Explaining the obesity paradox: cardiovascular risk, weight change, and mortality during long-term follow-up in men[†]

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Aims	To examine life-long weight trajectories behind the 'obesity paradox', and whether cardiovascular disease (CVD) risk contributes.
Methods and results	Cardiovascular disease risk and body mass index (BMI) at mean ages of 25, 47 (year 1974), and 73 years (year 2000) were available of a socioeconomically homogenous sample of 1114 men, without chronic diseases and diabetes in 1974. Overweight was defined as BMI > 25 kg/m^2, and 7-year mortality (2000–06) from the mean age of 73 years determined (188 deaths). Between 1974 and 2000, 44.3% ($n = 494$) were constantly overweight, 31.0% ($n = 345$) constantly normal weight, 12.2% ($n = 136$) moved from normal to overweight, and 12.5% ($n = 139$) moved from overweight to normal. The last group had highest CVD risk in midlife, and in late life more co-morbidities and greatest total mortality ($P < 0.001$). Adjusted mortality hazard ratio was 2.0 (95% confidence interval, CI 1.3–3.0; constantly normal weight group as referent). The hazard ratio remained similar (1.9, 95% CI 1.2–3.0) after adjustment for prevalent diseases in 2000.
Conclusion	In old age, both normal weight and overweight men are a mixture of individuals with different weight trajectories during their life course. Overweight and high-CVD risk in midlife with subsequent weight decrease predict the worst prognosis in late life.
Keywords	Obesity • Cardiovascular risk • Weight change • Frailty

Introduction

Numerous epidemiological studies[1–4] have identified obesity [body mass index (BMI) > 30 kg/m^2] as an established risk factor for cardiovascular disease (CVD) and death, whereas overweight (BMI > 25 kg/m^2)[3,4] has also been associated with favourable prognosis when compared with normal weight. This protective effect of overweight and even obesity has been shown especially in studies involving older people[5–8] or CVD patients.[9–15] Recently, this 'obesity paradox' has arisen much interest and several explanations have been presented.[14,15] However, if chronic diseases lead to gradual weight los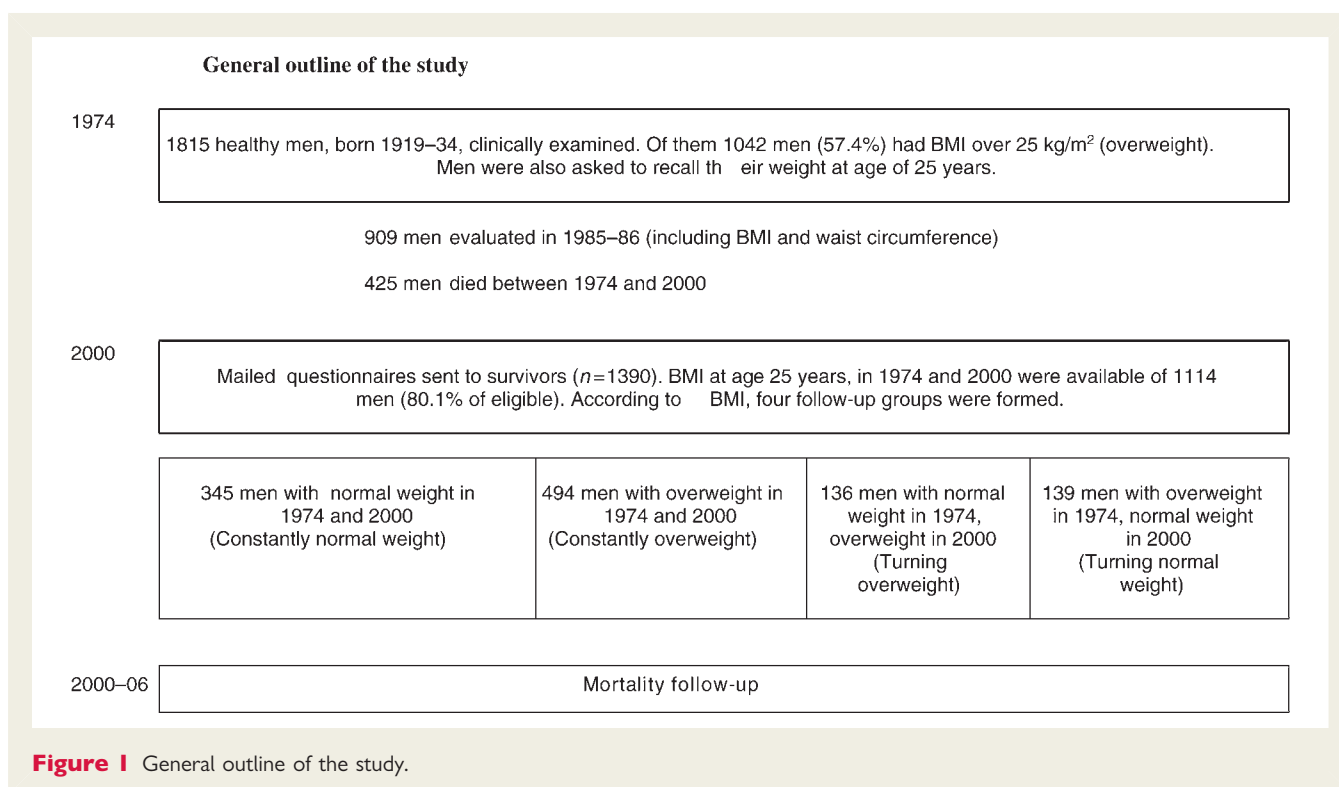s, it is quite obvious that in cross-sectional or short-term studies a link could be observed between greater weight and better prognosis simply through selection. Several well-known studies assessed the impact of weight variability during the 1990s,[16–18] but lessons from those seem to be forgotten. Transitions of weight trajectories during life course are important,[19,20] and the weight in old age, when most deaths occur, may not necessarily reflect earlier weight.[21] Because the obesity paradox is usually encountered in cohorts involving older people, it is possible that the development of frailty[22,23]—with possible links to CVD—could contribute to worse prognosis.

