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# Insulin metabolism and the risk of Alzheimer disease

## The Rotterdam Study

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### ABSTRACT

**Objective:** Diabetes mellitus has been associated with an increased risk of Alzheimer disease (AD), but how it exerts its effect remains controversial. Possible pathophysiologic mechanisms are glucose toxicity and a direct effect of insulin on amyloid metabolism. Most studies had short follow-up, and longer-term effects of diabetes on AD risk are unknown. We investigated whether fasting glucose and insulin levels and insulin resistance are associated with the risk of AD and whether this risk is constant over time.

**Methods:** The study was based on 3,139 participants of the Rotterdam Study, a population-based cohort study. All subjects were free from dementia, did not have a history of diabetes, and had fasting levels of glucose and insulin measured at baseline. Insulin resistance was estimated with the homeostasis model assessment. We investigated how fasting glucose, insulin, and insulin resistance are related to the risk of AD in 3 different strata according to time-to-event, using Cox proportional hazards models.

**Results:** During follow-up, 211 participants developed AD, 71 of them within 3 years of baseline. Levels of insulin and insulin resistance were associated with a higher risk of AD within 3 years of baseline. After 3 years, the risk was no longer increased. Glucose was not associated with a higher risk of AD. There was no interaction of *APOE*  $\epsilon$ 4 carriership and insulin metabolism on the risk of AD.

**Conclusions:** Our findings suggest that insulin metabolism influences the clinical manifestation of AD only within 3 years. *Neurology*® 2010;75:1982-1987

### GLOSSARY

**AD** = Alzheimer disease; **DSM-III-R** = *Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised*; **HDL** = high-density lipoprotein; **HOMA** = homeostasis model assessment.

Diabetes and Alzheimer disease (AD) are both common diseases in elderly individuals. Although many studies have suggested that patients with diabetes have a higher risk of developing AD,<sup>1,2</sup> the results are conflicting and the real relationship between diabetes and AD remains controversial.

Three characteristics related to type 2 diabetes that might underlie the effect of diabetes on the brain in the development of AD are insulin resistance, hyperinsulinemia, and hyperglycemia.<sup>3-5</sup> These mechanisms are thought to act on different pathways that are important in the pathophysiology of AD, either indirectly, through inflammation or the development of vascular disease, or directly, through effects on amyloid and tau metabolism and the formation of advanced glycation end products.<sup>1,5-7</sup>

We previously reported from the Rotterdam Study, a population-based cohort study, an association between diabetes and a higher risk of AD.<sup>2</sup> This study was based on the initial cohort that started in 1990 and had only a short follow-up of on average 2.1 years.<sup>1,2</sup> In 1997,

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at the third survey of the Rotterdam Study, fasting blood samples were drawn. Using this survey as baseline for our current study, we now have levels of fasting glucose and insulin available at baseline and a much longer follow-up, up to 10 years (average, 7.2 years).

To investigate the relationships that might underlie the effect of diabetes on the risk of AD, we determined whether fasting glucose and insulin levels and insulin resistance are associated with the risk of AD in persons without diabetes and whether this risk remains the same over a longer follow-up period.

**METHODS The Rotterdam Study.** The Rotterdam Study is a prospective population-based cohort study that is conducted among all inhabitants aged 55 years and older of Ommoord, a district of Rotterdam, the Netherlands.<sup>8</sup> Of 10,274 eligible subjects, 7,983 (78%) participated in the baseline examinations between 1990 and 1993. Follow-up examinations were conducted in 1993–1994, 1997–1999, and 2002–2004. In addition, through linkage with records of general practitioners, the total cohort was continuously monitored for morbidity and mortality.

**Study population.** This study was based on the third survey (1997–1999) of the Rotterdam Study in which fasting blood samples were obtained. Of the 5,990 participants of the original cohort who were still alive at that time, 4,797 participated, 3,795 of whom had fasting blood samples drawn. Of these participants, 3,432 were free of dementia and had complete data on glucose and insulin levels, cognitive function, and cardiovascular risk factors, including waist circumference, blood pressure, triglycerides, and high-density lipoprotein (HDL) cholesterol. We excluded 313 participants who had a history of diabetes at the time of the third survey. This resulted in a study population of 3,139 subjects.

**Standard protocol approvals, registrations, and patient consents.** The medical ethics committee at Erasmus University of Rotterdam approved the study, and written informed consent was obtained from all participants.

