Five-decade trajectories in body mass index in relation to dementia death: follow-up of 33,083 male Harvard University alumni

Short title: Body mass index trajectories and dementia risk

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ABSTRACT

Background: In prospective cohort studies, obesity has been linked with a *lower* risk of subsequent dementia. Reverse causality, whereby neurodegeneration preceding overt dementia symptoms may lower weight, is a possible explanation of these findings. To explore further the weight–dementia association we followed people from early adulthood, an age at which neurodegeneration has typically yet to begin.

Methods: 33,083 male participants in the Harvard Alumni Health Study underwent a medical examination as undergraduates (typically aged 18 years) during which height, weight, resting pulse rate, blood pressure, physical activity, and smoking status were assessed. Subsamples provided height and weight in 1962/6 (mean age 50.7 years), 1977 (58.6), 1988 (67.5), and 1993 (71.1). Dementia deaths were extracted from death certificates (mean follow up 53.1 years). We used latent class mixed models to create body mass index (BMI) trajectories; for comparison, we also constructed models with cardiovascular disease (CVD) death.

Results: We found no association between early life BMI and subsequent dementia (age-adjusted HR 0.94, 95% CI 0.85, 1.04). We identified two latent class groups based on different BMI trajectories – "early decliners" whose BMI began to decline around age 50 years and "late decliners" whose BMI declined about two decades later. The former experienced a raised risk of dementia-related death compared to the latter (multivariable-adjusted HR 1.57, 95% CI 1.14, 2.17). Expected associations were identified between CVD risk factors and CVD death.

Conclusions: In a population likely to be free of dementia neuropathology at BMI measurement, we found no association between BMI at baseline and subsequent dementia-related death. Earlier decline in BMI was, however, associated with dementia which suggests that findings associating BMI with dementia risk may be influenced by reverse causality.

Keywords: Obesity, overweight, dementia, Alzheimer's disease, risk factors, epidemiology, cohort, life course

INTRODUCTION

Dementia is a major and growing global public health concern. While the incidence of dementia may be falling, perhaps due to lifestyle changes in recent generations,[1, 2] global demographic changes mean that the number of people with this condition will continue to rise dramatically – estimated to reach 131.5 million people worldwide by 2050, with the majority of cases occurring in low-to-middle income countries.[3] Preventing or delaying the symptomatic onset of dementia would substantially reduce its public health burden.[4] However, the aetiology of dementia remains incompletely understood. Genetic factors explain about a third of the variance in risk and a further third is commonly attributed to risk factors such as diabetes, midlife hypertension and obesity, smoking, depression, cognitive inactivity, and low educational attainment.[5, 6] Thus, a substantial proportion of risk remains unexplained.

The assumption that midlife cardiovascular risk factors are associated with later dementia risk has been accepted largely on the strength of evidence from conflicting observational studies.[7] For example, many observational studies suggest that being overweight or obesity might be associated with an elevated risk of subsequent dementia.[8] However, a report based on data from 2 million British individuals found that being overweight or obese in midlife was actually associated with a lower risk of dementia.[9] Amongst much discussion regarding this unexpected finding, it was subsequently replicated in the original Whitehall cohort.[10]

Interpretation of these findings is substantially complicated by the long asymptomatic preclinical period of dementia during which neurodegenerative changes are present in the brain but there are no overt clinical symptoms.[11] This leads to the possibility of reverse causation – neurodegeneration preceding overt dementia symptoms may influence the risk factor, thus leading to spurious conclusions. For example, Whitehall II investigators examined trajectories of body mass index (BMI) over 28 years and found that individuals who developed dementia were more likely to be obese in midlife than subsequent decades but then lost weight in the preclinical phase.[12] Furthermore, an individual-participant meta-analysis of 39 studies led to the conclusion

that higher BMI was harmful but that studies with shorter periods of follow up could be affected by reverse causation to make higher BMI appear protective.[13] This could lead one to the erroneous conclusion that lower weight in later life is a risk factor for dementia. One solution to this conundrum is to recruit participants at an age when the brain changes of dementia are unlikely to be present to any degree – that is, before the preclinical period of dementia. Thus, we present reults from a longitudinal cohort study of University alumni recruited at the beginning of their undergraduate studies – typically aged 18 years – with long-term follow-up exceeding five decades.

