Cardiovascular risk factors and cognitive decline in older people with type 2 diabetes

Insa Feinkohl¹ · Markéta Keller¹ · Christine M. Robertson¹ · Joanne R. Morling¹ · Stela McLachlan¹ · Brian M. Frier²³ · Ian J. Deary³⁴ · Mark W. J. Strachan⁵ · Jackie F. Price¹

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Abstract

Aims/hypothesis The aim of this work was to assess the role of well-established cardiovascular risk factors in the late-life cognitive decline of patients with type 2 diabetes.

Methods Data from 831 participants (aged 60–75 years) attending the 4 year follow-up of the Edinburgh Type 2 Diabetes Study (ET2DS) were used. Smoking history (pack-years), BP, HbA₁c, plasma glucose and cholesterol were determined at baseline clinics (single time measurements) and/or from serial data recorded on a clinical management database from diagnosis until recruitment (‘historical’ data). Principal component analysis derived a factor, g, of general ability from seven cognitive tests. Linear regression models of follow-up g were adjusted for baseline g to represent 4 year cognitive change. ‘Accelerated late-life cognitive decline’ was defined as scoring in the lowest tertile of ‘4 year cognitive change’ regression scores. Analyses controlled for age and sex.

Results A baseline history of moderate/heavy smoking (≥10 pack-years) and a 1% increased historical HbA₁c (equivalent to an increase by 11 mmol/mol) predicted a 64% (OR 1.64; 95% CI 1.14, 2.34; p=0.007) and 21% (OR 1.21; 95% CI 1.00, 1.45; p=0.046) increased risk of accelerated cognitive decline, respectively. When treated as continuous measures, higher pack-years, historical HbA₁c and historical BP emerged as significant independent predictors of 4 year decline in g (standardised β range −0.07 to −0.14; all p≤0.05).

Conclusions/interpretation Increased smoking and poorer glycaemic control (with relatively weaker findings for BP) during the life-course were independently associated with accelerated late-life cognitive decline. Where possible, evaluation is warranted of these risk factors as targets for intervention to reduce the burden of cognitive impairment in diabetes.

Keywords Blood glucose · Blood pressure · Cardiovascular risk · Cholesterol · Cognitive impairment · Glycaemic control · Hyperglycaemia · Older age · Smoking · Type 2 diabetes

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Abbreviations

ACCORD-MIND Action to Control Cardiovascular Risk in Diabetes
ARIC Atherosclerosis Risk in Communities
BVFT Borkowski Verbal Fluency test
dDSC Digit Symbol Coding
ET2DS Edinburgh Type 2 Diabetes Study
g Factor of general cognitive ability
LM Logical Memory
LNS Letter–Number Sequencing
MR Matrix Reasoning
Introduction

People with type 2 diabetes are at greater risk of cognitive impairment in later life than their non-diabetic peers [1]. With the prevalence of diabetes expected to reach 15% in the USA within the current decade [2], researchers have attempted to identify underlying pathophysiological mechanisms and potentially modifiable risk factors that may be responsible for the observation. For instance, based on competition of insulin with β-amyloid peptide for degradation and recent reports identifying the amyloid precursor amylin, which is co-secreted with insulin from the pancreas, in brains of patients with diabetes (but not in diabetes-free controls), increased concentrations of β-amyloid and amylin are candidate links between type 2 diabetes and cognitive impairment [3, 4]. The role of vascular disease has also received increasing attention of late due to an increased prevalence in type 2 diabetes and plausible biological mechanisms linking the two conditions. Amylin, for instance, is known to contribute to cardiovascular disease, so similar effects on the vascular system of the brain may be plausible [4]. Recent epidemiological evidence has also shown a direct association between cognitive decline and markers of symptomatic and asymptomatic vascular disease in people with type 2 diabetes [5]. These observations suggest a potential role for smoking, hypertension, adverse lipid profiles and hyperglycaemia, all of which are established risk factors for adverse cardiovascular outcomes, in the development of cognitive impairment in people with type 2 diabetes. If such a role is repeatedly demonstrated, then future clinical trials targeting these risk factors should consider inclusion of cognitive endpoints (e.g. to determine whether a change in the threshold for existing clinical intervention may be indicated).

