Examining if being overweight really confers protection against dementia: Sixty-four year follow-up of participants in the Glasgow University alumni cohort study

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Abstract

Background: Recent large-scale studies suggest that obesity and overweight may confer protection against future dementia. This observation could, however, be generated by reverse causality. That is, weight loss in the incipient phase of dementia ascribed to diminished self-care, including sub-optimal nutrition, would have the effect of generating such an inverse association. One approach to circumventing this problem would be to measure weight in a population which is young enough to be free of the symptoms of dementia which is then followed up for dementia occurrence over many decades.

Methods: In a prospective cohort study, body mass index, and other potential risk factors, were measured in 9547 male university undergraduates (mean age 20.5 years) in 1948–68 who were then linked to national mortality registers.

Results: Of 2537 deaths over a mean of 50.6 years follow up, 140 were ascribed to dementia. There was no association between overweight and future dementia deaths (age-adjusted hazard ratio; 95 % confidence interval: 0.93; 0.49, 1.79).

Conclusion: In this cohort study of former university students, being overweight in youth did not confer protection against later dementia death.

Keywords: Cohort, Dementia, Epidemiology, Life course, Obesity, Overweight, Risk factors

Introduction

Dementia is a well-documented global health priority and, given projected demographic transitions, substantial increases in the absolute number of people with this disease are anticipated [1]. With current treatments having modest clinical benefit, an improved understanding of the aetiology of dementia is needed if the disorder is to be delayed or prevented. Observations that cerebrovascular pathology commonly co-occurs with Alzheimer’s disease [2], the leading dementia sub-type, has raised the possibility that dementia and cardiovascular disease (CVD) may share similar disease processes. Results from prospective cohort studies suggest that established CVD risk factors when measured in mid- or older-age – smoking, diabetes, physical inactivity, hypercholesterolaemia, and hypertension – are related to dementia risk [3, 4], although these are by no means universal findings [5, 6].

Some reports also suggest that another established CVD risk factor, overweight/obesity, might be associated with an elevated risk of dementia [7]. Other studies, however, including a cohort of 2 million British individuals [8], actually found that being overweight or obese in midlife conferred a lower risk of dementia. Results from a recent study accord with these findings [9]. In keeping with these and other discordant results, an expert consensus statement issued by the US National Institutes of Health has indicated that there was insufficient evidence to conclude that...
overweight/obesity, amongst other modifiable factors, was linked to cognitive decline or dementia [10].

The prolonged preclinical period of many dementias complicates interpretation of findings as to the potential risk factors for this disorder and may explain the controversial overweight/obesity–dementia relationship [11]. That is, the known reduction in weight in the incipient phase of dementia [12, 13] ascribed to diminished self-care, which includes sub-optimal nutrition, would have the effect of generating a potentially spurious inverse association. One approach to addressing this issue of reverse causality is to measure weight in populations which are young enough to be free of the symptoms of dementia who are then followed up for dementia occurrence over many decades. Being unaware of any such data, we report on the long term follow-up for dementia of male undergraduates who had a physical examination which included a measurement of weight, height, and other risk factors at university entry.

**Methods**

**Study population**

Participants were drawn from the Glasgow Alumni Study which has been described in detail elsewhere [14, 15]. In brief, with the establishment of a student health service at the University of Glasgow (Scotland, UK) in 1947, students were invited to a medical examination on entry.

**Measurement of weight and other risk factors**

During an interview and physical examination, a university physician recorded a series of characteristics. Height (inches converted to centimetres) and weight (stones and pounds converted to kilograms) were measured directly. Body mass index (BMI) was calculated using the standard formula (weight[kg]/[height[m]]²). Pulse rate (a marker of physical fitness), and systolic and diastolic blood pressure were also recorded. Enquiries were made about father’s occupation (coded according to the Registrar General’s social class schema), amount of physical exertion during recreation (coded as ‘sufficient’, ‘insufficient’), smoking status (nil, slight, moderate, heavy), and alcohol consumption (nil, occasional, regular).

**Ascertainment of dementia death**

Individuals enrolling in Glasgow university between 1948 and 1968 were traced using the procedures of the NHS Central Registers to obtain details of emigration, and, for deceased participants, date of death and contributing causes as recorded on death certificates from 1971 onwards. All diagnoses recorded on death certificates were coded according to the International Classification of Diseases (ICD) 9th and 10th revisions. Dementia cases were identified by any mention of codes 290.0 to 290.4, 294.9, 331.0 to 331.2, 331.9 (ICD-9), and codes F00, F01, F03, F09, G30, G31 (ICD-10) [16, 17]. Findings from two studies suggest that using data on dementia death captures the majority of dementia cases. In a UK study, 71.5 % of people with dementia confirmed at a tertiary-referral memory clinic who subsequently died during the next decade had the condition correctly recorded on their death certificates [18] and, in a separate group where multiple sources were used to identify dementia, 83 % of known cases were found using death certificates alone [19].

