Sociodemographic and lifestyle risk factors for incident dementia and cognitive decline in the HYVET*

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Abstract

Introduction: previous studies have suggested that smoking, living alone and having a high body mass index may increase risk of developing dementia whereas a normal body mass index, having received education and moderate alcohol consumption may decrease risk. Dementia risk also increases with age and is thought to be higher in hypertensives.

Method: we used data collected in the Hypertension in the Very Elderly Trial (HYVET), and cognitive function was assessed using the Mini-Mental State Examination (MMSE) at baseline and annually. Participants with a fall in MMSE to <24 or with a fall of 3 points in any 1 year were investigated further. The association of baseline sociodemographic, medical and lifestyle factors with incident dementia or decline in MMSE scores was assessed by regression models.

Results: incident dementia occurred in 263 of 3,336 participants over a mean follow-up of 2 years. In multivariate analyses, being underweight, BMI <18.5 (HR 1.90, 95% CI 1.06–3.39) or obese, BMI >30 (HR 1.84, 95% CI 1.24–2.72), increased risk of incident dementia as did piracetam use (HR 2.72, 95% CI 1.60–4.63). Receiving formal education was associated with a reduced risk (HR 0.59, 95% CI 0.45–0.78). There was no association with smoking, alcohol and gender. Similar results were found when examining mean annual change in the MMSE score.

Discussion: our results for BMI and education agree with those from other studies. The increased risk associated with piracetam may reflect awareness of memory problems before any diagnosis of dementia has been made. Trial participants may be healthier than the general population and further studies in the general population are required.

Keywords: dementia, cognitive decline, sociodemographic, predictor, elderly

Introduction

Dementia is a distressing condition and its prevalence increases with age. It is estimated to occur in up to 20% of those aged 80 and over and 40% at 90 and over [1]. Various sociodemographic and lifestyle factors have been shown to be associated with an increased risk of dementia, including smoking, high alcohol consumption or abstinence, low educational level, obesity and living alone [2–7]. The prevalence of dementia is also higher in females than in males, although this may be partly due to higher levels of education in males, or to other factors including post-menopausal loss of the anti-oxidant effects associated with oestrogen [8–10]. It has also been suggested that Chinese and European

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or European origin populations differ in terms of dementia type with the Chinese manifesting higher levels of vascular dementia and Europeans, Alzheimer’s disease although this is becoming less clear cut [11]. Whether this may have been due to genetic differences, physiological differences or lifestyle is not clear [11].

A recent meta-analysis of longitudinal studies found an increased risk for dementia with current smoking [12]. A systematic review and meta-analysis including only longitudinal studies concluded that low to moderate alcohol use was associated with a 37% reduced risk of incident dementia ($P < 0.0001$) [4]. It has been suggested that the anti-oxidant properties of the flavonoids in wine may help prevent the oxidative damage which has been associated with dementia [12–14]. Alcohol also increases levels of HDL cholesterol and fibrinolytic factors leading to lower platelet aggregation and possibly lower risk of stroke or ischaemia [15, 16]. A low body mass index (BMI) (<21) or high (>29) may increase risk of dementia or cognitive decline [17–20]. It may be that low BMI reflects the start of the dementia processes and associated weight loss prior to any observable change in cognitive functioning and that high BMI is associated with a generally higher cardiovascular risk.

Loneliness, living alone and a lack of close social ties have also been shown to increase the risk of developing dementia in longitudinal studies with relative risks (RR) reported at levels as high as 1.9 [95% confidence intervals (CI) 1.2–3.1] [5–7]. Conversely, education and learning seem to contribute to cognitive reserve and have either a protective or a masking effect against a deleterious change [21–24]. The apparent protective effects of education and cognitive activity need to be interpreted with caution as causality is far from clear.

