

# Obesity in middle age and future risk of dementia: a 27 year longitudinal population based study

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## Abstract

**Objective** To evaluate any association between obesity in middle age, measured by body mass index and skinfold thickness, and risk of dementia later in life.

**Design** Analysis of prospective data from a multiethnic population based cohort.

**Setting** Kaiser Permanente Northern California Medical Group, a healthcare delivery organisation.

**Participants** 10 276 men and women who underwent detailed health evaluations from 1964 to 1973 when they were aged 40-45 and who were still members of the health plan in 1994.

**Main outcome measures** Diagnosis of dementia from January 1994 to April 2003. Time to diagnosis was analysed with Cox proportional hazard models adjusted for age, sex, race, education, smoking, alcohol use, marital status, diabetes, hypertension, hyperlipidaemia, stroke, and ischaemic heart disease.

**Results** Dementia was diagnosed in 713 (6.9%) participants. Obese people (body mass index  $\geq 30$ ) had a 74% increased risk of dementia (hazard ratio 1.74, 95% confidence interval 1.34 to 2.26), while overweight people (body mass index 25.0-29.9) had a 35% greater risk of dementia (1.35, 1.14 to 1.60) compared with those of normal weight (body mass index 18.6-24.9). Compared with those in the lowest fifth, men and women in the highest fifth of the distribution of subscapular or tricep skinfold thickness had a 72% and 59% greater risk of dementia, respectively (1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04).

**Conclusions** Obesity in middle age increases the risk of future dementia independently of comorbid conditions.

## Introduction

With the ageing of the population it is expected that the incidence of dementia will increase 400% in the next 20 years.<sup>1</sup> Contrary to findings from cross sectional studies,<sup>2</sup> a recent prospective study found that obesity in elderly woman increases the risk of dementia.<sup>3</sup> The ratio of lean to fat mass changes with ageing,<sup>4</sup> resulting in a decreased body mass index. The subclinical phase and initial onset of dementia affect appetite and cause weight loss,<sup>2 5 6</sup> skewing the temporal association between weight and dementia. Thus, one study found that weight loss precedes onset of dementia in elderly adults.<sup>7</sup> Obtaining weight measurements many years before the onset of dementia, as well as other measures of adiposity, would provide stronger evidence of causality between obesity and increased risk of dementia. For example, skinfold thickness, another marker of obesity has not been examined in relation to dementia.

We determined the predictive value of mid-life adiposity, including body mass index and tricep and sub-

scapular skinfold thickness, on the risk of developing dementia in a large multiethnic cohort of men and women followed for an average of 27 years.


## Methods


**Study population**—We conducted a prospective analysis of 10 276 members of the Kaiser Permanente medical care programme who participated in voluntary health checks in San Francisco and Oakland, California, between 1964 and 1973 when they were aged 40-45. We identified participants who were still members of Kaiser Permanente when outpatient diagnoses of dementia were available in 1994 (n = 25 290). After exclusions, 10 276 remained for analysis. Kaiser Permanente covers more than a quarter of the population in the areas served, and members are representative of the sociodemographics of the local population in the service areas.

**Data collection and mid-life adiposity**—Participants were interviewed, underwent a clinical examination, and gave a blood sample. Information was collected on demographics and medical history. Height and weight were measured. We categorised body mass index (weight/height<sup>2</sup>) as obese ( $\geq 30$ ), overweight (25.0-29.9), normal (18.6-24.9), and underweight ( $\leq 18.5$ ). Subscapular and tricep skinfold thickness were measured.

**Diagnosis of dementia and other illnesses in later life**—We searched the databases of medical records from the care programme (from January 1994 to April 2003) for diagnoses of dementia and other illnesses. All cause dementia diagnoses included: dementia, Alzheimer's disease, and vascular dementia. We determined incidence of ischaemic heart disease, hypertension, stroke, hyperlipidaemia, and diabetes. We gathered information on mortality from the California automated mortality linkage system up to the end of 2000, and a matching linkage system, incorporating social security number, name, and address, from 2001 to the end of 2002.

**Statistical analysis**—We assessed the association between time to diagnosis of dementia and characteristics measured at the multiphasic exam and Cox proportional hazard models to identify independent predictors of risk of late life dementia. Person years were calculated from onset of follow-up (1 January 1994) until onset of dementia or the earliest of death, end of Kaiser Permanente membership, or end of study (3 April 2003). We determined if there were any significant differences in the mid-life measures of adiposity and covariates by health plan membership status in 1994 (see bmj.com).

 A further table on age and body mass index can be found on [bmj.com](http://bmj.com)

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## Results

From 1 January 1994 until 3 April 2003, 713 participants were diagnosed with dementia (table 1). Mean age at initial recorded diagnosis was 74.5 years (range 66-82). The mean time to start of ascertainment of dementia was 26.5 years. Those with the diagnosis were more likely to be older, to have finished schooling at age 12, and be unmarried in mid-life.

