Comorbid type 2 diabetes mellitus and hypertension exacerbates cognitive decline: evidence from a longitudinal study

LINDA B. HASSING1, SCOTT M. HOFER2, SVEN E. NILSSON4, STIG BERG4, NANCY L. PEDERSEN5,6, GERALD MccLearN3, BOO JOHANSSON1

1Department of Psychology, Göteborg University, Göteborg, Sweden
2Department of Human Development and Family Studies and 3Center for Developmental and Health Genetics, Pennsylvania State University, University Park, PA, USA
4Institute of Gerontology, School of Health Sciences, Jönköping, Sweden
5Department of Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden
6Department of Psychology, University of Southern California, Los Angeles, CA, USA

Address correspondence to: Linda B. Hassing, Department of Psychology, Göteborg University, Box 500, SE-405 30 Göteborg, Sweden. Fax: (+46) 31 773 4628. Email: Linda.Hassing@psy.gu.se

Abstract

Background: diabetes and hypertension are two highly prevalent diseases in the old population. They are highly related such that comorbidity is common.

Objectives: to examine (i) the independent impact of the respective diseases on cognitive decline in very old age and (ii) the interactive impact of the two diseases on cognitive decline.

Subjects: 258 individuals (mean age = 83 years), all non-demented at baseline. Of these, 128 individuals (non-cases) were free from diabetes and hypertension, 92 individuals had a diagnosis of hypertension, 16 had a type 2 diabetes mellitus diagnosis without hypertension, and 22 had comorbid diabetes and hypertension.

Method: a population-based longitudinal study of ageing (The OCTO-Twin Study), including four measurement occasions 2 years apart. The Mini-Mental State Examination was used to measure general cognitive function. Data were analysed using SAS Proc Mixed multilevel modelling.

Results: longitudinal trajectories indicated a steeper decline in cognitive function related to diabetes but not related to hypertension. However, the results indicated greatest cognitive decline among persons with comorbid diabetes and hypertension.

Conclusions: it is concluded that comorbidity of diabetes and hypertension produce a pronounced cognitive decline. This finding emphasises the importance of prevention and treatment of those highly prevalent diseases in the old population.

Keywords: hypertension, type 2 diabetes mellitus, cognitive decline, older age, longitudinal study, vascular disease

Introduction

Type 2 diabetes mellitus and hypertension are two highly prevalent diseases among the old that are known to be risk factors for vascular disease. The prevalence of type 2 diabetes is estimated to range between 15% and 25% in the age group of 65 years and older [1]. The corresponding numbers for hypertension range between 50% and 70% [1–3]. Diabetes and hypertension are furthermore highly related such that comorbidity is common [1].

Extensive research on the effects of diabetes on cognitive function in old age has provided mixed findings [4, 5]. Although the majority of the studies have found negative effects on cognitive functioning related to diabetes [6–8], several studies have reported no relationship [9, 10]. The effects of hypertension on cognitive function have also been a subject for extensive research [11]. Most studies indicate that hypertension is negatively related to cognitive test performance [12–14], although some studies report no association [15]. Variation in findings concerning the consequences...
of hypertension may be partially explained by age; thus, high blood pressure in young and middle age predicts lower cognitive performance whereas high blood pressure in old age has given mixed findings.

A methodological issue that may be a source of these conflicting results is that comorbid diseases are often not considered. The most important condition that has to be screened for or controlled when examining older samples is dementia. The significance of comorbid dementia was demonstrated in a recent study where it was found that initially observed differences between people with diabetes and people without diabetes in cognitive performance were no longer significant when dementia was accounted for [8]. It is also important to control for dementia when examining the impact of hypertension on cognitive function in old age, given that blood pressure decreases following the development of dementia. Thus, given the association between dementia and diabetes, respectively dementia and hypertension, it is possible that one reason for conflicting results as to whether hypertension and diabetes are related to lower cognitive functioning is that some studies control for dementia whereas others do not.

Little is known about the comorbid effect of diabetes and hypertension on cognitive function. For example, it is not known if it is more detrimental to have comorbid hypertension and diabetes than having only diabetes. Findings from the Framingham Heart Study indicated that comorbid diabetes and hypertension were associated with lower performance in tasks measuring visual organisation and memory [16]. Furthermore, Kuusisto and colleagues [17] found that people with comorbid hyperinsulinaemia and hypertension performed worse on several cognitive tasks compared with normoinsulinaemic hypertensive people.

