Association of depression with subsequent mortality, cardiovascular morbidity and incident dementia in people aged 80 and over and suffering from hypertension. Data from the Hypertension in the Very Elderly Trial (HYVET)

RUTH PETERS1, ELISABETE PINTO1, NIGEL BECKETT1, CAMERON SWIFT2, JOHN POTTER3, TERRY MCCORMACK4, MARIA NUNES5, JOHN GRIMLEY-EVANS6, ASTRID FLETCHER7, CHRISTOPHER BULPITT1

1Care of the Elderly, Faculty of Medicine, Imperial College London, Du Cane Road, London W12 0NN, UK
2Clinical Age Research Unit, Department of Clinical Gerontology, King’s College Hospital, Bessemer Road, London SE5 9PJ, UK
3Ageing & Stroke Medicine Section, School of Medicine, Health Policy and Practice, University of East Anglia, Norfolk NR4 7TJ, UK
4Whitby Group Practice, Spring Vale Medical Centre, Whitby YO21 1SD, UK
5Centro Universitário São Camilo, Rua Raul Pompéia, 144, São Paulo 05025-010, Brazil
6Nuffield Department of Clinical Medicine Division, John Radcliffe Hospital, Oxford OX3 9DU, UK
7Department of Epidemiology & Population Heath, London School of Hygiene and Tropical Medicine, Keppel Street, London WC1E 7HT, UK

Address correspondence to: Ruth Peters. Tel: +44 (0)20 75948974; Fax: +44 (0)20 740222150. E-mail: r.peters@imperial.ac.uk

Abstract

Background: depression is common in elderly people and may be associated with increased cardiovascular risk and incident dementia.

Method: participants in the Hypertension in the Very Elderly Trial (HYVET) completed a depression screening instrument, the Geriatric Depression Score (GDS), at baseline and annually. We examined the association of GDS score with incident stroke, mortality and dementia using Cox proportional hazards models (hazard ratios, HR and 95% confidence intervals, CI) adjusted for treatment group and other potential confounders.

Results: 2,656 HYVET participants completed the GDS. The mean follow-up was 2.1 years. A GDS score ≥6 was associated with increased risks of all-cause (HR 1.8, 95% CI 1.4–2.3) and cardiovascular mortality (HR 2.10, 95% CI 1.5–3.0), all stroke (HR 1.8, 95% CI 1.2–2.8) and all cardiovascular events (HR 1.6, 95% CI 1.2–2.1). Risk of incident dementia also tended to be increased (HR 1.28, 95% CI 0.95–1.73). Each additional GDS point at baseline also gave rise to a significantly increased risk of fatal and non-fatal cardiovascular events, all-cause mortality and dementia.

Conclusion: there was a strong association between baseline depression scores and later fatal and non-fatal cardiovascular endpoints over a mean follow-up of 2 years in a hypertensive very elderly group. The mechanism of this association warrants further study.

Keywords: cardiovascular diseases, aged, depression, hypertension, mortality

Introduction

Depression or depressed mood is common among older people with an average prevalence of clinically relevant syndromes estimated at 13.5% at ages ≥55 years [1, 2] and higher in women than in men [2]. Many studies have found an association between depression, poor quality of life and increased risk of cardiovascular disease [3–5]. Depression was associated with an increased risk of coronary disease in a meta-analysis [6] and with increased risk of all-cause mortality and stroke or transient ischaemic attack in the Framingham Heart Study [7, 8]. Plausible causal mechanisms have been put forward in the literature [9–13].
Depression may also be associated with increased risk of later dementia [14].

Depression is common after stroke, heart attack and in early dementia [13–15], and is strongly associated with disability [16, 17], raising the possibility that the association could be confounded or subject to reverse causation.

The Hypertension in the Very Elderly Trial (HYVET) [18] enrolled hypertensive people aged ≥80 years. As part of a quality-of-life sub-study, depression in HYVET was assessed at baseline and then annually using the Geriatric Depression Scale (GDS) [19], and provided an opportunity to study the association of depression with stroke, cardiovascular morbidity, mortality and dementia in a high-risk group of people.