METHODS

Study population

Participants were drawn from the Harvard Alumni Health Study which has been described in detail elsewhere.[14, 15] In brief, this is a prospective cohort study of men who matriculated as undergraduates at Harvard University between 1916 and 1950. Participants provided consent and approval was granted by the institutional review board of the Harvard T.H. Chan School of Public Health.

Measurement of weight and other baseline variables

At the time of matriculation as undergraduates, participants underwent an interview and physical examination with a university physician. Height (measured in inches and converted to centimetres) and weight (measured in stones and pounds and converted to kilograms) were measured directly. Body mass index (BMI) was calculated using the standard formula $\left(\frac{weight[\mathrm{kg}]}{height[\mathrm{m}]^2}\right)$. The amount of physical exertion the individual engaged in was recorded as number of hours of physical activity per week, and coded as five or more and four or fewer. Resting pulse rate (a marker of physical fitness, coded as <75, 75-94, and ≥95 beats per minute) and systolic and diastolic blood pressure (mmHg) were also recorded, as was smoking status (current smoker

or non-smoker). At a number of follow up waves, all surviving participants were invited to take part and over 60% did on each occasion:[16] height and weight were self-reported in either 1962 or 1966 (N=19,143; mean age 50.7 years), 1977 (N=16,222; 58.6 years), 1988 (N=11,253; 67.5 years), and 1993 (N=10,562; 71.1 years), allowing us to compute BMI at these time points.

Ascertainment of cause of death

Participants who had died on or before 31st December 1998 were identified from records maintained by the Harvard University Alumni office and causes of death were extracted from death certificates obtained from the state health departments (up to three coded causes in total). Completeness of mortality follow up is over 99% in this cohort.[17] Diagnoses recorded on death certificates were coded according to the International Classification of Diseases (ICD) 7th revision.[18] Dementia-related deaths were identified by any mention of codes 304 to 306 (senile psychosis, presenile psychosis, and psychosis with cerebral arteriosclerosis) or 794 (senility without mention of psychosis). For comparison, and to confirm expected risk factor-outcome relationships, we also constructed with cardiovascular disease death as the outcome; these deaths were identified by any mention of codes 330 to 334 and 410 to 446.

Statistical analyses

After ascertaining that the proportional hazards assumption had not been violated through visual inspection of plots, we constructed Cox regression models[19] for the association of baseline variables with dementia-related deaths. Continuous variables were standardised so that a unit increase denoted one standard deviation disadvantage in the risk factor, irrespective of the original orientation of the scale. Since age is an important risk factor for dementia, we included it in every model. Individuals with data missing for particular variables were excluded from analyses using those variables. The timescale was calendar days from examination date with follow-up

censored at the date of death from other causes or the end of December 1998 (whichever came first).

For a preliminary exploration of life course BMI data, we constructed Cox models examining the effect of adjusting individually for BMI measured at different time points. We explored the possible influence of missing data by adjusting effects for BMI measured at baseline including only individuals who had BMI measured in 1993 and comparing this to the complete data model of baseline BMI. To use all the information from BMI measurements across the life course we used the lcmm package[20] to construct latent class mixed models to explore whether there were distinct groups of BMI trajectory. Models were compared using the Bayesian Information Criterion (BIC) with a lower BIC indicating a better fit. The association between membership of the resulting groups and dementia-related death was then explored in Cox models. All analyses were conducted using R version 3.2.3.

