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Weight change in midlife and risk of mortality from dementia up to 35 years later

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Abstract

Background: The relationship between body mass index (BMI) and dementia is complex and controversial. This study investigates the association of weight change during midlife and later dementia related mortality.

Methods: Two BMI measurements (average of 9.0 years apart) were available for 43,721 participants in the Norwegian Counties Study (NCS), with mean age 42 years at first BMI measurement and 51 at the final measurement. NCS was linked with the Cause of Death Registry until year 2015 (mean follow-up time 25.9 years). Cox regression with a conditional growth model was used.

Results: Our study comprised 1,205 dementia related deaths. Weight loss was associated with increased dementia related mortality, irrespectively of baseline BMI and confounders; those with ≥10% loss had HR=1.52 (95 % confidence interval CI 1.09, 2.12) compared to those being stable (0-2.5% BMI gain), and those with 5-10% loss had HR=1.38 (95% CI 1.08, 1.76). Gaining weigh was associated with reduced dementia related mortality. Associations with BMI change did not vary by baseline BMI.

Conclusions: Weight loss during midlife was associated with increased dementia related mortality risk more than three decades later, while weight gain was associated with reduced risk. These associations held both for low and high baseline BMI. Weight loss was an independent risk factor for dementia related mortality and more strongly related with dementia related mortality than stable BMI (stable high or low). Overweight and obesity were associated with an increased risk for non-dementia related mortality, which was far more common than dementia related mortality.

Key-words: Dementia, dementia related mortality, body weight, growth, weight loss, conditional growth.

Introduction

The relationship between weight and dementia is complex (1). Some studies report overweight in midlife to be associated with increased dementia risk (2-4), others report a reduced dementia risk (5, 6) or a U-shaped association (1, 7, 8). The conflicting results may be attributable to the different ages at which weight was measured, which would imply that age matters (1, 7, 9). A better understanding of the association between body weight and dementia may be achieved by studying weight trajectories and patterns from midlife into old age (1). Studies with weight at multiple time points have generally reported weight loss (10-18) or weight instability (19) to be associated with increased dementia risk. However, many of these studies are limited to weight trajectories in old age, and might be prone to reverse causality because dementia and preclinical dementia might cause weight loss (1, 20). Therefore, to study weight and weight change as risk factors for dementia outcomes it has been proposed that midlife weight and changes in midlife into old age may be more appropriate (21). The few studies covering weight in both midlife and old age have been criticized for not taking into account baseline weight, and therefore one cannot disentangle if it is weight change per se or baseline weight, or even an interaction between the two which matters most regarding dementia risk (1).

Dementia related mortality has very high specificity and positive predictive values for clinical dementia diagnoses (22), and dementia related mortality might be a feasible proxy for clinical dementia diagnoses in epidemiological studies (23). In previous work we studied weight at single time points and found high body mass index (BMI) to be associated with decreased dementia mortality risk only when BMI was measured in old age, while low BMI was associated with increased risk regardless of age (8, 24). To expand upon these previous analyses, our aim was threefold; first to explore whether the effect of weight change in

midlife depends on baseline weight, and secondly to examine associations with changes in weight during midlife adjusted for baseline weight. Finally, we wanted to assess which is most important for dementia mortality: size through midlife or changes in size?

Methods

Study sample

Repeated height and weight measurements were collected three times in the Norwegian Counties Study during 1974-88 (25). Study participants were born 1925-45 and were 35-49 years at baseline, and 40-62 years at the final measurement (N=69,906), with an average of 9.0 years between measurements. Our study sample comprised participants with two or three measurements of height and weight (N=46,774) (see flow chart in Figure 1). Participants with less than 5 years between baseline and follow-up measurement were removed to get a more homogenous population regarding time between measurements (n=1,916). Participants with missing measurements were removed (n=710). To make follow-up time more homogenous, participants with three measurements (n=29,155), the first and last were used. Finally, those with missing covariate values were removed (n=417). The final number of participants was 43,721. The percentage of missing due to missing values for height, weight or covariates was 2.5%.

Body mass index

Each respondent had two body mass index (BMI) values calculated as kg/m^2. Baseline BMI was used as a continuous variable and as a categorical variable (<20 kg/m^2, 20-24.9 kg/m^2, 25-29.9 kg/m^2, ≥30 kg/m^2). Percentage change in BMI was calculated as 100*(final BMI - baseline BMI)/(baseline BMI). Time between BMI measurements ranged 5-13 years.

Dementia related mortality

Dementia related mortality was defined as a dementia diagnosis (ICD-9: 331.0, 294.1, 290.0-290.4; ICD-10: F00-F03 and G30) recorded on the death certificate in The Norwegian Cause of Death Registry, either as the underlying cause of death or as a contributory cause. Study members were followed from final BMI assessment until death, emigration or until January 1st 2015, whichever occurred first.

Covariates

Highest educational level in 1970 or 1980 was obtained from the National Education Data Base, and grouped: university degree and equivalents (high), advanced secondary qualifications (middle), and basic (public school/elementary school) (low). Based on self-reports at baseline, participants were dichotomized according to diabetes status. Similarly, participants were dichotomized according to CVD status based on a history of cardiovascular disease (CVD), heart attack, angina, stroke, medical treatment of CVD, or symptoms of such diseases. Baseline smoking was dichotomized as daily smoker or not daily smoker. Baseline leisure time physical activity was grouped in four as reading or watching television mostly, light walking, moderate exercise, or intensive exercise. Based on a non-fasting blood sample at baseline, total cholesterol level was grouped in four categories: 5.20 mmol/l, 5.20–6.49 mmol/l, 6.50–7.79 mmol/l and ≥7.80 mmol/l (26). The second measurements of resting diastolic and systolic blood pressures were used in the analyses. The respondents were categorized as hypertensive if they had systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg, and hypotensive if systolic pressure was ≤90 mmHg, or diastolic pressure was ≤60 mmHg (27).

Statistics

The association between BMI (and BMI change) with later dementia related mortality was analyzed using three sets of Cox regression models (with attained age as time variable). First, for validation purposes and being able to compare results to earlier studies, the association between baseline BMI (in categories) with dementia related mortality was analyzed, without taking into account later BMI change. Secondly, to explore whether the association of weight change in midlife with the outcome depends on baseline BMI, the association between percentage BMI change and dementia related mortality was analyzed separately for baseline BMI below and above 25 kg/m^2 as well as combined.

Thirdly, to examine the role of both baseline BMI and BMI changes through adulthood we fitted a conditional growth model that included both baseline BMI (BMI_0) and change in BMI ($BMI_1 - BMI_0$) in the same Cox model (specified in appendix [1]). Baseline BMI and BMI change was treated as continuous variables in the "Cox growth model", and interaction was investigated including baseline BMI multiplied by BMI change in the model. Additionally, to allow for deviation from linearity in the association between BMI (and BMI change) with dementia related mortality, the covariates of interest were modeled using linear splines with one knot, keeping the adjustment covariate continuous. So for example when BMI change was the main interest, change was modeled using two linear splines with a knot at 0, and baseline BMI was treated as a continuous variable. In the second model, linear splines were created for baseline BMI with a knot at 25 kg/m^2 while holding BMI change as a continuous variable.

To investigate the specificity of the associations, a second set of analyses, identical to those above were performed using non-dementia related mortality as outcome rather than dementia

related mortality. For sensitivity purposes additional analyses were run using dementia outcome restricted to underlying cause of death. Stata version 14.0 was used for analyses.