In the general population, hypercholesterolaemia, hypertension, smoking and hyperglycaemia have each been associated with a poorer level of cognitive function [6–8]. Lower childhood intelligence, however, potentially leads to increased vascular risk, as well as to lower cognitive ability and greater cognitive decline in later life [9]. Therefore, studies with a prospective design and, preferably, with a measure of pre-morbid cognitive ability, are required to help determine the direction of relationships between vascular risk factors and cognitive decline. Compared with previous prospective studies in the general population that suggest a degree of complexity and do not always provide a consistent picture of vascular risk and cognitive impairment [10, 11], such studies in diabetic populations are much more scarce and often sub-optimal in design not least due to the neglect of consideration of pre-morbid ability [12]. For smoking in particular, this type of evidence was lacking until a recent analysis of the Fremantle Diabetes Study, which showed that midlife smoking predicted an increased risk of future cognitive impairment [13].

Using data from a large prospective cohort of older adults with type 2 diabetes, the Edinburgh Type 2 Diabetes Study (ET2DS), we tested the associations of serum cholesterol, BP, glycaemic control and smoking with late-life cognitive decline. Given known strong correlations among vascular risk factors themselves, it was important to evaluate the relative independence of their contributions in our cohort. Our analyses had the additional advantage of using ‘historical’ data on BP and HbA1c covering the time between diabetes diagnosis and attendance at the clinic.

Methods

Study population

The baseline clinic of the ET2DS was attended by 1,066 community-dwelling adults aged 60–75 years [14], of whom 831 returned 4 years later. Ethical approval was obtained from the Lothian Medical Research Ethical Committee. Examinations complied with the Declaration of Helsinki and participants gave full written consent. Details of study recruitment and examination have been described previously [15].

Baseline clinical examination and historical data

Data obtained at baseline (‘clinic data’) and from a clinical management database between diabetes diagnosis and attendance at the baseline clinic (‘historical data’) were used. At baseline, blood samples were taken following an overnight fast to measure HbA1c, plasma glucose, serum LDL-cholesterol and HDL-cholesterol. The ratio of HDL-cholesterol/total cholesterol was used (‘cholesterol’) in subsequent analysis as such ratios may be preferable to non-ratio measures in cardiovascular risk prediction [16].

Questionnaires administered at baseline obtained data on education, smoking and medical history. Medical history data, together with Scottish Morbidity Record Data, responses on the World Health Organization chest pain questionnaire and 12-lead ECG data, identified angina, transient ischaemic attack, stroke and myocardial infarction [14]. Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥85 mmHg at the clinic visit and/or when participants self-reported taking medication to lower BP. Hypercholesterolaemia was defined as plasma total cholesterol ≥5 mmol/l and/or when participants self-reported taking medication to lower blood lipids.

Questionnaire items ascertained current and previous smoking, including years since cessation and number of

<table>
<thead>
<tr>
<th>TMT-B</th>
<th>Trail-Making Test-B</th>
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<tbody>
<tr>
<td>WAIS-III</td>
<td>Wechsler Adult Intelligence Scale, third edition</td>
</tr>
</tbody>
</table>
cigarettes, cigars or ounces of tobacco smoked per day. Each self-reported cigar smoked was converted to equal four cigaretes; each 20 cigarettes were converted to equal one pack. The number of packs was multiplied by the number of years participants had smoked to obtain ‘pack-years’ (1 pack-year is equivalent to 20 cigarettes/day for 1 year). For pipe smoking, 7,300 g of tobacco were equivalent to 1 pack-year. The measure of pack-years was additionally categorised into participants who had never smoked or had a history of light smoking (<10 pack-years) and those with a history of moderate to heavy smoking (≥10 pack-years).

Historical data from the Lothian Diabetes Register between 1988 and 2007 (the year of study recruitment) were used to obtain time-weighted mean measures of systolic and diastolic BP (‘historical systolic BP’; ‘historical diastolic BP’) and HbA1c (‘historical HbA1c’). Data from between one reading and 65 readings (median 19 readings, interquartile range 14–25 readings) were available for each individual and were used to calculate the time-weighted mean. Assessments captured by the register spanned between 0 years (single assessment) and 19.8 years (median 10.4 years, interquartile range 7.3–13.6 years). ‘Poor glycaemic control’ was defined as a historical HbA1c >7% (>53 mmol/mol). ‘Poor BP control’ was defined as historical systolic BP ≥140 mmHg and/or historical diastolic BP ≥85 mmHg. Clinical characteristics of the study population are shown in Table 1.

