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Diabetes, Glycaemia, and Cognition– a secondary analysis of the Finnish Diabetes Prevention Study

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Abstract

BACKGROUND

Type 2 diabetes is linked with cognitive dysfunction and dementia in epidemiological studies, but these observations are limited by lack of data on the exact timing of diabetes onset. We investigated diabetes, dysglycaemia, and cognition in the Finnish Diabetes Prevention Study (DPS), in which the timing and duration of diabetes is well documented.

METHODS

The DPS comprised middle-aged, overweight participants with impaired glucose tolerance (IGT) but no diabetes at baseline (n = 522), randomized to lifestyle intervention or a control group. After an intervention period (mean duration 4 years) and follow-up (additional 9 years), cognitive assessment with the CERAD test battery and Trail Making Test A (TMT) was executed twice within a two-year interval. Of the 364 (70%) participants with cognitive assessments, 171 (47%) had developed diabetes.

RESULTS

Cognitive function did not differ between those who developed diabetes and those who did not. Lower mean 2-h glucose at an oral glucose tolerance test (OGTT) and HbA_{1C} during the intervention period predicted better performance in the TMT (p = 0.012 and 0.024, respectively). Those without diabetes or with short duration of diabetes improved in CERAD total score between the two assessments (p = 0.001) whereas those with long duration of diabetes did not (p = 0.844).

CONCLUSIONS

Better glycemic control among persons with baseline IGT predicted better cognitive performance 9 years later in this secondary analysis of the DPS study population. In addition, learning effects in cognitive testing were not evident in people with long diabetes duration.

INTRODUCTION

Type 2 diabetes (later referred to as diabetes) is associated with an increased risk of Alzheimer's disease (AD) and vascular dementia (VaD) [1], and amnestic and non-amnestic mild cognitive impairment [2]. Cerebrovascular factors seem important mediators between diabetes and both AD and VD [3]. Compared with non-diabetic people, those with diabetes have lower cognitive performance [4-6], although cognitive deficits appear to be mild before the age of 70 years [7]. Improved diabetes control [8], and aerobic exercise [9] may delay cognitive decline in people with diabetes or impaired glucose tolerance (IGT).

Although the reasons behind the relationship between glycaemia and cognition are still uncertain, several potential mechanisms have been identified. In addition to cerebrovascular factors, such as infarcts and white matter lesions in the brain, also hyperinsulinemia, advanced products of glycosylation, inflammation, dysregulation in glucocorticoid metabolism, and oxidative stress are linked to both diabetes and poor cognitive functioning [10,11]. However, all pathways can either be causal or co-occur, and even reverse causality has been proposed [10], i.e. pre-clinical AD process causing impairment in glucose homeostasis. One of the reasons for this uncertainty is a lack of precise data on longitudinal measures of glycaemia, and onset and duration of diabetes.

The Finnish Diabetes Prevention Study (DPS) was a controlled lifestyle intervention trial that demonstrated a reduction of 58% in diabetes in the lifestyle intervention group [12]. Glycaemia and diabetes onset were further monitored annually with an observational phase, and cognitive assessments were conducted twice, on average 13 and 15 years after the baseline. We reported elsewhere that the lifestyle intervention allocation was not related to cognitive performance [13] .The aim of these analyses is to investigate the association of diabetes onset and duration, and glycaemia with cognitive performance in the DPS.