Results

Of the 43,721 study participants 18,312 died during follow-up and 1,205 were dementia related, either registered as the main cause or as the underlying cause of death (Table 1). Mean follow-up time was 25.9 years (minimum 0.22 years, maximum 35.0 years). Mean age at start of mortality follow-up (at second BMI measurement) was 51.0 years (minimum 39.9 years, maximum 62.0 years), and at end of follow-up the mean age was 76.9 years (minimum 41.5, maximum 90.0 years). The distribution of study participants across BMI categories at baseline was: 4% underweight (<20 kg/m^2), 52% normal weight (20-24.9 kg/m^2), 36% overweight (25-29.9 kg/m^2) and 8% obese (≥30 kg/m^2) (Table 2). At final BMI measurement the corresponding distribution was: 3%, 43%, 42% and 12%. Mean BMI at baseline was 25.1 kg/m^2 for men (SD 3.0) and 24.8 kg/m^2 (SD 4.1) for women (Table 1). At follow-up, mean BMI was 25.8 kg/m^2 (SD 3.2) in men and 25.7 kg/m^2 (SD 4.4) in women. Mean change in BMI for men was 0.7 kg/m^2 (SD 1.7) and 0.9 kg/m^2 in women (SD 2.2).

Not taking later weight change into account, low BMI (<20 kg/m^2) at baseline was associated with increased risk of dementia related mortality compared with normal weight participants (Table 2). Adjusting for potential confounders made little difference to the result; HR=1.50 (95% CI 1.13, 1.99) in a fully adjusted model. Neither baseline overweight nor obesity was associated with later dementia related mortality.

There was no evidence that having a lower BMI at baseline and maintaining that lower BMI (over a period of 5-13 years) carried any significant extra risk of dementia related mortality,

likewise, starting with a higher BMI and maintaining that extra BMI was not associated with risk of dementia related mortality (Figure A1). For baseline BMI values below 25 kg/m^2, a one unit higher BMI was associated with dementia related HR of 0.97, p=0.13, in a fully adjusted model, and for baseline BMI above 25 kg/m^2 it was 0.99, p=0.87. HR results for baseline BMI below and above 25 kg/m^2 did not significantly differ (test for difference in slopes above and below 25 kg/m^2: p=0.31), so in Figure A1 baseline BMI was modeled continuously throughout the whole BMI range without splines.

BMI loss of 10% or more was associated with a fifty two percent increased dementia related mortality risk compared with those with stable weight; HR=1.52, 95% confidence interval (CI) 1.09, 2.12 in a fully adjusted model (Table 3, Model 2). Also those with slightly less BMI loss (5-10%) had increased dementia related mortality risk; HR=1.38, 95% CI 1.08, 1.76. Gaining weight was not associated with increased dementia related mortality risk. These results on BMI change and dementia related mortality risk (in Table 3) were similar in men and women (p-value testing for gender interaction: 0.92). Furthermore, HRs for BMI-change were similar between low (<25 kg/m^2) and high (≥25 kg/m^2) baseline BMI (p-value testing for interaction: 0.62).

Losses in BMI, after covariate adjustment for baseline BMI, were associated with a higher risk of dementia related mortality, whereas BMI gains were associated with a lower risk (Figure A2); one unit BMI gain was associated with a significant dementia related HR of 0.95 (p=0.001). In a model where BMI change was modeled as linear splines with one knot at 0, the slopes for BMI loss and BMI gain were identical; a one unit change was associated with HR=0.95.

To investigate what matters more regarding dementia related mortality risk, baseline BMI or BMI change, we formally tested differences in coefficients for baseline BMI and BMI change in the Cox growth model (appendix [1]) where the coefficients were modeled linearly without splines. The assumption about linearity seems feasible, as the slopes above and below the knot did not differ significantly, neither for baseline BMI nor for BMI change. The HR coefficient for baseline BMI was 0.99 (95% CI 0.97, 1.01), and for BMI change it was 0.95 (95% CI 0.92, 0.98). Furthermore, the difference between these coefficients was significant (p=0.011), indicating that BMI change matters more than baseline BMI regarding the outcome. There was no evidence that dementia related mortality risk associated with BMI change differed in those with high and low baseline BMI (p=0.15 for the interaction term baseline BMI*BMI change).

Analyses of non-dementia related mortality showed a significant u-shaped association with BMI at baseline, and a significant mirrored J-shape with BMI change (strongest association for those losing weight and a small increased risk for those gaining weight) (Appendix Table A1, and Figures A3 and A4).

Discussion

The novel finding in the present study is that weight change matters most regarding dementia related mortality risk, not baseline weight; losing weight was associated with increased risk, while putting on weight was associated with lower risk. This was true both for those with low and high baseline BMI. Having stable BMI through midlife (either being thin or having high BMI through midlife) was not associated with higher risk of dementia related mortality. These findings fit with the apparent paradox that obesity in old age seems to reduce dementia risk, while no such reduction in risk is observed for obesity in midlife (8, 9).

Our result regarding weight loss being associated with increased dementia related mortality risk fits with studies using clinical dementia as end point (10-18). Most previous studies investigate weight change in old age, typically above 65 years or older, where reverse causality might be a plausible explanation for the association between weight loss and dementia. For example weight loss in late life was associated with dementia in the Swedish Kungsholmen study (age 75 or older at baseline) (11), in a study of African-Americans (12) and in a study of Yoruba Nigerians (13) (age at baseline was 65 years or older in both studies). It has been found that preclinical dementia may cause weight loss already in the late 50s, decades before the dementia diagnosis (20).

We identified five studies which have, like us, linked weight change from midlife into old age to dementia outcomes, and in accordance with our findings, weight loss was associated with increased dementia risk in all these studies (14, 17-19, 28). First, in the Honolulu-Asia Aging Study, a study of Japanese American men, where age at inclusion was from late 40s and 60s and follow-up was until 90s for the oldest, it was reported that men that developed dementia lost significantly more weight during the years prior to the diagnosis, especially during the three year period prior to the diagnosis (14). Secondly, in the Baltimore Longitudinal Study of Aging, women losing weight between their 30s and 40s were at increased risk for Alzheimer's disease (AD) (18). Thirdly, in The Prospective Population Study of Women (PPSW), where Swedish women aged 38 to 60 years at baseline were followed over nearly four decades, it was reported that women developing dementia had a lesser increase in BMI compared to the increase seen in other women (28), and these trajectories were modified by the ApoE genotype after age 70 years; Women carrying the ApoE ε4 allele had a steeper BMI decline than non-carriers after age 70 years (29). The authors argued that it is plausible that the ApoE ε4 allele, which is tightly related to increased risk of Alzheimer’s disease, is associated with weight loss through reverse causality.

However, before age 70 years there was no indication of any modification by the ApoE genotype on the BMI trajectories and it is suggested that the association between BMI loss before 70 and dementia is driven by other aspects of the early phases of the underlying dementia disease (29). We were not able to investigate this in detail, but we question if the dementia prodromal could cause weight loss as early as ages between 35 and 62 years. Fourth, in the Finnish CAIDE study, both men and women were included, and weight loss between age 50 and 70 years was associated a 20% increased dementia in risk per unit BMI loss, which was robust to adjustment for a range of health related variables (17). Fifth, midlife weight variability (in either direction) was associated with increased dementia risk in the Israel Ischemic Heart Disease Project (19). Unfortunately weight change and interaction with baseline weight status was not addressed in these five studies. This is essential, as noted in a recent review study (1), because loss or gain in BMI might be differently associated with dementia outcomes in initially normal weight individuals compared with initially obese individuals.