**Statistical analyses**

We excluded women in the cohort (N = 2701) as there were too few dementia events (N = 21 deaths) in this group to facilitate analyses. In order to focus on a pre-morbid sample, men aged greater than 30 years at university entry were also omitted (N = 482). This resulted in a sample of 11,271 men which, after exclusions for the reason of missing data, gave us an analytical sample of 9547. After ascertaining that the proportional hazards assumption had not been violated, we constructed Cox regression models [20] for the association of obesity/overweight and other baseline variables with dementia-related deaths. The timescale was calendar days from examination date with follow-up censored at the date of emigration, death from other causes, or the end of December 2012 (whichever came first). All analyses were conducted using R version 3.2.1.

**Internal and external comparison**

To contextualise our data, particularly for weight, we compared baseline characteristics in the Glasgow alumni study with those seen in three contemporary surveys of the Scottish male population (1995, 1998, 2003) [16, 17] in the same baseline age range (16–30 yr). Additionally, to show our data have predictive validity, we also report the associations of overweight/obesity and other risk factors with cardiovascular disease death in the Alumni study. Should known relationships be replicated, this gives us increased confidence in our very novel results for dementia.

**Results**

In Table 1 we show the baseline characteristics of the Alumni sample and compare these results with those of men of the same age range from three contemporary Scottish Health Surveys. Levels of CVD risk factors were generally more favourable in the Alumni. This was particularly evident for our principal exposure of interest, BMI: while obesity occurred in 10 % of the present day sample, it was essentially non-existent in the Glasgow Alumni (0.4 %) surveyed up to 55 years earlier. Corresponding values for overweight were 39.9 and 6.8 %. Alumni were also somewhat less likely to smoke and much less likely to drink alcohol but had higher blood pressure. In keeping with a privileged cohort of university students from the era, there
was a greater representation of alumni from higher social class backgrounds than in the population-wide Scottish Health Surveys. Comparison of the difference in other baseline characteristics, such as physical inactivity, are complicated by different measurement approaches.

In the analytic sample of 9547 men, an average of 50.6 years follow up gave rise to 2537 (26.6 %) deaths. Of these, 140 study members had dementia recorded on some part of their death certificate and 1157 had mention of CVD but no dementia (42 individuals had both recorded and were included in the dementia analyses but excluded from the CVD analyses). In Table 2 we depict the age-adjusted associations of overweight and other CVD risk factors with dementia and CVD death. In these analyses we collapsed the obese and overweight categories owing to insufficient numbers of dementia deaths (N = 2) in the obese group. As anticipated, many of the indices depicted in Table 2 were related to CVD mortality several decades later. This included body mass index where the category of overweight (hazard ratio; 95% confidence interval: 1.29; 1.05, 1.59) and a standard-deviation-increase in BMI (1.06; 1.00, 1.12) was associated with elevated CVD rates. Other risk factors shown to be related to CVD risk were low childhood socioeconomic status, reduced physical stature, smoking, and higher levels of each component of blood pressure.

In the main analyses where we related overweight and other confirmed CVD risk factors to dementia risk, there was little evidence of a gradient. Thus, BMI (one

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**Table 1** Comparison of obesity/overweight and other baseline characteristics of male University of Glasgow alumni (1948–68) with male Scottish Health Survey participants (1995, 1998, 2003)

|                      | Glasgow Alumni (N = 9547) | Scottish Health Surveys (N = 2362) |
|----------------------|---------------------------|-----------------------------------|
| Age (years) Mean (SD) Range | 20.5 (2.7)  | 23.7 (4.5) |
| Father’s occupation | I (high) N (%)  | 1836 (20.0)  | 128 (6.6) |
|                      | II N (%)   | 3276 (35.7)  | 301 (15.4) |
|                      | III N (%)  | 3401 (37.0)  | 946 (50.0) |
|                      | IV + V N (%) | 669 (7.3)   | 577 (30.0) |
| Physically inactive   | N (%)      | 1049 (12.7)  | 1346 (57.0) |
| Body mass index (kg/m²) Mean (SD) | 21.6 (2.2)  | 24.5 (4.1)   |
| Obesity              | N (%)      | 35 (0.4)     | 219 (10.0)  |
| Overweight           | N (%)      | 647 (6.8)    | 871 (39.9)  |
| Pulse rate (beats/minute) Mean (SD) | 74.5 (10.3) | 70.3 (11.4)  |
| Systolic blood pressure (mmHg) Mean (SD) | 130.7 (13.1) | 127.0 (11.1) |
| Diastolic blood pressure (mmHg) Mean (SD) | 77.2 (8.6)  | 65.3 (10.4)  |
| Smoker               | N (%)      | 3019 (33.3)  | 884 (37.9)  |
| Drinks alcohol       | N (%)      | 4483 (54.4)  | 1605 (75.2) |

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*Categorised according to the UK Registrar General classification of occupations into I (professional), II (intermediate), III (skilled), and IV + V (semi- and unskilled). BMI ≥30 kg/m² for obesity, BMI ≥25 kg/m² for overweight. *Categorised as any or nil. *Categorised as occasional/regular or nil (Alumni) or at least weekly (SHS).

