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The Association between Weight Change and Cardiovascular Mortality:

The HUNT Study, Norway

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Abstract

Background: Obesity has become a widespread health problem all over the world and is related to adverse levels of cardiovascular risk factors, which rapidly improve after weight loss. However, observational studies have shown that weight gain could both reduce and increase the risk of cardiovascular diseases (CVDs), whereas weight loss have been associated with higher CVD mortality in some studies. The purpose of this study was to examine the association between changes in body weight and the subsequent risk of cardiovascular death in Norwegian adults. We also assessed if the potentially increased risk was modified by physical activity.

Methods: Weight and height were measured among 18 798 males and 22 602 females aged ≥20 years who participated in two population based studies in the county of Nord-Trøndelag, Norway, first in 1984-86 (HUNT 1) and then in 1995-97 (HUNT 2). The participants completed a detailed questionnaire including physical activity, case history, smoking, education, and alcohol consumption, and based on standardized measures of body weight and height, we calculated change in weight and body mass index (BMI) between the two surveys. We utilized a linkage to the Cause of Death Registry at Statistics Norway, with follow-up from participation in HUNT 2 until 31st December 2008. Cox regression analyses were used to calculate mortality rate ratios in different groups of weight and BMI change, and to control for potentially confounding factors.

Results: People who lost most weight had the significantly highest risk of CVD death, even when we adjusted for several potential confounders (men: RR = 1.8, 95% CI: 1.3-2.4 and women: RR = 2.2, 95% CI: 1.7-2.9). Those who gained weight between the surveys had approximately similar risk as those who were weight stable. The same tendencies were shown in analysis of change in BMI categories, but these analysis also showed a higher risk associated with being obese at both surveys (1.3, 95% CI: 1.2-1.5) compared to being normal weight.

Conclusion: In this population-based study of Norwegian adults, we found that weight loss and stable obesity was associated with higher CVD mortality, even when physical activity was taken into account, though it is possible that the follow-up period was too short to exert an effect of weight gain. Although underlying diseases are likely to be our most plausible explanation, we may cautiously suggest that to prevent health consequences caused by overweight or weight changes, people should make early establishments of normal body weight and good habits, and prevent further weight changes.

Contents

Introduction

Obesity has gradually become a widespread health problem all over the world and the prevalence of overweight and obesity has increased substantially during the last decade [1]. More than 34% of US adults are overweight and additionally 34% are obese [2]. A large health study in Norway showed a substantial increase in the prevalence of overweight and obesity in all age groups below 70 years during a 10-year period, especially among the youngest. The proportion of people classified as obese increased from 7 % to 16 % among men and from 11 % to 21 % among women, and people aged 20-29 years had an increase in body weight of approximately 7 kg [3].

An individual's body weight is determined both by genetic and environmental factors, but it is likely that lifestyle and behavior are the main contributors to weight change [4]. Possible reasons for weight gain or weight variability includes dieting efforts, smoking cessation, depression, alcohol habits [5], or physical activity. It should be noted, however, that it is difficult to achieve weight loss by exercising alone, and other lifestyle changes, such as reduced dietary energy intake, should also be adopted [6]. Several diseases may induce weight loss, either due to reduced appetite, depressions, nausea, vomiting, or diarrhoea, or because of other catabolic effects [7]. Also, it is possible that several obese people are being advised to lose weight for health reasons [8]. Besides, during the lifespan, the body composition passes trough considerable changes [9] and the body weight changes systematically with age [2].

The net effect of overweight on morbidity and mortality is complicated to quantify, despite an extensive body of research [1]. However, numerous studies have shown that obese individuals have higher all-cause mortality and that obesity is an important risk factor for chronic disorders such as diabetes, hypertension, dyslipidemia, and cardiovascular diseases (CVDs) [8, 10, 11]. The risk of developing weight related diseases increases with the duration of overweight [3], and a relatively small weight gain may be associated with an increased risk [8]. Further, the risk seems to increase with increasing weight gain [8, 12]. However, studies have shown that cardiovascular risk factor levels (e.g. blood pressure, blood lipids, blood glucose), and risk of type 2 diabetes are rapidly improved after weight loss [11, 13]. Thus, it is reasonable to suggest that weight loss among obese persons should reduce cardiovascular risk and mortality. However, several observational studies have shown the opposite; that weight loss is related to a higher CVD mortality [7, 13, 14].

A study from the US showed that, compared to being weight stable, weight loss was associated with higher mortality if it was unintentional, whereas intended weight loss was associated with lower mortality [15]. A higher mortality among persons who have lost weight may be caused by an underlying undiagnosed disease. This mechanism is often referred to as reverse causation, i.e. it is not weight loss that cause the disease, but the disease that causes weight loss [2, 8]. However, others have found no association between change in body mass index (BMI) from early- to mid-adulthood and CVD mortality [16]. It is possible that established overweight or obesity may confine the possible cardiovascular benefits of weight reduction, since the cardiovascular damage is well established and may not easily regress [8]. Breeze and colleagues showed that a change in body weight during 30 years had a stronger relation to CVD mortality than the exact BMI at middle or old age, and both an increase and a decrease in BMI was associated with higher all-cause mortality and CVD mortality [17]. Accordingly, studies have reported that keeping a stable weight may be a preventive factor for developing CVD [12, 18].

Physical activity may, to some extent, compensate for the negative effects of obesity [19] and protect against all-cause mortality [20]. A study from Denmark by Sørensen and colleagues showed that the excess mortality associated with weight loss was worse in those who used dieting as their weight loss procedure compared to those using physical activity [21], indicating that activity should be promoted among persons indenting to lose weight [4, 19].

Sørensen and colleagues suggest that the best study design to assess the real consequences of intended weight loss in selected groups is randomized trials [21]. But on the other hand, the long-term effects of a weight loss will probably remain unknown, which rather promote a prospective cohort study. Also, few studies have focused on the possible favorable effects of physical activity.

The purpose of this prospective cohort study was to examine the association between long-term changes in body weight and the subsequent risk of cardiovascular death. Furthermore, we assessed if the potentially increased risk associated with weight change may be modified by physical activity.

Materials and methods

Study population

The HUNT study is conducted in the Nord-Trøndelag County in the middle of Norway. The population is considered representative for the whole Norwegian population, although the county does not have any big cities. Three cross-sectional waves of the HUNT study have been conducted; HUNT 1 (1984-86), HUNT 2 (1995-97) and HUNT 3 (2006-08), and the HUNT study is one of the world's largest health surveys ever conducted [22]. All inhabitants in Nord-Trøndelag aged ≥20 year have been invited to the study, and 88% (n=77 216) participated in HUNT 1, whereas in HUNT 2, 70% of the invited chose to participate (n=65 215), while 47 286 persons participated in both [22].