Therefore, our objective was to investigate how BMI changes over the life course relate to mortality in old age.

General outline of the study

| 1974 | 1815 healthy men, born 1919–34, clinically examined. Of them 1042 men (57.4%) had BMI over 25 kg/m² (overweight). Men were also asked to recall their weight at age of 25 years. |

909 men evaluated in 1985–86 (including BMI and waist circumference)

425 men died between 1974 and 2000

| 2000 | Mailed questionnaires sent to survivors (n=1390). BMI at age 25 years, in 1974 and 2000 were available of 1114 men (80.1% of eligible). According to BMI, four follow-up groups were formed. |

| 345 men with normal weight in 1974 and 2000 (Constantly normal weight) | 494 men with overweight in 1974 and 2000 (Constantly overweight) | 136 men with normal weight in 1974, overweight in 2000 (Turning overweight) | 139 men with overweight in 1974, normal weight in 2000 (Turning normal weight) |

| 2000–06 | Mortality follow-up |

Figure 1 General outline of the study.

In addition, a special aim was to investigate the role of midlife CVD risk.

Methods

Long-term follow-up is needed to reveal the underlying factors behind the obesity paradox, and therefore we examined the longitudinal cohort of the Helsinki Businessmen Study, in which we have BMI and CVD risk factor data from the age of 25 years to old age. Analyses were restricted to participants clinically healthy in midlife (average age 47 years in the year 1974), and alive at the average age of 73 years (in the year 2000), whereafter the BMI trajectory was projected to 7-year mortality (2000−06). Change in BMI status from overweight in midlife to normal weight in late life was used as a surrogate for frailty. General outline and study procedures from the year 1974 until 2007 are shown in *Figure. 1*. The study has been approved by the Ethics Committee of the Department of Medicine, University of Helsinki.