**Glucose and insulin assessments.** Fasting blood serum was drawn during the examination at the research center. The blood was stored at  $-80^{\circ}\text{C}$  in a number of 5-mL aliquots. Glucose levels were measured within 1 week of sampling using the glucose hexokinase method.<sup>9</sup> The remaining serum was kept frozen for later analyses. In 2008, stored serum that had not been thawed previously was used for insulin measurements. Serum insulin was determined by metric assay (Biosource Diagnostics, Camarillo, CA). This assay has no cross-reactivity with either proinsulin or C-peptide. All measurements were done at the clinical chemistry laboratory at Erasmus Medical Center in Rotterdam.

**Insulin resistance.** Data on fasting glucose and fasting insulin levels were used to calculate the degree of insulin resistance according to the homeostasis model assessment (HOMA).<sup>10</sup> The HOMA index, which is calculated by dividing the product of fasting levels of glucose and insulin by a constant, has been shown to correlate well with the euglycemic hyperinsulinemic clamp method,<sup>11</sup> which is the gold standard for measuring insulin resistance.

**Dementia case finding.** The diagnosis of dementia was made following a 3-step protocol.<sup>12</sup> Two brief tests of cognition (Mini-Mental State Examination<sup>13</sup> and Geriatric Mental State schedule<sup>14</sup> organic level) were used to screen all subjects. Participants with screen-positive results (Mini-Mental State Examination score  $<26$  or Geriatric Mental State organic level  $>0$ ) underwent the Cambridge Examination for Mental Disorders of the Elderly.<sup>15</sup> Subjects who were suspected of having dementia were, if necessary, examined by a neuropsychologist. In addition, the total cohort was continuously monitored for incident dementia through computerized linkage between the study database and digitized medical records from general practitioners and the Regional Institute for Outpatient Mental Health Care.<sup>12</sup> The diagnoses of dementia and AD were made in accordance with internationally accepted criteria for dementia (*DSM-III-R*),<sup>16</sup> and AD (National Institute of Neurological and Communicative Disorders and Stroke–Alzheimer's Disease and Related Disorders Association),<sup>17</sup> by a panel of a neurologist, neuropsychologist, and research physician. The follow-up with regard to dementia diagnosis was virtually complete (98.6%) until January 1, 2007.

**History of diabetes.** History of diabetes was defined as 1) self-reported history of diabetes (reported use of oral antidiabetes medication, or insulin use, or treatment by diet), 2) registration by a general practitioner as having diabetes, or 3) a previous diagnosis of diabetes during the 1990–1993 or 1993–1994 examinations (based on a random nonfasting plasma glucose level  $\geq 11.1$  mmol/L).<sup>18</sup>

**Newly diagnosed diabetes.** Newly diagnosed diabetes was defined as a fasting glucose level  $\geq 7.0$  mmol/L in participants without a history of diabetes.

**Covariates.** Educational level was assessed during the first interview that took place between 1990 and 1993 and was dichotomized into primary education (with or without an unfinished higher education) vs lower vocational to university education. *APOE* genotype was assessed on coded DNA samples using PCR without knowledge of the dementia diagnosis. *APOE*  $\epsilon 4$  status was defined as carriership of 1 or 2  $\epsilon 4$  alleles.

Blood pressure was measured at the right brachial artery using a random-zero sphygmomanometer with the participant in a sitting position. The waist circumference was measured in centimeters. HDL cholesterol levels were measured in fasting serum within 1 week of the visit to the research center. Serum levels of triglycerides were measured in 2008 at the same time the insulin levels were measured.

**Statistical analyses.** Because of a nonnormal distribution of insulin levels and HOMA, we used a  $\log_2$  transformation, which means that every unit increase on the logarithmic scale reflects a doubling of the absolute values.

We used Cox proportional hazards models to examine the associations of fasting levels of glucose and insulin, and insulin resistance with the risk of developing AD during follow-up.

All analyses were adjusted for age and sex, and additional adjustments were made for level of education, *APOE*  $\epsilon 4$  status, and the components of the metabolic syndrome (waist circumference, systolic and diastolic blood pressure, triglycerides, and HDL cholesterol).<sup>19</sup>

We added a time-dependent covariate to the model to test the proportionality assumption. Because this assumption was violated, we performed the analyses in 3 different strata according to follow-up time: 1) short follow-up (maximum 3 years), 2) medium follow-up (3–5.5 years), and 3) long follow-up (5.5–9.7