For the purpose of the present study, we selected 24 868 females and 21 728 (n= 46 596) males who took part in both studies. In every HUNT-study all participants completed self-administered questionnaires on health and lifestyle. Also, standardized measurements of physiological variables such as weight and height were registered [22]. The questionnaires and procedures were more comprehensive at HUNT 2 than at HUNT 1, and included more data on each person [23].

From the 46 596 persons who participated in our study, we excluded 4 802 who reported CVD (i.e. myocardial infarction, stroke, or angina) at HUNT 2 and 394 persons without information on CVD or central variables such as weight and height. In this master thesis, data from HUNT 1 and HUNT 2 will be used, and a complete number of 18 798 males and 22 602 (n= 41 400) females are included in the analysis.

Follow-up

Each participant's record at HUNT is attached to his or her unique 11-digit personal identification numbers, which enables linkage with other health registries [22]. In this study we utilized a linkage to the Cause of Death Registry at Statistics Norway. Each participant contributed person-years from the date of participation in HUNT 2 to the date of death or to end of follow-up at 31st December 2008. International Classification of Diseases was used to classify cardiovascular mortality. A few deaths that occurred in 1995 were classified according to the 9th revision (cardiovascular diagnoses codes 390-459) and thereafter the 10th revision (codes I00-I99) was used.

Weight change and change in BMI

Both height and weight were measured objectively by trained personal, wearing light clothes and without shoes. Weight was measured to the nearest half-kilogram and height to the nearest centimeter [23]. Weight change was determined by calculating the difference in weight from the first to the second survey (i.e. weight at HUNT 2 minus weight at HUNT 1). These results were recoded into seven different weight changing groups, where a stable weight was defined as a change of ±0.99 kg. This stable group (group 1) was used as the reference group in the statistical analyses. Weight loss consisted of two different categories; a loss of 1.00-9.99 kg (group 2) or ≥10.00 kg (group 3), while weight gain was separated in four different groups; 1.00-4.99 kg (group 4), 5.00-9.99 kg (group 5), 10.00-14.99 kg (group 6) or ≥15.00 kg (group 7).

Based on the measurements if height and weight, BMI was calculated as kilograms of weight divided by the squared value of height in meters (kg m^{-2}). Based on cut-offs recommended by the World Health Organization (WHO) [24], we categorized the subjects into three different groups in both surveys, defined as normal weight (18.5-24.9 kg m^{-2}), overweight (25.0-29.9 kg m^{-2}), and obese (≥30.0 kg m^{-2}). Those who were classified as underweight (<18.5 kg m^{-2}) were excluded from this analysis. We then combined the three categories of BMI status at HUNT 1 (initial BMI) and the three categories at HUNT 2 (final BMI), leading to a complete number of nine categories showing if people had been stable within a BMI category, or had gone up or down one or two categories.

Other study variables

Leisure time physical activity

The level of physical activity was obtained from two questions in the second survey (HUNT 2), where the subjects indicated the amount of leisure time physical activity that they usually engaged in during one week the past year. The first questions asked the participants to state the number of hours of light exercise (i.e. not sweat or out of breath) each week the past year, with four possible response options; "none", "<1 hour", "1-2 hours", or "≥3 hours". In the second question, the number of hours of hard exercise (i.e. sweat or out of breath) each week the past year was reported using the same response alternatives as for light activity. Further, these variables were recoded and the subjects were categorized into four different groups of physical activity level per week; "no activity", "<3 hours light and no hard", "≥3 hours light and/or <1 hour hard", "any light and ≥1 hour hard", or "unknown".

Smoking status

Participants were asked about smoking history using seven questions in HUNT 2. The first four questions were "Do you smoke cigarettes daily?", "Do you smoke cigars daily?", "Do you smoke pipe daily?", and "Have you never smoked daily?", with response options "yes" or "no". Three more specific questions followed; "If you have been a daily smoker, how long has it been since you stopped smoking?", "For how many years have you been a daily smoker?", and "How old were you when you became a daily smoker?". We used this information to construct a variable of smoking status defined as "never", "former", or "current" smoker. Those with missing information on smoking history were classified as "unknown".

Educational level

Since the level of education may indicate socioeconomic position we decided to take this variable into consideration in the analysis. Consequently, the participants were divided into a total number of four different categories; "middle school", "high school", "college/university", and "unknown".

Alcohol consumption

We classified alcohol consumption into three different groups based on how often the participants reported to drink per month. "0 times or teetotaler", "1-2 times", or "≥3 times". Persons with missing data were classified as "unknown".

Ethics

Each participant in the study signed a written consent upon participation, thus, the participation was completely voluntary. Also, the study has been approved by the Regional Committee for Ethics in Medical Research.

Statistical analyses

The baseline characteristics of the study population were analyzed using descriptive analyses and presented as frequencies and means with standard deviations (SDs), median with range, or as percentages. Descriptive statistics are presented within each weight changing group. Cox regression analyses were used to calculate both age-adjusted and multivariably adjusted mortality rate ratios (RRs) with 95% confidence intervals (CIs) associated with the different weight changing and BMI categories, using persons with stable weight (±0.99 kg) or normal

BMI (18.50-24.99) at both surveys as reference. The analyses were performed separately for males and females. Multivariably adjusted RRs were controlled for the potential confounding effect of age at the second survey (30-39, 40-49, 50-59, 60-69, 70-79 and ≥80 years), physical activity (no activity, <3 hours light and no hard, ≥3 hours light and/or <1 hour hard, any light and ≥1 hour hard activity per week, or unknown), smoking (never, former, current smoker, or unknown), education (middle school, high school, college/university, or unknown) and alcohol consumption ("0 times or teetotaler", "1-2 times", ≥3 times per month, or unknown).

In a supplementary analysis we excluded everyone with less than 5 years of follow-up to assess the potential influence of underlying pre-clinical disease. To further address the potential influence of undiagnosed disease, we repeated the main multivariably adjusted analysis only among participants who defined their general health at HUNT 2 as "good/very good", based on the question "How is your health nowadays?". Moreover, we examined whether the effect of weight change on mortality was modified by age by conducting stratified analysis using 65 years as cut-off.

To explore the potential importance of physical activity on the association between weight change and mortality, we conducted stratified analysis of weight change according to activity level, where participants were defined as either "inactive" ("no activity" or "<3 hours light and no hard") or "active" ("≥3 hours light and/or <1 hour hard" or "any light and ≥1 hour hard").