At mid-life, 10% of the cohort were obese, 36% overweight, 53% normal weight, and 1.3% underweight. The prevalence of a subsequent diagnosis of dementia was significantly higher for those who were obese or overweight at mid-life. Those in the highest fifth for subscapular and tricep skinfold measurements at mid-life were more likely to have dementia than those in the lowest fifth. Post hoc analyses of the 10 276 participants in the study compared with the 10 407 excluded, because they were no longer health plan members in 1994, showed no significant differences in any of the mid-life measures of adiposity or covariates by status of health plan membership in 1994. We also conducted post hoc analyses to ensure that there was no selection effect due to age, indeed participants who were obese or overweight were not older at time of ascertainment of dementia than those of normal weight (see table on bmj.com). We checked the proportionality of hazards for each covariate by entering interaction terms of the covariate by person years into the model. The P values for each were non-significant ( $P > 0.06$ ), indicating all hazards were proportional.

Compared with those with normal weight at mid-life, obese people had a 74% greater risk of dementia (table 2), while those who were overweight had a 35% greater risk. In sex specific models body mass index was associated with dementia more strongly in women (body mass index\*sex interaction term  $P = 0.06$ ). Obese women were 200% more likely to have dementia than women of normal weight, while obese men had a non-significant 30% increase in risk. Overweight women were 55% more likely to have dementia than women of normal weight, while overweight men had a non-significant 16% increase in risk compared with men of normal weight. There were no significant race interactions in the association between body mass index and risk of dementia ( $P > 0.15$  for race\*body mass index interaction term).

Measures of skinfold thickness at mid-life were significantly associated with risk of dementia at a magnitude similar to body mass index (see bmj.com). Those in the highest fifth of subscapular skinfold had a 72% increased risk, while those in the highest fifth of tricep skinfolds had a 59% increased risk compared with those in the lowest fifth (fully adjusted models: 1.72, 1.36 to 2.18, and 1.59, 1.24 to 2.04, respectively). Results did not vary by race in the association between skinfolds and dementia risk ( $P > 0.15$ , interaction term skinfold measures\*race).

## Discussion

Obesity and overweight in middle age as measured by body mass index and skinfold thickness were strongly associated with risk of dementia in later life, independent of sociodemographic characteristics and common

**Table 1** Demographic characteristics of the participants at mid-life by dementia status. Figures are numbers (percentage) of participants unless stated otherwise\*

	No dementia (n=9563)	Dementia (n=713)	P value†
Mean (SD) age at multiphasic exam (years)	42.45 (1.71)	42.89 (1.66)	<0.0001
Women	5168 (54.0)	396 (55.5)	0.8930
Men	4395 (46.9)	317 (44.5)	
Race:			
White	6864 (71.8)	489 (68.6)	0.0006
Black	1591 (16.6)	155 (21.7)	
Asian	636 (6.7)	36 (5.1)	
Other	471 (4.9)	33 (4.6)	
Level of education completed:			
Grade school (to age 12)	1159 (13.8)	129 (19.5)	<0.0001
High school (to age 18)	2895 (34.4)	214 (32.3)	
Trade or technical school	595 (7.1)	42 (6.3)	
College or university	3777 (44.8)	278 (41.9)	
Marital status:			
Married	7994 (84.5)	573 (81.5)	0.0451
Never married	489 (5.2)	38 (5.4)	
Divorced/widowed/separated	972 (10.3)	92 (13.1)	
Smoking:			
Yes	5002 (58.6)	408 (60.4)	0.0627
No	3539 (41.4)	268 (39.6)	
Alcohol use:			
≤2 per week	5745 (60.4)	406 (57.1)	0.0732
3-5 per week	774 (8.1)	55 (7.7)	
≥6 per week	204 (2.1)	20 (2.8)	
Current/unknown quantity	681 (7.2)	63 (8.9)	
Past drinker	132 (1.4)	6 (0.8)	
Never drinker	1977 (20.8)	161 (22.6)	

\*Missing data: education for 1185, marital status for 118, smoking for 1059, alcohol use for 52.  
†P values were calculated with log rank test.

comorbidities. To date, this is the first study to determine the contribution of mid-life adiposity and skinfold thickness to risk of dementia.

### Strengths and weaknesses of study

Strengths include the longitudinal design with skinfold measures from two parts of the body as well as body mass index, the long follow-up, the breadth of information on other diseases in middle and old age, and the well characterised representative sample with equal access to medical care. The participants were middle aged when risk factors were assessed, thus sub-clinical dementia at baseline is highly unlikely.