Method

Participants

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. Ethical and regulatory approvals were obtained prior to data collection.

All participants were hypertensive defined by a sitting systolic blood pressure of ≥160 mmHg and a standing pressure of ≥140 mmHg, with a baseline diastolic pressure of ≤110 mmHg. Trial participants were aged ≥80 years, had no clinical diagnosis of dementia at baseline and did not require daily nursing care. The trial had a 2-month placebo run-in phase with collection of baseline data on participant characteristics prior to randomisation. Participants gave informed consent and were recruited from hospital and general practice settings.

Depression scores were collected using the 15-item GDS administered as part of a Quality of Life (QoL) questionnaire at baseline and annually thereafter. The QoL questionnaire was completed by the respondents willing to participate in this sub-study to the main trial. Participants were asked to complete the questionnaire themselves prior to having their blood pressures measured and other clinical assessments. The QoL questionnaire was provided in large text and in the local language after being translated, checked and back-translated where validated language versions were not previously available. Sixty-nine percent of people entering HYVET completed the GDS in the baseline QoL questionnaire. Those participants completing the QoL questionnaire were from centres in Eastern (45.9%) and Western (1.8%) Europe, China (49.0%), North Africa (2.6%) and Australasia (0.7%). Respondents were instructed to respond ‘yes’ or ‘no’ to 15 questions relating to how they had been feeling in the preceding week.

Outcomes

All-cause mortality, incident stroke, incident and worsening heart failure, and incident myocardial infarction (MI) were reported by the trial investigators and validated by an independent endpoint committee blinded to trial treatment. Mortality was further categorised into cardiovascular and non-cardiovascular mortality. The endpoint committee required copies of the case report forms declaring the event and supporting documentation such as death certificates, hospitalisation reports, CT scan reports and information on the results of investigations. Where these were provided in a language other than English, translations were also obtained. The committee included members that were representative of the high recruiting countries in HYVET and who could read Chinese and Cyrillic scripts.

Dementia was suspected in those participants who had a mini-mental state examination (MMSE) score that fell to <24 or by >3 points annually, and in these cases further diagnostic information was requested in the form of the Diagnostic Statistical Manual criteria, a CT scan (a copy of the film) and completed Modified Hachinski Score. A contemporary MMSE was also requested. If the participant did not consent to a CT, a full Hachinski score was required. The CT scan was evaluated by two independent neuroradiologists, and an expert committee made a diagnosis of dementia using the diagnostic information in addition to other information that had been gathered in the course of

<table>
<thead>
<tr>
<th>Table 1. Baseline characteristics</th>
<th>Geriatric Depression Score &lt;6</th>
<th>Geriatric Depression Score ≥6</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age—years (SD)</td>
<td>83.3 (3.0)</td>
<td>83.7 (3.2)</td>
<td>0.003</td>
</tr>
<tr>
<td>Percent female (%)</td>
<td>56.6 (1,001)</td>
<td>68.7 (609)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Previous stroke (%)</td>
<td>8.3 (146)</td>
<td>8.9 (79)</td>
<td>0.605</td>
</tr>
<tr>
<td>Previous cardiovascular disease* (%)</td>
<td>11.2 (199)</td>
<td>15.4 (137)</td>
<td>0.002</td>
</tr>
<tr>
<td>Education* (%)</td>
<td>None</td>
<td>36.9 (653)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Some</td>
<td>63.1 (1,116)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean sitting systolic blood pressure (mmHg) at entry (SD)</td>
<td>172.8 (8.9)</td>
<td>174.0 (8.7)</td>
<td>0.001</td>
</tr>
<tr>
<td>Mean standing systolic blood pressure (mmHg) at entry (SD)</td>
<td>168.0 (11.9)</td>
<td>168.2 (11.8)</td>
<td>0.591</td>
</tr>
<tr>
<td>Smoker (%)</td>
<td>7.1 (126)</td>
<td>5.4 (48)</td>
<td>0.097</td>
</tr>
<tr>
<td>Consumes alcohol (%)</td>
<td>15.7 (278)</td>
<td>15.9 (141)</td>
<td>0.910</td>
</tr>
<tr>
<td>Mean number of co-morbidities (SD)</td>
<td>1.6 (1.4)</td>
<td>2.0 (1.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Living alone (%)</td>
<td>18.5 (328)</td>
<td>22.9 (203)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean GDS (baseline) (SD)</td>
<td>2.2 (1.6)</td>
<td>9.3 (2.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median GDS (baseline)</td>
<td>2 (2–4)</td>
<td>9 (9–12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>(interquartile range)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean MMSE (baseline) (SD)</td>
<td>24.7 (4.5)</td>
<td>24.4 (4.7)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median MMSE (baseline) (interquartile range)</td>
<td>26 (22–28)</td>
<td>25 (22–28)</td>
<td>0.008</td>
</tr>
</tbody>
</table>