Baseline examinations in 1974

The cohort and examinations of the Helsinki Businessmen Study have been described earlier.[24] Initially healthy men, mostly business executives born in 1919−34, had participated in structured health check-ups during the 1960s and early 1970s at the Institute of Occupational Health in Helsinki. They were evaluated with questionnaires and clinical and laboratory examinations in 1974, when they were also asked to recall their weight at 25 years of age. Perceived health was assessed with a five-step scale: 'very good', 'good', 'fair', 'poor', and 'very poor'. Weight and height were measured and BMI was calculated as weight (kilograms) divided by height (meters) squared. Overweight was defined as BMI over 25 kg/m², and normal weight below this. Waist circumference was not measured in 1974 or in 2000, but it was measured in 1985−86 when 909 men of the present cohort were evaluated. At that time, there was a strong correlation

between BMI and waist circumference ($r = 0.80$, $P < 0.001$), suggesting that BMI in general reflects abdominal obesity. The coronary heart disease risk was originally calculated according to Keys *et al.*[25] We did not use the Framingham equation, because HDL cholesterol was not available in the 1974 measurements. Altogether 1815 men were found to be clinically healthy, without history or clinical signs of chronic diseases including diabetes, electrocardiographic abnormalities, or regular medications such as anti-hypertensives or anti-diabetics.

The 2000 survey

In 2000, we sent a mailed questionnaire to 1390 survivors (re-mailed once for non-respondents), and 1231 (88.6%) men responded. The questionnaire included items on demographic variables, present body weight, lifestyle factors (smoking, alcohol consumption, physical activity), and history of chronic diseases. From the responses, a summary co-morbidity measure was assessed according to the Charlson index,[26] taking into account the number and severity of co-morbid conditions. In addition, the Finnish version of the RAND-36-Item Health Survey 1.0[27] (practically identical to SF-36 health survey and validated in the Finnish population) was embedded in the questionnaire. The eight domains of RAND-36 were aggregated into the physical (PCS) and mental (MCS) health component summary scores.

Among the respondents, there were 1114 men for whom the BMI at the age of 25 years, in 1974 and in 2000, was available (80.1% of eligible). These 1114 men formed the cohort for the mortality follow-up from 2000 onwards (*Figure 1*). According to the BMI in 1974 and in 2000, the following four groups were identified: (i) BMI ≤ 25 both in 1974 and in 2000 ('constantly normal weight' group, n = 345), (ii) BMI > 25 both in 1974 and in 2000 ('constantly overweight' group, n = 494), (iii) BMI ≤ 25 in 1974 and > 25 in 2000 ('turning overweight' group, n = 136), (iv) BMI > 25 in 1974 and ≤ 25 in 2000 ('turning normal weight' group, n = 139).

Mortality follow-up

Total mortality of the study population up to 31 December 2006, was retrieved from the Population Information System, which keeps registry of all Finnish citizens, and determination of vital status can thus be assessed to be virtually 100% complete. Causes of deaths (according to the International Classification of Diseases, available of 99% of the participants) were obtained from the cause-of-death bureau of Statistics Finland, where trained nosologists check and code the causes from death certificates. Deaths were grouped into the following major categories with International Classification Diseases-10 codes in parenthesis: (i) coronary (I20−I25); (ii) stroke (I60−I69); (iii) other CVD (I00−I99, excluding two previous groups); (iv) cancer (C00−C97); (v) other medical causes (A00−N99, excluding the four previous groups); and (vi) accidents or suicide (V01−Y98). These were calculated as deaths per 1000 men.

Statistical methods and covariates

The statistical software NCSS (version 2004, www.ncss.com) was used for the statistical analyses. The BMI change groups defined in the year 2000 were categorized as described above. *t*-Tests, non-parametric tests, and analyses of covariance (Bonferroni correction for pairwise comparisons) were used where appropriate to compare continuous variables, χ^2 and trend tests were used to compare proportions. Differences in survival curves were analysed with log-rank test. Hazard ratios [HR, with their 95 percent confidence intervals (CI)] for mortality associated with the BMI change groups were calculated using Cox's proportional hazards regression. The proportionality assumption was met (assessed using visual inspection of mortality curves and Schoenfeld residuals). In multivariable models, we aimed to a parsimonious model in order to demonstrate the face value of BMI change and mortality. Therefore, we did not use cardiovascular risk factors possibly intermediating the association between BMI change and mortality. However, we adjusted for smoking, which may affect energy balance and appetite and lead to weight change through other mechanisms. Inclusion of perceived health in 1974 was used to control for baseline status (perceived health predicts mortality in the whole Businessmen cohort, unpublished results); perceived health was dichotomized as very good or good = 0, fair or worse = 1. Inclusion of prevalent diseases (including diabetes and hypertension) in 2000 was aimed to tease out the effect of frailty as such, although this is necessarily inconclusive and principally aims to be hypothesis-generating for further studies. Of the covariates only age was continuous and graphic assessment was used to determine linearity assumption, which was met. In statistical analyses, two-tailed tests were used and two-sided *P*-values < 0.05 were taken as significant.

