Adiposity in middle and old age and risk of death from dementia: 40-year follow-up of 19,000 men in the Whitehall study

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Dementia , Obesity , BMI , Whitehall, Older people.

Keypoints:

- Loss of weight and BMI is associated with increased risk of dementia
- The association between BMI and dementia is stronger in old age compared to middle age
- This study casts doubt on previous suggestions that obesity protects against dementia

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Abstract

Aims and objectives

To examine the hypothesis that obesity is protective for dementia, we compared the associations of death from dementia with body weight and body mass index (BMI) in both middle and old age.

Design: Height and weight were measured in a prospective study of 19,019 middle aged men in the Whitehall study in 1967-1970 and in 6158 surviving participants at resurvey in 1997. Cox regression was used to examine the associations of death from dementia over a 40-year period with weight or BMI measured by health professionals in middle and old age adjusting for age, smoking habits, employment grade and marital status.

Setting: Central government employees in London, England

Main outcomes measure: Death due to dementia in 320 participants

Results: Body weight measured in middle age was weakly inversely associated with death from dementia (hazard ratio 0.98 [95%CI: 0.97 – 0.99] per kg), but neither height nor BMI were related to risk of dementia. In contrast, body weight in old age was more strongly inversely related to deaths from dementia (0.96; [0.95 – 0.98] per kg) as was BMI (0.92 [0.86 – 0.97] per kg/m^2). Weight loss over the 30 years between baseline and resurvey was associated with a higher risk of death from dementia, with an adjusted HR per kg/30 years of 1.04 [95%CI: 1.02-1.08] and the association with loss of BMI was even stronger (adjusted HR of 1.10 [1.03-1.19]) per kg/m^2 decrease).

Conclusions

The stronger associations of deaths from dementia with BMI in old age, compared with middle age, together with strong positive associations of loss of BMI or body weight between middle and old age casts doubt on previous suggestions that obesity protects against death from dementia.

Introduction

Dementia is a growing public health problem worldwide. Longer life expectancy and improvements in medical care have resulted in an increasing proportion of older people in the population and a higher prevalence of dementia.[1] The Global Burden of Disease Project estimated that dementia contributed 6.8 million years lived with disability in 2015 [1]. In the UK, it has been estimated that about 850,000 people currently suffer from dementia, but this is expected to increase to one million by 2025 and to two million by 2051 [2]. Traditionally, mid-life obesity has been linked with higher risks of dementia, but these results have been challenged by a 2-year follow-up cohort study of 2 million people which demonstrated lower risks of dementia in obese people [3]. It is unclear whether the hypothesis that obesity is protective for dementia is causal or an artefact of reverse causality. As dementia is a chronic progressive neurodegenerative disorder, where the pathological changes typically precede the onset of clinical symptoms by a decade or more [4], studies with serial measures of adiposity and prolonged follow-up may be able to assess the associations of adiposity with dementia and assess the extent to which such associations are causal or reflect the effects of reverse causality [5].

Data and Methods

The Whitehall I study is a prospective cohort study of central government employees in London (civil servants) designed to assess the relevance of cardiovascular risk factors and of employment grade with cardiovascular and other causes of death in the UK [6]. At baseline (1967-1970), 19,019 male civil servants aged between 40 and 69 years were invited to participate in the study [7]. Men were invited to complete a questionnaire, which included questions about their health and lifestyle, and had a medical examination in which blood pressure height and weight were measured. A postal resurvey in 1997 of the surviving participants in the cohort achieved an overall response rate of 82% for questionnaires and 72% for repeat measures of height and weight recorded by their GP (See Appendix 2 in the supplementary data on the journal website *http://www.ageing.oxfordjournals.org*) [8].

Follow-up to 30th September 2012 for mortality and vital status was conducted by the National Health Service Central Registry (NHS Digital), which also provided dates and underlying causes of death. The following ICD codes were used to define deaths from dementia: from ICD 8 and 9, codes 290-292, 294, 331, 333, 797 and 046 and from ICD 10, codes F00-F03, G30 and G31.

Analyses examined the associations of anthropometric measures (height, weight and body mass index [BMI]) recorded at baseline in 1967-1970 with death from dementia over a 40-

year follow-up period. This allowed assessment of whether measurements recorded in middle age were predictive of death from dementia. BMI was classified in two ways, using the standard WHO classification and using fifths, in order to examine the association with death across the distribution of BMI. A re-survey of surviving participants in old age in 1997 recorded repeat measurements of height, weight and BMI. The analyses of differences in weight and BMI between baseline and resurvey were used to estimate risks of death from dementia associated with changes in BMI and weight.