* Includes participants who reported having suffered from a stroke, myocardial infarction or heart failure prior to entry into the trial.

**Participants reporting having received no formal education compared to those who reported some level of formal education.
In common with other studies [20–22], we categorised the GDS score as a binary variable of a score ≥6 (to indicate depression) compared to <6. In secondary analyses, we also explored the GDS as a continuous variable. We used Cox proportional hazards models to investigate the association between the baseline GDS score with all-cause and cardiovascular mortality, fatal and non-fatal stroke events, fatal and non-fatal cardiovascular events (including cardiovascular mortality, all stroke, all heart failure and all MI) and incident depression.) compared to <6 are shown in Table 1.

Analyses were carried out for the association of GDS score with outcome (i) unadjusted, (ii) adjusted for treatment group and (iii) adjusted for multiple factors including age, sex, treatment allocation, country area, educational level, living alone, number of co-morbidities, previous cardiovascular disease, previous treatment and previously diagnosed hypertension. Proportional hazards assumptions were tested. This paper presents baseline GDS data and its relationship to subsequent trial endpoints. Effect of trial treatment on GDS scores will be published separately.

Results
A total of 2,656 completed questionnaires were received with GDS information and for 2,320 of these longitudinal MMSE data were also available (and therefore the possibility of assessment for incident dementia).

The participants who completed the QoL questionnaires were of a similar age to those who did not (mean age of those who completed the QoL was 83.5 years compared with 83.7 years) and sex, with 60.6% female compared with 60.2%. Mean follow-up was 2.06 years with only 17 participants being lost to follow-up during the HYVET.

A third of participants (n=887) had GDS scores of ≥6 indicating depressed mood, although investigators reported clinical depression in only 15 (0.6%). When this was examined by prior cardiovascular disease (stroke, myocardial infarction or heart failure; previous CVD), 32.3% of those without previous CVD reported GDS scores ≥6 compared to 40.8% in those with previous CVD.

The baseline characteristics of patients with a GDS of ≥6 compared with those with GDS <6 are shown in Table 1. A score of ≥6 was associated with being older, a female, a baseline history of CVD, some level of education, living alone, a slightly higher sitting systolic blood pressure, an increased number of co-morbidities and a slightly lower baseline MMSE.

Of those who completed QoL questionnaires, 294 (11%) participants died during follow-up; 146 (5.5%) of these were classified as cardiovascular deaths. There were 233 (8.8%) cardiovascular events and 173 (7.5%) cases of incident dementia.

A baseline GDS score of ≥6 was associated with a significantly increased risk of all-cause mortality [hazard ratio (HR) 1.8, 95% confidence intervals (CI) 1.4–2.3], all stroke...
95% CI 1.6 – ≥ calculated for a GDS of just adjusted model. When sensitivity and specificity values were calculated for a GDS of ≥6 compared to a GDS of <6, specificity was high, >90% for all-cause mortality, all stroke, cardiovascular mortality, cardiovascular events and dementia. Corresponding sensitivity values were low at 16% for all-cause mortality, 5% for stroke, 9% for cardiovascular mortality, 12% for cardiovascular events and 10% for dementia.

