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Citation for published version:

Möttus, R, Luciano, M, Starr, JM & Deary, IJ 2013, 'Diabetes and life-long cognitive ability', *Journal of Psychosomatic Research*, vol. 75, no. 3, pp. 275-278. <https://doi.org/10.1016/j.jpsychores.2013.06.032>

Digital Object Identifier (DOI):

[10.1016/j.jpsychores.2013.06.032](https://doi.org/10.1016/j.jpsychores.2013.06.032)

Link:

[Link to publication record in Edinburgh Research Explorer](#)

Document Version:

Peer reviewed version

Published In:

Journal of Psychosomatic Research

Publisher Rights Statement:

© Möttus, R., Luciano, M., Starr, J. M., & Deary, I. J. (2013). Diabetes and life-long cognitive ability. *Journal of Psychosomatic Research*, 75(3), 275-278. [10.1016/j.jpsychores.2013.06.032](https://doi.org/10.1016/j.jpsychores.2013.06.032)

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SHORT TITLE: Diabetes and life-long cognition

Diabetes and life-long cognitive ability

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Word count: 2,892 (main text)

Summary

Objectives: There is a widespread consensus that diabetes impairs cognitive functioning.

However, some recent findings have shown that many health conditions generally thought to be detrimental to cognitive functioning are in fact linked to pre-morbid cognitive ability, suggesting reverse causation. To better understand the causality in diabetes-cognition relationship, this study investigates the association of older-age diabetes with concurrent and childhood cognitive functioning. **Methods:** Lothian Birth Cohort 1936 participants (N = 1,017) completed the same general cognitive ability test at ages 11 and 70 years. Scores were compared between those with and without diabetes at age 70. Diabetes status was based on self-reports and haemoglobin A1c levels. **Results:** People with diabetes had lower mean cognitive ability scores at ages 11 and 70 when compared with those without diabetes. The effect size was roughly similar at both ages (Cohen's $d \approx 0.32$). When adjusted for age-11 cognitive ability, diabetes status was not associated with cognitive ability at age 70. The association between childhood cognitive ability and older-age diabetes was partly accounted for by body mass index and cholesterol level in older-age.

Conclusion: In this sample, diabetes was associated with poorer cognitive ability in old age but this was because of life-long lower cognitive ability in people with diabetes instead of diabetes impairing cognitive functioning.

Keywords: Diabetes, HbA1c, metabolism, cognition, cognitive ability.

Introduction

The prevalence of diabetes is increasing rapidly in the Western countries including the UK and US [1,2], which has several public health implications. According to a widespread consensus, diabetes is causally associated with an increased risk of cognitive decline and dysfunction [3–6]. Potential mechanisms that have been suggested for this associations include diabetes-related hyperglycemia, inflammation, rheological factors and dysregulation of the hypothalamic-pituitary-adrenal axis [7]. In this article, however, we consider the possibility of reverse causation.

Some adverse health outcomes that are often considered detrimental to cognitive functioning are, in fact, associated with lower pre-morbid cognitive functioning [8,9], which is what we mean by reverse causation in this context. That is, individual differences in cognitive ability, which are relatively stable across the life-course for most people [10], appear to contribute to the aetiology of some adverse health conditions rather than being among their outcomes. One example of such reverse causation is inflammation: it was found that childhood cognitive ability explained the cross-sectional association between cognitive ability and blood levels of C-reactive protein at age 70 [11]. To discover such instances of reverse causation, estimates of cognitive functioning long before and after the onset of the disease or its precursors are needed. For diabetes, such studies are rare. Studies have tested the associations of adult diabetes with either concurrent [6] or childhood [12] cognitive ability but not with both in the same study.

