



BMI and risk of dementia in two million people over two decades: a retrospective cohort study

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Summary

Background Dementia and obesity are increasingly important public health issues. Obesity in middle age has been proposed to lead to dementia in old age. We investigated the association between BMI and risk of dementia.

Methods For this retrospective cohort study, we used a cohort of 1958191 individuals derived from the United Kingdom Clinical Practice Research Datalink (CPRD) which included people aged 40 years or older in whom BMI was recorded between 1992 and 2007. Follow-up was until the practice's final data collection date, patient death or transfer out of practice, or first record of dementia (whichever occurred first). People with a previous record of dementia were excluded. We used Poisson regression to calculate incidence rates of dementia for each BMI category.

Findings Our cohort of 1958191 people from UK general practices had a median age at baseline of 55 years (IQR 45–66) and a median follow-up of 9.1 years (IQR 6.3–12.6). Dementia occurred in 45507 people, at a rate of 2.4 cases per 1000 person-years. Compared with people of a healthy weight, underweight people (BMI <20 kg/m²) had a 34% higher (95% CI 29–38) risk of dementia. Furthermore, the incidence of dementia continued to fall for every increasing BMI category, with very obese people (BMI >40 kg/m²) having a 29% lower (95% CI 22–36) dementia risk than people of a healthy weight. These patterns persisted throughout two decades of follow-up, after adjustment for potential confounders and allowance for the J-shape association of BMI with mortality.

Interpretation Being underweight in middle age and old age carries an increased risk of dementia over two decades. Our results contradict the hypothesis that obesity in middle age could increase the risk of dementia in old age. The reasons for and public health consequences of these findings need further investigation.

Funding None.

Introduction

Obesity in middle age might increase the risk of dementia at older ages,^{1–3} whereas obesity in old age could reduce the dementia risk.⁴ An understanding of the association of BMI (measured in kg/m²) with dementia is a public health priority because the number of people affected by dementia worldwide is expected to rise from 30 million in 2010, to 106 million in 2050,⁵ and the prevalence of obesity is also increasing worldwide.⁶ In England, the prevalence of obesity has almost doubled between 1993 and 2010,⁷ and the global burden of obesity in 2008 was estimated to be 1.46 billion overweight adults (BMI ≥25 kg/m²) and 502 million obese adults (BMI ≥30 kg/m²).⁸

However, the association between BMI and risk of dementia is far from clear. Several studies report that being overweight (BMI ≥25 kg/m²) in mid-life is associated with an increased risk of cognitive impairment and dementia in later life^{2,9} whereas being overweight in later life might be associated with reduced dementia risk.¹⁰ This situation has been cited as another example of the so-called obesity paradox.¹⁰ Furthermore, low BMI (<20 kg/m²) is associated with an increased risk of dementia in short-term studies of elderly people¹⁰ and weight loss reportedly occurs before a diagnosis of dementia.⁴ Inconsistencies might arise because previous studies have been quite small with short durations of

follow-up. We report our findings of the largest study so far of the association between BMI and risk of dementia.

Methods

We did a retrospective cohort study using routine UK primary care data from the Clinical Practice Research Datalink (CPRD). The CPRD contains patient information recorded during routine general practice, such as diagnoses, prescriptions, physiological measurements, diagnostic tests, lifestyle information, and referrals to secondary care. Data in the CPRD represent around 9% of the UK population. Data collection began in 1987 and we used data up to July, 2013, in our study.

We calculated BMI from weight and height records (weight in kg divided by height in m²). The index BMI (and index date) was the first eligible BMI value when participants were aged 40 years or older between Jan 1, 1992, and Dec 31, 2007. In our analysis, we used only the index BMI. Weight and height recorded on the same date were converted to BMI. If height was not recorded on the same date as weight, we used the most recent height within the previous 5 years, or, if unavailable, 5 years afterwards. We discarded weight records lower than 20 kg, height outside the range 121–214 cm, and BMI outside the range 15–50 kg/m² as being probable recording errors. We used standard BMI definitions for underweight (<20 kg/m²), healthy weight (20–24.9 kg/m²), overweight

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Research in context**Evidence before this study**

The most relevant systematic summary of the literature on the association between BMI, obesity, and dementia risk so far was published in January, 2015 by Emmerzaal and colleagues and we used this report to gather all relevant studies relating the risk of dementia to BMI. Adjustment was made for confounders in several studies, but the effect of duration of follow-up was small in most studies because few events were included. Subgroup analyses by age and sex were done in a few studies but the findings were statistically unreliable because the numbers of people and events were too few. Information was scarce for some confounders, such as smoking, blood pressure, and statins.

