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# **Survival in elderly men in relation to midlife and current BMI**

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Running heading: BMI and survival in men

## **Abstract**

**Background:** The relation between BMI and mortality is U-shaped in the elderly but may be modified by mid-life BMI and change in weight.

**Objective:** To elucidate mortality prediction by BMI trajectory in older men.

**Subjects:** The Oslo cohort of men born in 1923-32 were screened for BMI and cardiovascular risk in 1972-3. Survivors were rescreened at ages 68-77 years and all-cause mortality was followed from 2000 to 2011.

**Methods:** We calculated Cox regression proportional hazards for 11-year mortality rates in relation to BMI change among 5,240 men with no reported disease in 1972-3 and complete data. Models were adjusted for demographics, medications and disease. Men with BMI <25 kg/m<sup>2</sup> in midlife (1972-73) and in 2000 were the reference group.

**Results:** Men whose BMI changed from <25 kg/m<sup>2</sup> in midlife to 25-29.9 kg/m<sup>2</sup> in 2000 carried the lowest mortality risk (hazard ratio [HR] 0.84; 95% CI 0.75-0.94). Men with BMI ≥30 kg/m<sup>2</sup> in midlife were at highest risk (HR 1.79; 95% CI 1.12-2.88 if reclassified to 25-29.9 kg/m<sup>2</sup> in 2000 and HR 1.39; 95% CI 1.05-1.85 if BMI remained ≥30 kg/m<sup>2</sup> in 2000). Men with BMI 25-29.9 kg/m<sup>2</sup> in midlife that reclassified to <25 kg/m<sup>2</sup> in 2000 had increased risk. Findings were similar when percentage change in BMI was the outcome.

**Conclusion:** Survival in older men with normal weight at midlife was associated with BMI gain after midlife while midlife obesity increased risk regardless of subsequent change.

The World Health Organization defined BMI-based categories of underweight, normal weight and obesity in 1997 largely based on studies examining morbidity risk in young and middle-aged adults [1]. The category of BMI of 20 to 24.9 kg/m<sup>2</sup> has the lowest all-cause mortality in prospective studies of white adults who never smoked and did not have diagnosed major diseases [2]. A meta-analysis using a broader inclusion range, but with exclusion of the first 5 years of follow-up found that the optimum BMI may lie between 22.5-25 kg/m<sup>2</sup> [3]. Recently, a meta-analysis of more than 2.88 million individuals and more than 270,000 deaths found that overweight was associated with lower all-cause mortality compared to normal weight [4]. The "obesity paradox" conveys the notion that in some populations overweight or obesity may protect against premature mortality. Particularly among the elderly, the shape of the association between BMI and mortality remains controversial. In meta-analyses, a BMI in the overweight range among the elderly was not associated with increased mortality [5], and together with subsequent findings has led to calls to amend BMI risk categories in older persons [5-7].

An important consideration in the obesity-mortality relationship is the question of weight stability. Use of a single measure of BMI raises several methodological concerns particularly in the elderly. Underweight is likely to indicate disease or frailty which contribute to mortality and weight loss may be the underlying culprit. Weight in old age may not reflect earlier weight; both earlier and later weights have been shown to independently affect risk [8]. In line with this, a dynamic measure of weight or BMI seems to be more predictive of mortality among older adults than a static one [9]. Weight loss associates with the worst prognosis even in people who were overweight earlier in life [10, 11], while weight gain in old age appears not to increase risk [12]. Stable overweight was shown to increase risk in Californians who never smoked and belonged to a demonimation encouraging a healthy

lifestyle [13] in contrast to findings in a general, more representative US population [9]. The degree of weight change may also be of importance [9] with large losses or gains shown to increase cardiovascular and all-cause mortality [14]. Clinically, losses of ~5% are thought to be sustainable and lead to reductions in cardiovascular risk factors [15].

A further consideration is that studies of the BMI-mortality relationship conducted before the mid-1990s do not reflect changes in the environment that may affect the relationship. Public health efforts to stem the obesity epidemic may potentially flatten the risk curve (due to protective lifestyle changes). Medical risk factors like dyslipidemia and hypertension are increasingly identified and treated. Treatment of these risk factors in obese individuals may likewise ameliorate risk of premature mortality.

The Oslo cohort was established in 1972-3 when 40–49 year old men residing in Oslo took part in a cardiovascular risk and BMI screening program [16]. Unfortunately, women were not invited to this program. The men were reinvited in 2000 to an expanded screening with additional data collection and remeasurement of BMI [17]. At this screening, 28 years after the initial one, men were aged 68-77 years. We followed all cause mortality in this cohort from 2000 to 2011. Our objective was to explore the associations between BMI category in midlife, BMI category at older age (68-77 years) and weight change and 11-year all-cause mortality. We controlled for variables that may confound the association between weight change and mortality including illness, smoking, and medication use.