Using data from the Lothian Birth Cohort 1936 (LBC1936) [13], the present study investigates whether diabetes is associated with cognitive decline or is linked to the relatively stable life-long

trait of cognitive ability. In the LBC1936, scores from a well-validated [14] cognitive ability test are available for the same people at ages 11 and 70 years. Age 11 is prior to most diabetes diagnoses, whereas by age 70 many people will have developed diabetes (about 13% in Scotland) [15]. As a result, the following hypotheses can be put forward. Given the evidence that life-course diabetes as such is detrimental to cognitive functioning, people with and without a history of diabetes or current diabetes symptoms in old age should score more similarly in cognitive ability at age 11 than at age 70. More specifically, in order to rule out reverse causation, people with and without diabetes should have similar average cognitive ability scores at age 11 but different scores at age 70. This hypothesis is depicted in the top panel (A) of Figure 1. If this is not the case, partial or full reverse causation is a possibility. In the partial case, people with and without diabetes would differ in cognitive ability already in childhood but the difference would be larger in older age, providing evidence for some detrimental effect of diabetes on cognition. In the case of full reverse causation, people with diabetes would score lower, and by a similar effect size, in childhood and old age. The latter possibility would suggest that people with diabetes have lower life-long cognitive ability; this would provide little evidence for the detrimental role of life-course diabetes on cognition in this group of people.

Methods

Sample

On June 4th 1947, nearly all children born in 1936 and attending school in Scotland sat a general cognitive ability test as a part of Scottish Mental Survey 1947 (SMS1947) [14]. Between 2004

and 2007, 1,091 surviving, community-dwelling participants of the SMS1947 were recruited into LBC1936 [13]. Participants completed the same cognitive test (the Moray House Test No. 12; MHT) that they had taken 59 years earlier. The present study uses the data from 1,017 people for whom MHT data are available at both ages. At follow-up, their mean age was 69.5 ± 0.8 years (range: 67.6 to 71.3; 504 women; all Caucasian). Participants were tested and interviewed individually by a trained psychologist and a research nurse at the Wellcome Trust Clinical Research Facility at the Western General Hospital, Edinburgh. About 17% of participants had no educational qualifications, 40% had O-level, 17% had A-level and 26% had semi-professional education or a university degree. Among the participants, 39% had self-reported hypertension, and 24% had a history of cardiovascular disease. About 95% of participants had a BMI (determined at the clinic) between 21 and 38 kg/m^2 . Of the participants, 85 (8.4 %) reported having a diagnosis of diabetes (mostly type 2); 11 of them were on insulin and 41 used non-insulin diabetes medications. Descriptive information is given separately for those with and without diabetes in Table 1. Participants' mean Mini-mental state examination (MMSE) score was 28.8 ± 1.4 [7 people had a score below 24 (22 or 23); they were included]. Informed consent was obtained from all participants. Ethics permissions for the study were obtained from the Multi-Centre Research Ethics Committee for Scotland.

Measures

The MHT is group-administered test of general cognitive ability that includes mental tasks such as word classifications, proverbs, arithmetic, and spatial items. It has been validated against well-established general cognitive ability tests both at age 11 and in old age and also against tests of

more specific psychomotor skills in old age [14,16]. Raw scores were adjusted for age at times of testing and converted into standard (z) scores (mean = 0, SD = 1). In addition to self-reported diabetes status, haemoglobin A1c (HbA1c) levels were measured for 990 sample members using the Menarini HA8160 analyser. Based on the HbA1c levels, people were grouped into those with ($\geq 6.5\%$ [48 mmol/mol]; N = 116) or without ($< 6.5\%$; N = 874) current 'biochemical diabetes' [17]. We also used this diabetes classification in our analyses for cross-validation purposes. Among those with self-reported diabetes, 84.1% had HbA1c $\geq 6.5\%$; the percentage was 5.2 among those without self-reported diabetes. Among those with HbA1c $\geq 6.5\%$, 59.5% reported diabetes, whereas the percentage was 1.5 among people with lower HbA1c values. The agreement (Cohen's kappa) between the two diabetes classifications was thus 0.66. Cholesterol was measured using the Abbott Architect c16000 instrumentation (Abbott Laboratories, U.S.A).