All analyses were conducted using SPSS 17.0 for Windows (SPSS, Chicago, ILL, USA).

Results

Baseline characteristics

During 13 years of follow-up, a total of 6230 deaths (3163 males and 3067 females) were observed, and out of these 1177 men and 1166 women died from CVD (Table 1). Amongst males who lost weight, 37.0% (n = 1194) died (from any cause), compared to 11.7% (n = 1649) of those who gained weight. Similar figures for females were 34.1% (n = 1307) and 8.5% (n = 1474), respectively (Table 1).

Overall, 7.8 % of the men in the study population retained a stable weight, whilst 75.1% gained weight and 17.2% lost weight during the 11-year period from HUNT 1 to HUNT 2. Corresponding figures for women were 6.7%, 76.4% and 17.0%. On average, people who lost most weight (≥10 kg) had the highest weight at HUNT 1, and most of the study population increased their weight between 1.00 and 10.00 kg during the two surveys (Table 1). In males, the two groups of people who lost weight had the highest mean age at the second survey; 62.9 years, while the four groups who gained weight had the lowest; 52.7 years. The same tendencies were shown in females; mean age in the two groups was 64.3 years and 51.6 years, respectively.

Table 2 presents the baseline characteristics of the four possible confounders; physical activity, smoking, education, and alcohol consumption. Among those who lost weight, 31.3% of the males and 25.1% of the females are defined as physically active. Similarly, the figures for those who were stable were 31.6% for men and 28.5% for women, and for those who gained weight 30.7% and 30.8%, respectively. Among women the smoking habits are nearly equal between the different categories, contrary to men, where the differences are more extensive (Table 2). Thus, the absolutely largest percent of current smokers (46.9%) was found among those who lost most weight. Also, those who lost weight have an inferior level of education; 10.0% among men and 8.4% among women. Similar figures among those who gained weight were 18.6% and 15.9%. There are no extensive differences between the categories in alcohol consumption. It should be noted that the numbers presented in Table 1 and Table 2 are crude estimates, and it is likely that factors such as age are of importance for the reported mean values and percentages.

Table 1: The baseline characteristics of the study population included in the analysis; 18 798 males and 22 602 females, stratified by weight changing group and gender, and based on data from the two surveys, HUNT 1 (1984-86) and HUNT 2 (1995-97). Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2.

	Weight changing group, kg						
Variables	≤-10.00	-1.00 to -9.99	±0.99	1.00 to 4.99	5.00 to 9.99	10.00 to 14.99	≥15.00
Males							
No. of participants (% within gender)	207 (1.1)	3018 (16.1)	1464 (7,8)	5343 (28.3)	5512 (29.3)	2254 (12.0)	1000 (5.3)
No. of deaths (% within weight changing group)	130 (62.8)	1064 (35.5)	320 (21.9)	824 (15.4)	566 (10.3)	180 (8.0)	79 (7.9)
No. of CVD deaths (% within weight changing group)	52 (25.1)	400 (13.3)	127 (8.7)	291 (5.4)	216 (3.9)	64 (2.8)	27 (2.7)
Median follow-up time, years (range)	9.0 (0.2-13.4)	12.1 (0.03-13.4)	12.3 (0.1-13.4)	12.3 (0.1-13.4)	12.3 (0.1-13.4)	12.3 (0.4-13.4)	12.2 (0.5-13.4)
Mean age at CVD death, years (SD)	81.9 (8.1)	81.1 (8.9)	79.0 (9.9)	78.4 (9.9)	75.5 (9.7)	71.5 (12.3)	70.2 (12.6)
Mean age at second survey, years (SD)	68.8 (13.6)	62.5 (13.6)	58.4 (13.2)	55.1 (12.7)	50.9 (11.7)	47.8 (11.2)	44.9 (10.6)
Mean weight at first survey, kg (SD)	88.3 (14.8)	79.7 (10.9)	77.7 (10.2)	77.9 (9.7)	78.5 (9.8)	79.7 (10.5)	81.0 (11.9)
Mean weight at second survey, kg (SD)	75.1 (14.2)	76.3 (10.9)	77.8 (10.2)	80.7 (9.7)	85.5 (9.9)	91.5 (10.7)	99.7 (12.8)
Mean weight change (SD)	13.2 (3.7)	3.4 (2.2)	0,03 (0.4)	2.8 (1.1)	6.7 (1.4)	11.8 (1.4)	18.7 (4.0)
Mean BMI at first survey, kg m^{-2} (SD)	28.8 (4.4)	25.7 (3.1)	25.0 (2.9)	24.9 (2.8)	24.8 (2.8)	24.9 (3.0)	25.0 (3.5)
Mean BMI at second survey, kg m^{-2} (SD)	25.0 (4.2)	24.9 (3.1)	25.2 (2.9)	25.9 (2.8)	27.1 (2.9)	28.6 (3.1)	30.9 (3.9)
Mean change in BMI, kg m^{-2} (SD)	3.8 (1.3)	0.8 (0.8)	0.3 (0.4)	7.1 (0.5)	2.3 (0.6)	3.8 (0.6)	5.8 (1.3)
Females							
No. of participants (% within gender)	449 (2.0)	3383 (15.0)	1507 (6.7)	5860 (25.9)	6586 (29.1)	3123 (13.8)	1694 (7.5)
No. of deaths (% within weight change group)	238 (53.0)	1069 (31.6)	286 (19.0)	708 (12.1)	493 (7.5)	181 (5.8)	92 (5.4)
No. of CVD deaths (% within weight change group)	106 (23.6)	408 (12.1)	125 (8.3)	262 (4.5)	184 (2.8)	60 (1.9)	21 (1.2)
Median follow-up time, years (range)	11.6 (0.1-3.4)	12.1 (0.1-13.4)	12.3 (0.2-13.4)	11.6 (0.1-13.4)	12.4 (0.2-13.4)	12.3 (0.1-13.4)	12.3 (0.6-13.4)
Mean age at CVD death, years (SD)	84.6 (6.1)	84.7 (7.4)	84.9 (7.3)	83.1 (8.0)	80.8 (9.4)	75.4 (11.6)	75.2 (13.0)
Mean age at second survey, years (SD)	68 (15.1)	63.8 (14.1)	60.6 (14.4)	56.0 (13.4)	52.4 (12.1)	50 (10.8)	47.7 (10.3)
Mean weight at first survey, kg (SD)	81.4 (15.9)	68.7 (12.1)	65.7 (10.6)	64.4 (10.2)	64.5 (9.9)	65.6 (10.2)	68.5 (11.4)
Mean weight at second survey, kg (SD)	67.2 (14.8)	65.0 (11.9)	65.7 (10.6)	67.2 (10.2)	71.5 (10.0)	77.4 (10.4)	88.0 (12.9)
Mean weight change (SD)	14.3 (4.9)	3.7 (2.3)	0.04 (0.4)	2.8 (1.1)	7.0 (1.4)	11.9 (1.4)	19.4 (4.6)
Mean BMI at first survey, kg m^{-2} (SD)	30.7 (5.8)	26.0 (4.4)	24.8 (4.0)	24.1 (3.8)	23.9 (3.6)	24.1 (3.7)	24.9 (4.0)
Mean BMI at second survey, kg m^{-2} (SD)	26.0 (5.3)	25.1 (4.4)	25.1 (4.1)	25.4 (4.0)	26.6 (3.8)	28.6 (3.9)	32.0 (4.6)
Mean change in BMI, kg m^{-2} (SD)	4.8 (2.1)	1.0 (1.0)	0.4 (0.5)	1.3 (6.6)	2.8 (0.7)	4,6 (0.7)	7.2 (1.7)