Results

Characteristics of the groups according to body mass index change from 1974 to 2000

Characteristics of the BMI change groups in 1974 and 2000 are shown in *Tables 1* and *2*. In 1974, the median age was 47 years (inter-quartile range 44−50 years); in 2000, median age was 73 years (inter-quartile range 70−76 years). In 1974, the participants were clinically healthy and without regular medications. In 1974, both overweight groups tended to be characterized by higher levels of cardiovascular risk factors (blood pressure, cholesterol, triglycerides, and glucose, but not smoking) when compared with the groups with normal weight. However, the difference was usually statistically significant only for the overweight group, which subsequently lost weight after midlife (*Table 1*). This group also had the highest composite risk of coronary heart disease; it was also slightly older than the other groups (*Table 1*). In 2000, the status of both weight change groups was reversed: BMI and risk factor profile of the group turning from overweight to normal weight resembled those of the constantly normal weight group, and BMI of the group turning from normal weight to overweight was similar to that of the constantly overweight group (*Table 2*).

Analysis of the 909 men, of whom also 1985−86 data were available (including BMI and waist circumference), implicated a break-even point at an average age of 58 years between the turning normal weight group ($n = 114$, BMI 25.6 kg/m², SD 1.7; waist 95.7 cm, SD 6.0) and the turning overweight group ($n = 102$, BMI 25.3 kg/m², SD 1.4; waist 94.6 cm, SD 6.0). The differences in BMI and waist circumference were not statistically significant.

In 2000, the constantly overweight group had the largest prevalences of hypertension, diabetes, and musculoskeletal disorders, whereas the group turning from overweight to normal weight tended to have the largest prevalence of cerebrovascular disorders (*Table 3*). However, the latter group had the Charlson co-morbidity index comparable to that of the constantly overweight group, and lowest scores in the quality of life measures PCS and MCS (*Table 2*).

Mortality during follow-up

Overall, the adverse effect of overweight on mortality from midlife to late life was observed also in our cohort. Of the 1815 healthy men evaluated in 1974, 425 men (23.5%) had died by the year 2000; 25.8% ($n = 269$) and 20.1% ($n = 156$) of those overweight and normal weight in 1974, respectively ($P = 0.003$).

The situation was different when old age survivors were followed-up from the year 2000. Unadjusted total mortality ($n = 188$) between 2000 and 2006 among the 1114 men according to the BMI change groups is shown in *Figure 2*. Mortality was clearly highest in the group which had turned from overweight to normal BMI after midlife, and comparable between other groups (log-rank *P* between groups < 0.001). Increased mortality was due to a variety of causes: as calculated per 1000 men, the number of deaths due to coronary artery disease, stroke, cancer, and other medical causes was highest among men who turned from overweight to normal weight after midlife (data not shown). The mortality difference shown in *Figure 2* was similar but attenuated (log-rank *P* = 0.015), after those men with a history of cancer in 2000 were excluded. (data not shown). Analyses of mortality using the Cox proportional hazards models are shown in *Table 4*. With the constantly normal weight group as referent, mortality risk between 2000 and 2006 was not significantly different in those constantly overweight and among those men who turned overweight after midlife. The group with overweight in midlife but normal BMI in old age, in turn, had a significant two-fold increased mortality risk when compared with the constantly normal weight group (HR 2.0, 95% CI 1.3−3.0). This risk was only slightly reduced, when it was adjusted for prevalent diseases in 2000 (HR 1.9, 95% CI 1.2−3.0) (*Table 4*).