Added value of this study

Our data provide statistically reliable and robust evidence for a non-linear inverse association of decreasing risk of dementia with increasing BMI. Our study is the first to have adequate statistical power to examine this association reliably, providing precise estimates for both sexes and a wide age range, with follow-up extending throughout two decades. Our study

adjusted for important potential confounders: age, sex, smoking, alcohol, history of myocardial infarction, stroke and diabetes, use of recent anti-hypertensive drugs, and statins. Our study contradicts the positive association between BMI and dementia in several previous smaller studies that were, statistically, too unreliable to be conclusive.

Implications of all the available evidence

Further work is needed to establish reasons for the inverse association of BMI with risk of dementia. The establishment of a lower risk of dementia in people who are overweight and obese opens up an avenue in the search for protective factors for dementia. A re-think is necessary regarding how best to identify who is at high risk of dementia. Perhaps most important is the link between underweight and increased dementia risk; the causes and public health consequences of this association need attention by researchers and policy makers. The association found with all types of dementia invites the investigation of potential differences in risk between major dementia subtypes.

(25–29.9 kg/m²), and obese (≥30 kg/m²). We defined underweight as a BMI of less than 20 kg/m² (instead of the other commonly used cutoff of 18.5 kg/m²) to enable comparison with other studies assessing BMI and risk of dementia⁴ and for statistical stability.

People with a record of dementia before their index date were excluded. Additionally, people with fewer than 12 months historical data before the index date were also excluded, to improve the availability of covariates and to avoid missing cases of pre-existing dementia. Follow-up was until the practice's final CPRD data record, the end of the patient's record collection (because of death or leaving the practice), or the first record of dementia, whichever occurred first.

Validation of the CPRD has previously been done for many disorders, including dementia.¹¹ Patients were classified as having dementia if any of the following terms were recorded during follow-up: dementia, Alzheimer, Lewy body disease, or Pick's disease. Dementia recorded on a death certificate was also used to classify patients with dementia.

Statistical analysis

To relate BMI to risk of dementia, we used Poisson regression models to obtain incidence rates and rate ratios. Initially, we adjusted for age (in 5-year bands) and sex. We used age at risk (updating age bands as people moved through the age categories) rather than baseline age because age at risk was a more meaningful time point than age at first BMI record between 1992 and 2007. We then fitted adjusted models controlling for the following additional covariates at the time of index BMI measurement: smoking (never smoker, ex-smoker, current smoker, or unknown), alcohol consumption (never

drinker, ex-drinker, current drinker, or unknown), statin use (yes or no), antihypertensive use (yes or no), diabetes (yes or no), and previous myocardial infarction (yes or no).

We standardised incidence rates to the age and sex distribution of the study population as follows: rates from Poisson regression models were calculated for each combination of age, sex, and BMI category. We then multiplied these rates by the proportion of follow-up time (in the overall cohort) spent in each age and sex category. The sum of these rates within each BMI category gave the age and sex-standardised rates. Confidence intervals for standardised rates used the normal approximation to the Poisson distribution.

To investigate whether or not the association between BMI and dementia depended on the time since BMI measurement, we split follow-up time into five intervals (0–1 year, 1–5 years, 5–10 years, 10–15 years, and ≥15 years), and fitted separate Poisson regression models for each interval. To investigate the cumulative incidence of dementia by age, we used Kaplan-Meier estimates with age as the time scale.

We did a sensitivity analysis to account for the hypothesis that those who died would have had double the risk of dementia if they had survived. We matched each person who died during follow-up to one randomly chosen person who did not die during follow-up, had at least as much follow-up as the person who died, had the same baseline age (matched in 5-year bands), were of the same sex, and were in the same BMI category. For each person who died, we replaced their record by the record of the matched survivor, and counted as two events whenever the surviving individual developed dementia.

We used Stata version 11.2 and R version 3.0.0 for all statistical analyses.

