A Prospective Analysis of Elevated Fasting Glucose Levels and Cognitive Function in Older People

Results From PROSPER and the Rotterdam Study

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OBJECTIVE—To investigate the relationship between fasting glucose levels, insulin resistance, and cognitive impairment in old age. Diabetes is associated with cognitive impairment in older people. However, the link between elevated fasting glucose levels and insulin resistance in nondiabetic individuals, and the risk of cognitive impairment is unclear.

RESEARCH DESIGN AND METHODS—We analyzed data from, in total, 8,447 participants in two independent prospective studies: the PROspective Study of Pravastatin in the Elderly at Risk (PROSPER), 5,019 participants, aged 69–84 years, and the Rotterdam Study, 3,428 participants, aged 61–97 years. Fasting glucose levels were assessed at baseline in both studies; fasting insulin levels were assessed in the Rotterdam Study only. Cognitive function was assessed in both studies at baseline and during follow-up.

RESULTS—Subjects with diabetes had impaired cognitive function at baseline. In contrast, in people without a history of diabetes, there was no clear association between baseline fasting glucose levels and executive function and memory, nor was there a consistent relationship between elevated baseline fasting glucose levels and the rate of cognitive decline in either cohort. Insulin resistance (homeostasis model assessment index) was also unrelated to cognitive function and decline.

CONCLUSIONS—Elevated fasting glucose levels and insulin resistance are not associated with worse cognitive function in older people without a history of diabetes. These data suggest either that there is a threshold for effects of dysglycemia on cognitive function or that factors other than hyperglycemia contribute to cognitive impairment in individuals with frank diabetes. Diabetes 59:1601–1607, 2010

Diabetes has been shown to be associated with an increased risk of dementia and impaired cognitive function (1). Suggested biological mechanisms that are involved in this relation are accelerated cerebrovascular disease (1), accumulation of advanced glycation end products (2), and reduced amyloid β-clearance through disturbing the role of the insulin-degrading enzyme (3). The accumulating evidence that diabetes is involved in a number of health problems, ranging from retinopathy and cardiovascular symptoms to neurological complications, has started a discussion about the necessity to identify those people who are at increased risk for diabetes (3–6).

Classifying people based on levels of fasting glucose to indicate “impaired fasting glucose” has been suggested as a possible tool for risk assessment of the development of diabetes (5,6). However, the relationship between the preceding stage of diabetes, when impaired fasting glucose levels are present, and cognitive function has not been comprehensively elucidated. A number of studies have investigated the relationship between this “pre-diabetes” state and cognitive function but showed contradictory or inconclusive results (7–9), possibly due to relatively small sample sizes and limited numbers of participants with an impaired fasting glucose level. Alternatively, peripheral insulin resistance that could underlie the elevated fasting glucose levels in the pre-diabetes state may contribute to impaired cognitive function (10,11).

Therefore, in this study we investigated the association between fasting glucose levels and cognitive function and decline in a large sample of 8,447 participants for whom fasting glucose levels at baseline were available together with longitudinal data from a dedicated neuropsychological test battery. Additionally, we investigated the relationship between insulin resistance (using the homeostasis model assessment [HOMA] index) and cognitive function and decline in 3,342 participants.

RESEARCH DESIGN AND METHODS

Populations. The PROspective Study of Pravastatin in the Elderly at Risk (PROSPER) was a prospective multicenter randomized placebo-controlled trial to assess whether treatment with pravastatin diminishes the risk of major cardiovascular events in the elderly (12,13). Between December 1997 and May 1999, a total of 5,804 participants (aged 70–82 years) with preexisting vascular disease or increased risk of such disease due to a history of smoking, hypertension, or diabetes were recruited in Scotland, Ireland, and the Netherlands. The institutional ethics review boards of all centers approved the protocol, and all participants gave written informed consent. Participants with
very severe cognitive impairment (Mini-Mental State Examination [MMSE] score <24) were excluded for inclusion in the study.

The Rotterdam Study is a large prospective population-based cohort study that is conducted among all inhabitants aged ≥55 years of Ommoor, a district of Rotterdam, the Netherlands (14). The medical ethics committee of the Erasmus University of Rotterdam approved the study, and written informed consent was obtained from all participants. Of 10,275 eligible subjects, 7,983 individuals (78%) participated in the baseline examinations between 1990 and 1993 (mean age 71 ± 25 years, range 55–106 years). All participants were interviewed at home and visited the research center for further examinations.