MATERIALS AND METHODS

Subjects and setting

This study was an ancillary study to the DPS, which has been described in detail elsewhere [14]. In brief, the DPS was a randomized, controlled, multi-center lifestyle intervention study aiming at diabetes prevention in a high-risk population (ClinicalsTrials.gov NCT00518167). Participants in the DPS were middle-aged (mean 55 years, range 40 to 65 at randomization), overweight or obese (BMI > 25 kg/m^2), and all had IGT at baseline defined by the mean of two oral glucose tolerance tests (OGTT). The 522 subjects were randomized into two groups; the intervention group (n = 265) received individualized dietary, exercise, and weight reduction counseling whereas the control group (n = 257) received only general health advice. The intervention was planned to continue for 6 years, but it was prematurely discontinued based on interim endpoint analyses showing significant difference between the groups in diabetes incidence [12], and consequently, the duration of the intervention varied with an average of 4 years. In this paper, intervention period refers to the active study period, when participants were subject to intervention according to group allocation (intensive or control). After the active intervention period, annual post-intervention follow-up visits were initiated with an average of 9 years of post-intervention follow-up before the cognition study.

The study protocol was approved by the ethics committees of the National Public Health Institute in Helsinki (intervention period), and of the North Ostrobothnia Hospital District (follow-up period and the cognition study). All study participants gave written informed consent at baseline, at the beginning of post-intervention follow-up, and at the beginning of cognitive assessments.

Clinical Measurements

Annual study visits comprised 2-h OGTT, a medical history, and a physical examination with measurements of height (without shoes), weight (in light indoor clothes), waist circumference (midway between the lowest rib and iliac crest to the nearest 1 mm) and systolic and diastolic blood pressure (two measurements with a standard sphygmomanometer in sitting position, using the right arm, after 10 minutes of rest).

Diabetes was diagnosed according to the WHO criteria from 1985 [15], as either fasting plasma glucose of 7.8 mmol/L or more, or 2-h plasma glucose of 11.1 mmol/L or more at OGTT. The diagnosis was confirmed by a second test. Participants with a verified diabetes diagnosis before the first cognitive assessment were defined as having diabetes in the cognition study. The apolipoprotein E (apo E) genotypes were analyzed using the polymerase chain reaction (PCR) with slight modifications, as described earlier [16].

Cognitive function was assessed by study nurses trained to use the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) [17] neuropsychological test battery (standardized Finnish translation) and Trail Making Test A (letters) [18]. The cognitive assessment was repeated two years later. All eligible participants in both intervention and control groups (excluding those who had withdrawn from the study or died) were mailed an invitation letter to participate, for both rounds respectively.

The Finnish CERAD Battery is composed of 1) Verbal fluency (naming as many animals as possible in one minute) 2) Modified Boston Naming test (15 words) 3) Mini-Mental State Exam 4) Word List Memory (learning of ten words, three trials) 5) Constructional praxis (copying four figures out of a model) 6) Word List Recall (delayed recall of the ten words presented in word list memory task) 7) Word List Recognition (recognition of the previous ten words out of 20 words) 8) Constructional praxis recall (drawing the previous four figures, later and without a model) 9) Clock drawing. We calculated the CERAD total score (CERAD-TS) to measure overall cognitive performance according to Chandler et al [19]. The Trail Making Test A (TMT) was calculated as time in seconds without upper limit (longer time indicating worse performance).

All participants with at least one cognitive assessment (n = 364 for CERAD-TS and 362 for TMT) were included in the analysis of general cognitive functioning using the first observation for each participant, regardless of the assessment point. Participants with two assessments were further included in the analysis of the rate of change between the assessments (n = 282 for CERAD-TS and 277 for TMT).

Statistical methods

Differences in characteristics between the participants and non-participants as well as between the diabetic and non-diabetic participants were compared using t-test or χ^2-test as appropriate. Linear regression modeling was applied in all cognition analyses, except for testing significance of change between the cognitive assessments, where paired t-test was applied in the whole group and in each diabetes group separately. All regression analyses were adjusted for sex, age and educational attainment (Model A), and additionally for apo E4 carrier status, baseline smoking, baseline systolic blood pressure and baseline BMI (Model B). In linear regression analysis, diabetes status was included as factor variable with the non-diabetic group as a reference. Missing baseline systolic blood pressure values (n = 2) and smoking (n = 1) were replaced with values from year 1. Apo E4 carrier status was coded as 1 for any apo E4 allele and 0 for none. For those with missing apo E4 information (n = 10) replacement with value 0.5 was applied and variable was entered as continuous in the model. Educational attainment was a factor variable with 4 categories, and it was also entered as continuous, as well as blood pressure and BMI.