Results

Figure 1 shows the creation of the analysis dataset. Of 6098128 people in CPRD aged 40 years or older between 1992 and 2007, 2944587 had BMI data available. We excluded people who did not have at least 12 months of historical data, those judged to be outliers, and those with a previous history of dementia, leaving a total of 1958191 people (representing 18786640 person-years of follow-up) to include in our analysis. The median BMI was 26.4 kg/m² (IQR 23.5–30.0), the median age at baseline was 55 years (IQR 45–66), and 1072485 (55%) of the 1958191 participants were women. Table 1 shows the distribution of BMI by age and sex. The prevalence of obesity was higher at younger ages than in older participants. The prevalence of underweight (BMI <20 kg/m²) was higher in women than in men and increased with age in both sexes.

During a median of 9.1 years of follow-up (IQR 6.3–12.6), 45507 people had a first diagnosis of dementia, at an overall rate of 2.4 cases per 1000 person-years. The incidence rates of dementia by age at diagnosis and sex are shown in appendix p 1 and appendix p 8. Dementia was strongly associated with increasing age, and was more common in women than in men in those older than 70 years.

Table 2 shows the association of dementia incidence with BMI categories. Compared with people of a healthy weight, underweight people had a 34% (95% CI 29–38) excess risk of dementia. Furthermore, the incidence of dementia continued to fall for every increasing BMI category, with very obese people (BMI ≥40 kg/m²) having a 29% lower risk of dementia (95% CI 22–36) than those of a healthy weight. Further adjustment for six potential confounders (table 2) made little difference to this monotonic inverse association between BMI and dementia risk, and if anything seemed to slightly accentuate the trend.

We further explored the association of BMI with dementia by estimating age-adjusted and sex-adjusted rates of BMI in 28 categories, for which we used 1 kg/m² steps for most of the distribution and 2 kg/m² or 3 kg/m² steps in the tail ends of the distribution (figure 2). An increase in BMI was associated with a substantial steadily decreasing risk of dementia for BMI of up to 25 kg/m². At a BMI higher than 25 kg/m², dementia risk decreased more gradually, and this trend continued up to a BMI of 35 kg/m² or higher. Notably, underweight people (BMI <20 kg/m²) had a 64% higher risk of developing dementia (95% CI 57–71) than did those with a BMI around the median of 26–27 kg/m² (data not shown).

Figure 3 shows the cumulative probability of dementia by age separately for men and women, and how this depends on BMI category. For both sexes, this age gradient is steepest for underweight people. People of a healthy weight have the next highest cumulative incidence, whereas overweight and obese people have rather similar lesser cumulative risk patterns. For example, at 80 years of age, for both sexes combined, the cumulative incidence of

dementia was 9.9% (95% CI 9.5–10.3) for underweight people, 6.5% (6.4–6.6) for those of a healthy weight, 5.2% (5.0–5.3) for overweight people, and 4.9% (4.7–5.0) for obese people. Beyond the age of 80 years, the gradient in cumulative risk of dementia is steeper for women than men, irrespective of their BMI.

To explore whether or not the association varies by follow-up time after the recorded BMI value, we estimated the incidence of dementia in five intervals after the BMI measurement (0–1 year, 1–5 years, 5–10 years, 10–15 years, and >15 years; see appendix p 2). In all cases, underweight

