarra	908	1%	779	2%	40	2%	113	2%
San Sebastian	992	2%	820	2%	65	4%	186	4%
The Netherlands								
Bilthoven	677	1%	264	1%	9	1%	23	1%
Utrecht	5813	9%	3325	10%	126	7%	378	8%
Germany								
Heidelberg	4368	7%	3216	9%	141	8%	421	9%
Potsdam	5198	8%	3811	11%	190	11%	502	10%
Sweden								
Umea	3301	5%	–[c]	–[c]	–[c]	–[c]	–[c]	–[c]
Denmark								
Aarhus	4096	6%	2935	9%	150	9%	450	9%
Copenhagen	10 873	17%	7640	22%	448	26%	1336	27%
Total	64 077	100%[d]	34 239	100%[d]	1712	100%[d]	4942	100%[d]

[a]Without diagnosis of cancer, myocardial infarction, diabetes or stroke at enrolment, with a valid weight measurement at enrolment, with at least one re-assessment of weight during follow-up, and with known survival status as of March 2007.
[b]Amongst eligible subjects, cases were all deceased and an attempt was made to find three living controls per case, matching for study centre, gender, age at enrolment (exact year), date of recruitment (±0.5 year) and date of re-assessment of weight (±3 months).
[c]Data on weight re-assessment postenrolment were not available.
[d]Sums do not always add up to 100 because of rounding approximations.
EPIC-Elderly NAH, European Prospective Investigation into Cancer and Nutrition Network on Ageing and Health.

ences were in general in the predicted directions. Thus, in comparison to living controls, deceased cases were of lower educational level (P for trend <0.001), exercised less (P for trend 0.02), smoked more frequently (P for trend <0.001) and were less frequently moderate alcohol drinkers ($P < 0.001$).

In Table 3, somatometric characteristics of the study participants at recruitment, as well as changes in body weight until re-assessment (at the date most distant from-date-of-death) are shown. The median age at weight re-assessment was 68.19 years for cases and 68.12 years for controls. The median time between weight measurement at enrolment and weight re-assessment was amongst men, 4.3 years for cases and 4.9 for controls, and, amongst women, 4.6 years for both cases and controls. The data in Table 3 serve only descriptive purposes, because they do not take into account possible confounding influences; nevertheless the high prevalence of overweight

Table 2 *Characteristics at enrolment of 1712 cases (deceased)[a] and 4942 controls (alive)[a]*

	Males (3481)				Females (3173)			
	Cases		Controls		Cases		Controls	
Age (matched)								
≤65.00	688	76.3%	2019	78.3%	559	69.0%	1663	70.4%
65.01–70.00	123	13.6%	330	12.8%	189	23.3%	540	22.9%
≥70.01	91	10.1%	230	8.9%	62	7.7%	160	6.8%
Smoking status								
Never	173	19.2%	740	28.7%	446	55.1%	1464	62.0%
Former	328	36.4%	1117	43.3%	178	22.0%	502	21.2%
Smoker	401	44.5%	722	28.0%	186	23.0%	397	16.8%
Ethanol intake[b]								
Low	335	37.1%	895	34.7%	464	57.3%	1337	56.6%
Moderate	419	46.5%	1368	53.0%	255	31.5%	811	34.3%
High	148	16.4%	316	12.3%	91	11.2%	215	9.1%
Education								
None	147	16.3%	369	14.3%	131	16.2%	347	14.7%
Elementary	396	43.9%	1085	42.1%	295	36.4%	820	34.7%
Secondary	206	22.8%	586	22.7%	305	37.7%	881	37.3%
University or college	153	17.0%	539	20.9%	79	9.8%	315	13.3%
Physical activity								
Inactive	212	23.5%	509	19.7%	180	22.2%	478	20.2%
Moderately inactive	205	22.7%	632	24.5%	202	25.0%	578	24.5%
Moderately active	248	27.5%	704	27.3%	227	28.0%	662	28.0%
Active	237	26.3%	734	28.5%	201	24.8%	645	27.3%
Total	902	100.0%	2579	100.0%	810	100.0%	2363	100.0%

[a]Without diagnosis of cancer, myocardial infarction, diabetes or stroke at enrolment, with a valid weight measurement at enrolment, with at least one re-assessment of weight during follow-up, and with known survival status as of March 2007.
[b]Low: <5 g day^{-1} for women, <10 g day^{-1} for men; moderate: 5–25 g day^{-1} for women, 10–50 g day^{-1} for men; high: >25 g day^{-1} for women, >50 g day^{-1} for men.

and obesity amongst both men and women participants is characteristic of this cohort.

