

# Obesity and Longer Term Risks of Dementia in 65–74 Year Olds

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## Abstract

**Background:** overweight or obesity at ages <65 years associates with increased dementia incidence, but at ≥65 years estimates are paradoxical. Weight loss before dementia diagnosis, plus smoking and diseases causing weight loss may confound associations.

**Objective:** to estimate weight loss before dementia diagnosis, plus short and longer-term body mass index associations with incident dementia in 65–74 year olds within primary care populations in England.

**Methods:** we studied dementia diagnosis free subjects: 257,523 non-smokers without baseline cancer, heart failure or multi-morbidity (group A) plus 161,927 with these confounders (group B), followed ≤14.9 years. Competing hazard models accounted for mortality.

**Results:** in group A, 9,774 were diagnosed with dementia and in those with repeat weight measures, 54% lost ≥2.5 kg during 10 years pre-diagnosis. During <10 years obesity (≥30.0 kg/m<sup>2</sup>) or overweight (25.0 to <30.0) were inversely associated with incident dementia (versus 22.5 to <25.0). However, from 10 to 14.9 years, obesity was associated with increased dementia incidence (hazard ratio [HR] 1.17; 95% CI: 1.03–1.32). Overweight protective associations disappeared in longer-term analyses (HR, 1.01; 95% CI: 0.90–1.13). In group B, (*n* = 6,070 with incident dementia), obesity was associated with lower dementia risks in the short and longer-term.

**Conclusions:** in 65–74 year olds (free of smoking, cancer, heart failure or multi-morbidity at baseline) obesity associates with higher longer-term incidence of dementia. Paradoxical associations were present short-term and in those with likely confounders. Reports of protective effects of obesity or overweight on dementia risk in older groups may reflect biases, especially weight loss before dementia diagnosis.

## Keywords

obesity, dementia, epidemiology, paradox, older people

## Key points

- In older frailty-free groups, are overweight or obesity protective for later development of dementia?
- Using weight measures from primary care records, weight loss was common during the 10 years before dementia diagnosis.
- Longer-term (10–14.9 years from baseline), obesity increased the risk of incident dementia.
- Claimed benefit of being obese to avoid dementia at ages 65–74 years is likely an artefact of pre-diagnosis weight loss.
- Avoiding obesity may contribute to dementia prevention, even in older groups.

## Introduction

Dementia is a major health challenge and in the absence of a treatment, there is great interest in modifiable risk factors. For middle aged adults, most studies report increased dementia risk for body mass index (BMI) obese range ( $\geq 30.0$  kg/m<sup>2</sup>) subjects versus the normal range (18.5 to  $< 25.0$ ) [1–3]. However, an electronic health records analysis (ages  $\geq 40$  years) cast doubt on this association, reporting reduced dementia risks in overweight subjects versus BMI 20.0 to  $< 25.0$  [4]. However, a recent meta-analysis including this above study showed midlife (aged 35–65 years) obesity associates with increased dementia risk [5]. For older aged adults (aged  $\geq 65$  years) and especially 65–74 year olds, obesity and dementia associations are particularly unclear [6–10].

Weight loss precedes a clinical diagnosis of dementia by at least a decade [11–13] and could obscure BMI associations. Greater weight loss in the 6 years preceding dementia diagnosis (versus those without dementia) was reported in Japanese American men [11]. Knopman *et al.* [12] found increasing weight differences in women (but not men) present for 20 years before dementia diagnosis, with e.g. 8.0 pounds median weight loss 10 years pre-diagnosis versus 2.0 pounds (median) for those without dementia, with a similar finding from LeBlanc *et al.* [13]. Thus pre-diagnosis weight loss would lower BMI, and could potentially produce ‘reverse causation biases’ in shorter-term ( $< 10$  years) estimates. Examining associations with BMI measures  $> 10$  years before outcome ascertainment is less likely to be confounded by pre-diagnosis weight loss. Furthermore, smokers have lower weight but high mortality [14], tending to die of competing causes before dementia diagnosis. Additionally, smokers have been shown to be at a higher dementia risk [15]. We also showed that weight loss is most strongly associated with cancer, heart failure and multi-morbidity in older primary care patients [16].