Why weight loss is related to dementia is poorly understood, and there is an ongoing discussion on this issue (1). One explanation is that the dementia disease itself can cause weight loss (reverse causality). This explanation is supported by results from the American HRS study, which reported that preclinical dementia was associated with weight loss in cognitive normal study participants (20). Another study reported no BMI differences 20 to 30 years before dementia onset, but 10 to 20 years before onset of dementia women that developed dementia had lower BMI than controls, and this BMI gap widened the closer the year of dementia onset (16). Thus, weight loss seems to precede dementia diagnosis by several years, even decades. Some authors have suggested that this loss may be related to pre-dementia apathy, loss of initiative, and reduced olfactory function (16). Our results are less prone to reverse causality as weight change is observed at fairly young ages (between ages

35-49 years at baseline and 40-62 years at BMI follow-up) and linked with dementia related mortality occurring up to three to four decades later. This makes it less likely that frailty and general poor health, which is found to be associated with weight loss, to be the full explanation for the weight loss dementia mortality link.

As we have discussed previously (24, 30), using dementia related mortality as a proxy for clinical dementia diagnosis has its limitations (24, 30). Dementia cases still alive and those with dementia dying from other cause(s) than dementia will not be cases in our study. Hence, it is likely that cases in our study are those with the most severe dementia. The outcome variable in the present study included both those with dementia as accompanying and underlying cause of death, so we cannot rule out the possibility that there are other causes of death that are driving the observed associations with BMI. However, the results were similar when only underlying cause of death was used as dementia end point. Another possible source of bias in cohort studies is informative censoring. Most of the mortality in our study (93%) were non-dementia related, of which many occurred before reaching ages where dementia mortality is most prevalent (average age at death for non-dementia related mortality was 71 years, while for dementia related mortality it was 79 years). Baseline obesity and overweight was associated with increased hazard of non-dementia related mortality, such as mortality from cardiovascular events, and it is possible that these heavy participants would be of high risk for dementia if they had survived, thereby attenuating the true associations. However, informative censoring does not seem likely for the associations with weight change, as weigh gain was only weakly associated with non-dementia related mortality. Because of this possible informative censoring bias we cannot rule out that our findings are restricted to those who survive other, much more common causes of mortality. The underreporting of dementia on the death certificates (31) will possibly blur any weak true associations between BMI and dementia related mortality. A study revealed that only 38-39% of residents of nursing homes

in Norway with dementia had dementia mentioned in their death certificate, thus quite low sensitivity (22). However, all of those having dementia mentioned in their death certificate had a dementia diagnosis – thus, high specificity and positive predictive values (100%) (22). Our recent findings, which showed that dementia related mortality risk for the various ApoE genotypes were in line with other reports using clinical dementia diagnoses as end point, suggest that dementia related mortality might be a feasible proxy for clinical dementia diagnoses in epidemiological studies (23). We performed a complete cases analysis using only individuals with non-missing values for all covariates in the fully adjusted regression model. Restricting the sample this way may introduce bias, but we believe this bias to be small as the complete cases sample comprised 97.5% of the total analytical sample.

Interpretation

Our results suggest that losing weight during midlife is associated with increased dementia related mortality risk up to four decades later, while gaining weight reduces risk. These associations hold both for low and high baseline BMI. Weight loss is an independent risk factor for dementia related mortality risk and more strongly related with the outcome than stable high or stable low BMI. The mechanisms linking weight loss in midlife and dementia in old age are poorly understood and are probably not only due to reverse causality. We will emphasize that our results do not support a recommendation that individuals should attempt to gain weight during mid-life or that obesity is not an important health risk factor; Both overweight and obesity were associated with at increased risk for non-dementia related mortality, which were far more common than dementia related mortality.

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Table and figure captions

Table 1. Background table.

Table 2. BMI at baseline and dementia related mortality and non-dementia related mortality, estimated with Cox regression.

Table 3. BMI change and dementia related mortality hazard ratios (HR), estimated with Cox regression.

Figure 1. Study population, flow-chart

Tables

Table 1. Background table.

	Dementia deaths/N	Mean baseline BMI (SD)	Mean follow-up BMI (SD)	Baseline BMI<25	BMI Change* (%)		
				(%)	BMI loss	Stable BMI	BMI gain
Men	534/21725	25.1 (3.0)	25.8 (3.2)	51	17	33	50
Women	671/21996	24.8 (4.1)	25.7 (4.4)	61	20	26	54
Education							
Low	673/22325	25.3 (3.8)	26.0 (4.1)	52	20	28	51
Middle	453/17931	24.8 (3.4)	25.6 (3.6)	58	17	30	53
High	79/3465	24.1 (3.0)	24.9 (3.3)	67	14	33	54
Diabetic							
No	1201/43460	25.0 (3.6)	25.8 (3.8)	56	18	30	52
Yes	4/261	26.0 (4.7)	26.4 (4.5)	49	29	26	44
History of CVD							
No	1125/41161	24.8 (3.4)	25.6 (3.8)	57	18	30	52
Yes	80/2560	27.0 (4.7)	27.7 (4.8)	36	23	27	50
Daily smoking							
No	723/24558	25.3 (3.7)	26.1 (3.9)	52	17	30	53
Yes	482/19163	24.5 (3.4)	25.3 (3.8)	60	20	29	50
Physical activity, leisure time							
Reads/TV mostly	3674/8534	25.4 (4.0)	26.3 (4.3)	51	21	27	52
Light walking	10,154/26426	24.9 (3.6)	25.7 (3.9)	57	18	29	53
Moderate exercise	3,156/8355	24.8 (3.0)	25.5 (3.3)	57	16	33	51
Intensive exercise	128/406	24.2 (2.2)	25.0 (2.5)	70	14	32	54

Tot. cholesterol mmol/l							
<5.20	133/7557	24.1 (3.2)	25.0 (3.5)	67	15	30	55
5.20-6.49	515/18591	24.7 (3.5)	25.6 (3.8)	59	18	30	53
6.50-7.79	386/12795	25.5 (3.7)	26.2 (3.9)	49	20	29	51
≥7.80	171/4778	25.9 (3.7)	26.6 (4.1)	43	22	29	52
Hypertensive**							
No	1045/38444	24.7 (3.4)	25.5 (3.7)	59	18	30	53
Yes	160/5277	26.8 (4.4)	27.4 (4.5)	36	23	30	46
Hypotensive**							
No	1193/43155	25.0 (3.6)	25.8 (3.8)	56	18	30	52
Yes	12/566	23.1 (2.9)	24.1 (3.2)	79	14	25	61

* BMI loss defined as a BMI loss of 2.5% or more between baseline and follow-up; stable BMI is loosing or gaining less than 2.5%, and BMI gain is gaining more than 2.5%.

** The respondents were categorized as hypertensive if they had systolic pressure ≥160 mmHg or diastolic pressure ≥100 mmHg, and hypotensive if systolic pressure was ≤90 mmHg, or diastolic pressure was ≤60 mmHg.

Table 2. BMI at baseline and dementia related mortality and non-dementia related mortality, estimated with Cox regression.