## **Material and methods**

The Oslo Study has been described in detail elsewhere [16]. Briefly, 16,203 men born in 1923-32 participated in a screening examination in 1972-3 with an attendance proportion of ~65%. Conventional cardiovascular risk factors including nonfasting total cholesterol, blood pressure and cigarette smoking were assessed. In addition, body height and weight (but not

waist circumference) were measured and BMI calculated. In the year 2000 the surviving men (N=12,764) in this cohort were invited to a new screening examination and 6,016 (47.1%) took part [17]. In this rescreening, the same variables and methods were applied as in 1972-3; in addition, questions about educational length, occurrence of chronic diseases from 1972-3 to present and use of drugs were posed, including use of antihypertensive and lipid lowering drugs. Waist circumference was measured over the umbilicus. Men with a history of previous cardiovascular diseases, established hypertension or diabetes in 1972-3 were excluded in the current analyses due to the confounding effects of disease on BMI and mortality. Excluded men had higher major risk factor levels than men without the defined health problems as described previously [16]. This left 5,738 men. Of these 5,239 with complete data were included. All cause mortality was the end point for the analyses from screening in 2000 to December 31<sup>st</sup> 2011. The number of deaths was 2,145 among 5,239 men at risk.

This study was approved by a Regional Ethics Committee for scientific research in Norway, the Norwegian Data Inspectorate, and the Ministry of Health and the study complies with the Declaration of Helsinki.

## **Statistics**

Descriptive statistics were used to compare risk factors in men with complete versus incomplete data and in men who died compared with survivors using t-tests or Chi-square as appropriate. In Cox regression models, time to death was the dependent variable. BMI in 1972-3 and in 2000 were the main exposure variables and were categorized according to WHO as normal weight (BMI 18.5-24.9 kg/m<sup>2</sup>), overweight (BMI 25-29.9 kg/m<sup>2</sup>) or obese (BMI 30 ≥kg/m<sup>2</sup>). Those who were underweight (BMI <18.5 kg/m<sup>2</sup>) at either screening were excluded in the regression models (n=44). We also categorized BMI change according to percentage change between 1972-3 and 2000 with cut-offs of ±5% as the reference, and >5% increase or >5% decrease as comparators. Age, educational length, smoking, use of

antihypertensive or lipid lowering drugs, diabetes, previous myocardial infarction or cerebral stroke were adjustment variables in all analyses. A time variant Cox model tested the assumption of proportional hazards by adding a multiplicative interaction term between time and BMI in the model, with or without adjustments. None was found to be significant. Hazard ratios (HR) with 95 % confidence limits were calculated. Analyses were performed in SPSS 18.0.

## **Results**

At the rescreening in 2000, the median age of the subjects was 73 years (range 68-77 years). The 499 men who were excluded from the analyses because of missing data were slightly older (mean [SD] 73.0 [2.9] years versus 72.5 [2.8]), had a shorter education (11.4 [3.5] years versus 12.0 [3.8]) years, slightly higher BMI (26.8 [3.5] kg/m<sup>2</sup> versus 26.3 [3.3] and included a higher proportion of smokers (20.7% versus 17.3%), users of antihypertensive (60.5% versus 32.1%) and lipid-lowering medication (32.6% versus 19.3%) and individuals with a history of diabetes (12.2% versus 6.2%), myocardial infarction (16.6% versus 11.5%) or cerebrovascular disease (11.6% versus 7.1%).

Compared to survivors (n=3,094), men who died (n=2,145) were older with a mean age of 73.5 years (SD 2.8) than men who survived who had a mean age of 72.2 (SD 2.8). Men who died reported a shorter education of 11.7 years (SD 3.8) compared to men who survived who reported 12.3 (SD 3.8) years of education. Among men who died, 23.5% were smokers versus 13.1% of survivors, 37.6% used antihypertensive medication, versus 28.2% of survivors, 20.3% used lipid-lowering medication versus 18.6% of survivors, 8.6% had a diagnosis of diabetes versus 4.5% of survivors, 15.9% had experienced a myocardial infarction versus 8.5% of survivors and 10.3% had cerebrovascular disease versus 4.8% of survivors.

### *Association between BMI and mortality*

All-cause mortality was lowest in men with the mid-range of BMIs from 22.0-27.4 kg/m<sup>2</sup> in univariate analyses (Table 1). After adjustment for age, education, smoking, use of lipid-lowering or antihypertensive drugs, diabetes or cardiovascular disease only the extremes of the BMI distribution were associated with increased mortality (Table 1).