Cognitive scores were skewed to the right, indicating high proportion of good scores. Box-cox transformations [20] improved normality and all regression analyses were conducted with transformed variables. The transformation did not change results much and we chose to present the regression estimates using non-transformed model to facilitate interpretation. All *P*-values presented are based on models using box-cox transformation. One influential outlier in the CERAD-TS, scoring 38 points at both assessments, was removed from the final analysis. Keeping the outlier in the model would have strengthened some of the reported associations.

The duration of diabetes ranged from 0.1 to 14.5 years with a median of 7.5 years, which was used as a cut-point to separate groups with short duration of diabetes (n = 86) and long duration of diabetes (n = 85). First, we compared all participants with and without diabetes, and secondly, people with short or long duration of diabetes, respectively, to individuals free of diabetes at the time of the first cognition assessment. Among those with diabetes, duration was analyzed as a continuous variable as well (in years).

Fasting glucose, 2-h glucose, and HbA_{1C} were averaged over the intervention period (range 1–6 measurements) and the post-intervention follow-up (range 4–14 measurements), respectively. Mean values were categorized according to current WHO criteria [21] as fasting glucose in the normal (NFG), impaired (IFG) or diabetic range; and the 2-h glucose in the normal (NGT), impaired (IGT), or diabetic range. Categorization suggested by ADA [22] was applied for HbA_{1C} as normal, high risk (later referred to as prediabetes), or diabetic range. All participants who had at least one measurement during either intervention or follow-up period, respectively, were included.

Participants were further classified according to the direction of change in fasting glucose, 2-h glucose, and HbA_{1C}. Those having average levels during both the intervention and follow-up periods lower than the baseline level were classified as having permanent decrease; those with both averages higher than baseline level were had permanent increase; and those with fluctuating levels were classified as the middle group, for each measure separately. Participants having at least one measurement during both the intervention and follow-up periods were included. Analyses were conducted with STATA for Windows, release 11.2 (StataCorp LP, TX). *P*-value <0.05 was considered statistically significant.

RESULTS

Characteristics

Of the entire DPS cohort, 70% participated in the cognition assessment at least once, and 54% twice. Mean age at the first cognitive assessment was 68.3 ± 6.7 years. Diabetes duration was longer among the non-participants (mean 8.6 ± 2.8 years; $n = 68$) than among the cognition study participants (mean 7.2 ± 3.5 years; $n = 171$; $p = 0.005$). The former intervention and control groups had no difference in participation ($p = 0.924$). Altogether 26 DPS participants had died before the first cognitive assessment (5% of the whole cohort; 16% of the non-participants). The cognition study participants free of diabetes were older than those with diabetes, but had lower risk factor levels at baseline (e.g. glycaemia), and were more likely to have been in the intervention group (Table 1).

Those with only one cognitive assessment (n = 80) were older (mean 70.2 vs. 67.8 years, p = 0.004), and had a higher proportion of diabetes (61% vs. 43%, p = 0.005) compared with those participating in both assessments.

Table 1 - Characteristics of the DPS Cognition Study participants according to diabetes status at the time of the first cognition assessment.