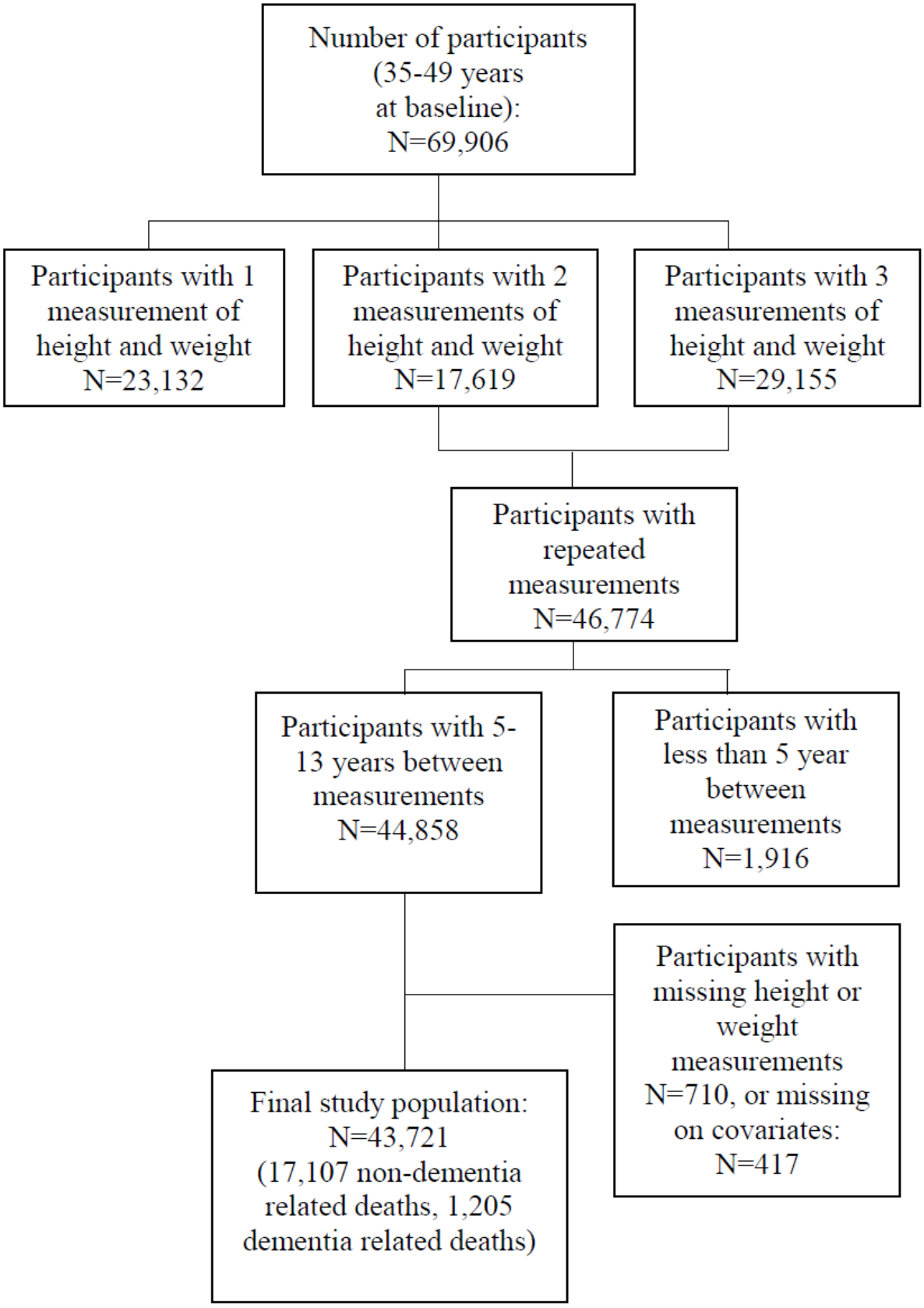
	Dementia related mortality HR (95% CI)	Non-dementia related mortality HR (95% CI)
BMI baseline, adjusted by sex (number of dementia related deaths/number of individuals)		
<20 kg/m^2 (54/1822)	1.52 (1.15-2.01)	1.52 (1.41, 1.64)
20-24.9 kg/m^2 (584/22604)	1.00	1.00
25-29.9 kg/m^2 (463/15676)	1.08 (0.96, 1.22)	1.13 (1.10, 1.17)
≥30 kg/m^2 (104/3619)	1.11 (0.90, 1.37)	1.66 (1.58, 1.75)
BMI baseline, fully adjusted*		
<20 kg/m^2 (54/1822)	1.50 (1.13-1.99)	1.38 (1.28, 1.49)
20-24.9 kg/m^2 (584/22604)	1.00	1.00
25-29.9 kg/m^2 (463/15676)	1.06 (0.94, 1.20)	1.13 (1.09, 1.16)
≥30 kg/m2 (104/3619)	1.04 (0.84, 1.29)	1.51 (1.43, 1.59)

* Adjusted by sex, total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking and blood pressure.

Table 3. BMI change and dementia related mortality hazard ratios (HR), estimated with Cox regression.

BMI change (number of dementia related deaths/number of individuals)	HR (95% CI) Model 1*	HR (95% CI) Model 2*
Loss 10% or more (44/1296)	1.62 (1.16, 2.26)	1.52 (1.09, 2.12)
Loss 5-10% (104/3093)	1.42 (1.11, 1.82)	1.38 (1.08, 1.76)
Loss 2.5-5% (113/3612)	1.27 (1.01, 1.61)	1.26 (0.99, 1.59)
Loss 0-2.5% (194/6552)	1.13 (0.92, 1.38)	1.12 (0.91, 1.37)
Gain 0-2.5% (167/6393)	1	1
Gain 2.5-5% (170/6753)	0.95 (0.76, 1.17)	0.95 (0.77, 1.18)
Gain 5-10% (255/9268)	1.10 (0.91, 1.34)	1.11 (0.91, 1.35)
Gain 10-15% (102/3999)	1.07 (0.83, 1.37)	1.05 (0.82, 1.35)
Gain 15-20% (42/1629)	1.12 (0.79, 1.57)	1.09 (0.77, 1.53)
Gain 20% or more (14/1126)	0.58 (0.33, 1.00)	0.56 (0.32, 0.96)

* Model 1: Adjusted by sex and time between BMI measurements;
Model 2: + adjusted by total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking and blood pressure.


Number of participants (35-49 years at baseline): N=69,906
Participants with 1 measurement of height and weight N=23,132
Participants with 2 measurements of height and weight N=17,619
Participants with 3 measurements of height and weight N=29,155
Participants with repeated measurements N=46,774
Participants with 5-13 years between measurements N=44,858
Participants with less than 5 year between measurements N=1,916
Participants with missing height or weight measurements N=710, or missing on covariates: N=417
Final study population: N=43,721 (17,107 non-dementia related deaths, 1,205 dementia related deaths)

Appendix

Conditional growth model to examine the role of both baseline BMI and changes in BMI through adulthood with dementia related mortality

We fitted a conditional growth model that included both baseline BMI (BMI_0) and change in BMI ($BMI_1 - BMI_0$) in the same Cox model as follows:

$$h(t, BMI_0, BMI_1) = h_0(t)\exp(\gamma_0 BMI_0 + \gamma_1(BMI_1 - BMI_0)) \quad [1]$$

Where $h(t, BMI_0, BMI_1)$ is the dementia related mortality hazard rate at time t for a model with two covariates; the baseline BMI_0 and the follow-up BMI_1, and baseline hazard $h_0(t)$. Coefficient γ_0 captures the association of the outcome with being a BMI unit bigger at baseline conditional on later BMI change; it therefore assesses the association between being bigger or being smaller through follow-up with dementia mortality. The coefficient γ_1 captures the association of the outcome with changes in BMI conditional on baseline BMI (1).

1. Wills AK, Silverwood RJ, De Stavola BL. Comment on Tu et al. 2013. A critical evaluation of statistical approaches to examining the role of growth trajectories in the developmental origins of health and disease. International journal of epidemiology. 2014;**43**:1662-1664.

Table A1. Change in BMI and non-dementia related mortality hazard ratios (HR), estimated in Cox regression with attained age as time scale.
N=43,721; 17,107 non-dementia related deaths.