Table 4 shows the association of annual weight change since recruitment with the risk of death overall, as well as by category of BMI at enrolment. When the data were stratified, only case–control sets in which both the case and the control(s) were in the same category of underweight/normal, overweight or obese were considered. Overall, weight loss >1 kg $year^{-1}$ was associated with a statistically significant increase in the risk of death (OR = 1.65; 95% CI: 1.41–1.92) and the effect was somewhat stronger amongst those who had a normal body weight (or were underweight) at enrolment. Overall, annual weight gain >1 kg $year^{-1}$ was also associated with an increase in the risk of death (OR = 1.15; 95% CI; 0.98–1.37) and the association was evident and statistically significant amongst the majority of subjects who were already overweight or obese at enrolment (OR = 1.55; 95% CI: 1.17–2.05). There was an indication for interaction ($P = 0.01$) of the weight loss association with mortality by gender. Thus, the overall estimate of 1.65 was amongst men 2.08 (95% CI: 1.68–2.57) whereas amongst women it was 1.28 (95% CI: 1.02–1.60). There was no evidence for interaction of the weight loss association with mortality by age, nor any evidence for interaction of the association of weight gain with mortality by either gender or age.

Table 3 *Somatometric characteristics at enrolment and postenrolment of 1712 cases (deceased)[a] and 4942 controls (alive)[a]*

	Males (3481) Median (IQR)[b]		Females (3173) Median (IQR)[b]	
Characteristic	Cases	Controls	Cases	Controls
At enrolment				
Height (cm)	171.00 (166.00–177.00)	171.70 (166.30–177.00)	159.80 (154.50–164.00)	160.00 (155.00–164.50)
Weight (kg)	79.40 (72.00–87.90)	80.00 (73.00–88.00)	67.35 (59.60–76.50)	67.30 (60.50–75.50)
BMI (kg m^{-2})	26.93 (24.64–29.59)	27.15 (25.00–29.52)	26.10 (23.36–30.56)	26.29 (23.52–29.78)
Normal/underweight: no. (%)[c]	263 (29.2%)	644 (25.0%)	323 (39.9%)	914 (38.7%)
Overweight: no. (%)[c]	445 (49.3%)	1364 (52.9%)	267 (33.0%)	890 (37.7%)
Obese: no. (%)[c]	194 (21. 5%)	571 (22.1%)	220 (27.2%)	559 (23.7%)
Waist circumference (cm)	98.00 (91.00–105.50)	98.00 (92.00–104.50)	85.00 (78.00–95.50)	85.00 (77.00–93.00)
Postenrolment				
Weight (kg)	79.00 (72.00–87.00)	80.00 (73.00–87.52)	66.01 (60.00–75.00)	68.00 (60.00–75.00)
Weight change (kg)	−0.35 (−3.80 to 2.50)	0.00 (−2.40 to 2.56)	−0.49 (−3.41 to 2.19)	0.10 (−2.20 to 2.50)
Annual weight change (kg $year^{-1}$)	−0.08 (−0.89 to 0.62)	0.00 (−0.55 to 0.55)	−0.11 (−0.82 to 0.53)	0.018 (−0.56 to 0.60)

[a]Without diagnosis of cancer, myocardial infarction, diabetes or stroke at enrolment, with a valid weight measurement at enrolment, with at least one re-assessment of weight during follow-up, and with known survival status as of March 2007.
[b]Unless otherwise specified.
[c](i) Underweight/normal weight: BMI <25.0 kg m^{-2}, (ii) overweight: 25 kg m^{-2} ≤ BMI ≤ 30 kg m^{-2}, (iii) obese: BMI >30.0 kg m^{-2}.
IQR, interquartile range.