Overall, there are consistent BMI dementia associations for ages  $< 65$  years, but it remains unclear whether raised BMI at ages 65–74 is a risk or protective factor for dementia. Here we used the Clinical Practice Research Datalink (CPRD) linked primary and secondary care health records for complete older populations in England registered with primary care providers. We considered two groups without dementia at baseline: group A excluding suggested confounders (i.e. smoking, cancer, heart failure or multi-morbidity at baseline) and group B with these confounders. First, we estimated the prevalence of BMI categories in those in group A who developed incident dementia in each year before diagnosis. We then estimated shorter (0 to  $< 10$  years from baseline BMI measure) and longer-term (10–14.9 years) associations between BMI and dementia diagnosis in groups A and B. Using this dichotomy allows us to take into account the 10 years pre-diagnosis weight loss, and to examine the prognostic value of BMI in the longer-term.

## Methods

### Data source

The CPRD includes health records from 674 UK primary care practices [17]. Our analysis included records linked to Hospital Episode Statistics data for admissions (linkage available for English practices only) and the Office for National Statistics (ONS) death certificates (see methods Appendix 1 for further details, in the supplementary data, available in *Age and Ageing* online).

### Participants

Previously we showed that BMI records were available from 1 January 2000 for 62% of patients ( $n = 955,031$ ) in CPRD practices aged  $\geq 60$  years [16]. We excluded extreme BMI values ( $< 14.0$  and  $> 56.5$ ) ( $n = 6,431$ ) and selected individuals aged 65–74 years with at least one recorded BMI and registered with a practice from 1 January 2000 to 17 November 2014. We stratified our analysis into non-smokers without cancer, heart failure, or multi-morbidity at baseline (termed group A, to minimise confounding) and those with these confounders (termed group B), as these conditions were most closely associated with weight loss in our previous analysis [16]. Patients with 6 or more Rockwood frailty index conditions (of 36) were defined as having multi-morbidity [18], using ResearchOne Electronic Frailty Index coding rules covering diagnoses, functional impairments, health attitudes and symptoms. We excluded patients with a dementia diagnosis at baseline and patients who were missing information on smoking history, alcohol status or relative socioeconomic status (Figure Appendix 2, in the supplementary data, available in *Age and Ageing* online).

### BMI records

The earliest age within the 65–74 years range at which BMI was recorded was used as the study ‘index’ (baseline) BMI for analysis. BMI (kg/m<sup>2</sup>) was categorised following the Global BMI Mortality Collaboration groupings [19] as BMI  $< 18.5$ , 18.5 to  $< 20.0$ , 20.0 to  $< 22.5$ , 22.5 to  $< 25.0$ , 25.0 to  $< 30.0$  and  $\geq 30.0$ . The higher risk for dementia reported in the lower end of the conventional normal range (BMI 18.5 to  $< 25.0$  compared to higher BMIs), may distort estimates: we therefore adopted the Global BMI Mortality Collaboration BMI groupings [19].

### Weight change

We analysed individual subject weight change (kg) for those who had dementia diagnosed during follow-up. We subtracted the median recorded weight in the 3 years immediately before dementia diagnosis from the median weight recorded 8–10 years before diagnosis, where available.

**Covariates**

We adjusted the models for: age, gender, smoking history, alcohol intake, relative socioeconomic status and calendar year (see methods Appendix 1 for further details, in the supplementary data, available in *Age and Ageing* online).

**Outcomes**

Outcomes included incident clinically diagnosed dementia (in primary care or hospital records), and mortality (from ONS death certificate data) to 17 November 2014.

**Statistical analysis**

For patients diagnosed with dementia during follow-up, we first calculated proportions of patients in each BMI category in the years before dementia diagnosis. We then calculated the weight change, where available, for those with incident dementia in group A. We used Fine and Gray competing risks models (with all-cause mortality as the competing risk) to estimate BMI category associations with incident dementia [20]. Adjustments were for age, gender, alcohol use, smoking history, calendar year and socioeconomic status. Sensitivity analyses (i) adjusted the model for prevalent stroke or prevalent depression at baseline and (ii) excluded those with diagnosed angina, myocardial infarction or diabetes at baseline. Stata statistical software (version 14.1) was used.

**Results**

**Group A: associations in subjects without suggested confounders**

Analyses included 257,523 non-smokers, without diagnoses of cancer, dementia, heart failure or multi-morbidity, aged 65–74 years at baseline. During the ≤14.9 years of follow-up there were 9,774 incident cases of dementia and 29,466 deaths. The mean baseline BMI was 27.7 kg/m<sup>2</sup> (sd 4.9 kg/m<sup>2</sup>), and 53.4% of the sample were females (Table 1).