Similar results were observed in the analysis for GDS as a continuous variable (Table 3). In these analyses, there was an additional association with increased risk of dementia both in unadjusted analyses and when adjusted for multiple confounders (Table 3). Further adjustment adding baseline sitting systolic blood pressure, smoking and consumption of alcohol at baseline to the multivariate analysis made little material difference to the effect sizes.

Further examination of these relationships by subgroups of gender, ethnicity (Chinese versus non-Chinese) and presence of previous cardiovascular disease resulted in point estimates over unity for all outcomes and the majority of subgroups retaining significance. Caution must be applied in this area as although the association of the GDS and subsequent events was planned a priori, the evaluation of subgroups was not. The subgroups are by definition smaller than the main data set and, in the case of ethnicity, are also affected by length of follow-up with the Chinese patients entering the trial later and therefore contributing less patient years.

Discussion

We found that a GDS score of ≥6 was associated with an increased risk of all-cause and cardiovascular mortality and cardiovascular morbidity. The relationship between depression, mortality and cardiovascular mortality and morbidity is likely to be complex, with potential for confounding and reverse causation as well as a possible causal relationship between depressed mood and mortality or cardiovascular outcomes.

Mood was worse in those with a prior cardiovascular event [11–13, 15]. The association between mood and outcomes was seen over a relatively short follow-up period of 2 years. These suggest the possibility of reverse causation: outcome cardiovascular events may have reflected the greater occurrence, on average, of recurrent events in those with cardiovascular disease at recruitment.

There is a possibility of confounding by unmeasured disability. But adjusting for prior events, or other potential confounders, did not alter the risk estimates (although the possibility of residual confounding remains).

A further possibility is that depressed mood causes cardiovascular disease and mortality. This could be by several mechanisms such as less physical exercise, worse diet, the effects of antidepressant drugs or other postulated pathways including hypertension, hyperlipidaemia, endothelial injury, progressive atherosclerosis and thrombus formation [3–5]. This raises the possibility that treatment of depression could reduce the risk of vascular disease. Our findings require replication and exclusion of some alternative possibilities (such as following up a population known to be free of vascular disease or disability at baseline, or carefully controlling for the confounding effect of disability) before testing in an intervention trial.

A third of participants in the quality-of-life sub-study of the HYVET had GDS scores of ≥6, indicating depressed mood. This is much higher than found in population studies [20–22], and a possible limitation of the study is the use of the GDS, especially across different countries and cultures. However, the GDS is a well-established and a good screening instrument for depression, and was designed for use among older people [23–31]. Multiple cut-off points have been used with varying levels of sensitivity and specificity, the most frequently used, as in our study, being 5/6 with higher scores indicating more severe depression [23]. With cut-offs <6/6+, the 15-item GDS has a specificity for depression of 93.7% and sensitivity of 50%, respectively.

Respondents who completed the GDS were representative of the HYVET population and were very elderly, with the majority being female. They were hypertensive but relatively healthy, with a mean number of co-morbidities of 1.7, and almost 20% were living alone. The mean MMSE of participants was 24.6 (SD 4.5), a score compatible with their age and varied levels of education [23].

A strength of the study was the administration of the questionnaire with the answers provided by the patients before commencing the trial clinical examination. This may have provided a more accurate representation of the respondents’ views than would be reflected in the low levels of depression reported by the investigators.

The HYVET is the first to study a large population of very elderly individuals with hypertension and to have included the assessment of depression using the GDS. However, there are several limitations. We report here the association between baseline GDS scores and later events; however, the study was not designed to investigate this and was stopped early at the time of the second interim analysis due to a positive finding in favour of active treatment, resulting in a relatively short mean follow-up of 2.1 years. Moreover, although participants were unable to enter the study if they required nursing care, we did not collect rigorous information about activities of daily living, disablemty levels or maintenance of social networks, socioeconomic status or activity level. Participants were all hypertensive, and although a proportion of them were reported to have previous cardiovascular disease, there may also have been unreported or subclinical disease that we were not able to take into account. There is, therefore, the potential for uncontrolled confounding from unmeasured factors, including those above, or of reverse causality.
whereby unreported or unrecognised ischaemic events lead to depression rather than the other way around.