RESULTS

After excluding seven individuals with missing or erroneous mortality or sex data, 236 individuals with matriculation dates before 1916 or after 1950 (who were not part of the main Harvard Alumni Health Study), and 33 individuals aged over 30 years at baseline, the analytic sample comprised 33,083 men aged 30 years or younger at baseline. In **Table 1** we show the baseline characteristics of participants. Levels of risk factors were generally favourable in these young, well educated men: 9% of the cohort was overweight (and approximately 1% obese) – a much lower prevalence than would be the case in a contemporary cohort – and mean blood pressure was 120/74 mmHg. However, approximately a third of participants smoked.

Over a mean 53.1 (SD 14.3) years follow up (range 109 days to 83.5 years), 16,478 participants (50%) were identified as having died. Of these, 390 had dementia mentioned on their death certificates and 6703 had cardiovascular disease mentioned. One hundred and three individuals had both dementia and cardiovascular disease mentioned on their death certificate;

they were included in the dementia analyses but excluded from the cardiovascular disease models, resulting in a total of 6600 participants dying with cardiovascular disease but no dementia. **Table 2** shows the results of the Cox regression models for the association between baseline risk factors and deaths related to dementia and cardiovascular disease. Other than increasing age (HR per five year increase 1.33, 95% CI 1.00-1.77), no other risk factors measured at baseline were associated with dementia-related mortality, although the HR for being overweight or obese was somewhat elevated but not at conventional levels of statistical significance. A sensitivity analysis using outcomes of (a) dementia but no cardiovascular disease and (b) any cardiovascular disease irrespective of the presence of dementia led to the same conclusions as the main analyses (Supplementary Table 1).

In preliminary life course analyses, there was an association between higher BMI and progressively lower risk of dementia-related death the later in life BMI was measured (**Table 3**). The age-adjusted HR of being at least overweight compared to not as measured at baseline was 1.33 (95% CI 0.90, 1.96). In contrast, the HR of dementia-related death for being at least overweight in 1993 (mean age 71.1 years) compared to not being was 0.36 (95% CI 0.18, 0.73). There was attrition during follow up but the age-adjusted HR for BMI measured at baseline in the subsample who had BMI reported in 1993 (mean age 18.3 years) did not show a similarly reduced hazard ratio (HR 2.78, 95% CI 1.08, 7.15) suggesting that this differential association depending on when BMI was recorded does not result from missing data. The association between BMI and cardiovascular disease deaths was not substantially altered by the time period when BMI was measured, apart from a null association between BMI measured in 1993 with cardiovascular disease deaths.

Figure 1 shows the two groups based on BMI trajectories across the life course derived from the latent class mixed models: (1) "early decliners" whose average BMI increased to a plateau of almost 25 between the ages of 30 and 50 years and then declined steadily thereafter; and (2) "late decliners" whose average BMI followed a similar pattern until the age of 50 but then

continued to increase until the age of approximately 70 years when it began to decline. Of all Harvard alumni, 17% (N=5717) were early decliners and 83% (N=27,230) were late decliners. Models with larger numbers of groups did have lower BIC values than two groups, but the groups themselves were too small to be included in models – 1-2% of the sample – with very few dementia cases. Therefore, a pragmatic decision was made to use two groups. **Table 4** shows the results of Cox models comparing early decliners with late decliners. Early decliners were at a 33% increased risk of dementia-related death than late decliners (age-adjusted HR 1.33, 95% CI 1.05, 1.68) and none of the covariates explained this increased risk. The multivariable-adjusted HR of dementia-related death for early decliners was 1.57 (95% CI 1.14, 2.17).

As expected, all of the risk factors were associated with cardiovascular disease death five decades later apart from low levels of physical activity (<5 hours per week) which was associated with a decreased risk of cardiovascular disease (HR, 95% CI 0.86, 0.80, 0.91). However, data on physical activity were missing in approximately a third of participants. Membership of the early decliners group was consistently associated with approximately 30% reduction in the risk of cardiovascular disease death.