In the 9,774 subjects with incident dementia, we calculated the proportions of patients in each BMI category in the years before diagnosis of dementia. This showed lower obesity prevalence in those diagnosed sooner after baseline (Figure 1), with for example 15.5% of those diagnosed with dementia in the first year of follow-up being obese, compared to 23.4% for those diagnosed in the 9th year of follow-up. Underweight (BMI < 18.5) and leaner normal weights (18.5 to <20.0) showed converse changes (Figure 1). We then analysed individual subject weight change (see Methods). Records allowed weight change calculations for 4,760 (48.7%) patients with dementia and of these 67.7% lost weight with 54.0% losing ≥2.5 kg during the decade before diagnosis.

Competing risk models (accounting for mortality) were adjusted for age, gender, smoking history, alcohol intake, socioeconomic status and calendar year. From analysis baseline to <10 years of follow-up (Figure 2), both obesity and overweight had protective associations for incident

**Table 1.** Characteristics of the study sample aged 65–74 years at baseline from the CPRD

	Group A <sup>a</sup>	Group B <sup>b</sup>
<i>n</i>	257,523	161,927
Follow-up years, mean (sd)	6.2 (4.1)	5.3 (3.8)
Age years, mean (sd)	68.3 (2.9)	67.8(2.8)
Gender		
Females, <i>n</i> (%)	137,583 (53.4)	75,584 (46.7)
BMI (kg/m <sup>2</sup> ), mean (sd)	27.7 (4.9)	27.7 (5.5)
BMI (kg/m <sup>2</sup> ), <i>n</i> (%)		
BMI <18.5	2,367 (0.9)	3,626 (2.2)
BMI 18.5 to <20.0	4,553 (1.8)	4,431 (2.7)
BMI 20.0 to <22.5	22,225 (8.6)	15,646 (9.7)
BMI 22.5 to <25.0	48,577 (18.9)	27,906 (17.2)
BMI 25.0 to <30.0	109,195 (42.4)	62,633 (38.7)
BMI ≥30.0	70,606 (27.4)	47,685 (29.5)
Alcohol status, <i>n</i> (%)		
Non-drinker	38,696 (15.0)	21,775 (13.5)
Current drinker	179,839 (69.8)	101,136 (62.5)
Ex drinker	34,264 (13.3)	36,299 (22.4)
Heavy drinker	4,724 (1.8)	2,717 (1.7)
Smoking status, <i>n</i> (%)		
Never	161,063 (62.5)	20,404 (12.6)
Ex-smoker	96,460 (37.5)	125,265 (77.4)
Currently smoking	–	16,258 (10.0)
Index of multiple deprivation quintiles (1 least deprived; 5th most deprived), <i>n</i> (%)		
1	66,513 (25.8)	29,009 (17.9)
2	68,028 (26.4)	36,590 (22.6)
3	54,263 (21.1)	34,208 (21.1)
4	44,326 (17.2)	35,192 (21.7)
5	24,393 (9.5)	26,928 (16.6)

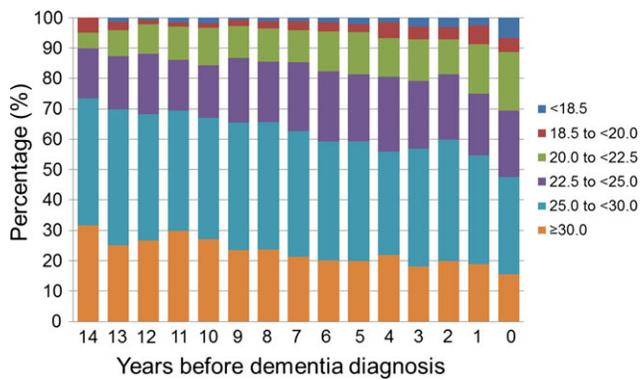
<sup>a</sup>Sample were non-smokers without recent cancer (within the previous 5 years except non-melanoma skin cancer), dementia, heart failure or multi-morbidity.

<sup>b</sup>Sample were patients who were either currently smoking, had a diagnosis of recent cancer (within the previous 5 years except non-melanoma skin cancer), heart failure or multi-morbidity.

dementia (obesity sub-Hazard Ratio [SHR], 0.69; 95% CI: 0.65–0.74, relative to BMI 22.5 to <25.0). However, for the longer-term follow-up (between 10 and 14.9 years from baseline), baseline obesity was associated with increased incidence of dementia (HR, 1.17; 95% CI: 1.03–1.32 versus BMI 22.5 to <25.0). In the longer-term follow-up, those defined as overweight had similar hazards for dementia to the control group. In models pooling shorter and longer follow-ups (Table Appendix 3, in the supplementary data, available in *Age and Ageing* online), the shorter-term protective associations predominated, although with smaller overall sub-Hazard Ratios than for the 0 to <10 year period only. Interestingly, low BMIs were consistently associated with raised risks of dementia in both the shorter and longer-term.