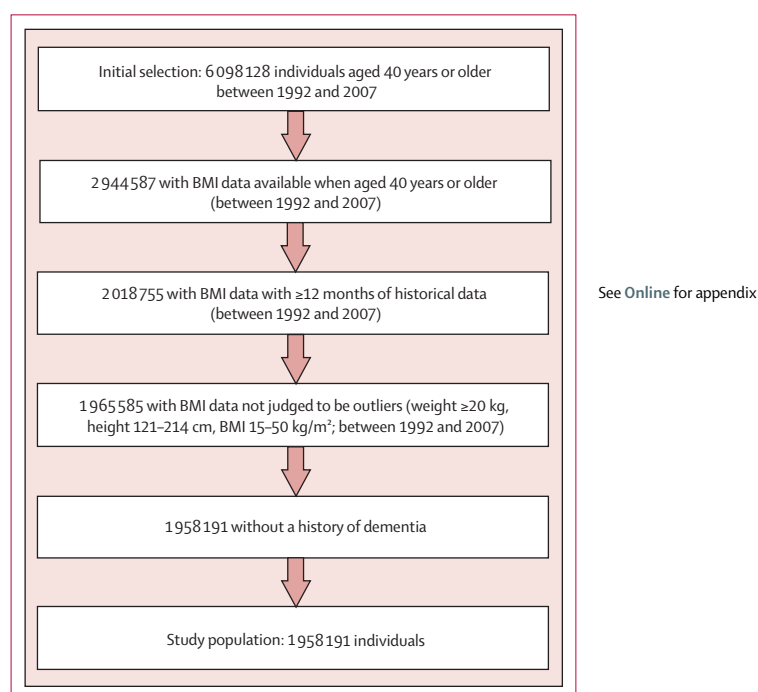


Figure 1: Creation of the dataset for analysis from the entire UK Clinical Practice Research Datalink

	Underweight (BMI <20 kg/m ²)	Healthy weight (BMI 20–24.9 kg/m ²)	Overweight (BMI 25–29.9 kg/m ²)	Obese (BMI ≥30 kg/m ²)
Men (n=885 706)				
40–49 years (n=315 037)	8699 (2.8%)	84 824 (26.9%)	130 379 (41.4%)	91 135 (28.9%)
50–59 years (n=237 978)	6129 (2.6%)	61 994 (26.1%)	105 806 (44.5%)	64 049 (26.9%)
60–69 years (n=184 703)	5829 (3.2%)	52 038 (28.2%)	84 641 (45.8%)	42 195 (22.8%)
70–79 years (n=111 213)	5540 (5.0%)	38 315 (34.5%)	49 264 (44.3%)	18 094 (16.3%)
≥80 years (n=36 775)	2725 (7.4%)	15 760 (42.9%)	14 598 (39.7%)	3692 (10.0%)
Women (n=1 072 485)				
40–49 years (n=405 027)	28 950 (7.1%)	151 996 (37.5%)	115 858 (28.6%)	108 223 (26.7%)
50–59 years (n=257 752)	13 969 (5.4%)	87 529 (34.0%)	85 711 (33.3%)	70 543 (27.4%)
60–69 years (n=201 083)	12 670 (6.3%)	63 432 (31.5%)	71 622 (35.6%)	53 359 (26.5%)
70–79 years (n=142 677)	13 510 (9.5%)	49 170 (34.5%)	50 159 (35.2%)	29 838 (20.9%)
≥80 years (n=65 946)	9273 (14.1%)	26 209 (39.7%)	21 309 (32.3%)	9155 (13.9%)

Data are n (%).

Table 1: Distribution of BMI measurements by age and sex

people had the highest dementia risk, followed by people of healthy weight. This pattern remained when we restricted our analysis to people whose BMI was measured before 55 years of age (appendix p 3).

Since the year of birth in our cohort ranged from 1892 to 1972, we assessed birth cohort effects and found that

they did not substantially affect the association between BMI and dementia (appendix p 4), and neither did analysis by age at diagnosis (appendix p 5).

Next, we considered the competing risk of mortality and whether or not that offers any explanation for our findings. The J-shape association of all-cause mortality with BMI is shown in appendix p 6 and appendix p 9. In an age-adjusted and sex-adjusted analysis, the highest mortality rates were in underweight people (BMI <20 kg/m²; rate ratio 1.53 [95% CI 1.51–1.55]) and those who were very obese (BMI ≥40 kg/m²; 1.57 [1.53–1.62]). Mortality rates were slightly lower in overweight people (0.90 [0.89–0.91]) than in those of a healthy weight (reference group) and the lowest mortality rate (12.78 per 1000 person-years) was for a BMI of around 26 kg/m². Our sensitivity analysis indicates that the increased mortality rate in obese people does not explain their low dementia risk. Table 2 presents rates and rate ratios for dementia in a hypothetical scenario in which dementia events that would have taken place had a person not died occurred at double the rate recorded in surviving individuals (ie, analysis adjusted for the effects of mortality). The rate ratios of dementia for obese versus healthy weight people became somewhat attenuated, but a more than 20% lower dementia risk persisted at all degrees of obesity. By contrast, this hypothetical adjustment for mortality slightly enhanced the excess risk of dementia in underweight people.

Discussion

This cohort study in which nearly 2 million people were followed retrospectively for two decades showed an inverse monotonic association between BMI and the incidence of dementia. The association was not explained by age, sex, duration of follow-up, or available baseline covariates.