The purpose of the present study was to examine the comorbid effects of type 2 diabetes and hypertension on cognitive decline across a 6-year interval in old individuals using the Mini-Mental State Examination [18].

Method

Participants

The participants were drawn from the ongoing population-based longitudinal study ‘Origins of variance in the Old-Old’ [19] which started in 1991. The full sample included 702 individuals at inclusion, in 351 like-sexed pairs, aged 80 years and older. The present study was based on the first four waves of the study and included a sample of individuals that survived the four waves, were not diagnosed with dementia at the first occasion (following DSM-III-R criteria), and had a MMSE score ≥23 at the first occasion. One hundred and twenty-eight individuals (non-cases) were free from diabetes and hypertension, 92 individuals had a diagnosis of hypertension, 16 had a type 2 diabetes mellitus diagnosis without hypertension, and 22 had comorbid diabetes and hypertension (see Table 1). The total sample size for analyses was 258.

Procedure

The participants were investigated in their home. A complete testing session, including rest periods, took about 3.5 to 4.0 hours. The participants were assessed four times at 2-year intervals beginning in 1991.

Table 1. Baseline participant characteristics and diseases across groups

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Non-cases (n = 128)</th>
<th>Hypertension without diabetes (n = 92)</th>
<th>Diabetes without hypertension (n = 16)</th>
<th>Diabetes and hypertension (n = 22)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years of age</td>
<td>M ± SD</td>
<td>82.5 ± 2.3</td>
<td>84.0 ± 3.9</td>
<td>83.1 ± 2.6</td>
</tr>
<tr>
<td>Years of education</td>
<td>M ± SD</td>
<td>7.4 ± 2.3</td>
<td>7.0 ± 2.1</td>
<td>7.6 ± 1.2</td>
</tr>
<tr>
<td>MMSE</td>
<td>M ± SD</td>
<td>28.2 ± 1.6</td>
<td>28.0 ± 1.7</td>
<td>28.0 ± 1.4</td>
</tr>
<tr>
<td>Sex (women) %</td>
<td>67</td>
<td>78</td>
<td>50</td>
<td>68</td>
</tr>
<tr>
<td>Never smoked %</td>
<td>59</td>
<td>73</td>
<td>63</td>
<td>55</td>
</tr>
<tr>
<td>Myocardial infarction %</td>
<td>12</td>
<td>11</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Angina pectoris %</td>
<td>14</td>
<td>19</td>
<td>25</td>
<td>23</td>
</tr>
<tr>
<td>Congestive heart failure %</td>
<td>13</td>
<td>17</td>
<td>13</td>
<td>18</td>
</tr>
<tr>
<td>Stroke %</td>
<td>9</td>
<td>12</td>
<td>0</td>
<td>18</td>
</tr>
<tr>
<td>TIA %</td>
<td>7</td>
<td>10</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
<td>M ± SD</td>
<td>24.2 ± 3.4</td>
<td>25.2 ± 3.4</td>
<td>24.0 ± 3.6</td>
</tr>
<tr>
<td>sBP (mm Hg)</td>
<td>M ± SD</td>
<td>149.9 ± 20.4</td>
<td>172.5 ± 24.2</td>
<td>155.9 ± 16.0</td>
</tr>
<tr>
<td>dBP (mm Hg)</td>
<td>M ± SD</td>
<td>80.2 ± 11.5</td>
<td>87.3 ± 13.6</td>
<td>80.0 ± 9.5</td>
</tr>
<tr>
<td>Years with diabetes</td>
<td>M ± SD</td>
<td>–</td>
<td>–</td>
<td>5.6 ± 4.6</td>
</tr>
<tr>
<td>Range</td>
<td>–</td>
<td>–</td>
<td>0–15</td>
<td>0–24</td>
</tr>
</tbody>
</table>

M = mean, SD = standard deviation, MMSE = Mini-Mental State Examination.
Medical information

During the interview the participants were asked for permission to review their medical records. Medical records for the period 1985–1998 were ordered from hospitals, outpatient clinics, district physicians, and primary health care centers, and multiple requests were made to secure the quality of information and to make sure that the records covered the entire time period and also contained a summary of diseases earlier in life. A physician (co-author Sven E. Nilsson) made a concurrent review of (i) medical records, including reported medical history; (ii) medicine use; and (iii) self-reported information about diseases. An independent 2nd opinion on classification performed by another physician in a 20% subsample produced only marginal amendment. Diagnoses were classified according to the ICD-10 [20]. The conditions of interest for subsequent analyses are hypertension (which was diagnosed in cases where either the records contained information of specific hypertension treatment, or in cases with more than one diastolic value of at least 95 mm Hg or systolic value higher than 160 mm Hg), type 2 diabetes mellitus (diagnosed using the 1980 WHO criteria when diagnostic level for venous whole blood glucose was 6.7 mmol/l [21]), congestive heart failure, myocardial infarction, angina pectoris, transient cerebral ischemic attack (TIA; that is defined as lasting shorter than 24 hours), stroke, and dementia.