**Sensitivity analyses for group A**

In a further analysis, we additionally adjusted for prevalent depression or prevalent stroke diagnosed at baseline, results were little changed (Table Appendix 4, in the supplementary data, available in *Age and Ageing* online). As obesity is a major risk factor for coronary artery disease (MI and angina) and diabetes we estimated the associations excluding



**Figure 1** Percentage of group A (non-smokers without recent cancer, heart failure or multi-morbidity) with incident dementia by BMI categories.

those diagnosed with these conditions, this reduced the sample size to 49,341 and attenuated the 10–14.9 year results only slightly (obesity HR, 1.16; 95% CI: 1.01–1.33) (Table Appendix 5, in the supplementary data, available in *Age and Ageing* online).

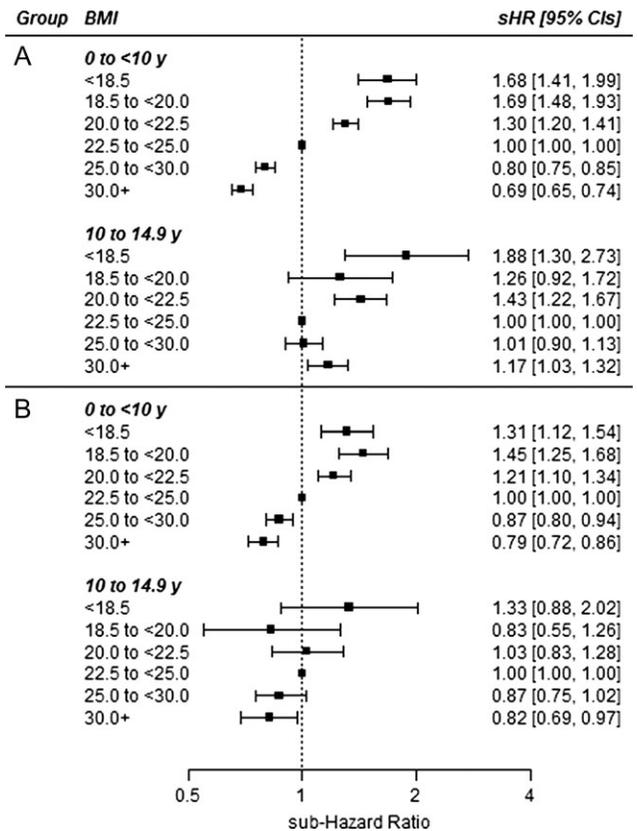
**Group B: associations in subjects with suggested confounders at baseline**

Analyses included 161,927 patients with either a diagnosis of cancer, heart failure, multi-morbidity or patients who were currently smoking. During the ≤14.9 years of follow-up there were 6,070 incident cases of dementia and 36,425 deaths. The mean baseline BMI was 27.7 kg/m<sup>2</sup> (sd 5.5 kg/m<sup>2</sup>), and 46.7% of the sample were females (Table 1).

From analysis baseline to <10 years of follow-up (Figure 2), obesity and overweight had protective associations for incident dementia (obesity SHR, 0.79; 95% CI: 0.72–0.86, relative to BMI 22.5 to <25.0). The risk of dementia remained reduced for the longer-term follow-up (between 10 and 14.9 years from baseline) (obesity SHR, 0.82; 95% CI: 0.69–0.97 versus BMI 22.5 to <25.0) (Figure 2). In the longer-term follow-up, those defined as overweight had similar hazards for dementia to the control group. There were increased dementia risks for those with low BMIs during the shorter term. In the longer-term, the hazards were similar to the control group.

**Discussion**

We studied shorter and longer-term associations between BMI and incident dementia in two groups within the older population: group A, excluding suggested confounders (i.e. smoking, cancer, heart failure or multi-morbidity at baseline) and group B with these confounders. Group A were selected to be typical of those targeted with general health advice about the risks of being overweight or obese, while group B would need specific advice tailored to their context. In group A we confirmed substantial weight loss for 10 years before dementia diagnosis. During the full follow-up obesity appeared paradoxically protective for dementia incidence,



**Figure 2** Competing hazards for incident dementia by BMI categories for Groups A and B, for 0 to <10 years and 10–14.9 years from baseline. Group A were non-smokers without recent cancer (within the previous 5 years except non-melanoma skin cancer), dementia, heart failure or multi-morbidity: Group B were patients who were either currently smoking, had a diagnosis of recent cancer (within the previous 5 years except non-melanoma skin cancer), heart failure or multi-morbidity.

but for longer-term outcomes (10–14.9 years after BMI measurement) the risk estimate reversed. Similarly, overweight protective associations disappeared in the longer-term. In group B with confounding conditions, raised BMI appeared protective for dementia in the short and longer-term, likely reflecting reverse causation with baseline BMI determined in part by smoking, cancers, heart failure and multi-morbidity, i.e. reflecting effect rather than cause.