In Table 5, the ORs of death in relation to annual weight change are shown by time interval between postrecruitment weight assessment and date of death. It is clear that weight loss is associated with increased risk of death mostly when it is proximal to the date of death. Thus, during the year preceding death, the risk of death appears to increase by 210% in relation to weight loss, whereas when the time interval exceeds 3 years, the corresponding excess is reduced to only 27%. With respect to weight gain, there is some evidence that it is associated with increased risk of death when it is relatively distant, rather than proximal, to the date of death. Indeed, when the analysis was limited to overweight/obese persons at the interval of more than 3 years, the OR was 1.58 (95% CI: 1.07–2.33).

When weight change was expressed as the per cent change in weight since enrolment, the results were very similar. In other analyses, the association of weight change with risk of death was found to be similar amongst smokers and amongst ex-smokers/non-smokers. In analyses by cause of death, the associations of weight loss or gain with subsequent death were similar for 538 cancer deaths (and 1528 matched controls) and for 498 deaths from circulatory diseases (and 1411 matched controls). However, the association of annual weight loss by more than 1 kg with death within 1 year was stronger for cancer (OR = 4.57; 95% CI: 2.36–8.85) than for deaths from circulatory diseases (OR = 3.16; 95% CI: 1.45–6.90).

Discussion

In the context of a large cohort study of men and women 60 years or older at enrolment from six European countries, who were followed-up for approximately 10 years, we have conducted a nested case–control study to investigate the relation of weight change with risk of death amongst persons who were apparently healthy at enrolment. Thus, survivors in this study would be about 70 years old at the end of the follow-up. Annual weight change was estimated as the difference in weight (in kg) from recruitment to the most distant from-date-of-death weight re-assessment, divided by the respective time interval. Evaluation of the consequences of weight change on risk of death was done for the period following that

Table 4 *Odds ratios*[a] *for death in relation to weight change since recruitment*

Weight change per year	Cases (%)	Controls (%)	Odds ratio	95% Confidence interval	*P*-value
All					
Minimal change[b]	1082 (63.2%)	3523 (71.3%)	Ref	–	–
Loss >1 kg year^{-1}	372 (21.7%)	746 (15.1%)	1.65	(1.41–1.92)	<0.001
Gain >1 kg year^{-1}	258 (15.1%)	673 (13.6%)	1.15	(0.98–1.37)	0.093
Underweight/normal[c]					
Minimal change[b]	301 (72.0%)	499 (76.1%)	Ref	–	–
Loss >1 kg year^{-1}	48 (11.5%)	39 (6.0%)	2.10	(1.28–3.44)	0.003
Gain >1 kg year^{-1}	69 (16.5%)	118 (18.0%)	0.90	(0.61–1.32)	0.579
Overweight/obese[c]					
Minimal change[b]	513 (60.9%)	968 (71.9%)	Ref	–	–
Loss >1 kg year^{-1}	208 (24.7%)	238 (17.7%)	1.70	(1.33–2.16)	<0.001
Gain >1 kg year^{-1}	122 (14.5%)	140 (10.4%)	1.55	(1.17–2.05)	0.003

[a]Adjusted for the following variables assessed at enrolment: measured BMI (underweight/normal weight, overweight, obese, categorically), measured waist circumference (continuously), ethanol intake (<10 g day^{-1} for men and <5 g day^{-1} for women g day^{-1}, 10–50 g day^{-1} for men and 5–25 g day^{-1} for women, >50 g day^{-1} for men and >25 g day^{-1} for women, categorically), smoking status (never, former, current, categorically) educational achievement (none, elementary school degree, secondary school or technical school degree, university degree or higher, categorically), physical activity (inactive, moderately inactive, moderately active, active, ordered) and energy intake (continuously). In analyses of 'underweight/normal' or 'overweight/obese', measured BMI at enrolment was still adjusted for continuously.
[b]Less than or equal to ±1 kg year^{-1}.
[c](i) Underweight/normal weight: BMI <25.0 kg m^{-2}, (ii) overweight/obese: BMI ≥25 kg m^{-2}.

required for assessment of weight change. We have found that weight loss >1 kg year^{-1} is associated with increased risk of death (OR = 1.65). Weight gain >1 kg year^{-1} was associated with higher risk of death only amongst overweight or obese (OR = 1.55), who, however, were the majority in this population. The lowest risk of death in all analyses was observed amongst individuals with minimal changes in body weight over time.