DISCUSSION

We found no association between BMI (and a range of other cardiovascular disease risk factors) measured in early life and subsequent dementia-related deaths with long-term mortality follow-up in men. Our finding of expected associations between cardiovascular risk factors and cardiovascular disease death provides some confidence in our conclusions regarding their likely lack of effect on dementia-related death. Exploring trajectories of BMI over the adult life course suggested that early decline in BMI (after the age of 50 years rather than after 70 years) was associated with an increased risk of dementia-related death.

To our knowledge, there are no other studies published which have investigated early life BMI in relation to dementia. A recent paper examining trajectories of BMI over 28 years reported

182 that obesity in midlife was associated with dementia risk and individuals who went on to develop
183 dementia declined in BMI in the preclinical period prior to diagnosis.[12] Our findings that early
184 decliners are more likely to die from dementia echoes these results. However, the Whitehall II
185 cohort was slightly more overweight than our Harvard Alumni Health Study cohort – e.g., BMI
186 26.1 (SD 4.2) compared to 24.3 (2.6) at approximately 50 years old (follow up waves in 1962/66
187 where mean [SD] age in those who had BMI measured was 50.7 [10.8]). Furthermore, our finding
188 that BMI measured later in life – and therefore associated with shorter follow up – was seen to be
189 increasingly protective of dementia is similar to the findings already mentioned from an
190 individual-participant meta-analysis of 1.3 million adults.[13] The mean age at which BMI was
191 recorded across all studies included in this meta-analysis was 45.8 (SD 3.4; range 36.3-55.2). This
192 confirms that the more sophisticated trajectory analyses carried out here including more of the
193 life course are necessary to analyse BMI data in relation to dementia adequately.
194 The large sample size and long duration of follow up in the present study gives us adequate
195 power to identify associations, if they existed. Of course, the study is not without its limitations.
196 Most risk factors were measured only once and risk factor levels will have changed in the
197 succeeding decades. Some – for example dietary factors and alcohol consumption – were either
198 not available or not measured in sufficient numbers of participants to be usable. BMI was
199 recorded at multiple time points throughout the period of follow up which gives a much richer
200 picture of each individual's exposure to this factor. There were missing data at each wave
201 (response proportions were 62-68% in the follow up waves[16]) which has the potential to bias our
202 findings through attrition and self-selection, but not to any greater extent than comparable
203 studies. However, such detailed data are scarce, particularly covering the early part of life in
204 combination with sufficient follow up time to identify the presence of dementia in later life. We
205 are unable to infer the reason for changes in BMI, perhaps most importantly distinguishing
206 individuals who lost weight intentionally which must limit the conclusions we can draw from our
207 observations. Moreover, we analysed data on men only, so the extent to which our results may be

generalized to women is unclear. Since they were recruited from a Higher Education Institution, participants had high educational attainment by definition. In 1940, 4.6% of the American population held an undergraduate degree by age 25 years – the proportion for 2016 was 33.4% (US Census data: https://www.census.gov/data/tables/2016/demo/education-attainment/cps-detailed-tables.html). Finally, hardly any individuals were initially obese – in contrast to contemporary populations – which excluded the possibility of investigating this category separately from those who were at least overweight.

We used death certification to identify dementia cases. Taking this approach raises concerns that a proportion of people who developed dementia are missed by using solely this approach. However, in support of this approach, findings from two studies suggest that using data on dementia death captures the majority of dementia cases. In a UK study, for instance, 71.5% of people with a robust diagnosis of dementia confirmed by rigorous assessment by a multi-disciplinary team at a tertiary-referral memory clinic who subsequently died during a decade of follow up had the condition correctly recorded on their death certificates.[21] There were also no differences in area-level deprivation or premorbid IQ (estimated by the National Adult Reading Test) at baseline between people who had dementia correctly recorded and those who did not (unpublished results available from the author on request) suggesting that there was no bias in reporting related to socioeconomic position or intelligence. In a separate population-based study, also in the UK, multiple sources were used to identify dementia occurrence in participants. Of those with dementia, 83% would have been identified had death certificates been the only source of information used.[22] On the other hand, clinical practice and coding conventions will have changed during the substantial period of follow up and there will have been variation in the extent of dementia identification in different areas as well as over time but it is unclear what impact, if any, this would have on our results. Furthermore, no fine-grained identification of dementia sub-types (e.g. Alzheimer's dementia, vascular dementia, Dementia with Lewy bodies) is possible to any extent with these data. In summary, while using death certification to identify

people with dementia is a limitation, it is likely to identify the majority of cases – particularly when any mention rather than the underlying cause is used (the immediate cause of death in people with dementia is often something else) – and, importantly for epidemiological purposes, is likely to be correct when it is recorded.