Table 2: The baseline characteristics of the possible confounders. The whole study population is included in the analysis; 18 798 males and 22 602 females, stratified by weight changing group and gender, and based on data from HUNT 2 (1995-97). Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2.

	No. of participants (% within weight changing group)						
	Weight changing group, kg						
Variable	≤-10.00	-1.00 to -9.99	±0.99	1.00 to 4.99	5.00 to 9.99	10.00 to 14.99	≥15.00
Males							
Physical activity[a]	55 (26,6)	953 (31,6)	462 (31,6)	1 602 (30,0)	1 704 (30,9)	732 (32,5)	290 (29,0)
Smoking habits[b]	97 (46,9)	1 194 (39,6)	516 (35,2)	1 610 (30,1)	1 450 (26,3)	522 (23,2)	246 (24,6)
Education[c]	16 (7,7)	306 (10,1)	191 (13,0)	908 (17,0)	1 067 (19,4)	479 (21,3)	176 (17,6)
Alcohol consumption[d]	94 (45,4)	1 517 (50,3)	720 (49,2)	2 625 (49,1)	2 556 (46,4)	1 047 (46,5)	495 (49,5)
Females							
Physical activity[a]	81 (18,0)	880 (26,0)	430 (28,5)	1 803 (30,8)	2 040 (31,0)	961 (30,8)	505 (29,8)
Smoking habits[b]	113 (25,2)	1 015 (30,0)	468 (31,1)	1 833 (31,3)	1 919 (29,9)	905 (29,0)	435 (25,7)
Education[c]	19 (4,2)	301 (8,9)	187 (12,4)	891 (15,2)	1 114 (16,9)	476 (15,2)	262 (15,5)
Alcohol consumption[d]	211 (47,0)	1 752 (51,8)	751 (49,8)	3 217 (54,9)	3 739 (56,8)	1 831 (58,6)	1 030 (60,8)

[a]≥3 hours light and/or <1 hour hard pr. week. [b]Current smoker. [c]Collage/university. [d]Drinks usually 1-2 times per month.

The risk of cardiovascular mortality

In analyses of weight change and the risk of cardiovascular death (Table 3) we found that participants who lost weight had a significantly higher CVD mortality compared with those who were weight stable. CVD mortality was approximately twice as high for people who lost most weight (≥10 kg) compared to those who were weight stable; adjusted RR = 1.8 (95% CI: 1.3-2.4) for men and 2.2 (95% CI: 1.7-2.9) for women. Similar associations were also found for total mortality, with an adjusted RR among those with the largest weight loss (≥10 kg) of 1.9 (95% CI: 1.6-2.4) for men and 2.4 (95% CI: 2.0-2.8) for women (Table 3). For non-CVD mortality, the associations were somewhat weaker. In contrast, people who gained weight had approximately similar risk of death as those who were weight stable, with non-significant RRs ranging from 0.8 to 1.2.

Table 3: Rate ratios (RRs) with 95% confidence intervals (CIs) of total mortality, cardiovascular (CVD) mortality and non-cardiovascular mortality associated with change in weight from HUNT 1 (1984-86) to HUNT 2 (1995-97). The 18 798 males and 22 602 females are included and stratified by weight changing group and gender. Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2.

		Total mortality			CVD mortality			Non-CVD mortality		
Weight changing group, kg	Person-years	No. of deaths	Age-adj.[a] RR	Multivariable[b] RR (95% CI)	No. of deaths	Age-adj.[a] RR	Multivariable[b] RR (95% CI)	No. of deaths	Age-adj.[a] RR	Multivariable[b] RR (95% CI)
Males										
≤-10.00	1 671	130	2.3	1.9 (1.6-2.4)	52	2.1	1.8 (1.3-2.4)	78	1.5	1.5 (1.1-2.0)
-1.00 to -9.99	31 526	1064	1.3	1.2 (1.1-1.4)	400	1.2	1.1 (0.9-1.4)	664	1.0	1.1 (0.9-1.2)
±0.99	16 530	320	1.0	1.0 (reference)	127	1.0	1.0 (reference)	193	1.0	1.0 (reference)
1.00 to 4.99	62 457	824	0.9	0.9 (0.8-1.0)	291	0.8	0.8 (0.7-1.0)	533	0.9	0.9 (0.8-1.1)
5.00 to 9.99	65 800	566	0.9	0.9 (0.8-1.0)	216	0.9	0.9 (0.7-1.1)	350	1.1	1.1 (0.9-1.3)
10.00 to 14.99	27 193	180	0.9	0.9 (0.8-1.1)	64	0.9	0.9 (0.7-1.2)	116	1.0	1.0 (0.8-1.2)
≥15.00	12 023	79	1.2	1.2 (1.0-1.6)	27	1.2	1.2 (0.8-1.8)	52	1.0	1.0 (0.8-1.5)
Females										
≤-10.00	4 116	238	2.5	2.4 (2.0-2.8)	106	2.3	2.2 (1.7-2.9)	132	1.2	1.2 (0.9-1.5)
-1.00 to -9.99	36 662	1069	1.5	1.4 (1.2-1.6)	408	1.2	1.2 (1.0-1.4)	661	1.0	1.0 (0.8-1.1)
±0.99	17 416	286	1.0	1.0 (reference)	125	1.0	1.0 (reference)	161	1.0	1.0 (reference)
1.00 to 4.99	69 919	708	0.9	1.0 (0.8-1.1)	262	0.9	0.9 (0.7-1.1)	446	0.9	0.9 (0.7-1.1)
5.00 to 9.99	79 965	493	0.8	0.8 (0.7-1.0)	184	0.9	0.9 (0.7-1.1)	309	0.9	0.9 (0.8-1.1)
10.00 to 14.99	38 050	181	0.9	0.9 (0.7-1.0)	60	0.9	0.9 (0.7-1.2)	121	0.8	0.8 (0.7-1.1)
≥15.00	20 550	92	1.1	1.1 (0.8-1.3)	21	0.9	0.8 (0.5-1.3)	71	1.0	1.0 (0.7-1.3)