**Table 1** Baseline characteristics<sup>a</sup>

	No. = 3,139
Age, y, mean (SD)	71.8 (6.7)
Women, %	58
Education, % only primary education	29
MMSE, points, mean (SD)	27.8 (1.9)
Waist circumference, cm, mean (SD)	
Men	97 (9)
Women	90 (12)
APOE $\epsilon 4$ allele present, %	28
Systolic blood pressure, mm Hg, mean (SD)	143 (21)
Diastolic blood pressure, mm Hg, mean (SD)	75 (11)
HDL cholesterol, mmol/L, mean (SD)	1.41 (0.40)
Triglycerides, mmol/L, mean (SD)	1.48 (0.71)
Fasting glucose levels, mmol/L, mean (SD)	5.65 (0.91)
Fasting insulin levels, mU/L, median (interquartile range) <sup>b</sup>	9.3 (6.6–13.3)
Insulin resistance, HOMA, median (interquartile range) <sup>b</sup>	2.26 (1.56–3.36)

Abbreviations: HDL = high-density lipoprotein; HOMA = homeostasis model assessment; MMSE = Mini-Mental State Examination.

<sup>a</sup> Data are presented as mean (standard deviations) or percentages.

<sup>b</sup> Median (interquartile range) are presented because of a skewed distribution.

years). Cutoffs were chosen to have approximately equal numbers of incident cases within the follow-up intervals. We repeated the analyses in strata of *APOE*  $\epsilon 4$  carriership. To test for interaction of *APOE*  $\epsilon 4$  status on the relationship of levels of glucose, insulin, and insulin resistance with the risk of AD, we first added an interaction term with *APOE*  $\epsilon 4$  status to the different models. This is the method that is usually performed to test for interaction and assesses interaction on a multiplicative scale, which, however, measures differences in rate ratios. When biological interaction occurs, one would expect to see interaction on an additive scale, which measures differences in absolute risks.<sup>20,21</sup> We used the relative risk due to interaction to test for interaction on an additive scale.<sup>22</sup> Although the number of patients with AD was small in the younger age group, we also performed stratified analyses by age median to test whether the associations of levels of glucose and insulin and insulin resistance with the risk of AD are different for younger vs older people.

All analyses were done using the SPSS statistical package 15.0 (SPSS Inc., Chicago, IL) or SAS 9.2 (SAS Institute Inc., Cary, NC).

**RESULTS** The baseline characteristics of the study population are shown in table 1. After a follow-up of 22,494 person-years (mean, 7.2 years; SD, 2.1), 211 participants developed AD, 71 of them within 3 years of baseline, 72 between 3 and 5.5 years, and 68 after 5.5 years. When we performed the analyses with the total follow-up period, fasting levels of glucose and insulin and insulin resistance were not associated with the risk of AD (data not shown).

Table 2 shows the associations of fasting insulin and glucose levels and insulin resistance with the risk of AD in the different follow-up strata. Fasting levels of glucose were not associated with the risk of AD after a short or medium follow-up time. There was a relation between higher levels of glucose and a lower risk of AD after 5.5 years (hazard ratio per SD increase, 0.61; 95% confidence interval, 0.41–0.89).

Fasting levels of insulin and insulin resistance were associated with a higher short-term risk of AD with an increase in risk of approximately 40% per doubling of insulin levels and insulin resistance in the fully adjusted model. Higher levels of insulin and insulin resistance were no longer associated with an increased risk of AD after 3 years, and the relation even seemed to invert, reaching borderline significance in some of the fully adjusted models.

Exclusion of 162 participants who had newly diagnosed diabetes based on their fasting glucose levels ( $\geq 7.0$  mmol/L) did not alter the results.

When we applied the fully adjusted model in strata of *APOE*  $\epsilon 4$  carriership, levels of glucose and insulin and insulin resistance were all associated with the short-term risk of AD in noncarriers of the *APOE*  $\epsilon 4$  allele (table 3). In these noncarriers, doubling of levels of insulin and insulin resistance increased the short-term risk of AD by 75%. In carriers of the

**Table 2** Hazard ratios (with corresponding 95% confidence intervals) of the association of fasting glucose and insulin levels and insulin resistance with the risk of Alzheimer disease according to time-to-event

	Short follow-up: maximum 3 years (n = 3,139)		Medium follow-up: 3–5.5 years (n = 2,881)		Long follow-up: 5.5–9.7 years (n = 2,566)	
	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>	HR (95% CI) <sup>a</sup>	HR (95% CI) <sup>b</sup>
Glucose (per SD)	1.08 (0.86–1.35)	1.16 (0.93–1.45)	0.79 (0.58–1.08)	0.85 (0.61–1.18)	0.70 (0.51–0.96)	0.61 (0.41–0.89)
Insulin (per log <sub>2</sub> )	1.12 (0.83–1.51)	1.41 (1.02–1.96)	0.65 (0.48–0.89)	0.71 (0.49–1.02)	0.83 (0.60–1.14)	0.74 (0.51–1.08)
Insulin resistance (HOMA per log <sub>2</sub> )	1.12 (0.85–1.46)	1.39 (1.04–1.86)	0.68 (0.51–0.89)	0.72 (0.52–1.01)	0.80 (0.60–1.07)	0.70 (0.50–0.99)

Abbreviations: CI = confidence interval; HOMA = homeostasis model assessment; HR = hazard ratio.