Table I Characteristics of the study groups (*n* = 1114) at baseline in the year 1974

Variable	Constantly normal weight (BMI ≤ 25 in 1974 and 2000), *n* = 345	Constantly overweight (BMI > 25 in 1974 and 2000), *n* = 494	Normal BMI in 1974, overweight in 2000, *n* = 136	Overweight in 1974, normal BMI in 2000, *n* = 139	*P*-value between groups
Age, year	47.6 (0.2)[3,4]	46.9 (0.2)[4]	46.4 (0.3)[1,4]	48.9 (0.3)[1−3]	<0.001
Height (cm)	177 (0.3)	176 (0.3)	177 (0.5)	177 (0.5)	0.19
Body weight (kg)	73.0 (0.4)[2−4]	86.5 (0.3)[1,3,4]	75.1 (0.7)[1,2,4]	82.7 (0.7)[1−3]	<0.001
Body mass index (kg/m^2)	23.2 (0.09)[2−4]	27.7 (0.08)[1,3,4]	23.9 (0.1)[1,2,4]	26.4 (0.1)[1−3]	<0.001
Body mass index at 25 years of age (kg/m^2)	21.8 (0.1)[2−4]	23.5 (0.09)[1,3]	22.3 (0.2)[1,2,4]	23.1 (0.2)[1,3]	<0.001
Weight gain from 25 years of age until 1974 (kg)	4.6 (0.4)[2,4]	13.2 (0.3)[1,3,4]	5.0 (0.6)[2,4]	10.6 (0.6)[1−3]	<0.001
Keys' risk index, %/5 years (*n* = 999)	1.59 (0.09)[2,4]	1.94 (0.07)[1,3,4]	1.42 (0.14)[2,4]	2.34 (0.13)[1−3]	<0.001
Blood pressure (mmHg)					
Systolic	137.4 (1.0)[2,4]	145.3 (0.8)[1,3]	137.7 (1.6)[2,4]	144.1 (1.5)[1,3]	<0.001
Diastolic	87.7 (0.6)[2,4]	94.2 (0.5)[1,3]	87.4 (1.0)[2,4]	92.3 (0.9)[1,3]	<0.001
Pulse rate (per min)	61.5 (0.6)[2]	65.0 (0.5)[1,3]	61.1 (0.9)[2]	62.8 (0.9)	<0.001
	Constantly normal weight	Constantly overweight	Turning overweight	Turning normal weight	
Cholesterol (mmol/L)	6.0 (0.06)[2,4]	6.2 (0.05)[1]	6.0 (0.09)[4]	6.3 (0.09)[1,3]	0.001
Triglycerides (mmol/L), median (inter-quartile range)	1.2 (0.9−1.5)[2,4]	1.5 (1.2−2.1)[1,3]	1.2 (0.9−1.6)[2,4]	1.5 (1.1−1.9)[1,3]	<0.001
One-hour glucose (mmol/L), median (inter-quartile range)	6.3 (5.2−7.6)[2]	6.8 (5.7−8.6)[1,3]	6.3 (5.3−7.3)[2]	6.4 (5.4−7.9)	<0.001
Smokers, no. (%)	82 (23.8)[3]	126 (25.5)[3]	50 (36.8)[1,2]	37 (26.6)	0.03
Alcohol, g/week median (inter-quartile range)	98 (42−182)[2,4]	126 (56−238)[1]	112 (56−238)	140 (56−280)[1]	<0.001

Age-adjusted except age and Keys' risk index (includes age). Mean (SE) unless otherwise stated. Superscript numbers denote groups from which the value is significantly different in pairwise comparisons (Bonferroni correction).