[a]Adjusted for age measured at the second survey (30-39 years, 40-49 years, …, ≥80 years). [b]Adjusted for the following variables measured at the second survey: age (30-39 years, 40-49 years, …, ≥80 years), level of physical activity per week (no activity, <3 hours light and no hard, ≥3 hours light and/or <1 hour hard, any light and ≥1 hour hard, unknown), smoking habits (never, former, current, unknown), education (middle school, high school, college/university, unknown) and usual alcohol consumption per month (0 times or teetotaler, 1-2 times, ≥3 times, unknown).

When we excluded everyone with less than five years of follow-up, the adjusted RRs were only moderately different from the main analysis (data not shown). Overall, there was no effect of weight gain, whereas women who lost ≥10 kg had a RR of 2.0 (95% CI: 1.4-2.8). The corresponding RR among men was 1.5 (95% CI: 0.9-2.5). Also the results from the supplementary analysis of participants who defined their general health as "good/very good" at HUNT 2 showed that both men and women who lost most weight (≥10.00 kg) had an increased risk of death from CVD. The adjusted RR was 1.6 (95% CI: 0.9-2.8) for men and 2.6 (95% CI: 1.6-4.1) for women. Moreover, the RRs for those who gained 10.00-14.99 kg were 0.9 (95% CI: 0.6-1.4) for men and 1.3 (95% CI: 0.8-2.1) for women. RR for those who gained most weight (≥15 kg) was 1.6 (95% CI: 0.9-2.7) in men and 0.6 (95% CI: 0.2-1.5) in women (data not shown).

In the analysis stratified by age ±65 years at HUNT 2, the risk associated with weight loss was slightly larger among the youngest participants than among the oldest (≥65 years); the RR was 3.3 (95% CI: 1.2-8.7) and 2.2 (95% CI: 1.6-3.1) in men and 3.0 (95% CI: 0.9-10.4) and 2.6

(95% CI: 2.0-3.4) in women. Overall, there was a non-significantly lower RR associated with weight gain in both age groups. The lowest risk was found in women who gained most weight (≥15 kg); RR among the youngest (≤65 years) was 0.7 (95% CI: 0.2-1.9) and 0.7 (95% CI: 0.4-1.2) among the oldest (≥65 years) (Appendix 1).

We also examined if the effect of weight change on mortality was modified by physical activity (Appendix 2). The results indicate no large differences between people who reported to be inactive and those who were physically active, and still, weight loss was associated with higher risk of CVD mortality. The significantly highest RR was among active females who lost most weight (≥10 kg); 2.9 (95% CI: 1.4-5.8). The corresponding RR among men was 1.8 (95% CI: 1.0-3.1). Both males and females who were inactive and lost most weight had a significantly higher RR; 2.0 (95% CI: 1.1-3.5) and 2.6 (95% CI: 1.8-3.9). The lowest RR, though non-significant, was associated with active females who gained most weight (≥15 kg); 0.7 (95% CI: 0.2-3.0), while the corresponding group of men had a slightly higher RR; 1.4 (95% CI: 0.8-2.7). Furthermore, those who were inactive and gained most weight (≥15 kg), had approximately similar risk of CVD mortality as those who were weight stable; 1.1 (95% CI: 0.5-2.2) for men and 1.1 (95% CI: 0.6-2.0) for women (Appendix 2).

Change in BMI categories

In the subsequent Cox regression analysis, which included the nine categories of change in BMI (Table 4), we found similar tendencies as those described above. Thus, overall there was a statistically significant association between a reduction in BMI and risk of cardiovascular death. Although non-significant, mortality was highest in those losing most weight (going from obese to normal weight), with a RR of 2.5 (95% CI: 0.9-6.7), whereas initially obese persons who became overweight had a RR of 1.8 (95% CI: 1.4-2.3) compared to the reference group of people who kept a stable normal weight. Being stable overweight was not associated with an increased risk (RR = 1.0; 95% CI: 0.9-1.1), while people who were obese at both surveys had a RR of 1.3 (95% CI, 1.2-1.5). Finally, an initial normal BMI (18.50-24.99) followed by weight gain was not clearly associated with the risk of CVD death. The RR was 0.9 (95% CI: 0.8-1.0) for those who became overweight, and 0.7 (95% CI: 0.3-1.6) for those who became obese. We also repeated the analysis stratified by gender, and the same pattern was evident for both sexes (data not shown).

Table 4: Multivariable-adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of cardiovascular mortality associated with the participants' change in BMI from HUNT 1 (1984-86) to HUNT 2 (1995-97). Those defined as "underweight" (BMI = <18.50) in HUNT 1 or HUNT 2 are excluded, thus 18 691 males and 22 081 females are included. Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2.

	Final BMI[a]		
Initial BMI[b]	Normal weight[c]	Overweight[d]	Obesity[e]
Normal weight[c]			
No. of participants (person-years)	13 825 (163 306)	9 368 (112 850)	491 (5 907)
No. of CVD deaths	573	273	6
Multivariable[f] RR (95% CI)	1.0 (reference)	0.9 (0.8-1.0)	0.7 (0.3-1.6)
Overweight[d]			
No. of participants (person-years)	875 (8 824)	8 953 (102 933)	3 845 (45 359)
No. of CVD deaths	133	684	231
Multivariable[f] RR (95% CI)	1.5 (1.2-1.8)	1.0 (0.9-1.1)	1.1 (0.9-1.3)
Obesity[e]			
No. of participants (person-years)	24 (215)	393 (3 806)	2 998 (33 667)
No. of CVD deaths	4	83	320
Multivariable[f] RR (95% CI)	2.5 (0.9-6.7)	1.8 (1.4-2.3)	1.3 (1.2-1.5)

[a]Estimated BMI (kg m^{-2}) at HUNT 2. [b]Estimated BMI (kg m-2) at HUNT 1. [c]BMI = 18.50-24.99. [d]BMI = 24.99-29.99. [e]BMI = ≥29.99. [f] Adjusted for gender and the following variables measured at the second survey: age (30-39 years, 40-49 years, …, ≥80 years), level of physical activity per week (No activity, <3 hours light and no hard, ≥3 hours light and/or <1 hour hard, any light and ≥1 hour hard, unknown), smoking habits (never, former, current, unknown), education (middle school, high school, college/university, unknown) and usual alcohol consumption per month (0 times or teetotaler, 1-2 times, ≥3 times, unknown).