Our findings indicate that, amongst the elderly, stable body weight is an important predictor of lower subsequent mortality. Weight gain, especially amongst overweight or obese elders, is associated with increased mortality. Weight loss amongst the elderly is also associated with increased mortality, most likely because it reflects the effects of underlying nosology (reverse causation).

The association of weight change with risk of death has been investigated in many studies conducted in populations of adults or elderly. Increased risk of mortality with weight loss has been found in many of these studies [35–41]. In some studies, an increased risk of death has also been associated with weight gain [41–44], whilst in others no association of mortality with weight loss or/and weight gain was evident [45, 46].

The time period over which weight change has been estimated varies across investigations. In some of the studies amongst the elderly, a long-term weight change has been evaluated, defined as the difference between 'current' (baseline) weight and a recalled weight in adulthood [16, 20, 26]. In some investigations, a short-term weight change has been estimated as the difference in weight between two study examinations [21, 22, 24, 25], whilst in others weight change has been assessed as a trend over a series of measurements undertaken at standard time intervals [23]. Studies also differ with respect to the length of follow-up after assessment of weight change, which ranges from <6 years in most of these studies [16, 20, 22, 23, 26] to more than 12 years in some of them [21, 24, 26]. In our study, median time interval between weight assessments was 4.6 years and median length of follow-up after weight change assessment was 5.0 years.

The results of our study indicate an association of weight loss with excess mortality. This probably reflects the effect of underlying morbidity on mortality

Table 5 *Mortality in relation to weight change (since recruitment), by time interval since weight re-assessment*

Weight change	Cases (%)	Controls (%)	Odds ratio[a]	95% Confidence interval	*P*-value
Time interval: <1 year[b]					
Minimal change[c]	129 (58.37%)	461 (72.14%)	Ref	–	–
Loss >1 kg year^{-1}	70 (31.67%)	100 (15.65%)	3.10	(2.03–4.72)	<0.001
Gain >1 kg year^{-1}	22 (9.95%)	78 (12.21%)	1.03	(0.59–1.79)	0.931
Time interval: ≥1 to ≤3 years[b]					
Minimal change[c]	391 (63.27%)	1300 (73.16%)	Ref	–	–
Loss >1 kg year^{-1}	133 (21.52%)	246 (13.84%)	1.85	(1.43–2.40)	<0.001
Gain >1 kg year^{-1}	94 (15.21%)	231 (13.00%)	1.18	(0.89–1.57)	0.249
Time interval: >3[b,d]					
Minimal change[c]	562 (64.38%)	1762 (69.75%)	Ref	–	–
Loss >1 kg year^{-1}	169 (19.36%)	400 (15.84%)	1.27	(1.02–1.58)	0.035
Gain >1 kg year^{-1}	142 (16.27%)	364 (14.41%)	1.18	(0.94–1.49)	0.147

[a]Adjusted for the following variables assessed at enrolment: measured BMI (underweight/normal weight, overweight, obese, categorically), measured waist circumference (continuously), ethanol intake (<10 g day^{-1} for men and <5 g day^{-1} for women g day^{-1}, 10–50 g day^{-1} for men and 5–25 g day^{-1} for women, >50 g day^{-1} for men and >25 g day^{-1} for women, categorically), smoking status (never, former, current, categorically), educational achievement (none, elementary school degree, secondary school or technical school degree, university degree or higher, categorically), physical activity (inactive, moderately inactive, moderately active, active, ordered) and energy intake (continuously).
[b]Estimated as the time between postrecruitment weight re-assessment and case date of death.
[c]Less than or equal to ±1 kg year^{-1}.
[d]For about 65% of cases in this category, the time intervals ranged from 3 to 5 years.