Statistical Analyses

We started by calculating mean values of cognitive ability test scores at ages 11 and 70 for those with and without diabetes. We then carried out logistic regressions, whereby diabetes status was predicted separately by cognitive abilities at ages 11 and 70, adjusting for exact age at follow-up testing and sex. The former model describing the link between age-11 abilities and diabetes was further adjusted for (a) BMI, (b) BMI and cholesterol, and (c) BMI, cholesterol and hypertension status; these adjustments tested for the possible mediating (or confounding) role of these variables in the cognition-diabetes association. Mediation (or confounding) was attested by attenuation of the effects after co-variate inclusion [attenuation equalled the decrease in regression coefficient (not odds ratio) as a result of adding the respective co-variates]. To test

whether diabetes status moderated the stability/change in cognitive ability between childhood and older age, a linear regression model was used to predict age-70 cognitive ability from that of childhood, along with diabetes status and their interaction term (also adjusting for exact age at the follow-up testing and sex). Diagnostics plots of the linear regression models were inspected to detect major violations of model assumptions. For statistical inference, 5% alpha level was used throughout. R [18] statistical software was used for these analyses.

Results

Mean and standard deviations of standardized cognitive ability test scores are illustrated in the panels B (for self-reported diabetes) and C (for HbA1c-based diabetes) of Figure 1, along with the hypothesized pattern of findings (panel A). Regardless of whether self-reported or HbA1c-based diabetes grouping was used, people with diabetes scored lower in cognitive ability at ages 11 and 70 than those without diabetes, with a similar effect size (Cohen's d of around 0.32) in childhood and older age. These observations clearly contrast with the expected pattern based on the consensus view that life-course diabetes lowers cognitive ability from a prior level and thereby increases any diabetes versus non-diabetes difference. The results were not likely caused by people with diabetes taking medications that could benefit cognition [for details see Supplementary Data, Table S1].

Table 2 gives the associations between childhood and older-age cognitive ability and diabetes, adjusted for sex and follow-up age. A standard deviation advantage in age-11 cognitive ability is associated with 26% lower odds of self-reported diabetes at age 70, and 24% lower odds of

HbA1c-determined diabetes. The associations of age-70 cognitive ability and these two diabetes diagnoses are almost identical to the age-11 associations. Table 2 also shows the associations between age-11 cognitive ability and diabetes after adjustment for BMI, hypertension and cholesterol, which we considered as potential mediators (or confounders). Adjusting for only BMI attenuated the association by 25.9% (self-reported diabetes) and 31.0% (HbA1c-based diabetes). Additionally adjusting for cholesterol level further attenuated the association by 21.5% and 20.2% (collective attenuations from the model with no co-variables were thus 41.9% and 44.9%), respectively. Further adjustments for hypertension lead to 8.7% and 14.3% increases in effect sizes (collective attenuations from the model with no co-variables were thus 33.6% and 40.1%), respectively. As a result, we conclude that there was evidence for BMI and cholesterol (but not hypertension) partly accounting for the childhood cognitive ability-diabetes association. There was also evidence for the effect of childhood cognitive ability on later diabetes being partly mediated by educational attainment (for details see Supplementary Data).

A general linear model was used to predict standardized cognitive ability at age 70 from age-11 ability scores and self-reported diabetes status along with their interaction term, age at follow-up testing and sex. This showed a significant age-11 ability effect on later cognition ($b = 0.70$, $p < 0.001$), but no diabetes effect ($b = -0.10$, $p = 0.25$). The interaction term between the age 11 cognitive ability test score and diabetes status was not significant ($p = 0.80$), indicating that diabetes status also had no effect on the stability of individual differences in cognitive ability between childhood and old age. When HbA1c-based diabetes status was used, the estimates were similar: $b = 0.69$ ($p < 0.001$) for age-11 ability, $b = -0.08$ ($p = 0.30$) for diabetes status, and $p =$

0.51 for the interaction term. No notable violations of model assumptions could be detected.

Discussion

People with self-reported and HbA1c-based diabetes at age 70 scored lower, by a similar amount, on the same well-validated general cognitive ability test at ages 11 and age 70 than people without diabetes. This suggests that the life-long trait of cognitive ability (relative stability estimate between ages 11 and 70 being about 0.70 in the present sample) predicts diabetes. Therefore, the often-observed differences between people with and without diabetes in cognitive functioning in later adulthood could at least partly reflect this life-long cognitive ability difference rather than there being a causal effect of life-course diabetes on cognitive function. In other words, these results supported full reverse causation as a plausible causal account for the diabetes-cognition association in this sample, with its particular characteristics.