Discussion

Major findings

In this population-based study of Norwegian adults, we found a higher mortality rate amongst people who had lost weight during the 11-year period between HUNT 1 and HUNT 2, compared to those who maintained a stable weight, both for CVD mortality, total mortality, and non-CVD mortality. Overall, weight gain showed little or no association with mortality, neither for all-cause nor cause specific deaths. The same tendencies were shown when we excluded everyone with less than five years of follow-up, and when we only included those who considered their health as good or very good. Likewise, analysis stratified by age ± 65 years showed the same pattern, with no material difference between the two age groups. The same did analysis stratified by physical activity; both active and inactive who lost most weight had the highest mortality rate. Similarly, going down one or more BMI category was associated with the highest risk, compared to being normal weight at both surveys, whereas people who were obese at both surveys had a slightly higher risk. People who increased their BMI category had no increased mortality.

Strengths and limitations

This prospective study has several important strengths, including the large number of both men and women who participated in the two surveys, the wide age range, the representative study population [23], and more than 10 year follow-up on cause specific mortality through the Cause of Death Registry at Statistics Norway. Moreover, body weight and height were measured standardized and objectively by trained personal and similar at both surveys [22]. A thorough administration of questionnaires and clinical examinations reduce the risk of selection and information bias. Although the possibility for residual confounding due to unmeasured or misclassified factors cannot be ruled out [7], data from HUNT 2 allowed us to adjust for the potentially confounding effect of factors such as physical activity, smoking, education, and alcohol consumption. The physical activity questions used in HUNT 2 have previously been validated, and unlike the “light activity” question, which had poor reproducibility and validity, “hard activity” correlated well with measured oxygen consumption [25]. However, it should be noted that this validation study was conducted on a small sample of young adult males. Finally, the latency time for developing cardiovascular- and other weight-related diseases is possibly several decades [3], and even though the present study had a quite long follow-up period, it may still be too short to exert an effect of weight gain on CVD mortality. Also, it must be noted

that in all analyses, some of the categories consist of very few deaths, thus the results may be somewhat uncertain.

Comparison with existing literature

Previous studies have reported higher CVD mortality in people who have lost weight compared to those who remain stable [7, 13, 14, 16], although other studies have not found this association [11]. Contradictory to studies who reported that weight gain may be associated with decreased CVD risk [26, 27], several studies have shown that an increase in weight or BMI tends to increase the risk of CVD mortality [8, 17, 18]. However, the causal pathway is somewhat enigmatic.

Overall, there was no clear association between weight gain and mortality, and based on the well known risk factors that follows with overweight and obesity, our findings appear to be somewhat paradoxical. Nevertheless, several studies have showed the same tendencies [26, 27]. The WHO-MONICA study by Kuulasma and colleagues showed that an increase in BMI trends tended to be associated with decreased coronary heart disease (CHD) rates among men, while there was no association between changes in BMI and CHD among women [26]. In a Korean study, a moderate weight gain in non-obese men seems to protect against cardiovascular death [27]. Contrarily, a Japanese prospective population study by Chei and colleagues from year 1990 to 2001 stated that in lean men weight gain appears to contribute to an increased risk (40%) of CHD, although no relation was found between weight change and the risk of CHD among women. A stable weight in lean men since 20 years of age may actually serve as a preventive factor for developing CHD [18], and according to the British prospective study by Wannamethee and colleagues, an increase in BMI tended to increase the risk of CVD, based on a 20 year follow-up period [8]. In our study there was at least a significantly higher risk of CVD mortality associated with being obese at both surveys.

Several previous studies have shown that intentional weight loss is not associated with any changes in mortality compared to those without any weight changes. While unhealthy subjects suffering from diseases are expected to benefit from weight loss (i.e. CVDs, diabetes etc) and reduce mortality, unintentional weight loss is generally associated with increased mortality [7]. However, the study by Wannamethee and colleagues reported little benefits in relation to CVD in obese men who lost weight. This could be explained by a regain in weight [8], and we cannot discount that this is also the case in our study.

Possible mechanisms

Both loosing and gaining weight seem to adversely affect longevity [5]. Weight gain is often followed by an intentional weight loss, which can be referred to as weight cycling, and may have the same unfavorable effect [5, 7, 28]. Especially, using diets to lose weight often causes repeated weight cycling, but even though weight variability is probably caused mainly by dieting, this association is not clearly related to increased risk of CVD [5]. However, it could be speculated that weight cycling may be the reason why people who lost most weight had the highest CVD mortality. Unfortunately this remains unknown to us, and we cannot even be sure of that everyone who was considered as "weight stable" truly belongs to this group. It is also conceivable that weight changes took place before our time interval.

The CVD risk factor profile that follows with obesity clearly improves shortly after weight loss, thus it seems likely that reduced adiposity would have beneficial long-term effects [7, 11, 21] (e.g. reduced blood pressure, improvements in glucose metabolism, serum lipid profile etc. [11]). It has been shown that weight loss is associated with increased mortality, whereas loss of fat mass is related to decreased mortality. Skinfold thickness at specific regions can estimate body fatness, although a reduction in skinfold thickness may not necessarily reflect loss in overall body fatness [29]. In the present study, there was no information about what type of body mass our participants lost.

BMI is useful in estimating the prevalence of obesity within a population and the risks associated with it, but does not account for the variation in the nature of obesity between different individuals and populations [24]. Since BMI is composed of two different components; fat mass and fat free mass, it may not be the most beneficial estimate of the impact of weight loss on mortality [11]. By using BMI, the body composition is unknown [1], thus it may hide different health consequences associated with the loss of fat- and lean body mass. Besides, changes in body composition seem to be more important with respect to longevity than the exact changes in body weight [11]. It is possible that the effects of weight loss on mortality is a balance between the effects of the loss of damaging abdominal fat and the corresponding loss of beneficial subcutaneous fat and lean body mass [13]. But unfortunately, the body composition is not known in the current study.

In agreement with previous studies [21], it seems plausible that weight gain partly reflects increase in lean body mass, with increased longevity as the result. This explanation puts a

major emphasis on the association between weight gain and reduced risk of CVD death, but it can probably not be our explanation based on the large number of participants we studied.