since weight loss, especially over relatively short periods, is likely to be a marker of existing disease. Indeed, in some of the earlier studies, weight loss was associated with previous illness [16, 20], whilst in others the association of weight loss with excess mortality was somewhat reduced after exclusion of the initial period of follow-up [23, 26]. In our study, we excluded subjects who, at enrolment, had cancer, myocardial infarction, stroke or diabetes. Nevertheless, the association of weight loss with excess mortality was much higher for deaths within 1 year of weight change assessment compared to deaths occurring more than 3 years from weight change assessment, a pattern compatible with the existence of underlying disease. The association of weight loss with excess mortality persisted even when deaths occurring after 3 years from weight change assessment were considered, which is likely to reflect the fact that medical progress has led to longer survival of patients afflicted with chronic diseases associated with intentional or unintentional weight loss, such as cardiovascular disease and several types of cancer. Similar results have been reported from previous studies which explored the effect of weight change in different follow-up periods [23, 25, 26].

It has been suggested that weight loss needs to be distinguished as intentional versus unintentional and failure to do this may bias the estimated effect so that weight loss would appear to adversely affect health [47]. We did not have data on reasons for weight change. However, results from studies of intentional/unintentional weight change are not consistent, with some showing an association of intentional weight loss with decreased mortality [48] or, of unintentional weight loss with increased mortality [49], some showing no association of either intentional or unintentional weight loss with mortality [50] and some showing a association of both, intentional and unintentional weight loss with increased mortality [51]. A recent meta-analysis on the effect of intentional and unintentional weight loss on all-cause mortality risk concluded that, unintentional/ill-defined weight loss was associated with an excess risk of 22–39%, whereas intentional weight loss had a small benefit only amongst individuals classified as unhealthy [52].

In our study, weight gain was associated with a statistically significant increase in mortality amongst the overweight and obese and the effect was more evident after 3 years from weight change assessment. Other studies amongst the elderly have also shown an association of weight gain with excess mortality [21, 23, 25, 26], although the association was not always statistically significant [21]. In two of these studies the follow-up period was similar to ours [23], whereas in the studies by Dey *et al.* [21] and Corrada *et al.* [26] the follow-up was considerably longer. It appears that the adverse consequences of weight gain are manifested after a long, rather than short, period of time. In our study, the detrimental effect of weight gain was larger amongst the overweight/obese rather than the normal weight subjects. Similar results have been reported from the two studies conducted amongst the elderly who explored the effect of weight gain across different categories of baseline BMI [23, 26].

Strengths of our investigation include its reliance on a well established cohort study, the inclusion of participants from several European countries across the continent and use of standardized instruments. We have adjusted for several confounding variables but the effect was limited, reducing the potential for substantial residual confounding [53]. The study was reasonably large for an elderly cohort, amongst whom the incidence of death is inherently high. An average follow-up time of about 10 years was quite long, but the need to use part of it to ascertain weight changes reduced the postweight re-assessment follow-up time to about half. Choosing controls amongst those who were alive, not only at the time of death of the corresponding case but also at the end of follow-up, was deemed appropriate to avoid including amongst controls persons who were already sick and had sickness-related weight changes. This approach may have led to slight overestimation of the effect estimates in our study as controls were probably healthier than those in the study base. Another limitation of our study is the use of self-reported rather than measured weight at re-assessment which is usually accompanied by underreporting of actual weight and, thus, of weight change. However, the effect of underreporting would be probably minimal in this case–control study as the degree of underreporting is not expected to be differential between cases and controls due to the original cohort design of EPIC from which the cases and controls were selected.

For the analyses of these data, we have opted for a nested case–control design because the times of weight re-assessments varied across participating centres. With the nested case–control design, which preserves all the attributes of the cohort design [54] we were able to overcome this problem by matching cases and controls on date of weight re-assessment and date of recruitment. A cohort design with time-dependent variables could perhaps address the same issues and incorporate repeated weight measurements, but it would introduce more complexity in the analysis.

In conclusion, we have found that amongst Europeans 60 years or older at recruitment, stable body weight is an important predictor of lower subsequent mortality. Weight loss amongst these elderly is associated with increased mortality, particularly in the short-term, most likely because it reflects the effects of underlying nosology. Weight gain, especially amongst overweight or obese elders, is also associated with increased mortality, particularly in the longer term.

Conflict of interest

All authors have declared no financial disclosures.

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