BMI change in % (number of individuals)	HR (95% CI) Model 1*	HR (95% CI) Model 2*
Loss more than 10% (710/1296)	2.05 (1.89, 2.23)	1.71 (1.57, 1.86)
Loss 5-10% (1468/3093)	1.47 (1.38, 1.57)	1.33 (1.25, 1.42)
Loss 2.5-5% (1594/3612)	1.24 (1.16, 1.32)	1.19 (1.11, 1.26)
Loss 0-2.5% (2691/6552)	1.08 (1.02, 1.14)	1.06 (1.00, 1.12)
Gain 0-2.5% (2447/6393)	1	1
Gain 2.5-5% (2469/6753)	0.95 (0.90, 1.00)	0.97 (0.92, 1.03)
Gain 5-10% (3241/9268)	0.96 (0.91, 1.02)	0.97 (0.92, 1.03)
Gain 10-15% (1462/3999)	1.10 (1.03, 1.18)	1.06 (0.99, 1.13)
Gain 15-20% (591/1629)	1.17 (1.07, 1.29)	1.08 (0.99, 1.19)
Gain 20% or more (434/1126)	1.35 (1.22, 1.50)	1.17 (1.06, 1.30)

* Model 1: Adjusted by sex and time between BMI measurements;
Model 2: + adjusted for cardiovascular/life-style factors at baseline (total cholesterol, physical inactivity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure.

Figure A1. Baseline BMI and dementia mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted for later BMI change, sex and risk factors. Cox regression with attained age as time scale and baseline BMI modeled as a linear variable, adjusted for later BMI growth, sex, time between BMI measurements, and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 1,205 dementia related deaths. Baseline BMI slope: HR=0.99, p=0.173. Model is described in [1] in appendix.

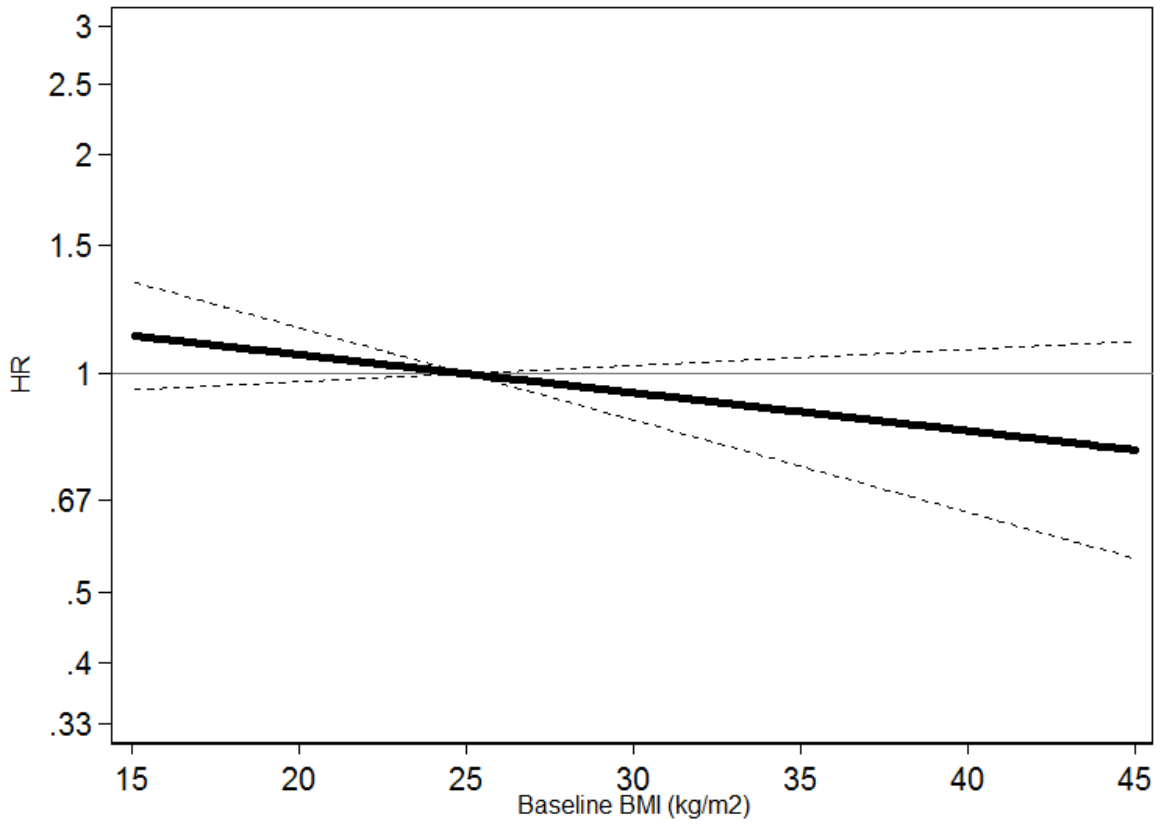


Figure A2. BMI change and dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted by baseline BMI, sex and risk factors. Cox regression with attained age as time scale and BMI change modeled as a linear variable, adjusted for baseline BMI, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721, and 1,205 dementia related deaths. BMI change slope: HR=0.95, p=0.001. Model is described in [1] in appendix.