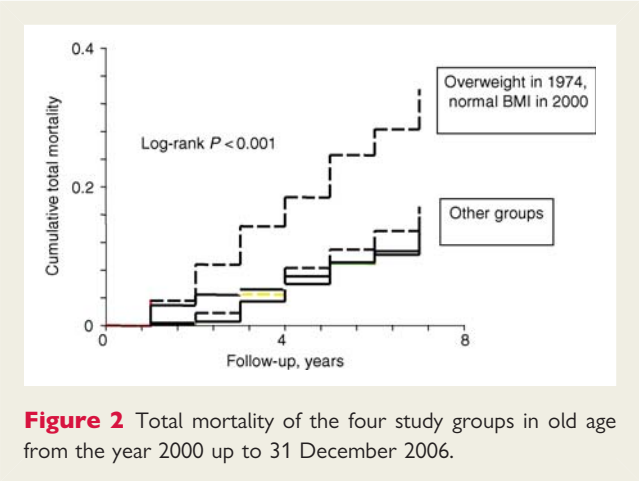**Table 2** Characteristics of the study groups in the year 2000

Variable in 2000	Constantly normal weight (BMI ≤ 25 in 1974 and 2000), n = 345	Constantly overweight (BMI > 25 in 1974 and 2000), n = 494	Normal BMI in 1974, overweight in 2000, n = 136	Overweight in 1974, normal BMI in 2000, n = 139	P-value between groups
Age, year	73.6 (0.2)[3,4]	72.9 (0.2)[4]	72.4 (0.3)[1,4]	74.9 (0.3)[1–3]	<0.001
Body weight (kg)	72.1 (0.4)[2–4]	87.9 (0.4)[1,3,4]	83.1 (0.7)[1,2,4]	74.4 (0.7)[1–3]	<0.001
Body mass index (kg/m^2)	22.9 (0.1)[2–4]	28.2 (0.09)[1,3,4]	26.5 (0.2)[1,2,4]	23.7 (0.2)[1–3]	<0.001
Weight change from 47 years of age (kg), median (inter-quartile range)	0 (−3 to +2)[2–4]	+1 (−3 to +5)[1,3,4]	+7 (+5 to +10)[1,2,4]	−8 (−4 to −11)[1–3]	<0.001
Reported blood pressure (mmHg) (n = 1016)					
Systolic	142.0 (0.9)	144.2 (0.7)	142.2 (1.4)	141.7 (1.4)	0.19
Diastolic	83.1 (1.2)	82.9 (0.9)	81.5 (1.8)	80.6 (1.8)	0.6
Reported cholesterol (mmol/L) (n = 801)	5.3 (0.06)	5.3 0.05)	5.3 (0.1)	5.1 (0.1)	0.41
Reported glucose (mmol/L) (n = 683) median (inter-quartile range)	5.1 (4.7–5.6)[2]	5.5 (5.0–6.2)[1]	5.3 (4.9–6.0)	5.1 (4.7–5.6)	<0.001
	Constantly normal weight	Constantly overweight	Turning overweight	Turning normal weight	
Smokers, no. (%)	37 (10.7)[2]	28 (5.7)[1,4]	10 (7.4)	19 (13.7)[2]	0.006
Alcohol, g/week (n = 879) median (inter-quartile range)	70 (28–154)[2]	98 (42–182)[1]	112 (28–210)	70 (14–140)	0.03
Reported exercise, h/week (n = 1109)	5.4 (0.3)	5.1 (0.3)	5.9 (0.5)	5.4 (0.5)	0.46
Charlson co-morbidity index	1.1 (0.07)[2,4]	1.5 (0.06)[1]	1.4 (0.1)	1.5 (0.1)[1]	<0.001
PCS (n = 923)	48.2 (0.5)[2,4]	45.3 (0.4)[1]	46.1 (0.8)	44.2 (0.9)[1]	<0.001
MCS (n = 923)	53.8 (0.6)	53.4 (0.5)	54.3 (0.9)	51.6 (0.9)	0.17

Age-adjusted except age. Mean (SE) unless otherwise stated. PCS and MCS denote physical and mental summary scores, respectively, of the RAND-36 health-related quality of life instrument. Superscript numbers denote groups from which the value is significantly different in pairwise comparisons (Bonferroni correction).