Cox regression was used to estimate hazard ratios for death from dementia. For the baseline analyses, follow-up was recorded from entry into the study, but for the resurvey analyses, follow-up was recorded from the date of resurvey questionnaire. Individuals were excluded if the cause of death was missing (n=43) or they were lost to follow-up (n=493).

Multivariate models were constructed, initially to adjust for age at the start of follow-up and calendar period of entry to risk, and subsequently for smoking, employment grade and marital status. Effect modification was tested for in each model using likelihood ratio tests.

Sensitivity analyses included assessment of associations of baseline weight and of BMI with death from dementia in the subset of men who participated in the resurvey. One of the primary objectives of the study was to assess the extent to which behaviour and dietary changes caused by developing dementia in the years before death might lead on to changes in body weight. Additional analyses excluded those deaths occurring within 5 years of resurvey to minimise reverse causality [9, 10]. Further, sensitivity analyses examined whether the associations persisted after censoring the follow-up at age 90 years to take account of inaccuracies in the causes of death in extreme old age.

This study was approved by the London School of Hygiene and Tropical Medicine ethics board with reference number 10729.

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Results

Descriptive characteristics

The distribution of participants at baseline and resurvey and risk of death from dementia by adiposity measures are shown in Table 1. Among 19,019 participants at baseline, there were 320 deaths due to dementia. Among the subset of 6158 surviving participants in the resurvey, there were 161 deaths due to dementia. The mean time from resurvey to death was 7.1 years. The mean age at resurvey was 77.0, and the mean weight and BMI were 75.6kg and 25.1kg/m^2 respectively. Complete data on socio-demographic confounders were available on almost all participants at both baseline and resurvey (see Supplementary table 1)

Multivariate analyses

All measures of adiposity were inversely associated with death from dementia in older ages (Figure 2, Appendix 3 and Appendix 4), while only weight was significant at middle age. The associations were slightly more extreme after adjustment for covariates, including smoking, employment grade and marital status. Analysis of change between baseline and resurvey indicated that the decline in both weight and BMI were both associated with higher risks of death from dementia after adjustment for confounders (Table 2, Appendix 5).

In a sensitivity analysis, in the subset of participants surviving to resurvey, the associations of anthropometric variables at baseline with mortality following resurvey (Appendix 6) were weaker than the association with anthropometric variables measured at resurvey (Appendix 4). This is consistent with some of the effect seen in Appendix 4being due to reverse causality as the measurements recorded at baseline, 30-40 years before death, are very unlikely to be a consequence of behaviours induced by dementia.

A further sensitivity analysis (Appendix 7) excluded any participants who died within the first 5 years following the resurvey [9, 10]. While this analysis had reduced power, due to there now being only 106 deaths due to dementia, the association with risk of death from dementia was still strong, with a similar magnitude and direction of association.

A final sensitivity analysis censored follow-up once a study subject reached the age of 90 years. This showed similar associations as in the uncensored analyses (Appendix 8).

Table 1. Distribution of anthropometric variables and deaths from dementia in middle and old age.

Anthropometric variables	Baseline participants			Resurvey participants		
	Number of individuals	Years of follow-up (1000s)	Deaths from dementia	Number of individuals	Years of follow-up (1000s)	Deaths from dementia
Height (cm)	-		-	-		-
<170	3267	78.0	61	2169	83.4	76
170-174.9	4805	125.7	81	1771	68.9	44
175-179.9	5576	152.2	98	1420	54.8	27
≥180	5368	151.8	80	752	29.0	12
Missing	3		0	46		2
Weight (kg)	-			-		-
<65	2506	62.6	49	1055	40.0	42
65-74.9	6256	169.1	117	2129	82.8	70
75-84.9	6599	181.1	115	1873	73.4	31
≥85	3657	95.1	39	1022	39.9	15
Missing	1		0	79		3
Obesity based on BMI (kg/m^2)						-
Underweight (<18.5)	239	5.4	6	80	2.9	5
Normal weight (18.5-24.9)	10201	281.7	185	3054	117.5	92
Overweight (25.0-29.9)	7764	202.2	121	2494	97.2	46
Obese (≥30.0)	812	18.4	8	441	17.0	14
Missing	3		0	89		4
BMI (kg/m^2)						
<22	3255	86.4	60	950	35.5	32
22-23.9	4446	124.6	83	1354	52.7	41
24-25.4	4092	112.1	74	1173	45.6	35
25.5-26.9	3366	89.7	54	1042	40.5	19
≥27	3857	95.1	49	1550	60.2	30
Missing	3		0	89		4
Total (per category)	19019		320	6158		161