Cognitive assessment

At baseline and at year 4, seven age-sensitive tests of cognitive function were administered. Executive function was measured by the Trail-Making Test-B (TMT-B) and the Borkowski Verbal Fluency Test (BVFT). The Digit Symbol Coding (DSC) subtest of the Wechsler Adult Intelligence Scale, third edition (WAIS-III) ascertained processing speed [17]. The Matrix Reasoning (MR) subtest of the WAIS-III measured non-verbal reasoning and the Letter–Number Sequencing (LNS) subtest measured working memory. The Logical Memory (LM) and Faces subtests of the Wechsler Memory Scale, third edition, assessed verbal and non-verbal declarative memory, respectively [18]. Scores on the combined junior and senior synonyms of the Mill Hill Vocabulary Scale (MHVS) [19], which have been shown to correlate with scores on other vocabulary-based tests [20], estimated pre-morbid cognitive ability. Vocabulary-based tests are used in this function on the grounds that vocabulary is part of ‘crystallised’ ability and hence is relatively immune to age-related cognitive decline [21]. The criteria used to identify participants with possible dementia by year 4 have been described previously [5].

Statistical analyses

Distribution was approximately normal for all measured variables; for TMTB and clinic plasma glucose, normal distribution was achieved following transformation to their natural logarithms. Normal distribution for pack-years was achieved using square root transformation. Missing data on cognitive ability tests other than Mill Hill Vocabulary (0.6–1.7% at baseline; 0.8–4.7% at year 4) were imputed, as described in detail previously [5]. Since people who perform well on one cognitive test tend to perform well on another, data reduction techniques may be applied to batteries of cognitive tests with complete data on all individual tests to obtain a factor of general ability [22]. The use of g is advantageous, because it is relatively unaffected by measurement error. Here, components with eigenvalues >1 were extracted in principal component analysis. All seven cognitive tests (those other than Mill Hill Vocabulary) loaded on a single component, accounting for 44.74% and 47.44% of variance at baseline and at year 4, respectively. Factor loadings ranged between 0.47 (Faces) and 0.80 (TMTB) at baseline and between 0.51 (Faces) and 0.81 (TMTB) at year 4 [5].

Linear regression analyses regressed cognitive function at year 4 and cognitive change between baseline and year 4 on each of the vascular risk factors (see Table 2 for analyses of g; see Electronic supplementary material [ESM] Table 1 for analyses of individual cognitive tests and ‘estimated lifetime cognitive change’, determined by adjustment of year 4 cognitive test scores for Mill-Hill Vocabulary). Four year cognitive change was represented by adjustment of year 4 scores for baseline scores (the procedure to ensure that baseline and year 4 g were standardised on the same sample has been described previously [5]). This method may be preferable to raw change scores because it is less dependent on individual differences in initial cognitive status [23].

Regression analyses of cognitive function at year 4 were adjusted for age and sex; those of 4 year cognitive change were adjusted for baseline cognitive scores, age and sex, before myocardial infarction, angina, transient ischaemic attack, stroke (‘vascular disease’) and duration of diabetes, and Mill-Hill Vocabulary were controlled for in two separate steps. For g, analyses that survived this adjustment were additionally controlled for mode of glucose-lowering treatment. Finally, pack-years, historical systolic BP, historical HbA1c and cholesterol were selected a priori (with the aim of avoiding multicollinearity) to be entered as predictors in a single model to ascertain the relative independence of associations. Additional categorisation of cognitive outcomes allowed the calculation of ORs for ‘poor’ cognitive function (scoring in lowest vs highest tertile of follow-up g) and ‘accelerated’ 4 year cognitive decline (lowest vs highest tertile of follow-up g adjusted
for baseline g) using logistic regression. All linear and logistic regression analyses of g were repeated separately with strati-