Discussion

The main finding of this study was of no association between overweight in youth and later dementia-related death over a period of up to 64 years. That we found no such link in a group of individuals who would have been free of the symptoms of dementia at weight measurement raises the possibility that the observation of an apparent protective effect of higher BMI against dementia [8, 9] is due to reverse causality. That is, the diminished self-care in people experiencing the early stages of dementia, as manifested by a poor diet, leads to weight loss and a spurious inverse BMI–dementia association. That smoking was associated with an elevated dementia risk appears to support some studies of middle- and older-aged populations [4]. The replication of associations between a range of risk factors and CVD gives us a degree of confidence in our new results for dementia.

The large sample size and long duration of follow up gives us adequate power to identify associations, if they
existed. Also, particularly for the era in which these alumni attended university, they would have been among a small, unusually well educated and therefore privileged elite. As such, there would have been very little heterogeneity in educational attainment in these alumni. In aetiological analyses such as our own, this is a distinct advantage: education, known to be related to overweight and dementia, cannot be a confounder in the present dataset when there is no variation in this characteristic.

The study is not of course without its limitations, however. Risk factors were measured only once and levels will have changed in the succeeding decades. Moreover, we analyzed data on men only, so the extent to which our results may be generalized to women is unclear. Lastly, our use of dementia death as our endpoint of interest is somewhat unconventional. As described, however, there is good evidence that the use of death certification captures the majority of dementia cases [18, 19]. As such, we [6, 16, 17, 21, 22], and other groups [9, 23–26], have used dementia death data in other contexts to provide insights into the aetiology of the disorder.

**Conclusion**

Overweight was unrelated to dementia deaths in this population of premorbid university alumni. This observation potentially calls into question the previously reported apparent protective role of overweight and obesity against dementia.

**Abbreviations**

BMI: Body mass index; CVD: Cardiovascular disease; ICD: International Classification of Disease

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**Availability of data and materials**

For data requests, please contact Professor George Davey Smith (KZ.Davey-Smith@bristol.ac.uk).

**Authors’ contributions**

GDB generated the idea for the study; GDB and TCR prepared the manuscript; BG, MJ, and GDS were responsible for the follow-up of the study participants; TCR conducted the analyses; and all authors revised the manuscript for intellectual content. All authors read and approved the final manuscript.

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**Table 2** Hazard ratios (95% confidence intervals) for the association of obesity/overweight and other baseline cardiovascular disease risk factors in relation to dementia and cardiovascular disease death: University of Glasgow male alumni (N = 9547)

|                      | Dementia                |                | Cardiovascular disease |                |
|----------------------|-------------------------|----------------|------------------------|----------------|
|                      | N                       | Deaths         | HR (95% CI)            | P value | Deaths | HR (95% CI) | P value |
| Body mass index      | 9493                    | 140            | 0.94 (0.80, 1.13)      | 0.55    | 1151   | 1.06 (1.00, 1.12) | 0.072   |
| Overweight           | 9493                    | 140            | 0.93 (0.49, 1.79)      | 0.84    | 1151   | 1.29 (1.05, 1.59) | 0.014   |
| Father occupation    | 9182                    | 140            | 1.24 (0.89, 1.73)      | 0.20    | 1137   | 1.13 (1.01, 1.27) | 0.040   |
| No physical activity | 8240                    | 135            | 0.50 (0.28, 0.89)      | 0.018   | 1090   | 0.93 (0.78, 1.11) | 0.41    |
| Height               | 9500                    | 140            | 0.89 (0.76, 1.05)      | 0.18    | 1151   | 1.08 (1.02, 1.14) | 0.010   |
| Pulse rate           | 9184                    | 139            | 0.96 (0.80, 1.15)      | 0.67    | 1141   | 1.04 (0.98, 1.10) | 0.18    |
| Systolic blood pressure | 9489                   | 140            | 0.81 (0.67, 0.98)      | 0.028   | 1156   | 1.15 (1.09, 1.22) | <0.001  |
| Diastolic blood pressure | 9468                   | 140            | 0.84 (0.71, 1.00)      | 0.054   | 1153   | 1.08 (1.02, 1.15) | 0.009   |
| Smoker               | 9068                    | 132            | 1.42 (1.00, 2.01)      | 0.047   | 1088   | 1.53 (1.36, 1.73) | <0.001  |
| Alcohol consumption  | 8245                    | 102            | 1.18 (0.79, 1.76)      | 0.42    | 860    | 0.88 (0.76, 1.01) | 0.060   |

*CVD cases were identified by any mention of codes 390–459 for ICD-9 and codes 100-199 for ICD-10 but no mention of dementia anywhere on the death certificate. Hazard ratios are age-adjusted and expressed per standard deviation disadvantage (height values were reversed). BMI ≥25 vs <25 kg/m². Occupational classes III, IV + V vs I + II (high). *Recreational physical activity categorised as ‘insufficient’ in the examining physician’s opinion. Any amount of tobacco vs nil. Occasional/regular drinker vs nil
Competing interests
The authors declare that they have no competing interests.

Consent for publication
Not applicable.

Ethics approval and consent to participate
Ethical approval to follow-up study members was granted by the Multi-Centre Research Ethics Committee in Scotland. With this being an historical data linkage study, it was not possible, nor required by this ethical committee, to gain informed consent from individual study members.

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