Figure 1: HR (95% CI) of death from dementia associated with weight or BMI in middle age and in old age

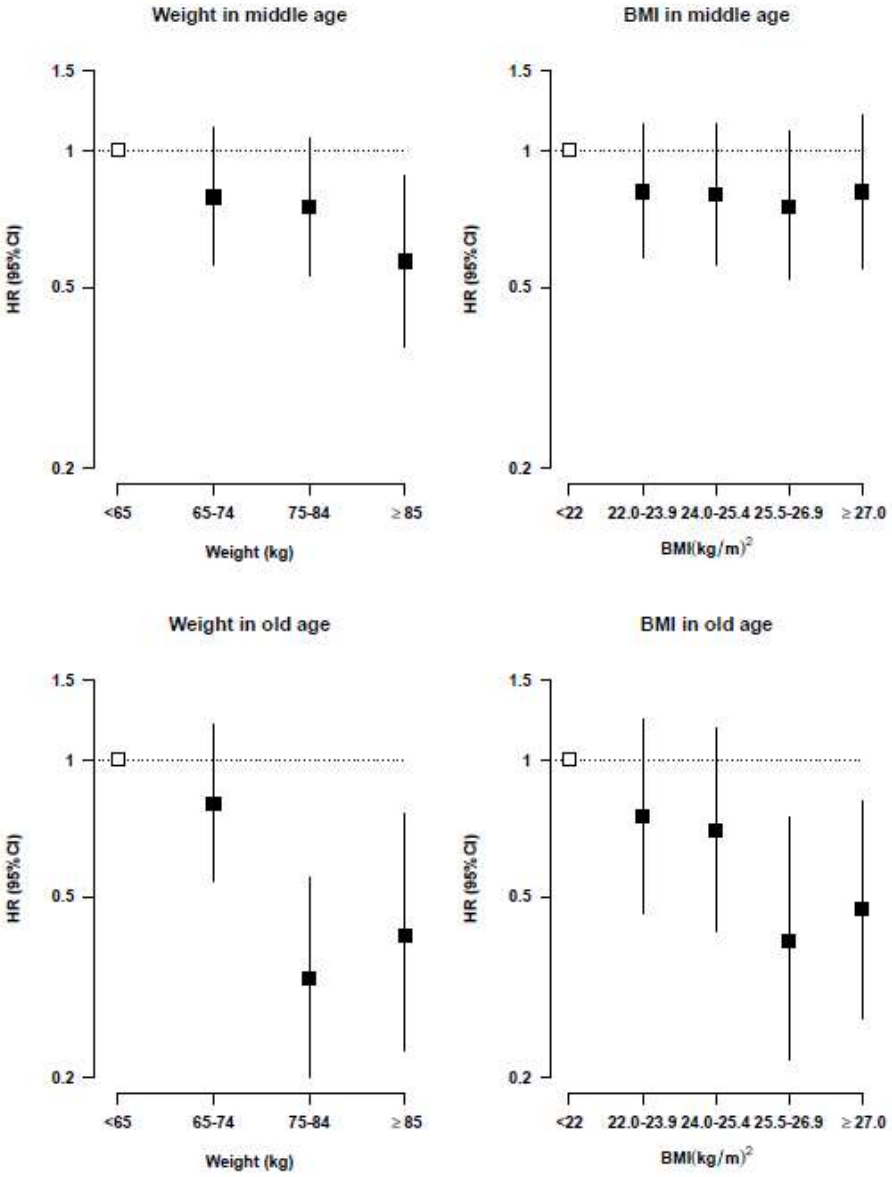

Table 2. Association of change in anthropometric measurements between baseline and resurvey with mortality from dementia