## Table 1  
Baseline demographics and clinical characteristics of attendees of the year 4 follow-up

<table>
<thead>
<tr>
<th>Characteristic/demographic</th>
<th>Total sample</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Age (years)</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>824</td>
<td>425</td>
<td>399</td>
</tr>
<tr>
<td>Insulin±oral glucose-lowering treatment</td>
<td>830</td>
<td>429</td>
<td>399</td>
</tr>
<tr>
<td>Oral glucose-lowering treatment alone</td>
<td>830</td>
<td>429</td>
<td>399</td>
</tr>
<tr>
<td>Diet alone as glucose-lowering treatment</td>
<td>830</td>
<td>429</td>
<td>399</td>
</tr>
<tr>
<td>Lipid-lowering treatment</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Hypercholesterolaemia</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Total cholesterol (mmol/l)</td>
<td>826</td>
<td>427</td>
<td>399</td>
</tr>
<tr>
<td>HDL/total cholesterol</td>
<td>826</td>
<td>427</td>
<td>399</td>
</tr>
<tr>
<td>Historical systolic BP (mmHg)</td>
<td>825</td>
<td>425</td>
<td>400</td>
</tr>
<tr>
<td>Historical diastolic BP (mmHg)</td>
<td>825</td>
<td>425</td>
<td>400</td>
</tr>
<tr>
<td>Clinic systolic BP (mmHg)</td>
<td>829</td>
<td>430</td>
<td>399</td>
</tr>
<tr>
<td>Clinic diastolic BP (mmHg)</td>
<td>829</td>
<td>430</td>
<td>399</td>
</tr>
<tr>
<td>Antihypertensive treatment</td>
<td>826</td>
<td>426</td>
<td>400</td>
</tr>
<tr>
<td>Hypertension</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Poor blood pressure control</td>
<td>825</td>
<td>425</td>
<td>401</td>
</tr>
<tr>
<td>Pack-years</td>
<td>803</td>
<td>410</td>
<td>393</td>
</tr>
<tr>
<td>Never smoked/history of light smoking</td>
<td>803</td>
<td>420</td>
<td>393</td>
</tr>
<tr>
<td>History of moderate/heavy smoking</td>
<td>803</td>
<td>420</td>
<td>393</td>
</tr>
<tr>
<td>Historical HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</td>
<td>825</td>
<td>425</td>
<td>400</td>
</tr>
<tr>
<td>Historical HbA&lt;sub&gt;1c&lt;/sub&gt; (mmol/mol)</td>
<td>825</td>
<td>425</td>
<td>400</td>
</tr>
<tr>
<td>Clinic HbA&lt;sub&gt;1c&lt;/sub&gt; (%)</td>
<td>804</td>
<td>415</td>
<td>389</td>
</tr>
<tr>
<td>Clinic HbA&lt;sub&gt;1c&lt;/sub&gt; (mmol/mol)</td>
<td>804</td>
<td>415</td>
<td>389</td>
</tr>
<tr>
<td>Clinic plasma glucose (mmol/l)</td>
<td>821</td>
<td>424</td>
<td>397</td>
</tr>
<tr>
<td>Poor glycaemic control</td>
<td>825</td>
<td>425</td>
<td>400</td>
</tr>
<tr>
<td>History of severe hypoglycaemia</td>
<td>816</td>
<td>425</td>
<td>391</td>
</tr>
<tr>
<td>Diabetic retinopathy</td>
<td>819</td>
<td>424</td>
<td>395</td>
</tr>
<tr>
<td>Waist–hip ratio</td>
<td>828</td>
<td>429</td>
<td>399</td>
</tr>
<tr>
<td>Carotid intima-media thickness (mm)</td>
<td>775</td>
<td>399</td>
<td>376</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Angina</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
<tr>
<td>Stroke</td>
<td>831</td>
<td>430</td>
<td>401</td>
</tr>
</tbody>
</table>

Total N=831

Poor glycaemic control was defined as historical HbA<sub>1c</sub> &gt;7% (>53 mmol/mol). Poor blood pressure control was defined as historical systolic BP ≥140 mmHg and/or historical diastolic BP ≥85 mmHg. Hypertension was defined as systolic BP ≥140 mmHg and/or diastolic BP ≥85 mmHg at the clinic visit and/or self-reported medication prescribed by a doctor to lower blood pressure. Hypercholesterolaemia was defined as plasma total cholesterol ≥5 mmol/l and/or when a participant self-reported medication prescribed by a doctor to lower blood lipid level. Never smoked/history of light smoking was defined as &lt;10 pack-years. History of moderate/heavy smoking was defined as ≥10 pack-years. Carotid intima-media thickness was measured at year 1 follow-up. Diabetic retinopathy was defined as mild or moderate/severe retinopathy on seven-field retinal photographs. History of severe hypoglycaemia was defined as self-reported history of at least one episode of hypoglycaemia requiring assistance by another person (for details, see [32]).

<sup>a</sup>p value for sex difference in χ<sup>2</sup> tests or t tests
The 4 year decline in historical systolic BP was marginally associated with a steeper decline on all of the seven individual tests (ESM Table 1), mainly due to an association with accelerated decline in reasoning abilities (Matrix Reasoning) (ESM Table 1). Upon exclusion of individuals with possible dementia, the finding for g (standardised $\beta=-0.06; p=0.069$) was attenuated. When analyses were repeated with non-imputed rather than imputed data, the marginal association with 4 year decline in g lost statistical significance ($-0.06; p=0.125$). BP was unrelated to risk of poor cognitive outcome (Table 3).