The Hypertension in the Very Elderly Trial (HYVET) was designed to investigate the risks and benefits of treating very elderly hypertensives and as such recruited a unique group at high risk of dementia. The main double-blind trial has now ended and has reported that treatment was associated with important reductions in mortality, stroke and heart failure [25]. The HYVET is unique in that it examined only those aged 80 and over and assessed incident dementia. Sociodemographic and lifestyle factors were collected at baseline thus allowing an investigation into the effect of risk factors, other than hypertension, on incident dementia [26].

**Method**

The HYVET was a randomised double-blind placebo-controlled trial and employed an antihypertensive treatment regimen of indapamide sustained release 1.5 mg with the optional addition of perindopril 2–4 mg if required to achieve a target blood pressure of 150/80 mmHg. All participants were hypertensive, requiring a sitting systolic blood pressure of $\geq 160$ mmHg and a standing pressure of $\geq 140$ mmHg. The baseline diastolic pressure was required to be $\leq 110$ mmHg. Trial participants were aged 80 and over, had no clinical diagnosis of dementia at baseline and did not require daily nursing care. Cognitive function assessment using the Mini-Mental State Examination (MMSE) was carried out at baseline and annually thereafter. The MMSE was administered in the local language and appropriate training was provided to the investigators. The trial had a 2-month placebo run-in phase and collected baseline data pertaining to sociodemographic characteristics at the baseline visit prior to randomisation. Participants were recruited from 195 hospitals and general practitioner-based centres in Western and Eastern Europe (56.8%), China (40.8%), Tunisia and Australasia (2.4%). The trial included 3,336 patients with longitudinal data on cognitive function. If participants had an MMSE score that fell to <24 or fell >3 points in any 1 year, they were assessed further in order to investigate possible incident dementia. Further assessment required data pertaining to the diagnostic criteria of dementia from the Diagnostic Statistical Manual (DSM) edition IV, a CT scan and Modified Ischaemic Score (MIS). If a CT brain scan was not obtained due to lack of available equipment or patient refusal then the full Hachinski Ischaemic Score (HIS) was collected. In cases where a CT scan was obtained, a copy of the film was assessed by two independent neuroradiologists based at Imperial College London and blind to all other patient data. An expert committee (the dementia committee detailed in the acknowledgements section) used the information above, in addition to serial MMSE scores and copies of clock drawing tests completed by the patients to arrive at a diagnosis. Baseline sociodemographic, lifestyle and other data were collected prior to randomisation and included living arrangements, gender, smoking and alcohol consumption, and educational level. Height and weight were measured and BMI was calculated (kg/m²). BMI was divided into categories using the recommended cutoffs of <18.5 underweight, 18.5–24 normal weight, 25–29 overweight and $\geq 30$ obese for those of European genetic descent and <18.5 underweight, 18.5–22.99 normal weight, 23–24.99 overweight, $\geq 25.7$ obese for the Chinese participants [27, 28].

The investigators were asked to collect information about all drugs currently being taken by the patient including use of nootropic drugs such as piracetam. The effect of the trial treatment on incident dementia and cognitive decline has been published and suggested a possibly reduced rate [hazard rate (HR) 0.86, 95% CI 0.67–1.09]. When combined with other similar placebo-controlled trials in a meta-analysis, the pooled RR was 0.87 (CI 0.76–1.00, $P = 0.045$) [29].

**Statistical analyses**

Cox proportional Hazard models were used to investigate the relationship between each baseline risk factor and incident dementia, both with and without adjustment for treatment group allocation and in a multivariate model with all risk factors examined here. Proportional hazard assumptions were tested. The association of baseline risk factor with the mean annual change in the MMSE score was also examined using
linear regression models both univariate and multivariate. All analyses were carried out in SAS version 9.1.

The HYVET trial was funded by grants from the British Heart Foundation and the Institute de Recherches Internationales Servier. The trial was co-ordinated by the Department of Care of the Elderly, Imperial College London. The Imperial College was the sponsor of the trial. The analysis, interpretation of the data, generation of the manuscript and decision to submit for publication were carried out independently of the funding bodies.