	Without diabetes [c] (n = 193)	Verified diabetes [c] (n = 171)	p-value
Intervention group, %	57.5	42.7	0.006
High education [a] , %	34.7	32.8	0.739
Women, %	68.9	68.4	1.000
Apo E 4 Carrier [b] , %	32.1	34.7	0.652
Smoker [a] , %	2.1	5.3	0.155
Age [c], yrs	69.6 ± 6.3	66.9 ± 6.8	<0.001
Follow-up duration [c], yrs	13.0 ± 1.1	13.5 ± 1.2	<0.001
Fasting glucose [a] , mmol/l	5.9 ± 0.6	6.3 ± 0.8	<0.001
2-h glucose [a] , mmol/l	8.5 ± 1.4	9.2 ± 1.5	<0.001
$HbA1_C$ [a,d] , %	5.5 ± 0.5	5.7±0.6	0.001
Body mass index [a], kg/m^2	30.1 ± 3.8	32.5 ± 5.1	<0.001
Systolic blood pressure [a], mmHg	137 ± 17	137 ± 18	0.666
Diabetes duration [c] , yrs		7.2 ± 3.6	

Data are presented as % of the population or as mean ± SD, and p values are based on chi2 test or ttest, as appropriate.

[a] At baseline of the DPS

[b] Data available for 354 participants (187 without and 167 with diabetes)

[c] At the first cognitive assessment

[d] Data available for 357 participants (190 without and 167 with diabetes)

Diabetes, cognition, and cognitive changes over time

The unadjusted mean for CERAD-TS was 82.0 ± 9.3 points (range 38 to 100, of maximum of 100) and for TMT 48.6 ± 19.6 seconds (range 21 to 151, no upper limit). Age-, sex-, and education adjusted means for the first assessment and for change between the two assessments are presented in Table 2. Among this population with baseline IGT, cognitive performance in the first assessment did not differ between those who had developed diabetes and those who had not.

Period between the two cognitive assessments was 2.0 years on average (range 1.6 to 2.4). The mean CERAD-TS improved from 82.8 to 83.8 (paired t-test, $p = 0.001$), whereas no change in TMT was detected ($p = 0.796$). Those with long-duration diabetes did not improve in CERAD-TS ($p = 0.742$), as did both the short-duration diabetes group ($p = 0.001$) and non-diabetic group ($p = 0.002$). Diabetes duration as a continuous variable was also associated with less improvement between the assessments: among those with diabetes the regression coefficient for change in CERAD-TS was -0.3 points for each year with diabetes (95% CI -0.6 to 0.0, $p = 0.042$ in fully adjusted model), and in TMT 0.8 seconds for each year (95% CI 0.0 to 1.6, $p = 0.042$ in fully adjusted model).

Previous dysglycaemia and cognitive function

Mean fasting plasma glucose during the active intervention period was 6.2 ± 0.7 mmol/l, 2-h glucose 8.6 ± 1.9 mmol/l, and HbA_{1C} 5.6 ± 0.5%**.** Participants were classified into three groups, as having non-diabetic, pre-diabetic, or diabetic glucose levels during the intervention period (Table 3). Those with diabetic glucose concentrations, defined by either 2-h glucose or $HbA_{1C,}$ performed more poorly in TMT than those with normal levels. Glycaemia levels measured during the post-intervention follow-up were not associated with the cognition (results not shown), but permanent increase in HbA_{1C} during the entire study (both intervention and follow-up levels higher than baseline) predicted poorer CERAD-TS (Table 4). Direction of change in glycaemia variables was not associated with the TMT (results not shown).

Table 2 - Cognitive function among the participants in the DPS cognition study according to the diabetes status.