This finding contradicts the general consensus view that any cognition-diabetes association should be understood to mean that diabetes has a detrimental causal effect on people's cognitive functioning. As a result, it must be questioned whether the design and results of the present study could have been flawed in some crucial ways and to what extent the present results are generalisable. Since exactly the same people were tested with exactly the same validated test about 59 years apart, biases due to sampling or instrument differences between the two measurement occasions were unlikely. This leaves us with three possible reasons why the current conclusion suggesting reverse causation as an explanation for the often-observed diabetes-related differences in cognition might be wrong.

First, the present sample may be in some ways unusual. This is possible but there is no identifiable evidence as to why this would be the case. For example, the findings corresponded to the expected pattern with respect to the diabetes-related differences in cognition in old age, such that people with diabetes did score lower than those without the diagnosis or its biochemical symptoms. And yet, the sample was relatively healthy; it was not intended to include cases of diabetes with major sequelae requiring constant medical attention. Also, almost all of the sample had MMSE scores that would imply no or little pathological cognitive impairment. Therefore, the study does not address the issue of more severe clinical diabetes and dementia and the cognitive sequelae found in the subset of people with more advanced diabetes and its multi-organ complications.

Secondly, it is possible that the test of general cognitive ability that was used in the present study is, for some reason, unsuited for properly detecting differences between people with and without diabetes. However, this explanation is not likely because, again, the test did detect the differences in older age precisely as expected. Moreover, the test is known to be correlated with other well-established tests of general and specific cognitive abilities, including tests of on-spot abstract reasoning, learning, psycho-motor speed, and visuospatial skills [14,16]. The test correlates with non-verbal general cognitive ability at $r = 0.67$ [16].

The third possible explanation is that a substantial minority of the participants already had symptoms of diabetes or its precursors at age 11 and that might also have influenced their cognition at that age. Given that the prevalence of diabetes in childhood and even in young

adulthood is relatively low [15] (and given the secular trends, it was probably much lower in the post-World War II Scotland, where food had been rationed for several years and sedentary life-style was less common than at present), early presence of diabetes or its important precursor obesity was not likely. It is also possible that the people who would later develop diabetes had some aspects of ill-health present at age 11 and that this was reflected in their lower cognitive ability test scores. For example, this might be due to: possible family history of diabetes, which could have complicated prenatal or early environment; shared genetic predisposition between diabetes and other conditions; or other reasons. However, it must be noted that, even if this explanation is correct, this does not necessarily support the idea that factors specific to diabetes impaired their cognition. Furthermore, this would still contradict the common explanations for diabetes-cognition associations such as those based on glycemic, inflammatory, or rheological functioning [7], given that these mechanisms are likely to unfold over the life-course whereas we observed the similar cognitive differences between people with and without diabetes at ages 11 and 70.

Therefore, assuming that the present findings point to the association of the life-long trait of cognitive ability with diabetes, how could the links be explained? A possible explanation is that people with higher cognitive ability might take better care of their health throughout life, possibly due to their higher education and socio-economic status [19] and the resources these provide, or due to better health-management skills [20]. For example, low childhood cognitive ability has been shown to predict smoking, physical inactivity, and poorer diet in later life [9] and these, in turn, may contribute to diabetes. The present finding that adjustments for BMI and cholesterol

levels resulted in substantial attenuation of the childhood cognitive ability-diabetes association is consistent with this explanation. Likewise, it has previously been found that childhood cognitive ability is associated with higher body mass index and metabolic syndrome in later life [21].