The Harvard Alumni Health Study population has previously been noted to be healthier than the general population.[23] Lower levels of dementia in this population may at least partially reflect study members' higher than average educational attainment and socioeconomic position. This observation is unlikely to impact on risk factor–disease associations, however. for instance, findings from other cohort studies based on select samples with a relatively low prevalence of a risk factor and/or incidence of a particular disease have been shown to find similar risk factor-disease associations to general population samples.[24]

In conclusion, we have shown that, in a population sufficiently young to be likely to be free of the earliest stages of dementia, there was no long-term association between BMI – or other cardiovascular disease risk factors – and dementia-related death. This suggests that the links between cardiovascular disease and dementia are potentially more complex than has been hitherto considered. Our BMI trajectory models suggests that change in BMI across the life course is relevant to dementia risk, specifically that early decline in BMI – which may partially be due to preclinical dementia – is associated with an increased risk of dementia-related death. More detailed life course studies are required to shed light on the pathogenesis of this important condition with the ultimate aim of identifying new factors in the primary prevention of dementia.

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Authors' contributions: GDB generated the idea for the study; GDB and TCR prepared the manuscript; IML and HDS were responsible for the follow-up of the study participants; TCR conducted the analyses with guidance in latent class modelling from GMT; and all authors revised the manuscript for intellectual content.

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TABLE 1: Baseline characteristics of study participants

Variable			**N**
Age (years)	mean (sd)	18.4 (1.8)	33,083
Height (cm)	mean (sd)	176.3 (7.1)	32,741
Body mass index (kg/m^2)	mean (sd)	21.6 (2.6)	32,692
Overweight or obese[a]	N (%)	2993 (9.2)	32,692
Pulse rate ≥75 beats per minute	N (%)	20,109 (62.2)	32,368
Systolic blood pressure (mmHg)	mean (sd)	120.4 (13.1)	32,256
Diastolic blood pressure (mmHg)	mean (sd)	73.9 (10.2)	32,198
Five or more hours physical activity per week	N (%)	10,533 (48.2)	21,853
Current smoker	N (%)	10,156 (36.3)	27,964

[a] Body mass index >25 kg/m^2

TABLE 2. Age-adjusted hazard ratios (HRs) (95% confidence intervals (CIs)) for the association between baseline cardiovascular disease risk factors measured at mean age 18.4 years and deaths related to dementia and cardiovascular disease: longitudinal study of 33,083 male Harvard alumni over five decades

	N	Dementia deaths	HR (95% CI)	P-value	CVD deaths	HR (95% CI)	P-value
Height[a]	32,741	385	0.94 (0.85, 1.04)	0.20	6515	1.08 (1.05, 1.10)	<0.001
Body mass index[a]	32,692	385	1.02 (0.91, 1.14)	0.77	6508	1.07 (1.05, 1.10)	<0.001
Overweight or obese[b]	32,692	385	1.33 (0.90, 1.96)	0.16	6508	1.27 (1.17, 1.39)	<0.001
Pulse rate ≥75 vs <75 bpm	32,368	378	1.03 (0.83, 1.29)	0.78	6409	1.15 (1.09, 1.21)	<0.001
Systolic blood pressure[a]	32,256	373	1.00 (0.91, 1.11)	0.99	6338	1.13 (1.10, 1.16)	<0.001
Diastolic blood pressure[a]	32,198	372	1.02 (0.93, 1.13)	0.67	6319	1.14 (1.11, 1.17)	<0.001
<5 hours physical activity per week[c]	21,853	211	0.93 (0.70, 1.23)	0.59	3801	0.86 (0.80, 0.91)	<0.001
Current smoker[d]	27,964	319	1.02 (0.80, 1.30)	0.88	5546	1.14 (1.07, 1.20)	<0.001