	The CERAD total score			Trail Making Test A		
	Mean (95% CI)	*p*, model A [a]	*p*, model B [b]	Mean (95% CI)	*p*, model A [a]	*p*, model B [b]
The first assessment						
All (*n* = 364)	82.1 (81.3 – 82.9)			48.6 (46.7 – 50.4)		
Without diabetes (*n* = 193)	82.6 (81.5 – 83.8)	*(ref)*	*(ref)*	47.4 (44.7 – 50.0)	*(ref)*	*(ref)*
Verified diabetes (*n* = 171)	81.5 (80.2 – 82.7)	*0.110*	*0.216*	49.9 (47.1 – 52.7)	*0.091*	*0.154*
Diabetes duration < 7.5 yrs (*n* = 86)	81.7 (80.0 – 83.4)	*0.218*	*0.402*	49.5 (45.6 – 53.4)	*0.254*	*0.276*
Diabetes duration > 7.5 yrs (*n* = 85)	81.2 (79.4 – 82.9)	*0.172*	*0.232*	50.3 (46.4 – 54.3)	*0.107*	*0.212*
The change between the assessments						
All (*n* = 282)	1.0 (0.3 – 1.7)			0.7 (-1.2 – 2.5)		
Without diabetes (*n* = 160)	1.3 (0.4 – 2.2)	*(ref)*	*(ref)*	0.8 (-1.6 – 3.3)	*(ref)*	*(ref)*
Verified diabetes (*n* = 122)	0.6 (-0.5 – 1.7)	*0.150*	*0.144*	0.5 (-2.4 – 3.3)	*0.606*	*0.661*
Diabetes duration < 7.5 yrs (*n* = 63)	1.6 (0.1 – 3.0)	*0.983*	*0.860*	-1.0 (4.9 – 2.8)	*0.167*	*0.222*
Diabetes duration > 7.5 yrs (*n* = 59)	-0.4 (-2.0 – 1.1)	*0.017*	*0.023*	2.1 (-1.9 – 6.2)	*0.528*	*0.564*

Data are presented as adjusted mean (95% CI), adjusted for age at the (first) cognitive assessment, educational attainment at baseline, and sex.

Better performance is indicated by higher CERAD-TS and shorter time in TMT in the first assessment. Improvement in follow-up is indicated by positive change in CERAD-TS and negative change in TMT.

[a] Model A with box-cox transformed cognition scores, adjusted for age at the (first) cognitive assessment, education at baseline, and sex

[b] Model B with box-cox transformed cognition scores, adjusted additionally for apo E4 carrier status, and smoking status, systolic blood pressure, and BMI at baseline.

Table 3 . Cognitive function according to the glycaemia variables during the original lifestyle intervention period.

	The CERAD total score				Trail Making Test A			
	Model A[a] b (95% CI)	*p*	Model B [b] b (95% CI)	*p*	Model A[a] b (95% CI)	*p*	Model B [b] b (95% CI)	*p*
Fasting glucose								
<6.1 (*n* = 176)	*(ref)*		*(ref)*		*(ref)*		*(ref)*	
6.1-7 (*n* = 143)	0.3 (-1.5 – 2.1)	0.768	0.7 (-1.1 – 2.5)	0.483	-0.8 (-4.9 – 3.3)	0.447	-0.4 (-4.6 – 3.8)	0.530
> 7 (*n* = 45)	-2.0 (-4.7 – 0.7)	0.253	-1.5 (-4.2 – 1.2)	0.433	1.1 (-5.1 – 7.3)	0.655	0.6 (-5.7 – 6.9)	0.807
P (trend)		0.453		0.759		0.991		0.939
2-hour glucose								
<7.8 (*n* = 124)	*(ref)*		*(ref)*		*(ref)*		*(ref)*	
7.8-11 (*n* = 197)	-1.6 (-3.4 – 0.3)	0.065	-1.3 (-3.1 – 0.5)	0.105	4.5 (0.3 – 8.6)	0.029	3.4 (-0.7 – 7.6)	0.090
> 11 (*n* = 43)	-2.4 (-5.2 – 0.5)	0.173	-2.1 (-5.0 – 0.7)	0.232	7.9 (1.6 – 14.3)	0.009	7.3 (0.9 – 13.7)	0.018
P (trend)		0.071		0. 112		0.004		0.012
HbA_{1C}								
<5.7 (*n* = 246)	*(ref)*		*(ref)*		*(ref)*		*(ref)*	
5.7-6.5 (*n* = 97)	-0.1 (-2.0 – 1.8)	0.824	0.0 (-1.8 – 1.9)	0.947	0.8 (-3.5 – 5.1)	0.379	0.0 (-4.3 – 4.3)	0.588
> 6.5 *n* = 20)	-4.7 (-8.5 – -1.0)	0.035	-4.1 (-7.8 – -0.3)	0.067	11.9 (3.5 – 20.2)	0.003	11.5 (3.1 – 19.9)	0.005
P (trend)		0.120		0.210		0.010		0.024