Cholesterol
People with higher cholesterol levels tended to have higher Mill Hill Vocabulary ($r=0.07; p=0.554$). A statistically significant association of higher cholesterol level with lower g did not survive adjustment for Mill Hill Vocabulary (ESM Table 1) or for baseline g (Table 2), and logistic regression analyses showed that cholesterol was unrelated to risk of poor cognitive outcome (data not shown).

Smoking
Pack-years was unrelated to Mill Hill Vocabulary ($p=0.157$), but was associated with lower g at baseline and with accelerated decline in g (Table 2). Neither inclusion of vascular disease, disease duration and Mill Hill Vocabulary (Table 2) nor of glucose-lowering treatment (data not shown) altered the results. In addition to g, pack-years was associated with decline on all of the seven individual tests (ESM Table 1). Overall, individuals with a history of moderate to heavy smoking had a 64% increased odds of accelerated 4 year cognitive decline after controlling for age and sex. To illustrate, independent of age and sex, each additional pack-year was associated with 1% increased odds of accelerated 4 year decline (Table 3).

### Results

#### Cohort characteristics

Eight hundred and thirty-one participants (51.7% male) of the ET2DS attended for follow-up cognitive testing. Clinical and cognitive differences between attenders and non-attendees have been described previously [5]. Baseline clinical and demographic characteristics of attendees (forming the study population for this analysis) are shown in Table 1. Mean age at baseline was 67.7 years, with median time since diabetes diagnosis of 6 years. Almost all participants suffered from hypercholesterolaemia (92.7%) and/or hypertension (87.7%); a majority had poor glycaemic control (67.9%) and around half (47.2%) had poor blood pressure control, according to our pre-specified criteria, respectively.

#### Vascular risk and cognition in total sample

**Blood pressure** Mill Hill Vocabulary was unrelated to historical diastolic (P=0.076) or systolic BP (P=0.701). Higher historical systolic BP was marginally associated with a steeper 4 year decline in g (Table 2), mainly due to an association with reasoning abilities (Matrix Reasoning) (ESM Table 1). Adjusting the association with 4 year decline in g for vascular disease, disease duration and Mill Hill Vocabulary did not alter the results in terms of effect size or statistical significance, and adjusting for glucose-lowering treatment led to statistical significance (standardised $\beta=-0.07; p=0.047$). Upon adjustment for baseline MHVS and other covariates, the marginal association with 4 year decline in systolic BP was attenuated. When analyses were repeated with non-imputed rather than imputed data, the marginal association with 4 year decline in g lost statistical significance ($-0.06; p=0.125$). BP was unrelated to risk of poor cognitive outcome (Table 3).

**Hypercholesterolaemia** People with higher cholesterol levels tended to have higher Mill Hill Vocabulary ($r=0.07; p=0.554$). A statistically significant association of higher cholesterol level with lower g did not survive adjustment for Mill Hill Vocabulary (ESM Table 1) or for baseline g (Table 2), and logistic regression analyses showed that cholesterol was unrelated to risk of poor cognitive outcome (data not shown).

**Poor BP control** Pack-years was unrelated to Mill Hill Vocabulary ($p=0.157$), but was associated with lower g at baseline and with accelerated decline in g (Table 2). Neither inclusion of vascular disease, disease duration and Mill Hill Vocabulary (Table 2) nor of glucose-lowering treatment (data not shown) altered the results. In addition to g, pack-years was associated with decline on all of the seven individual tests (ESM Table 1). Overall, individuals with a history of moderate to heavy smoking had a 64% increased odds of accelerated 4 year cognitive decline after controlling for age and sex. To illustrate, independent of age and sex, each additional pack-year was associated with 1% increased odds of accelerated 4 year decline (Table 3).
**Table 3** Incremental odds of poor cognitive performance at year 4 and of accelerated 4 year cognitive decline according to preceding vascular risk factors