### *Mortality relative to midlife BMI and change in BMI*

Of the total, 31.5% of men classified to the normal BMI category in 1972-3 and 2000, 30.2% moved from the normal to the overweight BMI category between 1972-3 and 2000, while only 1.8% moved from the normal to the obese category (Table 2). Among all men again, 3.1% moved from the overweight to the normal weight category, 22.3% stayed in the overweight category, while 8.8% moved from the overweight to the obese category. Finally, only two men in the obese category moved to the normal weight category, 0.5% moved from the obese to the overweight category, and 1.7% stayed in the obese category. As shown in table 2, in Cox regression models, men in the normal BMI category in 1972-3 who increased their weight to the overweight category had lower mortality compared to those in the normal BMI category in both 1972-3 and 2000 (reference group). Likewise BMI increase of >5% in this group was associated with lower mortality compared to the reference group with  $\pm 5\%$  change (Table 3). In obese men, reclassification to the overweight category or remaining in the obese category were associated with increased mortality (Table 3) as was weight loss of >5% or weight stability with  $\pm 5\%$  change in BMI (Table 3). Finally weight loss in overweight men in 1972-3 was associated with increased mortality (Tables 2 & 3).

## **Discussion**



Our 11-year follow-up study suggests that all-cause mortality in older men in their 7th to 8th decades is lowest in those with normal BMI in middle age, who reclassified to the overweight category in the course of aging. This group constituted just under one-third of the total population. Men who were obese in midlife had an increased risk of mortality regardless of weight stability or weight loss, but constituted a very small part of this cohort born in 1972-3 (about 2%). Men in the overweight category in midlife only had an increase in mortality if they lost weight, reclassifying to the normal weight category. Results were similar when examined as percentage BMI change rather than BMI classification.

Our findings are in line with other studies using similar designs [6-12], underscoring the notion that in aging men, current BMI categories may not describe risk precisely as in younger individuals. In a meta-analysis of 65 years or older men and women mostly residing in North America and Europe, the risk estimate for BMI within the overweight range was 1.0 and only a 10% increase in risk was estimated for the obese range [5]. Likewise among older individuals residing in Sweden, persons aged 70 to 95 in the overweight group had the lowest mortality of the cohort [6]. Among Framingham study participants, mortality risk was increased in obese persons who were obese at midlife, but not those who became obese in older age [8]. Strandberg et al studied a Finnish cohort of men parallel to the present one in time with baseline measurements in 1974 and follow-up in 2000 [10]. Among these 1,114 men, only those who reclassified from overweight to normal BMI experienced an increase in mortality. Zheng et al using attributable risk analyses found that trajectories of increasing obesity past 51 years of age reduced life expectancy, but the overweight stable trajectory had the lowest mortality risk followed by people in the overweight to obesity and normal weight upward classes [9].

The effect of excess weight may be obscured if body weight is measured after disease onset. Preexisting disease causing weight loss is an unavoidable confounder of the BMI-

mortality relation, and is observed even when death in the first years of follow-up are removed [3], and in non-smoker populations [2, 18]. Another limitation of observational studies is the possibility that in medium to long-term studies those individuals most susceptible to the effects of obesity will have succumbed earlier. Survivors may have a healthy form of obesity, providing advantages in aging [19]. However, this assumes that obesity was the cause of their underlying disease, which may not be the case [20]. These problems cannot be addressed with most observational data. We did not ask about intentionality of weight loss – in meta-analysis, intentional weight loss had a neutral effect on all-cause mortality, in contrast to ill-defined or non-intentional loss [21].

More difficult to explain is the observation that weight gain (but not in the obese) appears to lower mortality. Some evidence supports the notion that overweight and obesity may be less risky in recent compared to older studies. Obese people may come sooner to medical attention and be treated. Janssen & Mark in their 2009 meta-analysis found lower risk estimates (significantly  $<1.00$ ) for overweight and obese categories in studies with baselines measured after 1990 compared to studies between 1957-1990 [5]. Increased lean tissue and fat mass may protect against disease associated with aging. In the elderly fat mass increases due to an age-related loss of fat free mass and BMI may not reflect risk as accurately as fat mass, or abdominal adiposity. While meta-analysis supported this notion [22], a large study of subjects over 65 years of age found no association of waist circumference and mortality after adjustment for BMI [23]. We found no relation between waist circumference measured in 2000 and mortality in this cohort of men (data not shown). Findings from observational studies are buttressed by recent clinical data. The Look AHEAD trial found that lifestyle interventions leading to weight loss did not reduce cardiovascular events in middle-aged and elderly adults with diabetes [24].

We used the WHO-designated categorization of BMI [1] that is widely used as the standard for defining normal weight, overweight and obesity. However, the category of 18.5-24.9 kg/m<sup>2</sup> that defines normal weight may encompass individuals with clinical cachexia, and a cut-off of BMI <20.0 kg/m<sup>2</sup> which helps define cachexia in chronic disease may be more relevant [25].