Data are presented as unstandardized regression coefficient (95% CI) representing difference in cognitive scores compared with the reference group respectively, and *P* values for trend are also presented. Better performance is indicated by higher CERAD-TS and shorter time in TMT in the first assessment. Regression coefficients from model using non-transformed cognitions score and *P* values from models using box-cox transformed cognition scores.

[a] Model A adjusted for age at the (first) cognitive assessment, educational attainment at baseline, and sex

[b] Model B adjusted additionally for apo E4 carrier status; and smoking status, systolic blood pressure, and BMI at baseline

Table 4 - The CERAD total score according to the direction of change in glucose metabolism during the entire study period (from randomization until the end of the extended follow-up).

	Model A [d]		Model B [e]	
	b (95% CI)	*p*-value	b (95% CI)	*p*-value
Fasting glucose				
Decrease [a] (*n* = 95)	*(ref)*		*(ref)*	
Fluctuating [b] (*n* = 95)	-0.5 (-2.8 – 1.8)	0.601	-0.7 (-3.0 – 1.6)	0.489
Increase [c] (*n* = 167)	-1.5 (-3.6 – 0.6)	0.115	-1.7 (-3.8 – 0.3)	0.076
2 h-glucose				
Decrease [a] (*n* = 144)	*(ref)*		*(ref)*	
Fluctuating [b] (*n* = 84)	0.2 (-1.9 – 2.4)	0.980	0.2 (-1.9 – 2.4)	0.986
Increase [c] (*n* = 128)	-1.3 (-3.2 – 0.7)	0.134	-1.4 (-3.3 – 0.5)	0.092
HbA_{1C}				
Decrease [a] (*n* = 135)	*(ref)*		*(ref)*	
Fluctuating [b] (*n* = 102)	1.7 (-0.4 – 3.7)	0.139	1.4 (-0.6 – 3.4)	0.209
Increase [c] (*n* = 111)	-2.1 (-4.1 – -0.1)	0.013	-2.0 (-4.0 – -0.0)	0.015

Data are presented as unstandardized regression coefficient (95% CI) representing difference in cognitive scores compared with the reference group (respectively). Regression coefficients from model using non-transformed cognitions score and *P* values from models using box-cox transformed cognition scores.

[a] Decrease defined as both the intervention period mean and the follow-up period mean lower or equal than baseline level; [b] Fluctuating defined as either study period mean or follow-up mean higher than baseline; [c] Increase defined as both the study period mean or follow-up mean higher than baseline level

[d] Model A adjusted for age at the (first) cognitive assessment, educational attainment at baseline, and sex

[e] Model B adjusted additionally for apo E4 carrier status; and smoking status, systolic blood pressure, and BMI at baseline.

Age, diabetes, glycaemia and cognitive function

Because the group comprised both middle-aged and elderly participants (age range 52 to 82 years at the time of cognitive assessment), we repeated the analyses separately for those under and over the median age (70 years). Participants in the younger group performed better than the older one: in the first assessment mean difference was 5.5 points in CERAD-TS and -10.2 seconds in TMT ($p <$ 0.001, respectively). Despite better general performance, diabetes-related differences were more evident among those under 70 years: diabetes duration predicted worse performance in CERAD-TS in the first assessment (b -0.5 (95% CI -0.9 to-0.1) for each year with diabetes, $p = 0.020$ in fully adjusted model), as well as less improvement between the assessments.