Table 3 Self-reported diseases in study groups in the year 2000

Disease in 2000	Constantly normal weight (BMI ≤ 25 in 1974 and 2000), n = 345	Constantly overweight (BMI > 25 in 1974 and 2000), n = 494	Normal BMI in 1974, overweight in 2000, n = 136	Overweight in 1974, normal BMI in 2000, n = 139	P-value between groups
Hypertension	96 (30.0)	226 (48.2)	46 (36.5)	42 (33.1)	<0.001
Diabetes	15 (4.7)	56 (12.2)	8 (6.3)	8 (6.3)	0.001
Memory disturbance	47 (14.7)	82 (17.9)	22 (17.9)	29 (22.7)	0.25
Coronary heart disease	56 (17.6)	98 (21.2)	21 (16.7)	32 (25.0)	0.21
Congestive heart failure	30 (9.6)	71 (15.6)	17 (13.4)	20 (16.1)	0.09
Cerebrovascular disorder	35 (11.0)	44 (9.7)	19 (15.1)	23 (18.3)	0.04
Peripheral artery disease	39 (12.3)	64 (14.0)	20 (16.1)	16 (12.9)	0.74
Cancer	33 (10.4)	65 (14.2)	15 (11.9)	23 (17.8)	0.16
Pulmonary disease	28 (8.9)	33 (7.4)	11 (8.8)	11 (8.9)	0.86
Musculoskeletal disease	62 (19.6)	145 (31.6)	30 (24.4)	35 (28.0)	0.002

Data denote numbers (%) of men with disease state in the respective groups.

Figure 2 Total mortality of the four study groups in old age from the year 2000 up to 31 December 2006.

Discussion

Our long-term results show that those men who had normal weight in late life—but had been overweight in midlife—had the greatest mortality risk in old age. In contrast, the risk of those men who did not become overweight until after midlife did not differ from that of men with constantly normal weight. Importantly, the men turning normal weight in old age did have the highest CVD risk in midlife while overweight. These findings may: (i) suggest cardiovascular aetiology for developing frailty and (ii) give one explanation for the obesity paradox by showing that in old age both normal weight and overweight groups are actually mixtures of men with different weight and cardiovascular risk histories. Our results also support the implication that some weight gain may be beneficial after midlife for those who are not overweight in

early adult life.[28] However, even our long-term study does not yet cover the full life course, because median age was 80 years at the end of mortality follow-up.

The obesity paradox is one example of 'reverse epidemiology',[8,14] a frequent and often misunderstood topic both in geriatrics and recently in cardiovascular medicine. Many studies have shown that obese patients with CVD have better prognosis than those with normal weight.[9–15] Several explanations have been offered.[14,15] Low BMI may be a marker of disease severity, or harmful as such. Obesity can accentuate symptoms, such as dyspnea, and obese people may have better prognosis because they present earlier with heart failure. High BMI may also be associated with some protective factors.[29] On the other hand, intentional weight loss was associated with lower incidence of recurrent events among coronary patients.[11] In older individuals, this reverse epidemiology applies not only to body weight but also to blood pressure[30] and cholesterol,[31,32] and a shift in the treatment of these risk factors in old age has been called for.[8] However, reverse causation is probably at play. Findings from the Cardiovascular Risk Factors, Aging and Dementia (CAIDE[33]) study showed that the relationship between cholesterol and dementia is bidirectional: both high cholesterol earlier and low cholesterol in late life were associated with dementia. Furthermore, both cholesterol lowering[34] and anti-hypertensive treatment[35] have shown benefit among older persons also.

Overall, our results nevertheless indicate that—when mortality before later life is taken into account—lean men had better prognosis than overweight men, and this concurs with the results, for example from the Seven Countries Study.[17] Midlife obesity is also associated with non-fatal ill effects, such as disability in later life.[36] The present results further suggest that the development of frailty may be an intermediating mechanism between weight

Table 4 Multivariate-adjusted hazard ratios of total mortality during follow up from 2000 up to 31 December 2006

	(HR) with 95% CI[a]			
	Constantly normal weight (BMI ≤ 25 in 1974 and 2000), n = 345	**Constantly overweight (BMI > 25 in 1974 and 2000), n = 494**	**Normal BMI in 1974, overweight in 2000, n = 136**	**Overweight in 1974, normal BMI in 2000, n = 139**
Univariate	1.0 (referent)	1.1 (0.8−1.6)	0.9 (0.5−1.5)	2.3 (1.5−3.4)
Model A[b]	1.0	1.2 (0.8−1.7)	1.0 (0.6−1.7)	2.0 (1.3−3.0)
Model B[c]	1.0	1.2 (0.8−1.7)	0.9 (0.5−1.6)	2.0 (1.3−3.0)
Model C[d]	1.0	1.2 (0.8−1.7)	0.9 (0.5−1.6)	2.0 (1.3−3.0)
Model D[e]	1.0	1.1 (0.7−1.6)	0.7 (0.4−1.4)	1.9 (1.2−3.0)