Our finding of lower portions of subjects with obesity in those diagnosed sooner after baseline is consistent with previous reports of weight loss during the pre-clinical development of dementia [12]. Amongst those diagnosed with dementia (group A) 54% of those with repeat measures lost ≥2.5 kg during the decade before diagnosis. Stewart *et al.* [11] found that 30% of the Japanese American men who developed dementia lost ≥5 kg between two examination periods (1994–96 to 1997–99) compared to 12% of the men who did not develop dementia [11].

Our results for the whole follow-up period are partly in line with the previous analysis by Fitzpatrick *et al.* [8] who reported reduced dementia risk for those with obesity aged

65–97 years. Atti *et al.* studied a cohort aged  $\geq 75$  years, using an older cohort than used here, with overweight and obesity combined. For the whole follow-up period (0–9 years), overweight and obesity combined were associated with a reduced dementia risk (HR, 0.75; 95% CI: 0.59–0.96 versus BMI 20.0–24.9). After excluding the first 6 years the dementia risk estimates were only a little attenuated (HR, 0.66; 95% CI: 0.40–1.07) [21].

Our results, are in accordance with a recent analysis of individual level data from 39 cohorts, which showed a protective effect of BMI when measured closer to dementia diagnosis (<10 years), although the mean age at BMI measurement in these studies was under 65 years. However, in the longer-term higher BMI was associated with an increased dementia risk. The majority of the included cohorts had a baseline period pre 2000 (from 1965 to 1999) when the prevalence of overweight and obesity were much lower than they are now [22].

We additionally, estimated the short and longer-term BMI associations for patients who either had a diagnosis of cancer, heart failure, or multi-morbidity or were currently smoking (group B). These diseases were found to be associated with weight loss in our previous analysis using the CPRD [16], and as noted, smoking is associated with lower weight and high mortality [14]. As baseline BMIs in group B are likely influenced as a result of these factors, the paradoxical associations are difficult to interpret, and likely merely reflect reverse causation. Future work should examine associations with BMI recorded several years before the development of cancers, heart failure or multi-morbidity, to obtain valid estimates preferably in big enough groups to examine the effects of these factors separately.

Limitations include that the population studied was predominately of British ‘white’ ethnicity and more work is needed in other groups. Risks for dementia subtypes (mainly Alzheimer’s and vascular dementia) could not be examined, although dementia in older groups tends to have mixed pathologies [23, 24]. Unfortunately no data were available on some risk factors including head injuries or hearing loss, although it is difficult to see how these could confound obesity dementia associations. CPRD data are recorded during routine practice, with BMI often recorded opportunistically, e.g. at first registration with the practice, but also more frequently for patients with relevant conditions, possibly introducing selection biases. However, during the study period, GPs were financially incentivised to maintain a register of those with obesity [25]. Further, BMI recording were included in the NHS Health Check programme (implemented in our study period), which assess 40–74 year olds without diabetes or cardiovascular disease [26]. Both of these funded initiatives resulted in improved recording of BMI in primary care. Also recording biases from sicker patients seeing GPs more often are likely to affect the shorter-term associations, and be minimised by our analysis of outcomes 10 years after BMI recording.

This study also has considerable strengths, including the large complete older primary care populations plus no

informative loss to follow-up (i.e. loss of people who develop dementia) which is often seen in research cohorts [27]. The results extend previous findings for 65–74 year olds, and should encourage better management of excessive weight gain, without the confusion of claimed protective effects for dementia.

Future work could focus on testing longer-term associations with more detailed individual measures of weight dynamics. Additionally, potential interactions between weight loss and BMI categories should be examined using repeat BMI measures on a whole group of individuals rather than subsets of patients. Future studies could also examine longer-term associations between BMI and cognitive impairments.

## Conclusions

In 65–74 year olds (free of smoking, cancer, heart failure, multi-morbidity or dementia at baseline), being obese is associated with increased incidence of dementia in the longer-term. Paradoxical long-term associations were present in the group with likely confounders. Previous reports of protective effects of obesity or overweight on dementia risk in older groups likely reflect biases, especially weight loss during the pre-clinical development before dementia.

**Supplementary data** mentioned in the text are available to subscribers in *Age and Ageing* online.

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