Cognitive assessment

The MMSE is a measure of global cognitive functioning. The task reflects orientation, memory, attention, ability to follow verbal and written commands, writing, and copying. The maximum score is 30, indicating normal cognitive functioning.

Data analyses

Group differences in demographic and health conditions were analysed with one-way analyses of variance and Chi-square tests.

Random coefficients modelling using SAS Proc Mixed was used to estimate individual-level change and predictors of change while accounting for the dependency associated with twin pair status. The multilevel model was characterised by a fixed part which contained average effects for the intercept (initial status) and slope (rate of change) and a random part which contained individual differences (variance) in the intercept, slope, and the within person residual. A three-level linear growth model was composed of a level-1 component of individual outcomes over time, a level-2 component which models individual fixed and random effects of initial status and change over time (person-level covariates can be added at this level), and the level-3 component which models variance associated with twin-pair status. Thus, a three-level structure was characterised by longitudinal measurements nested within individuals which were nested within groups (twin dyad). The syntax for these models is presented in Appendix A.

The baseline model specifies a growth model with no level-2 covariates and was used to evaluate the fit of the growth model parameters. In this and subsequent models, zygosity was not modelled as a fixed effect because the expectation was for no or random differences among MZ and DZ twins in terms of average slope and rate of change. Random effects were, however, estimated separately by zygosity because we expected higher intraclass correlations for MZs than for DZs. Finally, we permitted different estimates of the residual (level-one) variance for the two zygosity groups.

Four nested models were estimated for MMSE as the outcome variable. A baseline model, without any covariates, was run to assess initial status and rate of change for the MMSE. Model A introduces the single covariate of hypertension status (0 = no, 1 = yes) adjusted for age, education, gender, smoking habit, angina, myocardial infarction, congestive heart failure, stroke, and TIA. Model B introduces the single covariate of diabetic status (0 = no, 1 = yes), adjusted for the same factors as in Model A. Finally, Model C introduces the interaction term of diabetes and hypertension, also adjusted for same factors as in Model A and B.

Results

Participant characteristics at baseline

Participant characteristics are presented in Table 1. No significant differences between groups in participant characteristics were observed except in systolic and diastolic blood pressure (PS < 0.05) which were higher among the two groups with hypertension as compared with the normotensive groups. The two groups with hypertension did not differ in systolic and diastolic blood pressure (PS > 0.05). Further, the two groups with diabetes did not differ with respect to how many years they had had the diagnosis of diabetes (P > 0.05).

Change in MMSE Scores across a 6-year Interval

Results from the growth curve modelling are reported in Table 2. The estimates of the average intercept (mean) and rate of change across persons (slope) in the Baseline model were significant. For example, the average person began with a score of 28.36 and declined by 0.33 points per 2-year interval.

Model A allows us to explore whether variation in intercepts and slopes is related to hypertension status as a lone covariate of interest after adjusting for age, education, gender, smoking habit, angina, myocardial infarction, congestive heart failure, stroke, and TIA. Neither estimates are significant, indicating that hypertension alone is not a significant factor for change in the MMSE. Model B examines the effect of diabetes. As seen in Table 2, diabetes is significantly associated with rate of change in the MMSE such that those with diabetes decline by an additional 0.29 points per 2-year interval as compared to those without diabetes. However, diabetes was not a significant predictor of initial status in the MMSE. Finally, Model C examines the effect of having co-morbid diabetes and hypertension. This model shows that there is a significant interaction between diabetes and hypertension in rate of change in the MMSE such that those with both diseases decline additionally by 0.42 points per 2-year interval as compared to those free from both diabetes and hypertension.
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Hypertension and diabetes. The rate of decline in the MMSE related to hypertension and diabetes is portrayed in Figure 1.