One of our key findings is that underweight people have a notably raised risk of developing dementia, and that this risk persists even 15 years after underweight is recorded. This finding might seem surprising, since some researchers have concluded that obesity in mid-life increases the risk of dementia. For example, a recent editorial in *The Lancet Neurology* stated unequivocally that “reduction of...risk factors such as midlife obesity and physical inactivity could substantially reduce the future prevalence of dementia”.¹² Similarly, a recent review⁴ concluded that “studies investigating the association between midlife BMI and risk for dementia demonstrated generally an increased risk among overweight and obese adults”, although the authors also noted that “when measured in late life, increased BMI has been associated with lower risk”. However, all these findings have been based on quite small studies. Overall, the evidence is not consistent, with some studies reporting a positive association between BMI and dementia^{9,13–17} and others reporting no association or a reduced risk.^{18–20} The reasons for the apparent differences in associations for mid-life and late-life dementia in some studies are not clear, but a long follow-up period (eg, 30 years²¹) might be necessary

	Rate (95% CI)	Rate ratio (95% CI)
Age and sex adjusted		
Underweight (<20 kg/m ²)	3.64 (3.52–3.77)	1.34 (1.29–1.38)
Healthy weight (20–24.9 kg/m ²)	2.73 (2.69–2.77)	1.00 (reference)
Overweight (25–29.9 kg/m ²)	2.24 (2.21–2.28)	0.82 (0.8–0.84)
Class I obese (<30–34.9 kg/m ²)	2.08 (2.03–2.13)	0.76 (0.74–0.79)
Class II obese (35–39.9 kg/m ²)	2.00 (1.92–2.08)	0.73 (0.69–0.78)
Class III obese (≥40 kg/m ²)	1.93 (1.81–2.05)	0.71 (0.64–0.78)
Further adjusted*		
Underweight (<20 kg/m ²)	3.70 (3.23–4.17)	1.34 (1.30–1.39)
Healthy weight (20–24.9 kg/m ²)	2.77 (2.19–3.34)	1.00 (reference)
Overweight (25–29.9 kg/m ²)	2.25 (1.98–2.51)	0.81 (0.79–0.83)
Class I obese (<30–34.9 kg/m ²)	2.05 (1.87–2.23)	0.74 (0.72–0.76)
Class II obese (35–39.9 kg/m ²)	1.95 (1.81–2.08)	0.69 (0.66–0.74)
Class III obese (≥40 kg/m ²)	1.84 (1.74–1.94)	0.67 (0.60–0.74)
Adjusted for the effect of mortality†		
Underweight (<20 kg/m ²)	4.57 (4.43–4.7)	1.39 (1.36–1.42)
Healthy weight (20–24.9 kg/m ²)	3.29 (3.24–3.33)	1.00 (reference)
Overweight (25–29.9 kg/m ²)	2.7 (2.66–2.74)	0.82 (0.81–0.84)
Class I obese (<30–34.9 kg/m ²)	2.5 (2.44–2.55)	0.76 (0.74–0.78)
Class II obese (35–39.9 kg/m ²)	2.49 (2.4–2.58)	0.76 (0.72–0.79)
Class III obese (≥40 kg/m ²)	2.59 (2.45–2.73)	0.79 (0.73–0.86)

All trends were associated with p values <0.0001. *These rates and rate ratios are adjusted for age, sex, smoking status, alcohol status, diabetes, previous myocardial infarction, statin use, and anti-hypertensive use. Excludes 73 310 participants with unknown smoking or alcohol status. †These rates and rate ratios are also adjusted for the above factors, and also assume a hypothetical subsequent rate of dementia two-times higher in those who died than in those still alive.