Results

There were 3,336 HYVET participants who had at least one follow-up MMSE and who were to be evaluated in accordance with the algorithm to determine possible incident dementia cases. A total of 263 cases were diagnosed, 126 in the active and 137 in the placebo groups. The baseline MMSE was a median of 26. The mean follow-up was 2 years for incident dementia with 7,400 patient-years of follow-up. The HYVET countries and centres started recruitment when they received all regulatory approvals and this meant that recruitment date varied, however when the trial was stopped early all patients remaining in follow-up at that time returned for a final visit and these took place between July 2007 and October 2007.

Baseline characteristics and the relationships between sociodemographic baseline risk factors and incident dementia are shown in Table 1. Just over 21% lived alone, and this was associated with a 29% reduction in risk of incident dementia (HR 0.71, 95% CI 0.52–0.97, \( P = 0.033 \)) when adjusted for trial treatment. People having received any education compared to those with no formal education were associated with a reduction in risk of 41% (HR 0.59, 95% CI 0.45–0.78, \( P = 0.0002 \)). Piracetam was the only nootropic used in any quantity and is usually used or prescribed (depending on the local drug regulations) for memory problems. In HYVET, piracetam use was associated with a more than 2-fold increase in risk despite the HYVET participants entering the trial without a clinical diagnosis of dementia. Low and high BMI were also associated with an increased risk of incident dementia with underweight participants twice as likely to develop dementia and obese participants at a 64% increased risk.

When all risk factors were entered into a multiple regression model education, piracetam use and being obese or underweight at baseline remained significant. Additional inclusion of baseline factors that may impact upon dementia, systolic blood pressure, previous cardiovascular disease reported at baseline and adjustment for region of recruitment resulted in a loss of significance but no change in the direction of relationship with regard to education (HR 0.70, 95% CI 0.46–1.06, \( P = 0.095 \)) and did not change the direction or significance of any other results. Proportional hazards assumptions were not violated.

Discussion

In univariate analyses of the same factors with mean annual change in MMSE as the dependent variable, living alone or being educated was associated with a very slight positive change in the mean MMSE change per year. Being older or underweight was associated with a slight negative change in the mean annual MMSE change. In multivariate analyses these factors remained significant, see Table 2.

Similarly, additional adjustment for systolic blood pressure, previous cardiovascular disease and region of recruitment did not result in any change in the direction or significance of results.

Sociodemographics and dementia in the HYVET

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Trial participants had a baseline median MMSE score of 26 which is consistent with studies published in the literature. Population studies have reported median values of 25 in people aged 80–84 with 5–8 years of education and 26 in those with 9–12 years of education. The corresponding value for 0–4 years of education was 16 with median values still lower in those aged 85 and over [30]. It is interesting to note that gender had no impact on incident dementia in these analyses and it may be that the gender differences are attenuated in these very elderly groups particularly with females several years post-menopause [9]. Smoking and alcohol consumption were not associated either with incident dementia or with change in MMSE. However, in our study the prevalence of reporting of smoking or regular dinking was very low possibly reflecting the effect of higher mortality rates in smokers or drinkers or inability to participate in the trial if these factors were associated with poorer cognitive function, earlier onset of dementia or other co-morbidities.

Moderate consumption of alcohol has been associated with a lower risk of dementia in studies of predominately younger elderly although it is not yet clear whether this still applies as the cardiovascular system ages and dementia risk increases. High and low BMI values have also been associated with increased risk of incident dementia in populations aged between 60 and 88 years [17, 18].