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Poor cognitive function at year 4&lt;sup&gt;a&lt;/sup&gt;</th>
<th>p value</th>
<th>Accelerated cognitive decline&lt;sup&gt;b&lt;/sup&gt;</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Entire sample (max N=831)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical systolic BP</td>
<td>1.00 (0.98, 1.01)</td>
<td>0.635</td>
<td>1.01 (0.99, 1.03)</td>
<td>0.228</td>
</tr>
<tr>
<td>History of moderate/heavy vs never smoked/history of light smoking</td>
<td>2.01 (1.38, 2.92)</td>
<td>&lt;0.001</td>
<td>1.64 (1.14, 2.34)</td>
<td>0.007</td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.001</td>
<td>1.01 (1.00, 1.01)</td>
<td>0.013</td>
</tr>
<tr>
<td>Historical HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>1.24 (1.02, 1.49)</td>
<td>0.029</td>
<td>1.21 (1.00, 1.45)</td>
<td>0.046</td>
</tr>
<tr>
<td>Men (max N=430)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical systolic BP</td>
<td>1.00 (0.97, 1.02)</td>
<td>0.651</td>
<td>1.02 (1.00, 1.05)</td>
<td>0.053</td>
</tr>
<tr>
<td>History of moderate/heavy vs never smoked/history of light smoking</td>
<td>2.09 (1.25, 3.52)</td>
<td>0.005</td>
<td>1.61 (0.97, 2.66)</td>
<td>0.065</td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.036</td>
<td>1.01 (1.00, 1.02)</td>
<td>0.154</td>
</tr>
<tr>
<td>Historical HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>1.34 (1.02, 1.77)</td>
<td>0.035</td>
<td>0.95 (0.73, 1.24)</td>
<td>0.706</td>
</tr>
<tr>
<td>Women (max N=401)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Historical systolic BP</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.932</td>
<td>1.00 (0.98, 1.02)</td>
<td>0.802</td>
</tr>
<tr>
<td>History of moderate/heavy vs never smoked/history of light smoking</td>
<td>1.83 (1.06, 3.17)</td>
<td>0.030</td>
<td>1.66 (0.99, 2.77)</td>
<td>0.054</td>
</tr>
<tr>
<td>Pack-years</td>
<td>1.02 (1.01, 1.04)</td>
<td>0.003</td>
<td>1.02 (1.00, 1.03)</td>
<td>0.023</td>
</tr>
<tr>
<td>Historical HbA&lt;sub&gt;1c&lt;/sub&gt;</td>
<td>1.14 (0.88, 1.45)</td>
<td>0.326</td>
<td>1.50 (1.15, 1.96)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Data are ORs (95% CIs) comparing incremental odds of scoring in the lowest tertile of the respective distributions vs the highest tertile. Analyses are multiple logistic regression analyses that were performed separately for each risk factor. Never smoked/history of light smoking was defined as <10 pack-years. History of moderate/heavy smoking was defined as ≥10 pack-years. Pack-years was untransformed in these analyses. Outcome variable is g at year 4. Analyses for entire sample were adjusted for age, sex and in sex-stratified analyses for age. Cut-points for follow-up g: lowest tertile <0.43; medium tertile 0.43 to 0.48; highest tertile >0.48. Cut-points for follow-up g adjusted for baseline g: lowest tertile <0.39; medium tertile 0.39 to 0.44; highest tertile >0.44.

<sup>a</sup>Model of reduced cognitive function at year 4 was defined as scoring in the lowest tertile of g at year 4

<sup>b</sup>Model of accelerated 4 year cognitive decline was defined as scoring in the lowest tertile of year 4 g adjusted for baseline g

**Historical HbA<sub>1c</sub>** Historical HbA<sub>1c</sub> was unrelated to Mill Hill Vocabulary (p=0.311), but was associated with lower g and with accelerated decline in g (Table 2). It was also significantly associated with decline on all tests except verbal memory (Logical Memory) and processing speed (Digit Symbol Coding; ESM Table 1). Adjustment for vascular disease, disease duration and Mill Hill Vocabulary (Table 2; ESM Table 1), or for glucose-lowering treatment (data not shown), did not alter the results. Each percentage (11 mmol/mol) increase in historical HbA<sub>1c</sub> was associated with a 21% increased odds of accelerated 4 year decline when age and sex were controlled for (Table 3).

**Relative independence of vascular risk associations with cognition in total sample**

Historical HbA<sub>1c</sub>, historical systolic BP, cholesterol and pack-years were entered in a single linear regression model controlling for age and sex. Significant contributors to 4 year change in g were pack-years (−0.14; p<0.001), historical HbA<sub>1c</sub> (−0.10; p=0.006) and historical systolic BP (−0.07; p = 0.052). The addition of vascular disease, duration of diabetes and Mill-Hill Vocabulary into the model did not alter the results: pack-years (−0.11; p=0.004), historical HbA<sub>1c</sub> (−0.09; p=0.014) and historical systolic BP (−0.07; p = 0.050) were each associated with a steeper 4 year decline in g. Cholesterol was not included in these models (both p>0.10).