Diabetic 2-hour glucose and Hba1c during the intervention period were related to the TMT in the whole sample, but among the under 70-year-olds association with the CERAD-TS was statistically significant as well. Lower performance was detected in the group having diabetic levels defined by either the 2-hour glucose (b -4.4; 95% CI -7.5 – -1.2, $p = 0.017$ in fully adjusted model), or the HbA_{1C} (b -7.6; 95% CI -12.1 – -3.1, $p = 0.007$), compared with normal glycaemia. Furthermore, in the younger group the performance in the TMT was significantly lower in the prediabetes group than in the normal group ($p = 0.032$ for IGT vs. NGT; and $p = 0.007$ for prediabetic vs. normal HbA_{1C}), in addition to the difference between normal and diabetic groups shown in Table 3.

DISCUSSION

Cognitive functioning among the DPS participants was in general rated good, and within two years average cognitive scores improved, consistent with learning effects. Developing diabetes was not related to cognitive performance among this population with baseline IGT, but longer diabetes duration predicted less improvement between the two assessments. High 2-hour glucose and HbA_{1C}, measured approximately 9 years before the cognitive assessment, predicted poorer processing speed while current diabetes diagnosis did not. All associations appeared stronger among those aged under 70 years.

Higher risk of dementia and AD among individuals with diabetes is well established [23-27], but cognition studies among non-demented individuals with diabetes are less consistent. We found no difference in cognitive function between persons with and without diabetes, and only some studies report such a cross-sectional difference [28,29]. Diabetes-related differences were only evident among those with long diabetes duration (over 7.5 years), consistent with previous reports showing no differences between non-diabetic people and those with newly diagnosed diabetes [30,31]. In many previous studies [29,32] the non-diabetic group has been younger whereas in our setting they were older, which may dilute the differences despite the age-adjustment in the analysis. Furthermore, usually in cohort studies there is no upper limit for diabetes duration; in the DPS all participants were free of diabetes at baseline, which may result in less variability, especially considering that the DPS did not include participants with normal glucose tolerance but all had IGT at baseline. Of note, previous studies included people with normal glycaemia in the non-diabetic group [28,29] as opposed to people with IGT in our study. On the other hand, as diabetes status has often been based on self-report, it is very probable that the "normoglycaemic" control group actually included non-diagnosed cases of diabetes and an even larger proportion of people with IGT of IFG.

Diabetes-free participants were able to improve their cognitive performance in our study, whereas those with long duration of diabetes showed no improvement or even decline. Over a longer period, 5 to 12 years, people with diabetes show greater cognitive decline in other studies [28,29,32]. With a 4-year follow-up differences are smaller [33] and even improvement in some cognitive domains has been reported previously [34]. Because of the relatively short time between the tests, the change over time in our study is more likely an indicator of learning (practice or learning effects). However, practice effects are increasingly recognized as important predictors of progression of

cognitive impairment that can be used as outcomes in clinical trials [35] and have clinical significance. Learning and memory deficits are commonly affected by type 2 diabetes [2,7], but in most studies they are defined as poor performance in neurocognitive tests measuring short-term learning, such as word list test.

We found that the 2-h glucose and HbA_{1C} levels measured approximately 9 years before the cognitive assessment were better predictors of cognition than the diabetes diagnosis at the time of the assessment, suggesting that the association between glycaemia and cognition follows a continuum, rather than having a threshold, among persons with IGT. Furthermore, among those under 70 years, there was a difference not only between those having normal and diabetic glucose levels, but also between the normal and pre-diabetes groups defined by either 2-h glucose or HbA_{1C}. This is consistent with findings showing that the continuum of hyperglycaemia in the general population is related to a higher risk of dementia [36] and cognitive impairment [6]. In the whole group, the glycaemia variables measured during the post-intervention follow-up, closer to the cognition study, did not correlate with cognition scores. The lack of such associations may be due to selective drop-out, and the high proportion of participants with diabetes. As approximately half of the participants were diagnosed with diabetes, medication use could confound the associations between those with and without diabetes. Alternatively, the glycaemia variables measured during the intervention period may also be markers of successful lifestyle changes (e.g weight loss or dietary changes), which have independent protective effects as reported previously [37].