### *Limitations*

We studied solely white men, and looked only at total mortality, not cause-specific mortality. The shape of the BMI-mortality curve differs by the cause of mortality [14]. Our cohort included only a small number of individuals that were obese at baseline and does not represent current cohorts who may be obese from an earlier age. Despite the low number we found that obesity in midlife significantly increased risk to old age. We lacked childhood and early adult measures of BMI, thus, we did not capture the lifelong trajectory of BMI. Mortality risks appear higher in persons who attained a high BMI at a younger age than those who gain weight later in life [26].

Subjects with missing data were unhealthier than the rest of the cohort; the effect of such selection is difficult to estimate. Missing data may lead to diluted associations because of restriction of variation in risk factors. We did not perform a multiple imputation analysis as distributions of missing factors cannot be assumed to be the same as in those without missing data.

### **Conclusions**

Survival in older men with normal BMI at midlife was associated with BMI gain after midlife. The counterpart of this finding was that midlife obesity reduced longevity regardless of subsequent change in weight. These findings underscore the importance of studying the life trajectory of the BMI-mortality relationship.

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Table 1 Relationship between BMI measured in the year 2000 in 5,239 men and mortality between 2000 and 2011 (number of deaths, 2,145). Hazard ratios with 95% confidence intervals are shown.

BMI category, kg/m <sup>2</sup>	Univariate hazard ratio (95% CI)	Adjusted* hazard ratio (95% CI)
18.5-21.9	1.36 (1.16-1.59)	1.31 (1.12-1.54)
22.0-24.9	Referent	Referent
25.0-27.4	0.93 (0.83-1.04)	0.91 (0.78-1.00)
27.5-29.9	0.90 (0.79-1.02)	0.86 (0.76-0.98)
30.0-34.9	1.27 (1.10-1.47)	1.15 (0.99-1.33)
≥35	1.38 (0.95-2.01)	1.26 (0.86-1.83)
P (RD)**	<0.001	<0.001

\*Adjustment factors: age, years of education, smoking (never, previous, current), use of antihypertensive medication, use of cholesterol lowering medication, diabetes, myocardial infarction, and cerebrovascular disease.

\*\*RD= global differences in relative risk between BMI groups.

Table 2. Number of deaths/men at risk and hazard ratios for mortality between 2000 and 2011 according to BMI category in 1972-3 and BMI category in 2000. Data are adjusted for age, years of education, smoking (never, previous, current), use of antihypertensive medication, use of cholesterol lowering medication, diabetes, myocardial infarction, and cerebrovascular disease. Men with BMI <18.5 kg/m<sup>2</sup> in year 2000 are excluded due to underweight.

BMI in 1972-3	BMI in 2000 18.5-25.0 kg/m <sup>2</sup>	BMI in 2000 25-29.9 kg/m <sup>2</sup>	BMI in 2000 ≥30 kg/m <sup>2</sup>
Normal 18.5-25 kg/m <sup>2</sup>	670/1,636 1.0 (Reference)	546/1,571 0.84 (0.75-0.94)	38/93 1.01 (0.73-1.40)
Overweight 25-29.9 kg/m <sup>2</sup>	93/162 1.43 (1.15-1.78)	484/1,160 0.93 (0.82-1.05)	214/455 1.12 (0.96-1.31)
Obese ≥30 kg/m <sup>2</sup>	1/2 2.79 (0.39-19.9)	18/26 1.79 (1.12-2.88)	53/90 1.39 (1.05-1.85)



Table 3. Number of deaths/men at risk and hazard ratios for mortality between 2000 and 2011 according to BMI category in 1972-3 and % change in BMI between 1972-3 and 2000. Data are adjusted for age, years of education, smoking (never, previous, current), use of antihypertensive medication, use of cholesterol lowering medication, diabetes, myocardial infarction, and cerebrovascular disease. Men with BMI <18.5 kg/m<sup>2</sup> are excluded due to underweight.

BMI in 1972-3	>5% decrease in BMI between 1972-3 and 2000	± 5% change in BMI between 1972-3 and 2000	>5% increase in BMI between 1972-3 and 2000
Normal 18.5-25 kg/m <sup>2</sup>	106/159 2.01 (1.62-2.49)	384/950 1.0 (Reference)	764/2,191 0.87 (0.77-0.99)
Overweight 25-29.9 kg/m <sup>2</sup>	99/165 1.46 (1.17-1.83)	262/603 0.99 (0.85-1.17)	430/1,009 1.02 (0.89-1.18)
Obese ≥30 kg/m <sup>2</sup>	20/28 1.68 (1.06-2.65)	25/40 1.68 (1.12-2.54)	27/50 1.35 (0.91-2.00)