<sup>a</sup> Adjusted for age and sex.

<sup>b</sup> Adjusted for age, sex, level of education, *APOE*  $\epsilon 4$  status, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, triglycerides, and waist circumference.

**Table 3** Hazard ratios (with corresponding 95% confidence intervals) of the association of fasting glucose and insulin levels and insulin resistance with the short-term risk of Alzheimer disease according to APOE  $\epsilon 4$  carriership, with *p* values for interaction

	HR (95% CI) <sup>a</sup>		<i>p</i> Values for interaction	
	APOE $\epsilon 4$ carriers	APOE $\epsilon 4$ noncarriers	Multiplicative	Additive
Glucose (per SD)	0.91 (0.49–1.67)	1.25 (1.03–1.52)	0.165	0.751
Insulin (per log <sub>2</sub> )	1.16 (0.65–2.06)	1.75 (1.16–2.64)	0.087	0.988
Insulin resistance (HOMA per log <sub>2</sub> )	1.10 (0.66–1.84)	1.74 (1.21–2.51)	0.050	0.519

Abbreviations: CI = confidence interval; HR = hazard ratio.

<sup>a</sup> Adjusted for age, sex, level of education, systolic blood pressure, diastolic blood pressure, high-density lipoprotein cholesterol, triglycerides, and waist circumference.

APOE  $\epsilon 4$  allele, higher levels of glucose and insulin and insulin resistance had no apparent effect on the short-term risk of AD. There was no significant interaction of APOE  $\epsilon 4$  status and glucose levels, insulin levels, and insulin resistance on an additive scale and a borderline significant interaction of APOE  $\epsilon 4$  status and insulin and insulin resistance on a multiplicative scale.

The risk of AD after a medium or long follow-up did not differ between carriers and noncarriers of the APOE  $\epsilon 4$  allele (*p* values for multiplicative and additive interaction >0.25).

In the stratified analyses by age median (71.0 years), there was no effect of glucose levels on the risk of AD, and higher insulin levels and insulin resistance were also not associated with an increased risk of AD after 3 years of follow-up in both age groups.

**DISCUSSION** The major strengths of our study are the prospective population-based design, the large number of participants, and the long follow-up period with almost no loss to follow-up. The latter in particular is important because theoretically the strength of a longitudinal association may diminish or even invert if there is selective attrition of people who develop dementia over the follow-up period. We are confident, however, that through our very dense and complete case finding and follow-up, selective attrition cannot explain the findings in our study.

Unfortunately, we had no repeated glucose and insulin measurements over time. Therefore, we could not assess whether changes in glucose and insulin levels have an impact on the longer-term risk of AD, and we might underestimate the longer-term risk of AD.

We considered whether the assessment of insulin levels after 10 years of storage at  $-80^{\circ}\text{C}$  might have affected the stability of the samples. Although we are not aware of a study on the stability of insulin levels after long-term storage of serum, there are several studies on the stability of other proteins and hor-

mones that show that long-term storage at  $-25^{\circ}\text{C}$  and especially at  $-80^{\circ}\text{C}$  does not affect the stability of the measurements and that the expected stability of materials stored at  $-80^{\circ}\text{C}$  is at least 10 years.<sup>23–25</sup> Furthermore, any change in insulin levels after 10 years of storage should affect all samples, without any relation with our outcome AD.

Because we had no fasting blood samples at the start of the Rotterdam Study, we used the third survey as the baseline for the current study. This was a selection of more healthy participants, with fewer cognitive deficits and less diabetes, who came to the research center and had fasting blood drawn. However, because we excluded patients with prevalent AD and participants with a history of diabetes, we consider it unlikely that this selection will have influenced our results.