Previous studies have consistently reported that higher educational level is associated with lower rates of incident dementia [8, 21–24]. Lifetime exercise of higher cognitive functions and occupational attainment may also be associated with reduced incidence of dementia [8, 21–24]. We did not collect occupational data in HYVET because of the difficulties in assessing previous work history and job and leisure behaviour, but education tended to protect against dementia. Although the proportion of people taking piracetam was very low, piracetam use was associated with an increased risk of dementia. Although we excluded people with a clinical diagnosis of dementia from the trial, it is possible that participants prescribed piracetam had sought medical advice for memory problems indicating early undiagnosed cases of dementia or cognitive decline. There is evidence in the literature to suggest that self-report of memory problems could indicate an early stage in dementia [31]. We found that
Lives alone (%) 21.2 (707) HR 0.71 (95% CI 0.66–0.76).
Consumes alcohol (%) 17.6 (588) HR 0.92 (95% CI 0.86–0.99).
Current smoker (%) 6.1 (202) HR 1.30 (95% CI 1.13–1.50).

BMI normal weight (%) 48.9 (1,630) 1 (referent group) 1 (referent group) 1 (referent group).
BMI (overweight) (%) 39.4 (1,313) HR 1.10 (95% CI 0.84–1.45).
BMI (obese) (%) 8.6 (287) HR 1.61 (95% CI 1.09–2.37)**.

Educational level (%)
None 27.4 (915) 1 (referent group) 1 (referent group) 1 (referent group).
Some 72.6 (2,421) HR 0.59 (95% CI 0.59–0.78)*.

Piracetam use (%) 2.2 (72) HR 2.52 (95% CI 1.38–3.90)*.

**P < 0.05, *P < 0.01.

Table 2. Relationship between baseline risk factors and mean annual change in the Mini-Mental State Examination score

<table>
<thead>
<tr>
<th>Linear regression—unadjusted</th>
<th>Linear regression—adjusted for trial medication</th>
<th>Multivariate linear regression—adjusted for risk factors detailed in this table and trial medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Relationship of baseline risk factor with annual change in MMSE Slope [95% confidence intervals (CI)]</td>
<td>Relationship of baseline risk factor with annual change in MMSE Slope [95% CI]</td>
<td>Relationship of baseline risk factor with annual change in MMSE Slope [95% CI]</td>
</tr>
<tr>
<td>Age at baseline</td>
<td>−0.06 (−0.09; −0.03)*</td>
<td>−0.06 (−0.09; −0.04)*</td>
</tr>
<tr>
<td>Gender</td>
<td>−0.09 (−0.26; 0.08)</td>
<td>−0.09 (−0.26; 0.08)</td>
</tr>
<tr>
<td>Current smoker</td>
<td>0.02 (−0.33; 0.36)</td>
<td>0.02 (−0.33; 0.36)</td>
</tr>
<tr>
<td>Consumes alcohol</td>
<td>0.10 (−0.12; 0.32)</td>
<td>0.10 (−0.12; 0.32)</td>
</tr>
<tr>
<td>Lives alone</td>
<td>0.26 (0.05; 0.47)**</td>
<td>0.26 (0.05; 0.47)**</td>
</tr>
<tr>
<td>Body mass index (underweight)</td>
<td>−0.65 (−1.13; −0.16)*</td>
<td>−0.65 (−1.13; −0.16)*</td>
</tr>
<tr>
<td>Body mass index (overweight)</td>
<td>0.09 (−0.08; 0.26)</td>
<td>0.09 (−0.08; 0.26)</td>
</tr>
<tr>
<td>Body mass index (obese)</td>
<td>0.21 (−0.09; 0.51)</td>
<td>0.21 (−0.09; 0.51)</td>
</tr>
<tr>
<td>Educated</td>
<td>0.34 (0.15; 0.52)**</td>
<td>0.34 (0.15; 0.52)**</td>
</tr>
<tr>
<td>Piracetam use</td>
<td>−0.49 (−1.08; 0.11)</td>
<td>−0.49 (−1.09; 0.11)</td>
</tr>
</tbody>
</table>

**P < 0.05, *P < 0.01.

Living alone was associated with a reduced risk of dementia in univariate analyses and this is in contrast to studies in the literature which have found living alone to be associated with an increased risk [5–7]. However, the association was attenuated in multivariate analysis. This difference may, in part, reflect the fact that participants in our study were a healthier group than might be found in studies of the general population.