**Vascular risk and cognition in stratified analyses**

Subgroup analysis by glucose-lowering treatment mode showed that findings on historical HbA<sub>1c</sub> in the total sample were driven by insulin-treated patients: for this treatment group, effect sizes in linear regression analyses appeared to be particularly strong (fully adjusted model for 4 year decline in g, standardised β −0.22; p<0.001). Findings on historical HbA<sub>1c</sub> also appeared to be driven by female sex, whereas those for historical systolic BP were restricted to the subsample of men (ESM Table 2). When historical HbA<sub>1c</sub>, historical systolic BP, cholesterol and pack-years were entered in a single model controlling for age, vascular disease and duration of diabetes, significant predictors of a steeper 4 year decline were pack-years (−0.13; p=0.011) and historical systolic BP (−0.12; p=0.018) for the subsample of men (p>0.05 for cholesterol and historical HbA<sub>1c</sub>, respectively), and pack-years (−0.11; p=0.003).
BP, those for a measure of mean HbA1c collected over a time
celerated late-life cognitive decline short of dementia. Overall
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Smoking history, long-term exposure to raised BP and poorer

Discussion

Smoking history, long-term exposure to raised BP and poorer
glycaemic control were independently associated with an ac-
celerated late-life cognitive decline short of dementia. Overall
effect sizes were modest but, compared with the findings on
BP, those for a measure of mean HbA1c collected over a time
period of up to 20 years prior to cognitive testing and for
lifetime smoking history appeared to be more robust across
the total sample. Independent of age and sex, a history of
moderate to heavy smoking and each percentage increase in
HbA1c (an increase that is equivalent to 11 mmol/mol) was
associated with a 64% and 21% increased risk of an accel-
cerated cognitive decline during 4 year follow-up, respectively.
Cholesterol was associated only cross-sectionally with cogni-
tion. While our findings are not directly transferable to a clin-
cal setting (since our definition of accelerated decline was
arbitrary and sample-specific), they should serve to increase
awareness of cognitive impairment and the potential impor-
tance of treatment of vascular risk factors in patients with type
2 diabetes.

To date, the relationships between cardiovascular risk fac-
tors and cognition have only infrequently been studied in peo-
dle with diabetes. The present study has extended earlier evi-
dence of cross-sectional associations of hypertension [24, 25]
and poorer glycaemic control [26, 27] with reduced cognitive
function in type 2 diabetes by demonstrating prospective asso-
ciations with accelerated late-life cognitive decline. The
association of smoking history with cognitive decline supports
recent findings from the Fremantle Diabetes Study, in which
midlife smoking was associated with the risk of cognitive
impairment in later life [13]. Findings on glycaemic control
in the present cohort are also consistent with a recent analysis
of the Atherosclerosis Risk in Communities (ARIC) study,
which reported that people with diabetes in midlife declined
cognitively at faster rates during a 20 year follow-up period
compared with diabetes-free individuals [28] and which addi-
tionally suggested a role for severity of hyperglycaemia [28].
In our study, the corresponding association of historical blood
glucose levels with cognitive decline in people with diabetes
in later life was particularly evident for tests of executive
function, which again is consistent with findings from the
ARIC study [28] and with reports of vulnerability of that do-
main in people with diabetes [29]. The suggestion of stronger
findings for glycaemic control in insulin-treated patients in the
present study may be due to the advanced disease stage and
comorbidity in these patients and, in women, merits further
investigation.

Many previous studies on a similar range of risk factors
have investigated single factors, despite complex relationships
among them. The present study makes an important advance
by showing that associations of each of the risk factors iden-
tified as being predictive of cognitive decline were indepen-
dent of one another. Although observational findings do not
correspond to causality, it is possible that each factor is asso-
ciated with cognition in separate pathophysiological path-
ways. Their modifiable nature suggests the potential for each
risk factor as a separate target for intervention to reduce pa-
tients’ risk of cognitive impairment. Observational data from
studies of people with type 2 diabetes appear to support this
possibility (e.g. with associations of antihypertensive treat-
ment with reduced risk of dementia as an endpoint of cogni-
tive decline [30]) but current evidence from trials is limited
and inconclusive. In the Memory in Diabetes study of the
Action to Control Cardiovascular Risk in Diabetes
(ACCORD-MIND) trial, a trend was observed for decelerated
cognitive decline in the treatment arm that was subjected to
intensified glucose-lowering treatment [31]. However, some
evidence suggests that hypoglycaemia (a side effect of more
intensive therapy) may increase the rate of cognitive decline
[32–35], thereby potentially counteracting the beneficial ef-
ecteds of improved glycaemic control. Future trials comparing
glucose-lowering agents that cause different degrees of
hypoglycaemia may help to clarify this. Trials on smoking
cessation are complicated by confounding and are scarce even
in the general population, with a single study showing decel-
erated 2 year cognitive decline in people who successfully quit
smoking compared with those who were unsuccessful [36]. A
Cochrane review of randomised trials in the general popula-
tion concluded that antihypertensive therapy was of no benefit
in slowing cognitive decline [37] and in the ACCORD-MIND
study, intensive lowering of BP in people with type 2 diabetes
had no effect on cognitive decline [38].