Fasting glucose levels. In PROSPER, fasting glucose levels were assessed at baseline and after follow-up (fourth survey) in 3,428 participants. Of the 5,599 participants, 590 did not have all cognitive function tests available at baseline. All of the resulting 5,019 participants had full data available for other cardiovascular risk factors including BMI, systolic and diastolic blood pressure, and HDL cholesterol levels at baseline. This resulted in a study sample of 5,019 participants for PROSPER.

In the Rotterdam Study, fasting glucose levels were assessed at the third survey in 5,019 participants. Of these participants, 3,664 were free of dementia, and 3,550 of those had data available for other cardiovascular risk factors including BMI, systolic and diastolic blood pressure, and HDL cholesterol levels. Of these 3,550 participants, 122 did not have all cognitive function tests available at the start of the third survey. This resulted in a study sample of 3,428 participants for the Rotterdam Study. Additionally, in 3,342 of these 3,428 participants, fasting insulin levels were assessed at the third survey.

In both the PROSPER and the Rotterdam sample, fasting glucose levels were additionally measured during follow-up. There were 4,690 of the 5,019 participants in the PROSPER sample and 2,364 of the 3,428 participants in the Rotterdam sample who underwent at least one additional measurement of fasting glucose level in addition to the initial examination. These data were used to study the variability of the fasting glucose levels over time and to assess the appropriateness of using a single baseline fasting glucose measurement to assess the relationship between fasting glucose and cognitive function and decline.

History of diabetes. At baseline, history of diabetes was defined by self-reported history of diabetes (reporting the use of oral antidiabetes medication, the use of insulin, treatment by diet, or registration by a general practitioner as having diabetes) in both study samples.

Cognitive function. Global cognitive function was measured with the MMSE (15) in both studies. In addition, a dedicated neuropsychological test battery was used to assess executive function and memory. Executive function was assessed with the Letter–Digit Substitution Task (LDST) (16) and the abbreviated Stroop test part 3 (17) in both studies, as well as with the Word Fluency Test (WFT) (18) in the Rotterdam Study only. Memory was assessed with the 12-Picture Learning Test (12-PLT) immediate and delayed recall (10), in PROSPER only.

Individual test scores were transformed into standardized z scores [z score = (individual score – mean population score)/SD population score]. A compound cognitive test score for global cognitive function was calculated by averaging the z scores of the MMSE, the LDST, and the abbreviated Stroop test part 3. A compound cognitive test score for the 12-PLT was calculated by averaging the z scores of the 12-PLT immediate and the 12-PLT delayed recall test.

In PROSPER, cognitive function was measured at six time points during the study: before randomization, at baseline, after 9, 18, and 30 months, and at the end of the study. The time point of the last measurement was different for the participants and ranged from 36 to 48 months after baseline. Therefore, we performed the analyses with their individual varying time point but report the results for the mean of these time points (at 42 months). The preregistered measurement was discarded in the analyses to preclude possible learning effects. This resulted in a mean follow-up of 3.2 years. Change in cognitive function could be assessed in 4,767 participants for whom at least one follow-up examination of cognitive function was available after the initial measurement.

In the Rotterdam Study, cognitive function was assessed at the third survey (1997–1999) and additionally at the fourth survey (2002–2004). This resulted in a mean follow-up of 4.6 years. Of the 3,428 participants of the Rotterdam sample who were present at the third survey, 2,601 remained in the study until the end of follow-up (fourth survey) and were available for the assessment of change in cognitive function.

Additional assessments. In both samples, level of education, BMI, systolic and diastolic blood pressure, HDL cholesterol level, and APOE ε4 carriership were assessed at baseline (PROSPER) or at the third survey (Rotterdam Study). Level of education was dichotomized into primary education or less (low) and more than primary education (high) (Rotterdam Study) and into age when leaving school <13 years (low) and age when leaving school ≥13 years (high) (PROSPER).

Statistical analyses. The relationship between baseline (PROSPER) or third survey (Rotterdam Study) fasting glucose levels and cognitive function and decline was assessed by use of linear mixed models. Data from the PROSPER sample and the Rotterdam Study sample were merged into one large sample of 8,447 participants. All analyses were adjusted for age, sex, level of education, study (PROSPER or Rotterdam Study), BMI, systolic and diastolic blood pressure, HDL cholesterol level, APOE ε4 carriership, country, use of pravastatin, and, where appropriate, test version. Analyses were carried out using the SPSS statistical package (release 12.0.1; SPSS, Chicago, IL).