Key points

• Depressed mood is common in older people with hypertension.
• Higher depression scores were associated with an increased risk of a subsequent cardiovascular event, mortality and possibly dementia.
• These associations occurred over a short period of time, mean follow-up 2.1 years.
• The association may or may not be causal.

Acknowledgements

All persons mentioned in the acknowledgements have given written consent.

Conflict of interest

Imperial College received funding from the British Heart Foundation and Servier International to run the trial and support salary and consultancy costs for staff including Christopher Bulpitt, Nigel Beckett, Ruth Peters and Elisabete Pinto. Honoraria for speaking at symposia have also been received by Christopher Bulpitt, Nigel Beckett and Ruth Peters. No other authors report conflicts of interest.

Funding

The HYVET trial is registered with ClinicalTrials.gov number NCT00122811 http://clinicaltrials.gov/

The committee members and investigators for HYVET were as follows: Co-ordinating Centre: C.J. Bulpitt (lead investigator), A.E. Fletcher (co-investigator), N.S. Beckett (trial co-ordinator), R. Peters (deputy trial co-ordinator), HYVET co-ordinating team at Imperial College London (1999–2006);


Investigators: (*national co-ordinators)


We wish to acknowledge the work of Professor C. Nachev (Steering Committee member, National Co-ordinator of Bulgaria and HYVET investigator from 1998 until his death in 2005).

References

Agreement between self-reported and measured height, weight and body mass index in old age—a longitudinal study with 20 years of follow-up

ANNA K. DAHL†, LINDA B. HASSENG†, ELEONOR I. FRANSSON†, NANCY L. PEDERSEN‡

†Institute of Gerontology, School of Health Sciences, Box 1026, Jönköping University, 551 11 Jönköping, Sweden
‡Department of Psychology, University of Gothenburg, Göteborg, Sweden

Address correspondence to: A. Dahl. Tel: +46 36 10 13 24; Fax: +46 36 10 11 80. Email: anna.dahl@hhj.hj.se

Abstract

Background: self-reported body mass index (BMI) based on self-reported height and weight is a widely used measure of adiposity in epidemiological research. Knowledge about the accuracy of these measures in late life is scarce.

Objective: the study aimed to evaluate the accuracy and changes in accuracy of self-reported height, weight and BMI calculated from self-reported height and weight in late life.

Design: a longitudinal population-based study with five times of follow-up was conducted.

Participants: seven hundred seventy-four community-living men and women, aged 40–88 at baseline (mean age 63.9), included in The Swedish Adoption/Twin Study of Aging.

Methods: participants self-reported their height and weight in a questionnaire, and height and weight were measured by experienced research nurses at an in-person testing five times during a 20-year period. BMI was calculated as weight (kilogramme)/height (metre)².

Results: latent growth curve modelling showed an increase in the mean difference between self-reported and measured values over time for height (0.038 cm/year) and BMI (0.016 kg/m²/year), but not for weight.

Conclusions: there is a very small increase in the mean difference between self-reported and measured BMI with ageing, which probably would not affect the results when self-reported BMI is used as a continuous variable in longitudinal studies.

Keywords: body mass index, height, weight, reliability, elderly

Introduction

Older people are at a high risk of functional impairment and morbidity. Body mass index (BMI), calculated as kg/m², might give an estimation of a person’s health status. In the prediction and treatment of various diseases, the trajectory of BMI over time might be of greater clinical value than a single assessment. In epidemiological studies, BMI values are often based on self-reported weight and height (henceforth called self-reported BMI). The accuracy of self-reported BMI in old age has been evaluated by only a few studies, and to our knowledge, the accuracy of self-reported height, weight and BMI has not been previously studied in a longitudinal trial including older people.