The present findings are consistent with those of a number of
studies that have reported links of higher midlife or late-life
cholesterol, or of lower HDL-cholesterol, with lower late-life
cognitive function or with a steeper cognitive decline in peo-
dle with diabetes [11, 39, 40]. However, these studies did not
adjust for pre-morbid ability. Here, we found evidence for
reverse causality: lower pre-morbid ability predisposed partic-
ipants to a higher late-life level of cholesterol and to lower
late-life cognitive function, and so confounding of previous
cross-sectional (and potentially prospective) evidence is like-
ly. In line with the present null findings for prospective asso-
ciations of either cholesterol (without regard to lipid-lowering
treatment) or of presence of hypercholesterolaemia (partly de-
finied by use of lipid-lowering treatment), ACCORD-MIND
revealed no effect of addition of fenofibrate to simvastatin
therapy on 3 year cognitive decline [38].
The prospective design and extensive clinical and cognitive characterisation are clear strengths of the ET2DS. Adjustment for estimated peak pre-morbid ability helped to counteract potential reverse causality. The dropout of 22\% over 4 years was relatively high but acceptable considering the diabetic status and age of the cohort. The associated survivor bias favouring healthier individuals to attend follow-up is likely to have led to an underestimate in effect sizes, so that associations may be stronger than reported here. Our overall results are further strengthened by the use of historical data. Despite data heterogeneity (historical data were available for between 1 and 65 readings), which may decrease the overall reliability of our findings, the approach substantially reduced the influence of measurement error compared with single measurement data. The calculation of a $g$ factor allowed the analysis of decline in overall cognitive function that was independent of the specific test battery used to measure cognitive function [41]. A resulting neglect of test-specific variance [42] was partly offset by additional consideration of findings from individual cognitive tests. Multiple testing will have increased the risk of type I statistical error and subgroup analysis by sex will have reduced statistical power, limiting the reliability of all findings and of those stratified by sex in particular. Replication in other cohorts with type 2 diabetes is therefore essential. Readers should also note that the category of accelerated cognitive decline was specific to the current, predominantly dementia-free cohort, and should not be mistaken for the presence of dementia. Finally, we did not consider the role of treatment of vascular risk, and so potential moderation of risk factor associations with cognitive decline by treatment cannot be excluded. The contributions of insulin or risk factor trajectories between baseline and year 4 follow-up to findings were also not assessed; such analyses are currently planned as part of future follow-up waves of the ET2DS.

Should associations of long-term exposure to vascular risk with cognitive decline prove to be causal, the present findings suggest that interventions targeting a range of vascular risk factors (rather than single factors such as hyperglycaemia only) may be needed to help reduce the risk of cognitive impairment in people who either have diabetes or who go on to develop type 2 diabetes in older age. Our findings support recent evidence that late-life cognitive change may be determined over the course of decades prior to the age at which deficits typically occur [28].

Overall, we have provided strong observational evidence showing that smoking history, higher BP and poorer glycaemic control are independently associated with accelerated late-life cognitive decline in people with type 2 diabetes. Further research into the usefulness of each risk factor as a target for intervention to reduce age-related cognitive decline in this patient population is now warranted.

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Access to research materials Samples and data of the ET2DS may be accessible subject to requests passing the study's usual data sharing and collaboration processes, which include protection of participant anonymity.

Duality of interest MWJS has received fees for speaking from Novo Nordisk, Eli Lilly and Pfizer and BMF has received honoraria for lecturing and attending advisory boards from Novo Nordisk, Eli Lilly, Sanofi-Aventis, MSD, Janssen and Boehringer Ingelheim. All other authors declare that there is no duality of interest associated with their contribution to this manuscript.

Contribution statement JFP and MWJS conceived and designed the ET2DS and oversaw the acquisition and analysis of data. MK, JRM, CMR, SM and IF were involved in the collection of data. IF performed the literature search, the statistical analysis and drafted the manuscript with supervision from JFP, MWJS, BMF and JID. MK, CMR, JRM, SM, IJD, BMF, MWJS and JFP were involved in the interpretation of findings, the drafting of the manuscript and its critical revision for important intellectual content. All approved the final version of the manuscript for publication. IF is the guarantor of this paper and as such had full access to all the data in the study, and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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