The eligibility criteria for HYVET excluded people requiring nursing care or with conditions likely to severely limit survival. In our healthier trial participants, living alone might reflect higher functioning (physical and cognitive) and greater levels of health compared to those living with spouses, families or in supported housing [32]. Our results from examining risk factors for cognitive decline showed similar outcomes to those from the HYVET study.
for incident dementia, with older age associated with a negative change in mean annual MMSE. This is consistent with the literature related to cognitive function and ageing [33].

It is of course possible that the different cultural backgrounds and levels of education across our population plus unmeasured confounders such as health status at midlife may impact upon our results. However, case identification was based both on crossing a threshold <24 and an annual fall >3 points on the MMSE and this should have aided case finding in those with low levels of education whose baseline performance may have been lower. In addition to this adjustment for region of recruitment and further factors that have been associated with dementia incidence, resulted in education losing its significance as a protective factor but did not change other findings.

In summary, low or high BMI was the most important factor influencing risk of dementia or cognitive decline with educational level almost certainly an important factor. As there are a few studies in this age group, however, and as the trial participants may not be representative further studies are needed to confirm or refute these results.

Key points
- In a very elderly (≥80 years) hypertensive population with a mean follow-up of 2 years, incident dementia was significantly more likely to occur in those that were overweight [body mass index (BMI) <18.5] at baseline.
- Similarly, being obese (BMI >30 Europeans and >27.5 Chinese) at baseline also significantly increased likelihood of incident dementia.
- There were no associations between baseline smoking, alcohol consumption or gender and incident dementia. Receiving higher levels of education was associated with lower levels of incident dementia.
- The findings for BMI and education agree with previous findings in differing populations.

Acknowledgements
We wish to acknowledge all HYVET committee members, country co-ordinators, investigators (see appendix) and the work of Professor C. Nachev (Steering committee member, National Co-ordinator of Bulgaria and HYVET investigator from 1998 until his death in 2005).

Conflicts of interest
The HYVET trial was funded by grants from the British Heart Foundation (a charity) and Servier International. The trial medication was provided by Servier International. These grants were made to Imperial College London who was the sponsor of the trial and employed the staff at the co-ordinating office. Salary support and speaker fees were received for Dr Nigel Beckett and Dr Ruth Peters. Salary support was received for Ms Ruth Poulter. Consultancy fees were received by Professor Bulpitt. Investigator fees were paid to trial investigators in accordance with the contractual arrangements between Imperial College and trial investigators. No additional fees were paid from these grants to any co-authors.

Appendix
References


Predictors of mortality among a national sample of elderly widowed people: analysis of 28-year mortality rates

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Abstract

Objective: to identify predictors of mortality among a national sample of elderly widowed people 28 years post-baseline interview.

Design and setting: face to face home interview survey across England.

Measures: physical, psychological, social, and socio-economic status and circumstances.

Results: excess risk of mortality, which had been noted up to six months post bereavement among males aged 75+, had disappeared. In contrast to findings up to 13 years post-bereavement, neither psycho-social factors, social circumstances nor social class independently predicted differentials in mortality when analysed up to 28 years post-bereavement. The most significant, independent predictors, up to the 28-year term, were, as would be expected, male sex, older age, poorer physical functioning, and expressed ‘relief at the death of the spouse’. When the sample was split by duration of widow(er)hood male sex and older age retained significance.

Conclusion: the increasing frailty of the sample overall, and reduced statistical power in split-sample analyses, may explain the loss of significance of physical functioning and ‘expressed relief at the death’ in the split-sample results. The psycho-social risk factors for mortality after bereavement reduce over time, although further examination of expressed relief would be worthwhile.

Keywords: physical functioning, survival, mortality, bereavement, old age, elderly

Introduction

Large studies across the developed world have indicated that married people have lower mortality rates than those who are widowed, divorced, separated or single [1–3]. Murphy, Grundy and Kalogirou (2007) [4] investigated mortality differentials by marital status among people aged 40–89 for seven European countries, and confirmed the mortality