Recently, a lot of interest has been focused on the higher "normal" glucose levels: worsening cognition with higher glucose levels that are still in the non-diabetic range has been reported [38], as well as elevated dementia risk [36]. In our data there were linear associations between the cognition and glycaemia variables in the whole group, but the dataset was too small to carry out analyses among non-diabetic people stratified by normal and prediabetic levels. Importantly, we showed, that among people with IGT those whose glucose levels were reduced to the normal range during the original intervention trial period had better cognitive performance later on. The association between better cognitive performance and long-term decrease in Hba1c, regardless of the baseline level, supports the idea of relationship between glycaemia and cognitive functions at any level of glycaemia.

We observed that younger participants performed markedly better but yet their performance appears to be more affected by diabetes or previous dysglycaemia. One explanation for this could be a

different risk profile. Both age groups had IGT and were overweight at the beginning of the study, but the older participants who had nevertheless managed to remain free from diabetes longer (mean age at inclusion 61 vs. 49 yrs in the younger group) may have other factors protecting them from both diabetes and cognitive impairment. This is supported by the observation that diabetes occurring at mid-life seems to have stronger effect on dementia risk than does diabetes incident at older age [27,39] and similar could apply for cognitive functioning before clinical dementia. Older participants with longer diabetes duration also appear underrepresented in the data: of the 70-year-olds, those with long-duration of diabetes were less likely to attend the cognition study.

The strength of our study is reliable diagnosis of diabetes and precise information on diabetes duration and glycemic control throughout the follow-up: participants underwent laboratory tests annually and diabetes was always confirmed with a repeated OGTT. Because of this frequent testing, we had an extensive dataset of trends in glycaemia variables over a long period of time prior to the assessment of cognition. Many previous studies used self-report of diabetes status or only fasting glucose, which showed no association with cognition in our data. For AD and diabetes, risk ratios appear to be lower in studies using self-report than in those with blood sampling [1]. This reflects the fact that the "normoglycaemic" control group actually includes also undiagnosed diabetes cases which attenuates the observed effect size. The diagnostic criteria we used, however, was from 1985 [15] and more participants would have been categorized as having diabetes using current criteria [21] because of lower fasting glucose threshold. The main limitation of this study is the cognition study design, which was basically cross-sectional although the cognitive assessment was executed twice. The first assessment was on average 13 years after the baseline (9 years after the end of the intervention period), and no baseline cognition data were available. A drawback related to the long follow-up is cohort attrition; especially those with cognitive dysfunction or other health issues may have been unable or unwilling to participate. Data support this assumption since participants had lower blood pressure compared with non-participants at baseline, and they also had shorter duration of diabetes. Such participation bias would be more likely to result in underestimation of the observed associations. Furthermore, we were not able to include a measure of depression, which is a potential confounder, in the analyses. In a sub-cohort of the DPS (n = 140), it was shown that only 21% of the participants had elevated depression score at baseline and participation in the study in general lowered the depression scores, with no specific group effect [40]. Therefore it is not likely that depression played a significant role in the associations presented in this paper. Finally, it is important to consider that the results of our study are only generalizable to persons with IGT and those who develop diabetes. Persons with baseline NGT were not included

in our study. However, persons with prediabetes represent an important proportion of the adult population, over a third in Finland [41] and the United States [42].

In conclusion, longer diabetes duration was associated with worse longitudinal cognitive performance. Two-hour glucose and HbA_{1C} levels, measured over several years prior to the cognition assessment, were better predictors of cognitive functions than current diagnosis of diabetes. Maintaining lower glycaemia, also among persons already diagnosed with IGT, may help in maintaining memory functions.

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