Exposure variable	Model 1 - Hazard ratio (95% CI)* adjusted for age and period	Model 2 - Hazard ratio (95% CI)** additional adjustment for employment grade, smoking and marital status
Decrease in height (cm)		
<2.5	1	1
2.5 -4.9	1.52 (1.03-2.24)	1.59 (1.06-2.40)
5- 7.4	1.37 (0.86-2.17)	1.28 (0.78-2.10)
≥7.5	1.92 (1.02-3.62)	1.87 (0.96-3.64)
P value for heterogeneity	0.19	0.09
Change per cm decrease	1.03 (0.98-1.09)	1.02 (0.97-1.08)
P value for linear trend	0.24	0.33
Change in weight (kg)		
>7.5	1.24 (0.68-2.27)	0.97 (0.50-1.89)
7.5-2.4	0.98 (0.58-1.67)	0.88 (0.50-1.55)
2.5- -2.4	1	1
-2.5 – 7.4	1.49 (0.97-2.27)	1.46 (0.93-2.29)
≥-7.5	1.73 (1.08-2.76)	1.90 (1.17-2.10)
P value for heterogeneity	0.53	0.51
Change per kg loss	1.03 (1.01-1.05)	1.04 (1.02-1.08)
P value for linear trend	0.02	<0.001
Change in BMI (kg/m^2)		
>2.5	0.96 (0.60-1.52)	0.70 (0.41-1.18)
2.5-0.9	0.96 (0.62-1.48)	0.94 (0.60-1.48)
1 - -0.9	1	1
-1 - -2.4	1.23 (0.77-1.95)	1.29 (0.80-2.10)
≥-2.5	1.45 (0.83 -2.51)	1.57 (0.87 -2.78)
P value for heterogeneity	0.78	0.14
Change per BMI unit loss	1.05 (0.98- 1.12)	1.10 (1.03-1.19)
P value for linear trend	0.14	0.006

All models based on same subset of 6158 individuals with 161 deaths
* Model 1 adjusts for age at resurvey and period.
**Model 2 adjusts for age at resurvey, period and employment grade, marital status and smoking habit at resurvey.

Discussion

The present study demonstrated that adiposity in old age was strongly associated with a lower risk of death from dementia. However, our study casts further doubt on whether this should be interpreted as indicating a protective role for obesity as has been previously suggested. Our key finding of a higher risk of death from dementia associated with losses of both weight and BMI between middle and old age over a 30-year follow-up period suggests that reverse causality is likely to account for the inverse association observed.

The findings of the present study are consistent with previous reports of decline in weight and BMI in later life reflecting the consequences of dementia occurring for several decades before diagnosis or expected onset of symptoms of dementia [11-13]. These effects may reflect changes in appetite or other aspects of behaviour that result in reduced energy intake. Thus, claims from previous studies that underweight increases the risk of dementia may be an artefact of the effects of reverse causality.

Strengths and limitations

The strengths of this study are its prospective design, large sample size and that the exposure measurements were recorded at two points in time, allowing changes in these to be calculated. The present study is one of a few studies that has measured adiposity in both middle age and in old age, and the changes between them, in the same participants rather than across multiple participants.

One of the major limitations of the present study was the use of death from dementia rather than incident cases of dementia. Thus, our conclusions can only be applied to mortality from dementia rather than the incidence of dementia. In addition, as only underlying cause of death was available, individuals where dementia is mentioned elsewhere on the death certificate will not be counted as dementia deaths. This means that the study has a smaller number of events to analyse than would be the case if multi-cause data was available. This will have reduced the total number of events detected, lowering the power of the study, but is unlikely to cause bias to the estimated point estimates, as there is not a plausible reason for diagnosis of dementia in life and at death to be differentially associated with BMI, and we have found no evidence to suggest this. A second possibility of bias is that older people are more likely to die from more clear causes of death, such as myocardial infarction, thus displacing dementia as the underlying cause of death. Evidence against this possibility is seen in two of the most recent and largest studies, [3] [11] and show a higher BMI in old age is associated with lower risk of dementia even though they use used dementia diagnosis in life as the primary outcome. There is the possibility the underreporting of dementia as a

cause of death could lead to reporting bias, if such underreporting on death certificates varied by, for example, age or place of death.

Loss to follow up is unlikely to be a source of bias as the exit from risk in the study was death. The UK has a high-quality system for collection of the vital statistics, and less than 3.5% of participants were lost to follow up. While several of the most common confounders are adjusted for, there is the possibility of residual confounding, by failure to control for other variables. There is the potential for confounding from socio-economic position, education level and physical activity. Employment grade and difficulty with undertaking activities of daily living act as partial surrogates for these factors but there is certainly some residual confounding which would cause overestimation of the true effect. However, as noted above, adjustment for these confounders either had minimal effect, or in the case of change in weight and BMI, strengthened the effect.