Table 2: Rates of dementia per 1000 person-years and rate ratios compared with healthy weight by category of BMI, adjusted in various ways

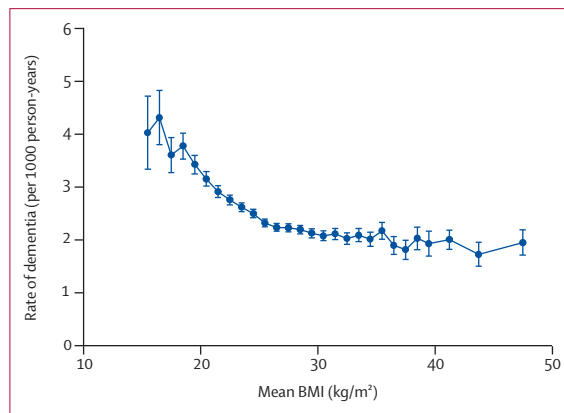


Figure 2: Age and sex-standardised rates of dementia per 1000 person-years by BMI
Plotted points are mean rates of dementia; error bars are 95% CIs.

to detect an increased risk of dementia from mid-life overweight and obesity.

Our study is substantially larger than previous studies, and is apparently the first to report an inverse association between BMI and dementia risk in both mid-life and later life. The strength of the association was quite constant even after 15 years of follow-up, including in people 40–55 years of age at the time of BMI measurement. Our findings question the belief that obesity in mid-life is associated with an increased risk of dementia. Claims that reducing obesity in middle age could help to prevent dementia in older age might therefore be ill founded.^{2,3,12}

If increased weight in mid-life is protective against dementia, the reasons for this inverse association are unclear at present. Many different issues related to diet, exercise, frailty, genetic factors, and weight change could play a part. Factors postulated to explain the previously observed protective effect of increased BMI on late-life dementia include low late-life blood pressure; high late-life cholesterol levels; higher leptin levels; age-related regulatory changes in carbohydrate, lipid, or protein metabolism;⁴ and increased intake of vitamin E anti-oxidant²² and vitamin D.²³

Our study has several strengths. It is the largest study so far of the association between BMI and dementia, with almost 2 million people followed for up to 20 years or longer with 45 507 cases of dementia. The CPRD is population based, geographically widespread, and representative of the UK population, which helps to ensure the generalisability of our findings. This statistical power allows precise age-specific risks of dementia with more detailed BMI categories and a longer duration of follow-up than previous studies. The fact that our findings are consistent across different subgroups (age, sex, and duration of follow-up) and that they remain consistent after adjustment for covariates supports their validity. Additionally, a sensitivity analysis accounting for the association of BMI with all-cause mortality had little effect on the association between BMI and dementia. Reverse causality (ie, whether onset of dementia could lead to reduced BMI) does not seem to be an explanation since similar patterns occur over 15 years after recording of BMI. Regression dilution is small for BMI.²⁴ Birth cohort effects and age at diagnosis had little effect on the association between BMI and dementia.

Our study has several potential limitations. Selection bias might exist because 48% of eligible people did not have a BMI record and 31% of people with BMI records were excluded for not having at least 12 months of previous health records—a requirement to ensure good-quality baseline data. If BMI is more likely to be measured in people with comorbidities than in healthy people, which might in turn be associated with dementia risk, then some bias is possible. However, since recording of BMI became routine in 2004, we undertook analyses by calendar year of BMI reading, and this did not affect the relation between BMI and dementia (data not shown).