As reported by Sørensen and colleagues, those who lose weight by dieting have worse excess mortality than those who use exercise, which probably reflects the favorable effect of fat free mass [21] and the positive association between this and physical activity. Thus, the association between weight loss and increased mortality could be explained by loss of lean body mass. However, neither adjustment for nor stratification by physical activity did change the results.

According to Pischon and colleagues waist circumference is positively associated with the risk of death even at a low BMI, which can indicate that a low BMI often means low muscle mass. This supports the use of waist circumference or waist-to-hip ratio (WHR) in addition to BMI in the assessment of the risk of death [30]. But in our data, WHR was not available. Overall, former studies points out the importance of information about how our participants lost weight and their possible changes in body composition.

Duration and severity of obesity seem to limit the cardiovascular benefits which may be caused by weight loss. That is, even though the weight loss may result in improved blood pressure and blood lipid profiles, cardiovascular damage may be well established and cannot be regressed easily. Also, the association between weight loss and CVD seems to be dependent on initial BMI, at least to some extent [8]. This may be the reason why there is an overall higher risk associated with a high initial BMI in our analysis. Besides, based on a cohort study of Danish schoolchildren at 7-13 years of age, Baker and colleagues determined that higher values in BMI during childhood are associated with a greater risk of CHD in adulthood. This increased risk may be a result of the early establishment of the risk factors for CHD [31]. Unfortunately, we have no information about possible established risk factors.

Once obesity is well established in an individual, it seems likely that the energy balance changes [32]. Pietailinen and colleagues stated in 2008, based on a longitudinal twin cohort study, that poor fitness in adolescence captured the risk for obesity in adulthood, independent of genetic effects. A vicious circle takes place; established obesity causes extremely low habitual physical activity, which may lead to increased adiposity, while genes seem to confer dispositions, not destinies. Thus, it is likely to believe that obese persons often fall below the level of physical activity they might need to maintain cardiovascular health [32]. There is

convincing evidence that physical activity appears to protect somewhat against the risk for CVDs that follows with obesity [19]. We tried to consider this, though without any substantial effect, but it must be noted that we have no information about the level of physical activity at earlier stages in life. However, the overall impression tells us that habitual physical activity should be promoted at young age and maintained during adulthood. Besides, high physical activity is associated with improved maintenance of body weight [6], and perhaps the optimal strategy to prevent increased mortality among overweight individuals is to remain stable [21]. If this is the case, prevention of overweight should definitely be globally promoted, fully independent of the weight at the present moment.

The intentions of weight change are unknown in our study. This is very difficult to validate, though in most studies, unintentional weight loss is associated with increased mortality and may signal underlying disease, which is referred to as reversed causation [7, 28]. Involuntary weight loss may be a sign of serious illness, even among people who appear healthy at baseline. But in several epidemiological studies, persons diagnosed with possible underlying diseases which may induce weight loss, (i.e. some sorts of cancers, diabetes, hyperthyroidism, celiac disease, chronic inflammatory bowel disease, and Alzheimer's disease) have been excluded, and nevertheless, weight loss was still associated with increased mortality, mainly caused by CVDs. However, pointing out diseases that may result in weight loss is usually very complicated, and these diseases may also go unrecognized for a long period [7], in fact no good way exists to control for this bias, and the methods proposed may even cause bias [32]. Firstly, we tried to prevent reverse causation by excluding participants with less than five years of follow-up, but without any considerable changes in the associations. Secondly, in the analysis of participants who defined their general subjective health as "good" or "very good" we tried to exclude persons with any possible underlying disease or depressions, because depressions can as well lead to weight loss and are a strong independent risk factor of CVDs and mortality [7]. However, no substantial change in the estimated associations were observed in analysis of men, whereas for women the RR associated with weight loss became somewhat stronger.

In the current study, those who lost most weight had the initially highest weight. Overall, it seems plausible that overweight brings about diseases that cause weight loss, but it is not known to us where our individuals are during this course. For instance, type 2 diabetes can remain undiagnosed for several years and may induce weight loss [21]. This is a possible explanation for some of our cases, but can probably not explain the whole complexity.

However, it is possible that some participants knew that they were more susceptible to harmful effects of overweight and obesity that to a greater extent encouraged them to lose weight than those without this susceptibility [11].

Ageing is generally associated with changes in body composition [34]. Weight loss in younger adults primarily means changes in fat mass whereas weight loss in older people reflects decrease in fat, lean body mass (i.e. sarcopenia) or underlying diseases, and the younger the age at intervention the greater the probable benefit of weight loss [8]. From this, the overall impression is that participants aged 65 years or younger should gain health benefits from their weight loss, and we tried to consider age as an effect modifier because it seemed plausible that the effect of weight changes was different dependent on age. But in our study the youngest group has the definitive highest RRs, which is not very likely to reflect decreased fat mass, and besides, it is not very usual to lose much weight at young age. Thus, this association may reflect reverse causation.

Based on the observational study by Newman and colleagues, the lean body mass tends to be conserved to a greater extent than fat mass with weight change in both men and women aged 70-79 years. This study showed that when older people lose weight, they are generally sicker than those who gain weight or remain stable [34] and it is conceivable that this is also the case in younger age groups. At least, this study may support our findings that when aged 65 years or older, weight loss increases the risk of CVD death, and the fact that those who lost most weight (and have the highest RRs) had the overall highest mean age at the second survey.

The weight change may also be caused by changes in the causes of obesity. Little is known about these causes, but these possible changes may be the reason why several subjects lose weight [7]. On the other hand, the possible reverse causation is likely to be less of a problem in studies of the incidence of CVD than in studies on death alone, like our study, because the impact of obesity on mortality seems to be lower than the impact on morbidity [8]. It is conceivable that the distinction between what we observe and the reality we may wish to infer would have been less critical by considering this. Besides, we cannot exclude the possibility for a selected survival; individuals with low tolerance for overweight tend to die before they reach old age. Moreover, the paradox may be partly attributable to the lower incidence of CHDs during recent decades and the fact that mortality from CHDs has decreased substantially, both because reductions in important risk factors and as a result of better treatment of CHDs [35].

Conclusion

This study has shown that weight loss, unlike weight gain, is associated with higher CVD mortality compared with maintaining a stable weight, in both men and women. While being obese at both surveys were associated with a slightly higher risk, going down one or more BMI categories was associated with the highest risk. Although reverse causation is likely to be the most plausible explanation for our findings, one may speculate in other potential mechanisms. It is possible that the results would have been different with a few more years of follow-up, and since mortality rather than morbidity was in focus, the final results may depend both on incidence of disease and survival from the disease. We may cautiously suggest that to prevent adverse health consequences caused by overweight or weight changes, people should aim at keeping a stable normal body weight. In this respect, lifestyle factors such as physical activity could be of importance.