Survival, prevalent, and incident dementia across groups

As shown in Table 3 the overall survival rate (based on the initial sample of 702 individuals) between T1 and T4 was 52%. The lowest survival rate was observed in the diabetes groups (44% and 46%), however, there was no statistically significant difference between groups ($P > 0.05$). Prevalence of dementia at baseline across groups is reported in Table 3 (note that demented persons at baseline were excluded). The highest prevalence of dementia at baseline was seen among the people with hypertension and diabetes (24%). Further, the highest incidence rate of dementia at T4 was seen among the people with hypertension and diabetes (23%), although the difference between groups was not statistically significant.

Discussion

In the present study, we examined the effects of comorbid hypertension and diabetes on change in MMSE score across a 6-year interval. The participants were drawn from a longitudinal population-based study and were measured on four occasions. Individuals with dementia at baseline were excluded. The main findings showed that all groups had declined after the 6-year follow-up period. Further, differential cognitive change was observed between the groups reflecting the greatest decline among those with comorbid hypertension and diabetes.

Our results showed that people with diabetes demonstrated greater cognitive change across the 6-year interval as compared with people without diabetes. This finding is in agreement with other longitudinal studies that report increased cognitive decline related to diabetes [6, 7] and an increased risk of dementia [22, 23]. On the other hand, the impact of hypertension on cognitive function was not statistically significant, although the hypertensives had a somewhat greater decline than the non-cases. A greater decline among the hypertensives would have been expected given the many findings showing this result [12–15, 24–26]. These findings may possibly be a result of the high age of our sample, as several investigations suggest that the negative effects associated with hypertension may vary with age such that greater effects are found among young samples as compared to old samples. For example, Waldstein [27] suggested that non-significant association between hypertension and cognitive function in old age might reflect selective attrition. Another possibility would be that early-onset hypertension confers greater risk for cognitive impairment [11].

Although hypertension alone was not related to significantly greater cognitive decline our results suggest that comorbid hypertension and diabetes is combined with hypertension and diabetes. The rate of decline in the MMSE related to hypertension and diabetes is portrayed in Figure 1.

Table 3. Survival, prevalent, and incident dementia across groups

<table>
<thead>
<tr>
<th></th>
<th>Non-cases</th>
<th>Hypertension</th>
<th>Diabetes</th>
<th>Diabetes + hypertension</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival until T4</td>
<td>171/331 (52%)</td>
<td>135/251 (54%)</td>
<td>29/52 (44%)</td>
<td>31/68 (46%)</td>
<td>366/702 (52%)</td>
</tr>
<tr>
<td>Prevalent dementia at T1*</td>
<td>51/331 (15%)</td>
<td>30/251 (12%)</td>
<td>11/52 (21%)</td>
<td>16/68 (24%)</td>
<td>108/702 (15%)</td>
</tr>
<tr>
<td>Incident dementia between T1 and T4b</td>
<td>10/128 (8%)</td>
<td>12/92 (13%)</td>
<td>3/16 (19%)</td>
<td>5/22 (23%)</td>
<td>30/258 (12%)</td>
</tr>
</tbody>
</table>

*a* These individuals were excluded from this study.

*b* Based on the sample that met the criteria for inclusion in the data analyses (see Methods).
increased risk for cognitive impairment. These results are consistent with prior research [15–17]. When looking into the underlying mechanisms through which diabetes and hypertension interact it should be kept in mind that these conditions may be a part of a larger metabolic syndrome, including hyperglycaemia, hyperinsulinaemia and dyslipidaemia. Thus, several pathways for how these conditions may interact and cause cognitive impairment have been suggested [28]. For example, hyperglycaemia has been shown to be related to loss of cortical neurons as well as a decrease in acetylcholine synthesis and release in the brain of rats [29]. Dyslipidaemia as well as hyperinsulinaemia are related to arteriosclerosis, although it should be noted that hyperinsulinaemia is not always apparent in type 2 diabetes. Furthermore, hypertension is a known risk factor for cerebrovascular disease, lacunar brain infarct, and white matter lesion [30]. In our study we found that there was a higher prevalence of stroke among those with comorbid diabetes and hypertension as compared to people with diabetes without hypertension. This reflects increased vulnerability among those with both diabetes and hypertension. It is also of interest to note that this group had had diabetes for a longer period of time than those with diabetes only. Thus, it may be the case that the longer the period with diabetes, the greater the risk of hypertension and of cognitive impairment. When comparing the incidence rates of dementia across groups in our study we find the highest rate among people with comorbid diabetes and hypertension, followed by people with diabetes without hypertension. However, these figures are based on very small numbers and should therefore be treated cautiously.