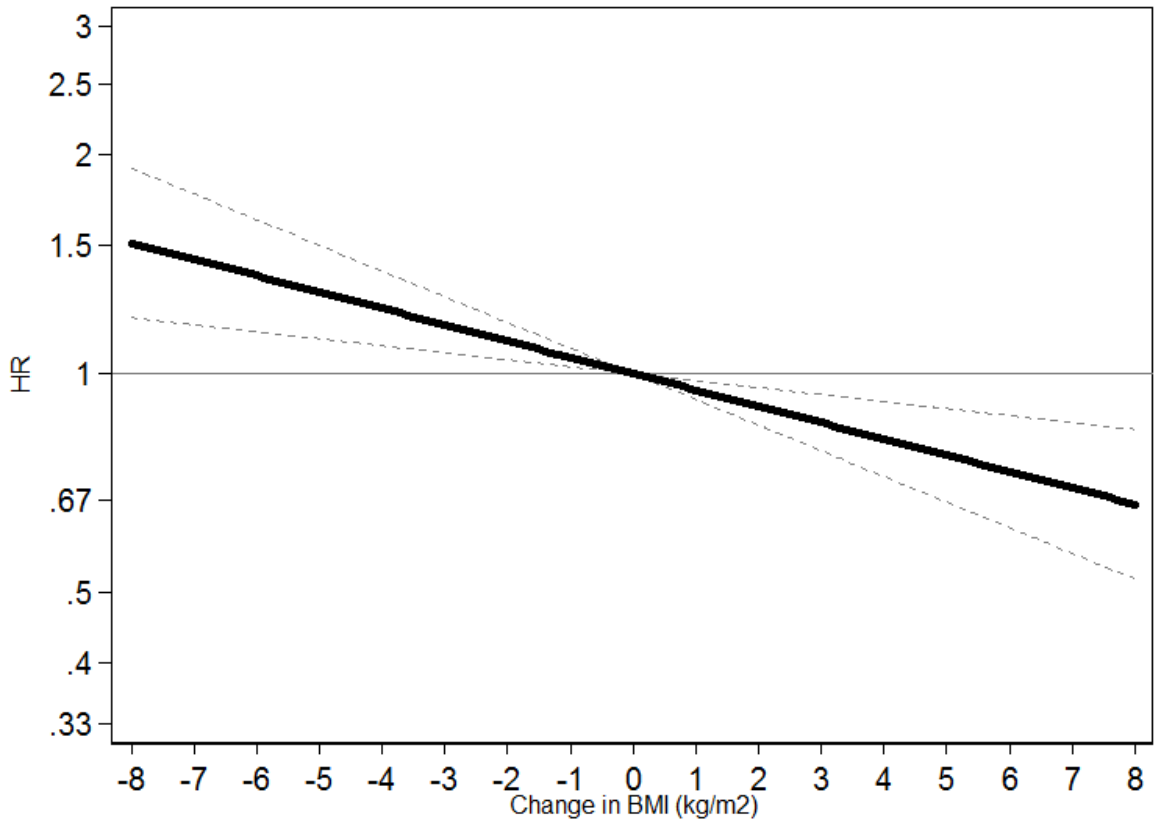


Figure A3. Baseline BMI and non-dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted for later BMI change, sex and risk factors. Cox regression with attained age as time scale and baseline BMI modeled as linear spline with one knot at 25, adjusted for BMI change, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 17,107 non-dementia related deaths. (Slopes test for difference from zero: spline 1 (BMI <25): HR=0.97, p<0.001, spline 2 (BMI >25): HR=1.05, p<0.001. Test for difference in baseline BMI slopes above and below 25: p<0.001). Model is described in [1] in appendix.

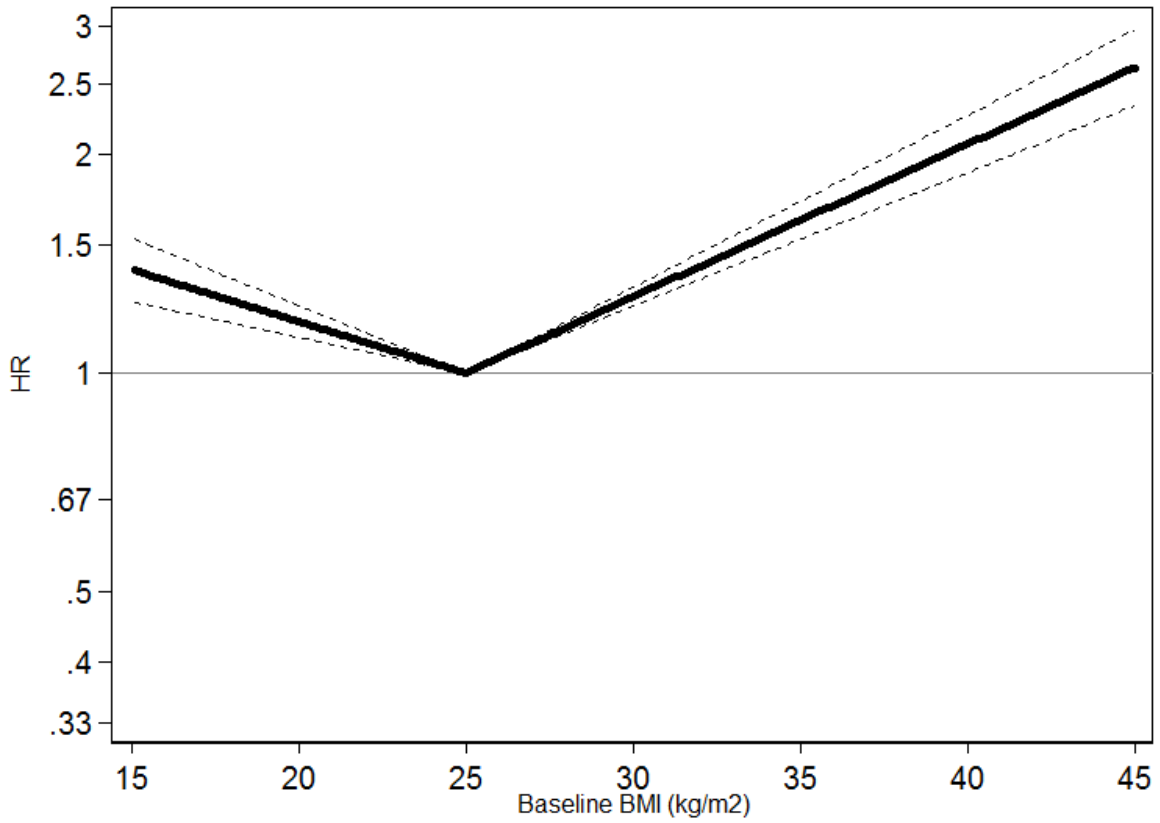


Figure A4. BMI change and non-dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted by baseline BMI, sex and risk factors. Cox regression with attained age as time scale and BMI change modeled as linear spline with one knot at 0, adjusted for baseline BMI, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 17,107 non-dementia related deaths. (Slopes test for difference from zero: spline 1 (change below 0): HR=0.95, $p<0.001$, spline 2 (change above 0): HR=1.004, $p=0.47$. Test for difference in slopes above and below 0: $p<0.001$). Model is described in [1] in appendix.