Our results show that characteristics related to diabetes, especially higher levels of insulin and insulin resistance, are associated with a higher risk of AD only within 3 years. This supports our previous finding of an association of diabetes with a higher risk of AD with an average follow-up of 2.1 years.<sup>2</sup> Another recent study from our cohort showed no association of higher levels of glucose and insulin resistance with cognitive decline after on average 4.6 years in participants without a history of diabetes. In that study, there was selective nonparticipation with regard to the outcome of cognitive decline of those who were diagnosed with dementia in between cognitive examinations and did not visit the research center for the follow-up assessment.<sup>26</sup> These are the participants who developed dementia mainly within 3 years of baseline, which is the time period in which we find an increased risk of AD with higher levels of insulin and insulin resistance.

Several other studies have shown associations of the glucose and insulin metabolism with the risk of AD.<sup>27–32</sup> Most of these studies had an average follow-up time of around 5 years. The studies that had a longer follow-up time often did not find a higher risk of AD with disturbances in the insulin metabolism. A recent study from the Uppsala Longitudinal Study of Adult Men showed no association of 6 of 7 measures of insulin metabolism including fasting insulin levels and insulin sensitivity, determined by the euglycemic insulin clamp method, with the risk of AD after a median follow-up of 12 years. A low early insulin response to oral glucose challenge was, however, associated with a higher risk of AD.<sup>29</sup> In the Framingham Study after a long follow-up period of on average 12.7 years, diabetes did not increase the overall risk of dementia and AD.<sup>33</sup> If we look at the risk of AD over the total follow-up period in our study, without dividing the time to event into



strata, we also find no association of our 3 measures and the risk of AD.

The higher short-term risk of AD that disappears after 3 years of follow-up might be explained by several mechanisms. First, because the underlying neuropathologic changes that cause AD are already ongoing years before the clinical diagnosis can be made, our results might reflect reversed causality or a common pathophysiology instead of a causal role of insulin metabolism in AD. Second, we hypothesized that diabetes and disturbances in insulin metabolism only increase the risk of AD for a short time period by advancing the onset in those already on the verge of getting AD. This would mean that disturbances in the insulin metabolism are not a cause of the neuropathologic changes that result in AD but do influence and accelerate those changes, leading to an earlier onset of AD.

We found that after 3 years of follow-up the risk of AD was no longer increased and even inverted. It seems unlikely that the inversion of the effect on AD risk reflects a true biological mechanism. It is more likely that competing risks might explain these findings: people with diabetes or prediabetes are at a higher risk of cardiovascular diseases and death, which makes them no longer at risk of AD, especially in the long term.

Although there was a difference in the effect size on the short-term risk between carriers and noncarriers of the *APOE*  $\epsilon 4$  allele, there was no interaction on an additive scale. The borderline significant negative interaction on a multiplicative scale suggests that the differences in risk ratio can be explained by the differences in baseline absolute risks and not by a true interaction between *APOE*  $\epsilon 4$  status and insulin metabolism.<sup>20</sup>

Different studies reported conflicting results on the influence of the *APOE*  $\epsilon 4$  allele on the relation between diabetes or insulin metabolism and the risk of AD. A number of studies reported higher effect estimates in noncarriers of the *APOE*  $\epsilon 4$  allele, although none of these studies reported whether testing for additive interaction was done.<sup>32,34,35</sup> The Uppsala Longitudinal Study of Adult Men showed a stronger effect of a low acute or early insulin response, assessed at midlife<sup>28</sup> and at age 71,<sup>29</sup> on the risk of AD in noncarriers of the *APOE*  $\epsilon 4$  allele. However, in the same study, higher levels of fasting insulin and HOMA, both assessed at midlife, were associated with the risk of AD only in carriers of the *APOE*  $\epsilon 4$  allele, which conflicts with our results.<sup>28</sup> We assessed our measurements at an older age, which might explain these differences. Several other studies also showed a stronger effect of diabetes and hyperinsulinemia on the risk of AD in carriers of the *APOE*

$\epsilon 4$  allele.<sup>31,36,37</sup> Investigators from the Kungsholmen Project initially reported an effect of diabetes on the risk of AD only in carriers of the *APOE*  $\epsilon 4$  allele,<sup>37</sup> yet in a later study they found an effect of borderline diabetes, defined as a random plasma glucose level of 7.8–11.0 mmol/L, on the risk of AD only in noncarriers.<sup>38</sup> These discrepant results fit our finding of no interaction between *APOE*  $\epsilon 4$  status and insulin metabolism on the risk of AD.

## AUTHOR CONTRIBUTIONS

Statistical analysis was conducted by Dr. Elisabeth M.C. Schrijvers.

## DISCLOSURE

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