Data on fasting glucose and fasting insulin levels from the Rotterdam Study sample were used to calculate the degree of insulin resistance according to HOMA (20). The HOMA index is calculated by dividing the product of fasting levels of glucose and insulin by a constant and has been shown to correlate well (r = 0.82, P < 0.0001) with the euglycemic-hyperinsulinemic clamp method (21).

RESULTS

Table 1 shows the baseline characteristics of the total sample and for participants with a history of diabetes at baseline (PROSPER) or at the third survey (Rotterdam Study). In PROSPER, the fasting glucose levels ± SD differed among the three countries from which the participants were enrolled: Scotland 5.62 ± 1.27, Ireland 5.09 ± 1.34, and the Netherlands 5.76 ± 1.64 mmol/l. This resulted in a lower mean fasting glucose level for the PROSPER study sample compared with that of the Rotterdam Study sample. Participants with a history of diabetes had a higher fasting glucose level, BMI, and systolic blood pressure and lower levels of HDL cholesterol compared with participants without a history of diabetes.

In PROSPER, fasting glucose levels were assessed during follow-up after 3, 6, 12, 24, and 36 months, in addition to the baseline assessment. In 3,491 participants without a history of diabetes, fasting glucose levels were available at baseline and after 36 months of follow-up. The mean glucose levels slightly increased over time. The quintiles of the mean fasting glucose ± SD at baseline and after 36 months were 4.30 ± 0.20 and 4.77 ± 0.67 mmol/l for the lowest quintile (quintile 1), 4.70 ± 0.08 and 4.95 ± 0.47 mmol/l for quintile 2, 5.00 ± 0.08 and 5.21 ± 0.67 mmol/l for quintile 3, 5.33 ± 0.11 and 5.46 ± 0.70 mmol/l for quintile 4, and 6.25 ± 0.83 and 6.30 ± 1.40 mmol/l for the highest quintile (quintile 5). In the Rotterdam sample, fasting glucose levels were assessed at the third survey as well as at the end of follow-up (fourth survey) in 2,209 participants without a history of diabetes. The quintiles of fasting glucose levels at the third survey and at the end of follow-up were 4.82 ± 0.24 and 5.07 ± 0.39 mmol/l for the lowest quintile (quintile 1), 5.20 ± 0.08 and 5.36 ± 0.42 mmol/l for quintile 2, 5.50 ± 0.08 and 5.55 ± 0.50 mmol/l for quintile 3, 5.84 ± 0.11 and 5.86 ± 0.57 mmol/l for quintile 4; and 6.73 ± 0.98 and 6.76 ± 1.44 mmol/l for the highest quintile (quintile 5).

Of the 8,447 participants who were present at baseline, 6,641 remained in the study sample until the end of follow-up, 985 withdrew from the study, and 821 died during follow-up. The 1,806 participants without a final examination comprised 20.8% of the participants without a history of diabetes and 26.3% of the participants with a history of diabetes at baseline (PROSPER) or at the third survey (Rotterdam Study).

Figure 1A shows the relationship between fasting glucose levels and cognitive function at baseline for the 8,447 participants of the merged study sample. Study-specific quintiles of the distribution of fasting glucose levels in participants without a history of diabetes were constructed to account for the differences in fasting glucose.
levels between the studies. Cognitive test scores are shown for quintiles of the distribution of fasting glucose levels in participants without a history of diabetes and for participants with a history of diabetes. In participants without a history of diabetes, a rise in fasting glucose levels in the nondiabetes range was not associated with impairment in cognitive function, for any of the cognitive tests. Additionally, we compared the cognitive test scores at baseline for participants with and without a history of diabetes (Fig. 1A) and showed that participants with a history of diabetes had worse cognitive function across the majority of tests at baseline when compared with participants without a history of diabetes (P < 0.05 for all tests except for the WFT in the Rotterdam Study sample).

In the longitudinal analyses of the study population, there was no clear association between baseline fasting glucose levels and change in cognitive function during follow-up in participants without a history of diabetes (Fig. 1B). In the PROSPER sample, higher levels of fasting glucose were associated with a decreased rate of decline on the 12-PLT (P_trend = 0.039), but this was not seen for any of the other cognitive tests. Furthermore, participants with a history of diabetes did not show an increased rate of decline for any of the cognitive tests.