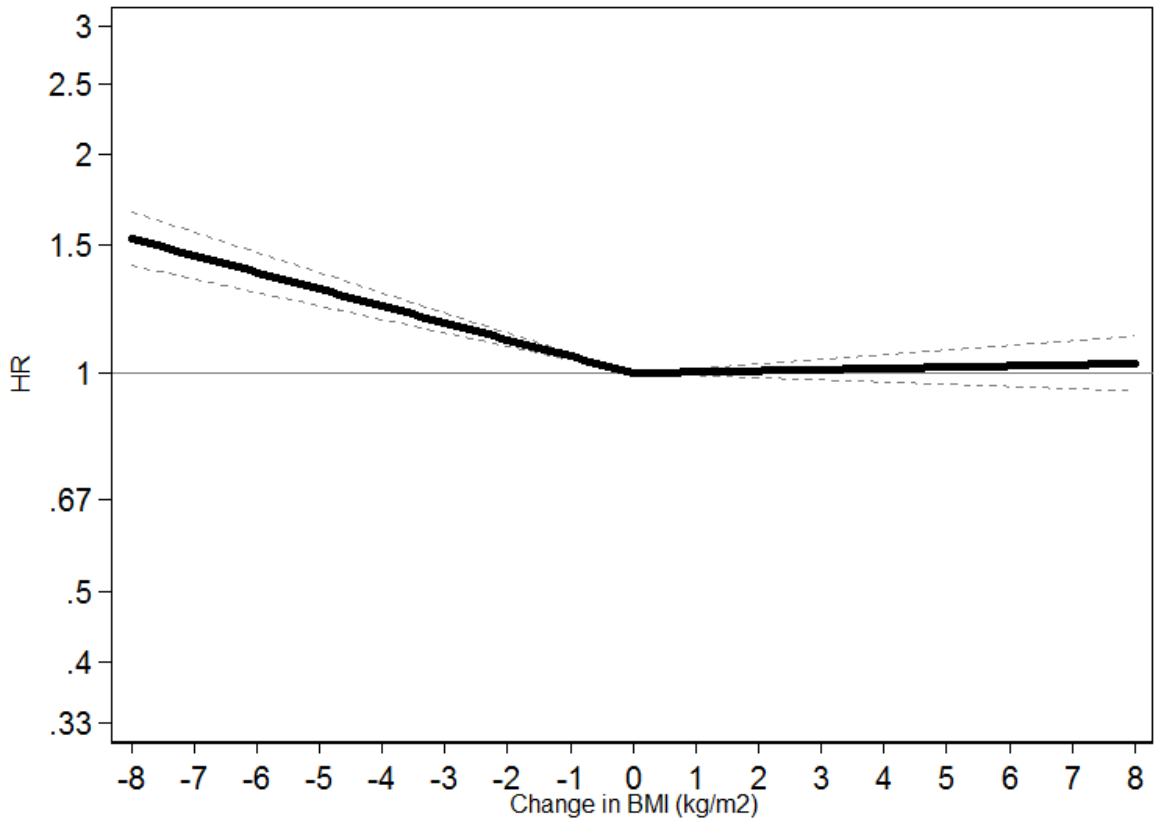


Figure legends for figures in Appendix

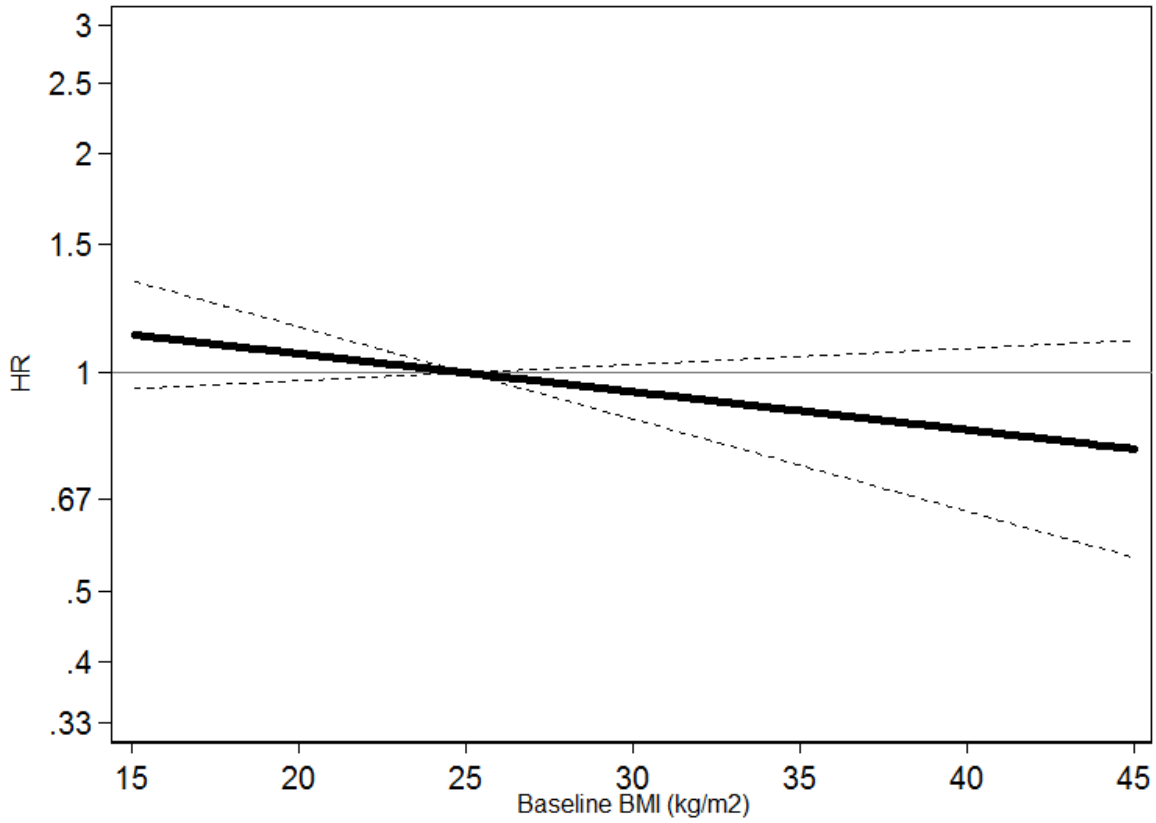
Table A1. Change in BMI and non-dementia related mortality hazard ratios (HR), estimated in Cox regression with attained age as time scale.
N=43,721; 17,107 non-dementia related deaths.

Figure A1. Baseline BMI and dementia mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted for later BMI change, sex and risk factors. Cox regression with attained age as time scale and baseline BMI modeled as a linear variable, adjusted for later BMI growth, sex, time between BMI measurements, and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 1,205 dementia related deaths. Baseline BMI slope: HR=0.99, p=0.173. Model is described in [1] in appendix.

Figure A2. BMI change and dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted by baseline BMI, sex and risk factors. Cox regression with attained age as time scale and BMI change modeled as a linear variable, adjusted for baseline BMI, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721, and 1,205 dementia related deaths. BMI change slope: HR=0.95, p=0.001. Model is described in [1] in appendix.

Figure A3. Baseline BMI and non-dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted for later BMI change, sex and risk factors. Cox regression with attained age as time scale and baseline BMI modeled as linear spline with one knot at 25, adjusted for BMI change, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 17,107 non-dementia related deaths. (Slopes test for difference from zero: spline 1 (BMI <25): HR=0.97, p<0.001, spline 2 (BMI >25): HR=1.05, p<0.001. Test for difference in baseline BMI slopes above and below 25: p<0.001). Model is described in [1] in appendix.