The strength of the present study is availability of information on cognitive functioning of the same people long before most of them were likely to develop diabetes and after a proportion had developed it. Given that randomized experimental studies on the cognition-diabetes association will probably never be available, the present observational design is arguably about as strong as an observational study can be. A weakness is that there was no information on more specific ability domains at both time-points. Also, ideally there could have been information on cognitive and diabetes-related variables between ages 11 and 70 as this would have allowed for testing for the stability of diabetes-related cognitive ability differences throughout most of adulthood and to investigate potential mechanisms of the association. However, we do note again that the cognitive differences between those with and without diabetes were almost identical in childhood and older age. Finally, information on family history of diabetes and childhood health would have allowed for controlling of these factors.

A recent systematic review concluded: “Cognitive dysfunction should therefore be added to the list of chronic complications of diabetes.” [5, p. 246]. The present results suggest, however, that cognitive function may sometimes contribute to the aetiology of diabetes rather than being its outcome. There is no doubt that diabetes is a health condition with numerous adverse consequences but, at least, its causal detrimental effect on cognition may be less evident among

those with the range of diabetes that were studied here.

Acknowledgements

The data were collected as part of the Age UK-funded Disconnected Mind project. The work was conducted within The University of Edinburgh Centre for Cognitive Ageing and Cognitive Epidemiology, part of the cross council Lifelong Health and Wellbeing Initiative (G0700704/84698). We thank the Scottish Council for Research in Education for allowing access to the SMS1947. René Mõttus is grateful to European Social Fund for supporting this post-doctoral studies (Estonian Research Council grant MJD44). Funders have no role in the particular study and have in now ways influenced its results or conclusions. Authors have no competing interests to report.

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Figure Captions

Figure 1. Expected (A) and observed mean differences (with 95% confidence intervals) in cognitive test scores between people with and without self-reported diabetes (B) or HbA1c-based diabetes groupings (C) at ages 11 and 70 years. Solid lines = people without self-reported or HbA1c-based diabetes grouping. Dashed lines = people with self-reported or HbA1c-based diabetes grouping. Note that the same people were tested at both ages.

Table 1. Descriptive statistics separately for participants with either self-reported or HbA1c-based diabetes and for participants without any indication of diabetes.

| | No diabetes (N = 885) | | Self-reported or HbA1c-based diabetes (N = 132) | |
|------------------------|-----------------------|-------|-------------------------------------------------|-------|
| | N | % | N | % |
| Female | 449 | 50.73 | 55 | 41.67 |
| Hypertension | 315 | 35.59 | 84 | 63.64 |
| Cardiovascular disease | 190 | 21.47 | 55 | 41.67 |
| | M | SD | M | SD |
| Age at follow-up | 69.51 | 0.84 | 69.68 | 0.79 |
| Educational level | 1.71 | 1.30 | 1.31 | 1.18 |
| HbA1c | 5.72 | 0.36 | 7.29 | 1.01 |
| Body Mass Index | 27.42 | 4.18 | 30.44 | 4.75 |

NOTE: M = mean; SD = standard deviation.

Table 2. Associations (odds ratios) between diabetes and standardized cognitive ability at ages 70 and 11 with the latter association being adjusted for various co-variates.

| | Self-reported diabetes | | HbA1c-based diabetes | |
|--------------------------------------------------|------------------------|-------|----------------------|-------|
| | OR [95% CI] | p | OR [95% CI] | p |
| Age 70 cognitive ability | 0.76 [0.62;0.92] | 0.005 | 0.78 [0.66;0.93] | 0.004 |
| Age 11 cognitive ability: | | | | |
| No adjustments other than sex and age | 0.74 [0.60;0.91] | 0.005 | 0.76 [0.64;0.92] | 0.004 |
| Adjusted for BMI | 0.80 [0.65;1.00] | 0.04 | 0.83 [0.69;1.01] | 0.06 |
| Adjusted for BMI + cholesterol | 0.84 [0.68;1.05] | 0.12 | 0.86 [0.71;1.05] | 0.13 |
| Adjusted for BMI + cholesterol + hypertension | 0.82 [0.65;1.03] | 0.08 | 0.85 [0.70;1.04] | 0.11 |

NOTE: All associations are adjusted for sex and follow-up age. OR = odds ratio; 95% CI = 95% confidence intervals; BMI = body mass index.