Additionally, we assessed the relationship between insulin resistance and cognitive function and decline for the 3,342 participants of the Rotterdam Study sample for whom fasting insulin levels were available (Fig. 2A). The HOMA that was calculated for these participants was correlated with the fasting glucose levels (r = 0.54, P < 0.001), although the overlap between quintiles of the HOMA index and quintiles of fasting glucose levels was limited: only 35% of the participants without a history of diabetes were in the same quintile of the distribution for both fasting glucose and HOMA index. The relationship between insulin resistance and cognitive function was in accordance with findings on fasting glucose levels and cognitive function: in participants without a history of diabetes, rising insulin resistance was not associated with cognitive function. Similarly, there was no clear relationship between levels of insulin resistance and change in cognitive function during follow-up (Fig. 2B). When the data from the PROSPER sample and the Rotterdam Study sample were analyzed separately, the findings were consistent with the results of the merged sample of 8,447 participants.

**DISCUSSION**

Our study shows that, in an unprecedented large number of individuals from two independent prospective studies, higher levels of fasting glucose in the absence of a history of diabetes are not associated with cognitive function or cognitive decline. Furthermore, there was no association between insulin resistance (HOMA index) and cognitive function and decline in people without a history of diabetes. However, participants with a history of diabetes did have worse cognitive function at baseline than those without diabetes, although the magnitude of the observed effects was relatively small.

The results of our analyses do not fully correspond with previous findings in the Rotterdam Study, in which diabetes was found to be related to an increased risk of developing dementia (22). Although our data show that those with a history of diabetes have worse cognitive function at baseline than those without, one could argue
that the effect sizes are lower than expected based on the previous report of an almost twofold increased risk of dementia for people with diabetes (22). It is possible that the measurement of cognitive function compared with the assessment of participants with dementia in the Rotterdam Study underlies this discrepancy. In the Rotterdam Study, we are able to continuously monitor the total cohort for incident dementia through computerized linkage between the study database and digitalized medical records from the general practitioners and the Regional Institute for Outpatient Mental Health Care. In contrast, in the Rotterdam sample, cognitive function assessments were performed with a 4.6-year interval, which could have limited the accuracy of cognitive examination in participants without a history of diabetes (n = 6,649) and participants with a history of diabetes (n = 719). Estimates are based on the maximum number of participants available per cognitive test: global cognitive function (n = 8,447), WFT (n = 3,518), and 12-PLT (n = 5,223).

B: Fasting glucose levels and change in cognitive function. z scores (SEM) represent annual change in cognitive test scores for study-specific quintiles of fasting glucose levels in nondiabetic participants (from lowest [quintile 1] to the highest [quintile 5] levels of fasting glucose) and for participants with a history of diabetes (DM). P values reflect the trend over the quintiles of fasting glucose levels, as well as the difference between participants without a history of diabetes (n = 7,368) and participants with a history of diabetes (n = 2,639), and 12-PLT (n = 4,960). Linear mixed models were used, adjusted for age, sex, level of education, study (PROSPER or Rotterdam Study), BMI, HDL level, systolic blood pressure, diastolic blood pressure, country, treatment group, and test version where applicable.

FIG. 1. A: Fasting glucose levels and cognitive function. z scores (SEM) for different cognitive test scores are plotted for study-specific quintiles of fasting glucose levels in nondiabetic participants (from lowest [quintile 1] to the highest [quintile 5] levels of fasting glucose) and for participants with a history of diabetes (DM). P values reflect the trend over the quintiles of fasting glucose levels, as well as the difference between participants without a history of diabetes (n = 7,368) and participants with a history of diabetes (n = 2,639). Estimates are based on the maximum number of participants available per cognitive test: global cognitive function (n = 8,447), WFT (n = 3,518), and 12-PLT (n = 5,223).

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did not differ from the analyses that were unadjusted for these covariates.

Furthermore, the participants in PROSPER were included based on their increased cardiovascular risk profile: having either preexisting vascular disease or increased risk of such disease due to a history of smoking, hypertension, or diabetes. The known association between these cardiovascular risk factors and cognitive function and decline might have interfered with our investigation of the relationship between fasting glucose levels and cognitive function without a history of vascular disease. However, when we excluded the 2,823 participants in PROSPER who had a history of vascular disease from the sample of 5,019 participants, the relationship between fasting glucose levels and cognitive function at baseline did not markedly differ from our findings in the total sample: there was no clear relationship between fasting glucose levels and cognitive function in participants without a history of vascular disease. Moreover, after exclusion of the 2,823 participants, there was no significant relationship anymore between history of diabetes and baseline global cognitive function. The relationship between fasting glucose levels and change in cognitive function did not markedly change after exclusion of the participants with a history of vascular disease. The same was seen for the analyses on the relationship between history of diabetes and change in cognitive function. Therefore, we do not think that the inclusion of participants with preexisting vascular disease in PROSPER has masked a possible association between fasting glucose and insulin resistance on cognitive function.