[a] Hazard ratio per standard deviation disadvantage (1 SD: height 7.1cm; BMI 2.6kg/m^2; systolic BP 13.1mmHg; diastolic BP 10.2 mmHg)

[b] BMI >25kg/m^2 compared to BMI ≤25kg/m^2

[c] compared to five or more hours of physical activity per week

[d] compared to current non-smoker

TABLE 3. Age-adjusted hazard ratios with accompanying 95% confidence intervals for the association between body mass index measured on multiple occasions and deaths related to dementia and cardiovascular disease: longitudinal study of 33,083 male Harvard alumni over five decades

	Mean (SD) age	% overweight or obese	N	Dementia deaths	HR[b] (95% CI)	P-value	CVD deaths	HR (95% CI)	P-value
Body Mass Index - hazard ratio per standard deviation (2.6kg/m²) disadvantage									
Baseline	18.4 (1.8)	9.1	32,692	385	1.02 (0.91, 1.14)	0.77	6508	1.07 (1.05, 1.10)	<0.001
1962/6	50.7 (10.8)	38.0	19,143	283	0.85 (0.75, 0.96)	0.010	3459	1.16 (1.13, 1.20)	<0.001
1977	58.6 (9.1)	38.5	16,136	249	0.82 (0.72, 0.94)	0.005	2498	1.19 (1.14, 1.24)	<0.001
1988	67.5 (8.0)	42.5	11,253	103	0.72 (0.57, 0.90)	0.003	1016	1.15 (1.08, 1.23)	<0.001
1993	71.1 (7.3)	55.5	10,562	40	0.59 (0.41, 0.85)	0.004	540	0.98 (0.90, 1.08)	0.71
Baseline (1993 subsample)[a]	18.3 (1.8)		10,464	40	1.11 (0.82, 1.50)	0.49	537	1.15 (1.06, 1.25)	<0.001
Overweight – hazard ratio for BMI >25kg/m² compared to BMI ≤25kg/m²									
Baseline	18.4 (1.8)	9.1	32,692	385	1.33 (0.90, 1.96)	0.16	6508	1.27 (1.17, 1.39)	<0.001
1962/6	50.7 (10.8)	38.0	19,143	283	0.78 (0.61, 1.00)	0.049	3459	1.25 (1.17, 1.34)	<0.001
1977	58.6 (9.1)	38.5	16,222	250	0.65 (0.49, 0.86)	0.003	2298	1.29 (1.19, 1.40)	<0.001
1988	67.5 (8.0)	42.5	11,253	103	0.57 (0.36, 0.91)	0.018	1016	1.25 (1.10, 1.41)	<0.001
1993	71.1 (7.3)	55.5	10,562	40	0.36 (0.18, 0.73)	0.004	540	0.92 (0.77, 1.09)	0.31
Baseline (1993 subsample)[a]	18.3 (1.8)		10,464	40	2.78 (1.08, 7.15)	0.034	537	1.88 (1.42, 2.50)	<0.001

[a] HR for baseline BMI in relation to outcomes but only in sub-sample who had BMI recorded in 1993; 98 individuals had missing BMI at baseline but BMI recorded in 1993

[b] HRs are adjusted for age at the time BMI was measured

HR = hazard ratio
CI = confidence interval

TABLE 4. Age-adjusted hazard ratios with accompanying 95% confidence intervals for the association between latent groups derived from life course body mass index trajectory (early decliners and late decliners) and deaths related to dementia and cardiovascular disease: longitudinal study of 33,083 male Harvard alumni over five decades