The main strength of the present study is the longitudinal design, which provides us with the opportunity to simultaneously explore the long-term effects of two risk factors of cognitive impairment. There is also an advantage in using a population-based sample, which minimises selection bias and increases generalisability. However, we need to be cautious when interpreting our results, as there are some limitations to our study. The first limitation is the small sample size. This is, however, a result of the high attrition rate, common for longitudinal studies of very old samples. Furthermore, the attrition rate is especially problematic when studying diseases that are associated with a greater mortality rate, such as diabetes. In our study the survival rate among people with diabetes was somewhat lower as compared to people without diabetes. Another limitation is that cognitive performance was only measured by a global measure that may be too insensitive to detect more subtle and differential change in various cognitive domains.

To summarise, this study demonstrates that comorbid diabetes and hypertension further increases the risk of cognitive decline. Thus, it underlines the importance of prevention and treatment of these two common diseases.

**Diabetes, hypertension, and cognitive decline**

*• People with diabetes and hypertension are at a greater risk for cognitive decline than normotensive people with diabetes.*

**Acknowledgements**

The OCTO Twin Study is an ongoing longitudinal study conducted at the Institute of Gerontology, School of Health Sciences, Jönköping, Sweden, in collaboration with the Center for Developmental and Health Genetics at the Pennsylvania State University, USA and the Department of Medical Epidemiology and Biostatistics at the Karolinska Institute in Stockholm, Sweden. The authors want to thank RNs Lene Ahlbäck (1991–2001), Agneta Carlholt (1992–2002), Gunilla Hjalmarsson (1991–1993), Eva Georgsson (1993–1995), and Anna-Lena Wetterholm (1993–1994) who travelled throughout the country and examined the participants. There are no conflicts of interest in this study.

**Funding**

This study is supported by a grant from the National Institute on Aging (NIA: AG 08861) of the National Institutes of Health, The Swedish Council for Working Life and Social Research, The Wenner-Gren Foundations, Wilhelm and Martina Lundgrens Foundation, Knut and Alice Wallenberg Foundation, and The Adlerbertska Foundation.

**References**


Received 13 June 2003; accepted in revised form 29 December 2003
Appendix A

Baseline Model

\textbf{proc mixed} method = ml noitprint covtest noclprint;
   class id id2; *where zyg = 1;
   model mmse = year0/s;
   random intercept/sub = id type = un group = zyg; *Level 3
      Variance Component;
   random intercept year0/sub = id2 (id) type = un gcorr
      group = zyg;
   repeated/sub = id2 (id) group = zyg;
   title ‘MZ Twins: Stacked No covariates’;
   run;

Model A

\textbf{proc mixed} method = ml noitprint covtest noclprint;
   class id id2; *where zyg = 1;
   model mmse = year0 age educ sex smok mi ap chf stke
      tia hyper hyper*year0/s;
   random intercept/sub = id type = un group = zyg; *Level 3
      Variance Component;
   random intercept year0/sub = id2 (id) type = un gcorr
      group = zyg;
   repeated/sub = id2 (id) group = zyg;
   title ‘MZ Twins: Stacked fixed effects age, education, sex, smoking, miocardial infarction, angina pectoris,
      congestive heart failure, stroke, TIA, diabetes’;
   run;

Model B

\textbf{proc mixed} method = ml noitprint covtest noclprint;
   class id id2; *where zyg = 1;
   model mmse = year0 age educ sex smok mi ap chf stke
      tia diab diab*year0/s;
   random intercept/sub = id type = un group = zyg; *Level 3
      Variance Component;
   random intercept year0/sub = id2 (id) type = un gcorr
      group = zyg;
   repeated/sub = id2 (id) group = zyg;
   title ‘MZ Twins: Stacked fixed effects age, education, sex, smoking, miocardial infarction, angina pectoris,
      congestive heart failure, stroke, TIA, diabetes and hypertension’;
   run;

Model C

\textbf{proc mixed} method = ml noitprint covtest noclprint;
   class id id2; *where zyg = 1;
   model mmse = year0 age educ sex smok mi ap chf stke
      tia diab*hyper diab*hyper*year0/s;
   random intercept/sub = id type = un group = zyg; *Level 3
      Variance Component;
   random intercept year0/sub = id2 (id) type = un gcorr
      group = zyg;
   repeated/sub = id2 (id) group = zyg;
   title ‘MZ Twins: Stacked fixed effects age, education, sex, smoking, miocardial infarction, angina pectoris,
      congestive heart failure, stroke, TIA, diabetes and hypertension’;
   run;