We used fasting insulin levels that were available for almost the entire sample of the Rotterdam Study to calculate the HOMA index as a measure of insulin resistance to further investigate the relationship between glucose metabolism and cognitive function. However, the relationship between insulin resistance and cognitive function and decline showed similarities with the association between fasting glucose levels and cognitive function.
between fasting glucose levels and cognitive function and decline: in participants without a history of diabetes, insulin resistance was not associated with cognitive function or decline.

Previous population-based studies that investigated the relationship between glucose metabolism and cognitive functions suggested a number of possible biological mechanisms that could be involved, ranging from accumulation of advanced glycation end products (2) and accelerated cerebrovascular disease (1) to the role of the insulin-degrading enzyme on amyloid β metabolism (3). Although it is difficult to address the role of these suggested mechanisms, our study of >8,000 participants shows that the effect of increased fasting glucose levels on cognitive function seems to be long-term and independent of other cardiovascular risk factors like BMI, blood pressure, and HDL cholesterol levels.

The observed differences in cognitive test scores between people with and without a history of diabetes were relatively moderate and may therefore lack clinical significance for individuals. However, small effect sizes do not automatically imply irrelevance of the observed effect, as small effects on the group level can indeed represent large effects for a number of participants.

In the analyses of the annual decline in cognitive function, the PROSPER sample failed to show a clear decline in MMSE score over time, although this was seen in the Rotterdam sample with participants of comparable age. It is possible that a potential learning effect of the MMSE had a higher impact on the PROSPER sample compared with the Rotterdam Study sample because of the shorter time span between cognitive measurements (19). Additionally, the selection criteria for participants in PROSPER (baseline MMSE score ≥ 24) may have resulted in a sample of participants with slightly better cognitive function, which is also represented in the difference in MMSE scores of both samples at baseline and might have had an effect on the annual decline of MMSE score that was measured in PROSPER.

The strengths of this study consist of the prospective design, the large number of participants in both studies, and the dedicated neuropsychological test battery that was used in both samples. Furthermore, we had the possibility of studying the variability of fasting glucose levels during follow-up and of examining the appropriateness of using a single measurement of fasting glucose level to assess the association between fasting glucose levels and cognitive function and decline. A large variation in fasting glucose levels over time could have disturbed our analyses through the phenomenon of “regression-to-the-mean.” However, the levels of fasting glucose during follow-up did not materially differ from the baseline or third survey in both study samples. Therefore, we decided to use the baseline or third survey fasting glucose measurement in our analyses.

Some limitations need to be addressed. Participants who were present at baseline but did not undergo follow-up examinations were predominantly present in the group with a history of diabetes. They had worse cognitive function at baseline compared with the participants who stayed in the study until the end of follow-up. This selective attrition of participants with relatively high levels of fasting glucose and concurrent low levels of cognitive function could have resulted in an underestimation of our estimates of cognitive decline for participants with a history of diabetes. We also recognize that some individuals with diabetes would have been missed because of lack of oral glucose tolerance testing. More importantly, undiagnosed diabetes would be more prevalent in those in the higher quintiles for fasting glucose and would have biased the study toward an association of higher quintiles and cognitive decline, not the other way around. Thus, lack of oral glucose tolerance testing does not negate our findings; rather it gives us added confidence that our observations are valid.

In conclusion, elevations in fasting glucose levels are not clearly associated with impaired cognitive function or with an accelerated rate of cognitive decline in participants without a history of diabetes. Furthermore, there was no clear relationship between insulin resistance (HOMA index) and cognitive function and decline in participants without a history of diabetes. These data suggest that cognitive decline accelerates strongly once a person is diabetic but not with lesser degrees of dysglycemia. As a result, preventing individuals at risk from developing diabetes through lifestyle changes may also lead to large societal gains by preventing such individuals from undergoing accelerated cognitive decline.

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REFERENCES

1. Biesalski HJ, Stackenborg S, Brunner E, Brayne C, Scheltens P. Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5: 64–74
2. Munch G, Schinzel R, Loske C, Wong A, Durany N, Li JJ, Vlassara H, Smith MA, Perry G, Riederer P. Alzheimer’s disease—synergistic effects of glucose deficit, oxidative stress and advanced glycation endproducts. J Neural Transm 1998;105:439–461
3. Craft S. Insulin resistance syndrome and Alzheimer’s disease: age- and obesity-related effects on memory, amyloid, and inflammation. Neurobiol Aging 2005;26(Suppl. 1):65–69
4. Lindahl B, Weinheil L, Asplund K, Hallmans G. Screening for impaired