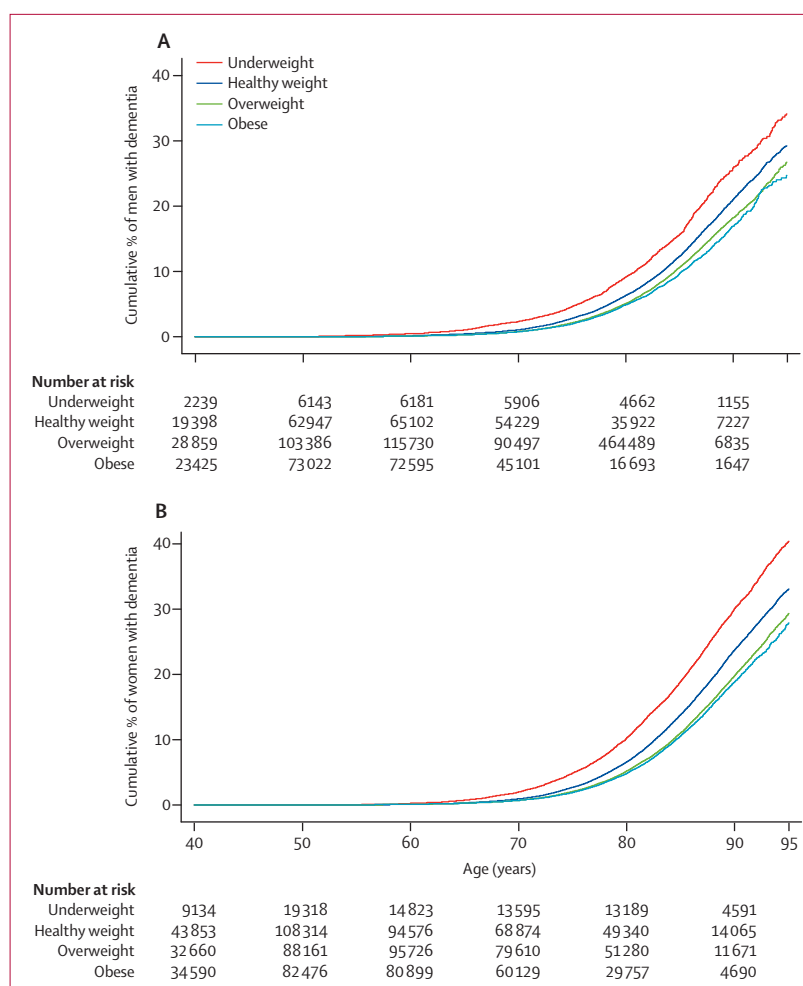


Figure 3: Cumulative risk of dementia with increasing age by BMI category in men (A) and women (B)

This consistency of our findings indicates that selection bias is an unlikely explanation. We also compared our BMI data with that of the Health Survey of England²⁵ and noted a similar distribution by age and sex. Furthermore, we confirm in our dataset the known J-shape associations of BMI with all-cause mortality (appendix p 9) and risk of stroke (data not shown).

The small set of variables available for covariate-adjusted analyses leaves the possibility of residual confounding. For example, we adjusted for anti-hypertensive agents and statins and not for blood pressure and blood lipid values, which do affect the associations of BMI with myocardial infarction and stroke;²⁴ thus, our adjustment might have been suboptimal. Other unavailable potential confounders, such as physical activity level, socioeconomic status, and ethnic origin, might change the recorded association between BMI and dementia. The amount of missing data for adjusted covariates was small (appendix p 7) and unlikely to affect the association between BMI and dementia, as confirmed by a complete case analysis. Might people at high risk of dementia be removed from follow-up

by being transferred out of practice or being admitted to an institution? Such loss to follow-up did not depend on BMI. We focused on all types of dementia since reliable data for specific dementia subtypes were not available. Specific diagnoses, such as vascular dementia and Alzheimer's disease, might show different associations with BMI. Although rarer and genetic causes of dementia occur more frequently in younger people than in older patients, the most common subtypes of dementia in patients younger than 65 years of age are similar to those in patients older than 65 years.²⁶ Only in people younger than 45 years do the common causes of dementia cease to dominate, and we recorded only 18 cases of dementia in people less than 45 years of age. Although some dementias might be secondary to other diseases (eg, alcoholism and AIDS) that are associated with weight loss, these causes are too rare to substantially affect the recorded association between BMI and dementia.

A further issue is the definition and classification of dementia. The degree of under-diagnosis of dementia in CPRD is unknown but, even if this were substantial, it would be unlikely to materially change the associations recorded. Data about dementia severity are not reliably available in CPRD but should not affect the overall association between BMI and dementia. Contact with general practitioners (and other physicians) might be higher for people in the extreme tails of the BMI distribution, which could potentially lead to increased reporting of dementia,²⁷ which might inflate the dementia risk in underweight and obese people.

We intend to do further research to better understand this inverse association between BMI and dementia risk. Specifically, the use of several BMI readings taken across a few years helps the study of changes in BMI, and it will be interesting to see whether weight loss is linked to a raised risk of dementia.

In conclusion, our study shows a substantial increase in the risk of dementia over two decades in people who are underweight in mid-life and late-life. Our findings contradict previous suggestions that obese people in mid-life have a higher subsequent risk of dementia. The reasons for and public health consequences of these findings need further investigation.

Contributors

All authors contributed to the study design and data interpretation. NQ and MEJ wrote the proposal. KW was responsible for data management. JG did the statistical analysis. NQ, SJP, JG, and MEJ wrote the first draft of the report. All authors contributed to further drafts and approved the final version.

Declaration of interests

We declare no competing interests.

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