Figure A4. BMI change and non-dementia related mortality hazard ratios (HR) with 95% confidence intervals marked with dotted lines. Model is adjusted by baseline BMI, sex and risk factors. Cox regression with attained age as time scale and BMI change modeled as linear spline with one knot at 0, adjusted for baseline BMI, sex, time between BMI measurements and risk factors (total cholesterol, physical activity, history of heart disease/conditions, history of diabetes, education, smoking, blood pressure). N=43,721 and 17,107 non-dementia related deaths. (Slopes test for difference from zero: spline 1 (change below 0): HR=0.95, p<0.001, spline 2 (change above 0): HR=1.004, p=0.47. Test for difference in slopes above and below 0: p<0.001). Model is described in [1] in appendix.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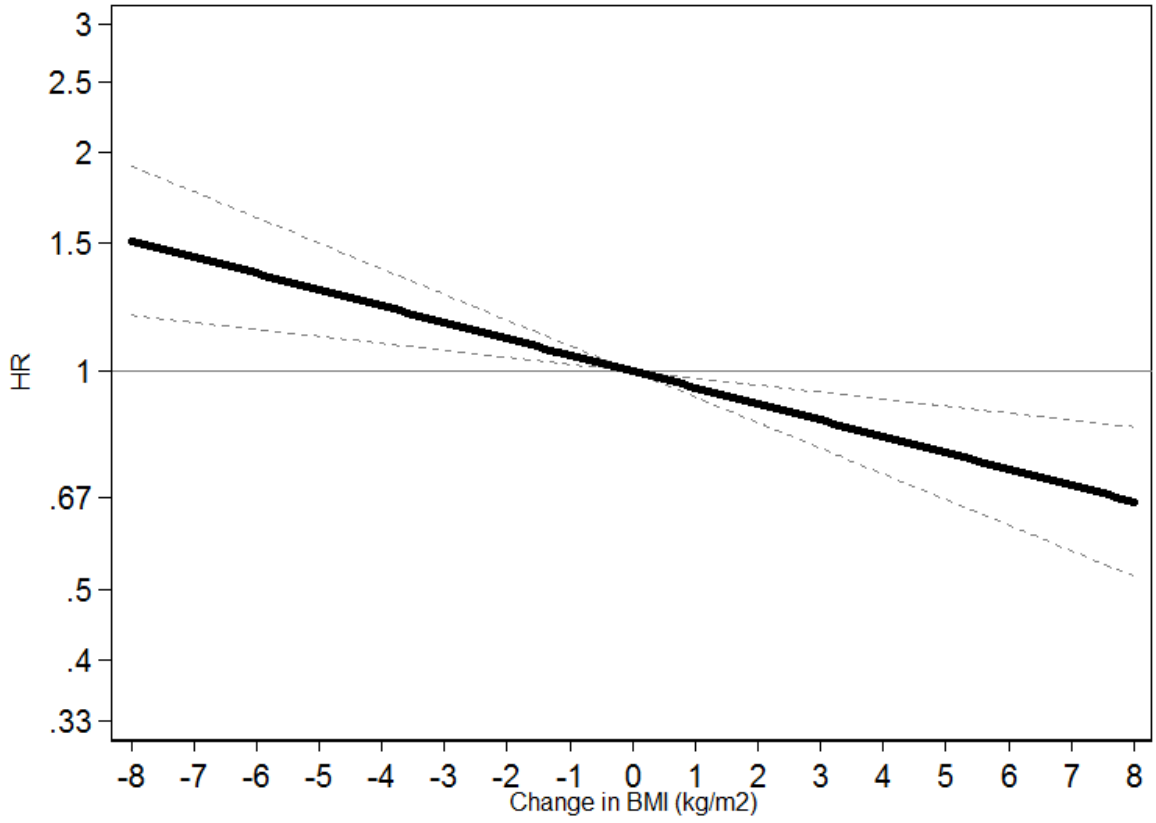
Baseline BMI (kg/m2)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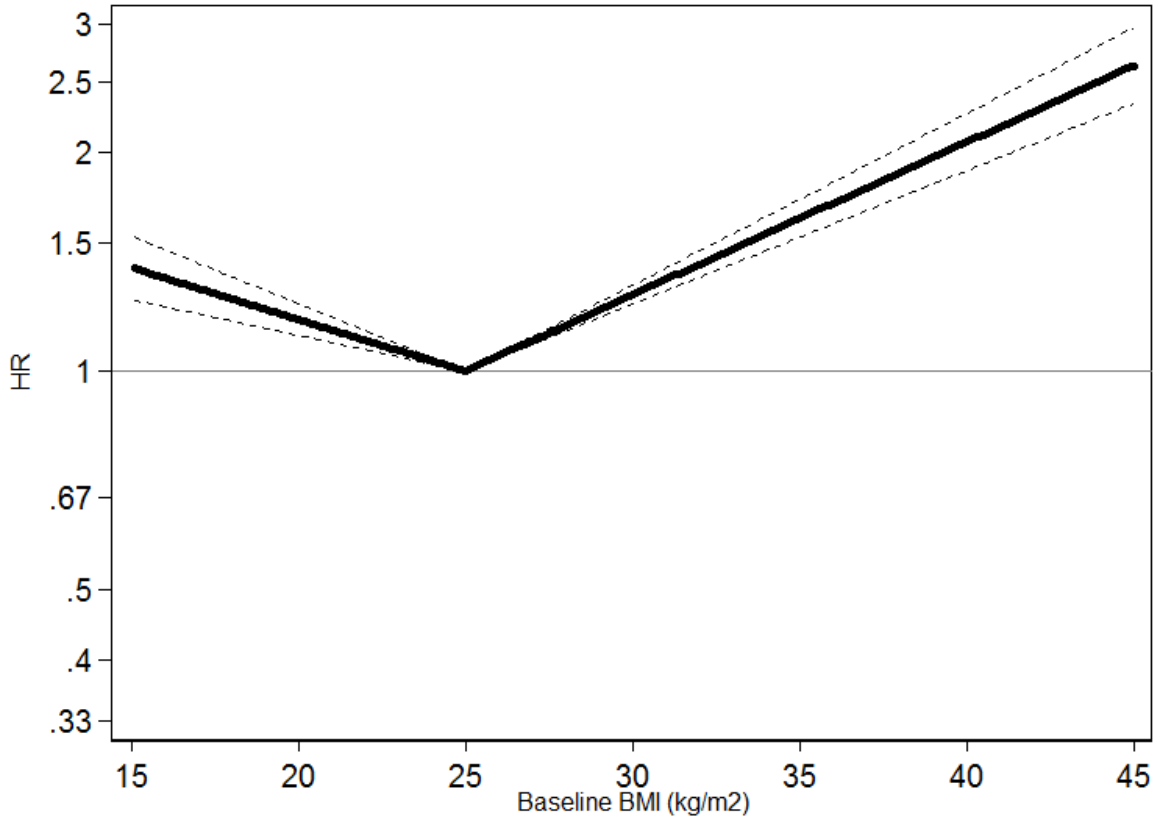
Change in BMI (kg/m2)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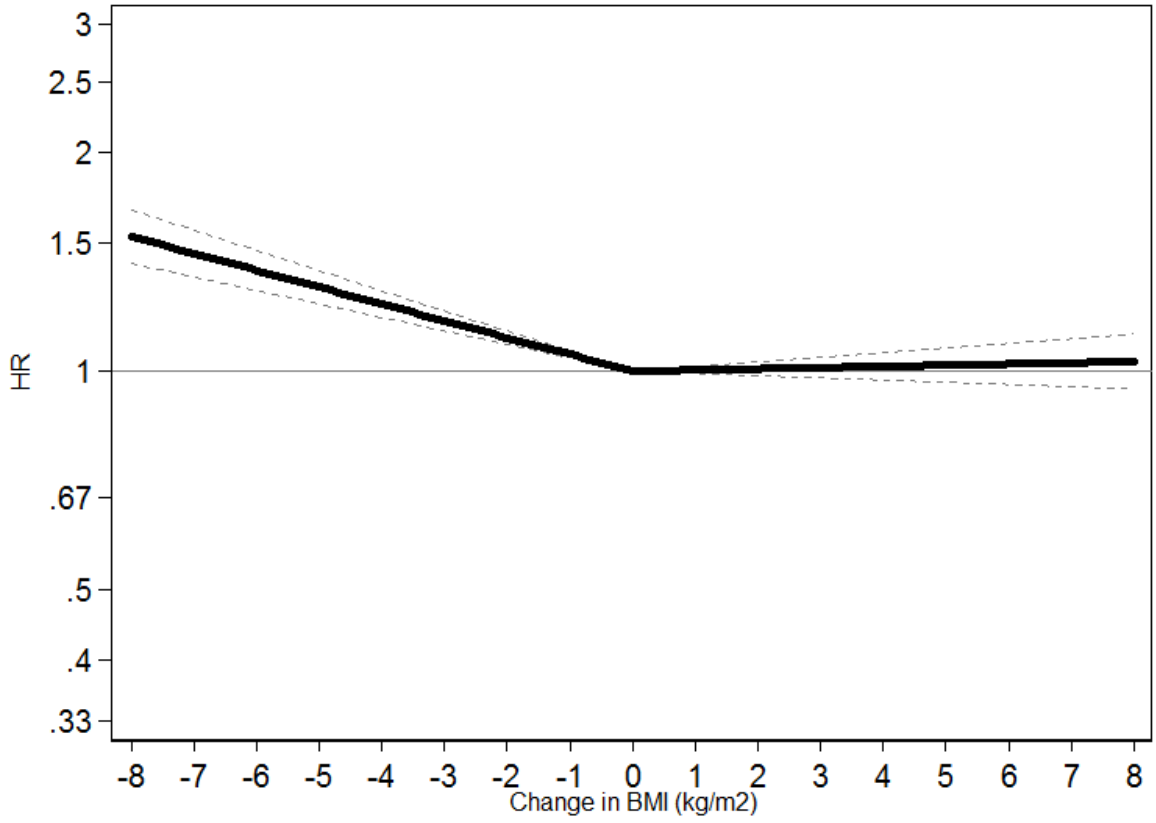
Baseline BMI (kg/m2)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Change in BMI (kg/m2)