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Appendix 1

The risk of cardiovascular mortality

Split file ≤ vs. ≥ 65 years of age

Table 5: Multivariable-adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of cardiovascular mortality (CVD mortality) associated with the participants' change in weight from HUNT 1 (1984-86) to HUNT 2 (1995-97). Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2. The 18 798 males and 22 602 females are stratified by gender, weight changing groups and ≤ vs. ≥ 65 years of age.

	≤65 years	CVD mortality		**≥65 years**	CVD mortality	
Weight changing group, kg	Person-years	No. of deaths	Multivariable[a] RR (95% CI)	Person-years	No. of deaths	Multivariable[a] RR (95% CI)
Males						
≥-10.00	810	5	3.3 (1.2-8.7)	861	47	2.2 (1.6-3.1)
-1.00 to -9.99	19 499	49	1.6 (0.9-2.6)	12 077	351	1.2 (1.0-1.5)
±0.99	11 899	19	1.0 (reference)	4 631	108	1.0 (reference)
1.00 to 4.99	50 128	67	1.0 (0.6-1.6)	12 329	224	0.8 (0.6-1.0)
5.00 to 9.99	58 558	71	0.9 (0.6-1.6)	7 242	145	0.8 (0.6-1.0)
10.00 to 14.99	25 069	28	0.9 (0.5-1.6)	2 124	36	0.7 (0.5-1.0)
≥15.00	11 404	14	0.9 (0.5-1.8)	619	13	0.9 (0.5-1.5)
Females						
≥-10.00	1 831	4	3.0 (0.9-10.4)	2 285	102	2.6 (2.0-3.4)
-1.00 to -9.99	19 158	22	1.7 (0.7-3.9)	17 503	386	1.3 (1.0-1.6)
±0.99	10 602	7	1.0 (reference)	6 814	118	1.0 (reference)
1.00 to 4.99	52 508	25	0.8 (0.4-2.0)	17 411	237	0.8 (0.6-1.0)
5.00 to 9.99	67 294	29	0.8 (0.4-1.9)	12 672	155	0.7 (0.6-0.9)
10.00 to 14.99	34 521	19	1.0 (0.4-2.5)	3 529	41	0.7 (0.5-0.9)
≥15.00	19 410	7	0.7 (0.2-1.9)	1 140	14	0.7 (0.4-1.2)

[a]Adjusted for the following variables measured at the second survey: level of physical activity per week (No activity, <3 hours light and no hard, >3 hours light and/or <1 hour hard, any light and ≥1 hour hard, unknown), smoking habits (never, former, current, unknown), education (middle school, high school, collage/university, unknown) and usual alcohol consumption per month (0 times or teetotaler, 1-2 times, ≥3 times, unknown).

Appendix 2

The risk of cardiovascular mortality

Split file "inactive" vs. "active"

Table 6: Multivariable-adjusted rate ratios (RRs) with 95% confidence intervals (CIs) of cardiovascular mortality (CVD mortality) associated with the participants' change in weight from HUNT 1 (1984-86) to HUNT 2 (1995-97). 1661 males and 3226 females are excluded because they are in lack of information on physical activity. The 17 137 males and 19 376 females are stratified by gender, weight changing groups and "inactive" vs. "active". Everyone is assessed as healthy in HUNT 1, i.e. free from CVD and/or diabetes 2.

			CVD mortality		
	Weight changing group, kg	Person-years	No. of deaths	Age-adj.[a] RR	Multivariable[b] RR (95% CI)
Males	**Inactive**[c]				
	≥ -10.00	537	19	2.3	2.0 (1.1-3.5)
	-1.00 to - 9.99	9 431	131	1.3	1.2 (0.9-1.8)
	±0.99	4 832	36	1.0	1.0 (reference)
	1.00 to 4.99	19 556	93	0.8	0.8 (0.6-1.2)
	5.00 to 9.99	21 216	89	1.1	1.1 (0.7-1.6)
	10.00 to 14.99	9 712	25	0.9	0.9 (0.5-1.5)
	≥15.00	4 832	9	1.1	1.1 (0.5-2.2)
	Active[d]				
	≥ -10.00	809	17	2.1	1.8 (1.0-3.1)
	-1.00 to -9.99	17 963	161	1.1	1.1 (0.8-1.5)
	±0.99	10 115	60	1.0	1.0 (reference)
	1.00 to 4.99	38 139	119	0.7	0.8 (0.6-1.1)
	5.00 to 9.99	40 716	77	0.8	0.8 (0.6-1.2)
	10.00 to 14.99	16 182	27	0.9	1.1 (0.7-1.7)
	≥15.00	6 642	12	1.3	1.4 (0.8-2.7)
Females	**Inactive**[c]				
	≥ -10.00	1 547	52	2.6	2.6 (1.8-3.9)
	-1.00 to -9.99	14 551	188	1.2	1.2 (0.9-1.6)
	±0.99	6 259	52	1.0	1.0 (reference)
	1.00 to 4.99	26 337	97	0.8	0.8 (0.6-1.1)
	5.00 to 9.99	33 439	75	0.7	0.8 (0.5-1.1)
	10.00 to 14.99	17 368	27	0.7	0.8 (0.5-1.2)
	≥15.00	9 631	15	1.1	1.1 (0.6-2.0)
	Active[d]				
	≥ -10.00	1 349	14	3.2	2.9 (1.4-5.8)
	-1.00 to -9.99	13 949	68	1.6	1.6 (0.9-2.6)
	±0.99	7 553	19	1.0	1.0 (reference)
	1.00 to 4.99	33 884	54	1.1	1.1 (0.7-2.0)
	5.00 to 9.99	38 710	37	1.1	1.1 (0.6-2.0)
	10.00 to 14.99	17 655	16	1.7	1.8 (0.9-3.7)
	≥15.00	9 250	2	0.6	0.7 (0.2-3.0)

[a]Adjusted for age measured at the second survey (30-39 years, 40-49 years, …, ≥80 years). [b]Adjusted for the following variables measured at the second survey: age (30-39 years, 40-49 years, …, ≥80 years), smoking habits (never, former, current, unknown), education (middle school, high school, collage/university, unknown) and usual alcohol consumption per month (0 times or teetotaler, 1-2 times, ≥3 times, unknown). [c] "no activity" or "<3 hours light and no hard". [d]"≥3 hours light and/or <1 hour hard" or "any light and ≥1 hour hard".