	N	Dementia deaths	HR[f] (95% CI)	P-value	CVD deaths	HR (95% CI)	P-value
Early decliners	32,947	389	1.33 (1.05, 1.68)	0.016	6568	0.69 (0.64, 0.73)	<0.001
+ pulse rate	32,253	377	1.37 (1.08, 1.73)	0.0098	6382	0.69 (0.64, 0.74)	<0.001
+ systolic and diastolic blood pressure	32,089	371	1.31 (1.03, 1.67)	0.0025	6298	0.69 (0.65, 0.74)	<0.001
+ activity	21,779	210	1.55 (1.14, 2.11)	0.0049	3783	0.72 (0.65, 0.78)	<0.001
+ smoker	27,866	318	1.53 (1.19, 1.97)	<0.001	5521	0.71 (0.66, 0.77)	<0.001
Multivariable[a]	20,433	189	1.57 (1.14, 2.17)	0.0058	3436	0.73 (0.66, 0.80)	<0.001
Non-missing datasets							
Early decliners (pulse)[b]	32,253	377	1.37 (1.08, 1.73)	0.0098	6382	0.69 (0.64, 0.74)	<0.001
Early decliners (blood pressure)[c]	32,089	371	1.31 (1.03, 1.67)	0.026	6298	0.69 (0.64, 0.74)	<0.001
Early decliners (activity)[d]	21,779	210	1.55 (1.14, 2.11)	0.0049	3783	0.71 (0.65, 0.78)	<0.001
Early decliners (smoker)[e]	27,866	318	1.53 (1.19, 1.97)	<0.001	5521	0.71 (0.66, 0.77)	<0.001

[a] Adjusted for all variables in the table

[b-e] Age-adjusted (age at baseline) HRs for group 1 membership compared to group 2 in a dataset with no missing data for:

[b] pulse rate

[c] systolic and diastolic blood pressure

[d] activity level

[e] smoking

[f] HRs are for the early decliners group compared to the late decliners group adjusted for age at baseline

HR = hazard ratio
CI = confidence interval

Figure 1. Latent class groups (early decliners [N=5717] and late decliners [N=27,230]) derived from life course body mass index trajectories: longitudinal study of 33,083 male Harvard alumni over five decades

SUPPLEMENTARY TABLE 1. Age-adjusted hazard ratios (HRs) (95% confidence intervals (CIs)) for the association between baseline cardiovascular disease risk factors measured at mean age 18.4 years and deaths related to dementia (with no CVD) and cardiovascular disease (whether or not dementia was recorded): longitudinal study of 33,083 male Harvard alumni over five decades

	N	Dementia deaths (no CVD)	HR (95% CI)	CVD deaths (all)	HR (95% CI)
Height[a]	32,741	283	0.92 (0.82, 1.04)	6617	1.07 (1.05, 1.10)
Body mass index[a]	32,692	283	0.94 (0.83, 1.08)	6610	1.07 (1.05, 1.10)
Overweight or obese[b]	32,692	283	0.97 (0.57, 1.63)	6610	1.29 (1.18, 1.40)
Pulse rate ≥75 vs <75 bpm	32,368	276	0.94 (0.72, 1.21)	6511	1.15 (1.09, 1.22)
Systolic blood pressure[a]	32,256	276	0.97 (0.86, 1.09)	6435	1.13 (1.10, 1.16)
Diastolic blood pressure[a]	32,198	275	0.97 (0.86, 1.08)	6416	1.14 (1.12, 1.17)
<5h physical activity per week[c]	21,853	154	0.93 (0.67, 1.30)	3858	0.86 (0.80, 0.92)
Current smoker[d]	27,964	236	1.15 (0.87, 1.52)	5629	1.13 (1.07, 1.19)

[a] Hazard ratio per standard deviation disadvantage (1 SD: height 7.1cm; BMI 2.6kg/m^2; systolic BP 13.1mmHg; diastolic BP 10.2 mmHg)

[b] BMI >25kg/m^2 compared to BMI ≤25kg/m^2

[c] compared to five or more hours of physical activity per week

[d] compared to current non-smoker