**Table 2** Cox proportional hazards model of body mass index at mid-life and risk of dementia. Figures are hazard ratios (95% confidence intervals)

Body mass index*	Adjusted for age at mid-life exam and education	Also adjusted for age at diagnosis, race, marital status, sex	Also adjusted for mid-life and late life comorbidity†
<b>All</b>			
Obese	1.38 (1.10 to 1.72)	1.56 (1.24 to 1.96)	1.74 (1.34 to 2.26)
Overweight	1.16 (1.01 to 1.34)	1.22 (1.04 to 1.42)	1.35 (1.14 to 1.60)
Underweight	1.41 (0.82 to 2.39)	1.46 (0.84 to 2.54)	1.24 (0.70 to 2.21)
<b>Women</b>			
Obese	1.59 (1.21 to 2.08)	1.80 (1.35 to 2.39)	2.07 (1.49 to 2.89)
Overweight	1.34 (1.09 to 1.63)	1.36 (1.10 to 1.68)	1.55 (1.22 to 1.97)
Underweight	1.63 (0.93 to 2.84)	1.73 (0.97 to 3.08)	1.45 (0.79 to 2.67)
<b>Men</b>			
Obese	1.08 (0.74 to 1.58)	1.22 (0.83 to 1.79)	1.30 (0.84 to 1.87)
Overweight	1.01 (0.82 to 1.25)	1.07 (0.86 to 1.33)	1.16 (0.91 to 1.46)
Underweight	0.55 (0.07 to 3.92)	0.55 (0.08 to 3.96)	0.53 (0.07 to 3.82)

\*Obese (≥30), overweight (25.0-29.9), normal (18.5-24.9), underweight (<18.5); reference group is those with normal body mass index.

†Mid-life comorbidity includes hypertension, diabetes, and high cholesterol; late life comorbidity includes hypertension, stroke, diabetes, ischaemic heart disease, and hyperlipidaemia.

This study also has limitations. We could assess dementia status only among participants who were still members of the health plan when dementia was diagnosed. However, there were no differences in adiposity or sociodemographic characteristics in those who didn't continue in the health plan. Information on weight cycling, dieting, nutrition, or mid-life measures of cognitive functioning was not collected. A measure of central obesity, such as waist circumference was not collected. As diagnoses of dementia were made during medical visits, some cases of dementia may have been missed in those who did not participate in visits. This would bias results in an underestimation of the effects of obesity on dementia.

#### Mechanisms of effects

Adiposity is one component of the metabolic syndrome, which has also been shown to cause cognitive decline, particularly in those with high levels of inflammation.<sup>8</sup> Perhaps adiposity has a direct effect on neuronal degradation. Genetically obese, leptin receptor deficient rodents have impaired performance on spatial memory tasks<sup>9</sup> and long term potentiation of neurones in the hippocampus.<sup>10</sup> C reactive protein, an inflammatory marker, is increased in those with greater adiposity<sup>11</sup> and is associated with dementia<sup>12</sup> and cognitive decline.<sup>8, 13</sup> Recently, obesity in elderly women was shown to be associated with greater cerebral atrophy<sup>14</sup> and white matter hyperintensity.<sup>15</sup> Future studies of cytokines produced in fat cells and neuronal functioning should be useful.

Another study found that high skinfold thickness in mid-life was associated with Parkinson's disease.<sup>16</sup> Perhaps adiposity works together with other risk factors to increase neurodegenerative disease.

Body mass index predicted dementia more strongly among women. These findings, however, are consistent with the only published prospective study on body mass index and dementia.<sup>3</sup> There could be several reasons. There were fewer obese and overweight men, thus the power to detect an effect was reduced. Current body mass index categories may be insensitive indicators of adiposity in men because of less variation in the distribution of visceral fat.<sup>4</sup> Perhaps body mass index and risk of dementia in women is mediated through central obesity, which is highly associated with insulin resistance, cardiovascular disease, increased adipocytokines, and inflammatory markers. All of these conditions could contribute to dementia. Diabetes and cardiovascular disease did not attenuate the effect, though the role of central obesity, inflammation, and adipocytokines on our findings is unknown and should be looked at in future research.

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#### What is already known on this topic

A recent study found that high body mass index in old age is associated with an increased risk of dementia in women, though body mass index is an insensitive measure of adiposity in elderly people and the subclinical phase of dementia causes weight loss

No studies have prospectively evaluated the effect of obesity in middle age on the subsequent risk of future dementia, and no studies have determined whether skinfold thickness is associated with dementia

#### What this study adds

People who were obese in mid-life were 74% more likely to have dementia, while overweight people were 35% more likely to have dementia compared with those with normal weight

Increased adiposity in the subscapular and tricep region in middle age was associated with a 60-70% increase in risk of dementia

These findings were not attenuated by presence of comorbid diseases in middle and late life

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#### Endpiece

#### Too much or too little

Old age is having too much room in the house and not enough in the medicine cabinet.

Robert Orben, American humorist

Fred Charatan, retired geriatric physician, Florida