HR, hazard ratio; CI, confidence interval.
[a]Calculated using the Cox proportional hazards model.
[b]Model A: adjusted for age.
[c]Model B: adjusted for age and smoking in 1974.
[d]Model C: adjusted as above plus perceived health in 1974.
[e]Model D: as above plus reported diseases (systemic hypertension, diabetes, memory disturbances, cerebrovascular disorders, coronary heart disease, congestive heart failure, pulmonary disease, musculoskeletal disease, and cancer) in 2000.

loss after midlife and late life mortality. Adjustment for prevalent diseases did not abolish the weight loss−mortality association (although lower end of CI was close to unity), and excess mortality was due to a variety of causes and not only, for example, to cancer. Our data also indicate that midlife CVD risk may be an important—although masked—pathophysiological factor for old age frailty. This is in perfect accordance with data from the Cardiovascular Health Study,[37,38] showing that sub-clinical CVD predicted not only incident CVD but frailty as well.

Strengths and limitations

Besides the long-term follow-up, the strengths of our study include a homogenous and healthy group at baseline in 1974. Thus, socioeconomic factors and gender do not confound the results, but on the other hand, generalizability is limited. The response rate was good in 2000 and non-responders were not different from responders as to earlier body weight and weight gain. The mortality results are based on a long follow-up with reliable verification using national registers. Besides limited generalizability, there are also other limitations in our study. The weight at age 25 years was based on recall in 1974, and weight in 2000 was based on self-report in the questionnaire. However, both recall and self-report have been used repeatedly in epidemiological studies,[39,40] and considered appropriate methods. The same applies to self-report of diseases in 2000, which has been assessed to be a satisfactory method at least for more severe diseases in epidemiological research.[41] Importantly, the Charlson co-morbidity index based on reported diseases predicted mortality in our cohort (unpublished result). The use of the term frailty can be aptly criticized in our study. We could not use established criteria[22] for this condition in 2000, and BMI change loss after midlife was taken as a surrogate. However, the Charlson index and the low component summary scores of RAND-36 support the presence of frailty among the group turning from overweight to normal weight. Whether weight loss was intentional or unintentional was not asked, and this may be seen as an important limitation. However,

drawing a strict line between these two is very difficult in older people, and weight loss in this age group has been considered to be mainly associated with physiological changes and/or underlying somatic or psychiatric diseases.[42] Furthermore, available data hardly support the idea that truly intentional weight loss as such, even in older adults, would be harmful.[11,43,44] However, the development of sarcopenia should obviously be avoided.

Finally, the small differences in mortality risk from old age onwards between the overweight groups and constantly normal weight group may be due to a relatively short follow-up of 7 years. The overweight groups may just be entering the weight loss (frailty) phase and their characteristics in the year 2000 (*Table 2*) indeed suggest that the prognosis probably worsens during more extended follow-up. It is of note that although BMI in our cohort was cross-sectionally in 1985 closely correlated with waist circumference, this does not rule out the possibility that overweight developing first after midlife would be metabolically different from overweight developing earlier in life. The question whether constant overweight and 'late-developing' overweight have different impact on the development of sarcopenic obesity[45] is beyond the scope of the present analysis, but this clearly calls for further studies.

Conclusions

Although life-long normal body weight is the best option, our study revealed that in old age, men with normal weight and overweight are a mixture of individuals with different weight history during their life course. Despite being a mortality risk in midlife, overweight or even obesity in late life may thus disguise itself as a protective factor in epidemiological studies. Importantly, those men who subsequently moved from overweight to normal weight had had the highest CVD risk in midlife and worst prognosis in late life.

Funding

Conflict of interest: none declared.

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