The study population was restricted to men, the vast majority of whom are white and born in the UK. Since there are anthropomorphic differences between men and women, associations with dementia may differ. Likewise, the incidence of dementia varies by gender [14,15], and women are known to have a different distribution of body fat reflecting differences in hormone levels [16,17]. If such hormones also influence the development of dementia, then it is possible that the associations of BMI with death from dementia could differ between men and women.

The strong dose-response of greater loss in BMI and weight between baseline and resurvey resulting in greater risk of death from dementia argues that adiposity in old age is unlikely to be protective for dementia (Supplementary Tables 1-4), but instead indicates that incipient dementia can lead to weight loss. It has been shown that changes in the brain occur up to 20 years before a diagnosis of dementia is made, and weight loss could reflect effects in the pre-clinical period due to changes in eating habits [18]. Moreover, two of the observed associations are consistent with the effects of reverse causality.

Comparison with other studies

A recent meta-analysis has demonstrated an association of midlife obesity and dementia, but the findings about any association of midlife underweight with dementia were inconclusive [19]. A second meta-analysis showed that an increasing BMI appeared protective when followed up at 10 years, but harmful when followed up after over 20 years, leading to a conclusion that reverse causality may be important [20].

Examining the studies included in these meta-analyses and in subsequent studies, illustrates the difficulty in attempting to pool the results of higher BMI and associations with dementia.

Most of the literature has been based on cross-sectional studies, has examined anthropometric measurements at a single point in time and, has not looked at the changes in measurements over time. There is a lack of consistency in results about the effects on risk of dementia of high BMI, both in older age and at mid-life. Study results include positive associations between increasing BMI and dementia [12], to a U-shaped relationship with both low and high BMI being associated with increased risk of dementia [21], and more complicated relationships where high BMI at mid-life appears to be a risk factor, while in old age it appears to be protective [22,23]. A prospective cohort study of weight in university students who were followed-up for 50 years reported no association of overweight in early adult life with death from dementia [24]. One other study examined change in weight and its association with dementia, and reported a significant association, although it only looked at weight rather than BMI and weight and had an older cohort with a shorter follow up [25]. Studies that examine changes in weight or BMI over time appeared to indicate that those whose measurements decrease the most over time have the highest risks of dementia [26, 27].

The results of our study are consistent with a large retrospective cohort study of 2 million people[3] that reported that increased BMI at older ages was associated with lower risk of dementia. However, contrary to the authors of this report, we have found evidence that this is most likely to be due to reverse causality rather than being a true protective effect.

Generally there is a consensus that a low BMI was associated with an increased risk of developing dementia both when measured in early life and when measured in cases with probable Alzheimer's disease [28]. In one large study across 8 countries, a weight loss of over 10 lbs in the last 3 years was associated with an increased risk of dementia, however this used cross-sectional surveys of the general population spaced 7 years apart, rather than following up a defined cohort [29]. The Whitehall II study [11] also found that being underweight in middle age was associated with an increased risk of dementia.

Studies looking at other anthropometric measurements are rare, but generally an increase in adiposity measure results are an increased risk of dementia [21]. Finally, other studies suggest it may be the type of obesity that is important, with central (or abdominal) obesity being the risk factor, independent of BMI [30]. What this study adds to the body of literature is the prolonged follow-up time with two measurements recorded on the same individuals. This study allows change in weight or BMI to be assessed as exposure variables and their association with subsequent dementia described.

Implications and further research opportunities

The increased risk of death from dementia associated with low BMI or weight in later life, or from the loss of weight or BMI through mid-life has implications for public health strategies for prevention of dementia. Regular weight checks could provide an easily measured marker for risk of frailty and subsequent detection of dementia. Whether this could allow early interventions to improve dementia outcomes could also merit further investigation. However, although these associations could point to a simple and cost-effective way to identify those at risk with regular weight checks using electronic records, the current evidence indicates weak associations at baseline, so the predictive value of such checks is likely to be low. Moreover, the strong likelihood of reverse causality argues against the causal relevance of any such checks on body weight. Overall, the discrepant associations of dementia with BMI recorded in middle and old age, together with strong positive associations with loss in BMI between middle and old age casts doubt on previous suggestions that obesity protects against dementia.

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