# Fasting Insulin Levels and Cognitive Decline in Older Women without Diabetes

Marieke van Oijen[a] Olivia I. Okereke[b, c] Jae Hee Kang[c] Michael N. Pollak[f]
Frank B. Hu[c, e] Susan E. Hankinson[c, d] Francine Grodstein[b–d]

[a]Departments of Epidemiology/Biostatistics and Neurology, Erasmus Medical Center, Rotterdam, The Netherlands; [b]Division of Aging and [c]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital, and Harvard Medical School, [d]Departments of Epidemiology and [e]Nutrition, Harvard School of Public Health, Boston, Mass., USA; [f]Departments of Medicine and Oncology, Lady Davis Research Institute of the Jewish General Hospital and McGill University, Montreal, Que., Canada

**Key Words**
Diabetes · Insulin, cognitive performance · Aging, cognitive decline · Dementia

**Abstract**
***Background:*** Type 2 diabetes has been associated with an increased risk of dementia. To assess possible independent effects of insulin, we investigated the relation of insulin levels to cognitive decline in nondiabetic women. ***Methods:*** Fasting plasma insulin levels were measured in mid-life in 1,416 nondiabetic Nurses' Health Study participants, who also completed cognitive testing that began 10 years later (current age: 70–75 years). Over 4 years, 3 assessments of general cognition, verbal memory, category fluency and attention were administered. Primary outcomes were the Telephone Interview for Cognitive Status (TICS) performance, the global score (average of all tests) and verbal memory (average of verbal recall tests). Linear mixed-effects models were used to calculate the association between insulin and cognitive decline. ***Results:*** Higher insulin levels were associated with a faster decline on the TICS and verbal memory. For analysis, batch-specific quartiles of insulin levels were constructed. Compared to the lowest quartile, adjusted differences in the annual rates of decline (with 95% CI values in parentheses) for the second, third and fourth quartiles were: TICS, −0.06 (−0.16, 0.03), −0.14 (−0.24, −0.04), and −0.09 (−0.19, 0.01) points (p trend = 0.04); verbal memory, −0.01 (−0.04, 0.02), −0.05 (−0.08, −0.02), and −0.02 (−0.05, 0.01) units (p trend = 0.02). These associations remained after multivariable adjustment. ***Conclusions:*** Our study provides evidence for a potential role of higher fasting insulin levels in cognitive decline, possibly independent of diabetes.

## Introduction

Type 2 diabetes mellitus has been associated with an increased risk of cognitive decline and dementia, including Alzheimer disease, in numerous epidemiologic studies [1–4]. Several mechanisms underlying this association have been proposed, including cerebrovascular disease that commonly accompanies type 2 diabetes mellitus, and toxic effects of chronic hyperglycemia and hyperinsulinemia [4]. In particular, increasing evidence suggests

that higher insulin levels may increase the risk of cognitive decline, even in the absence of clinical diabetes. While higher insulin may adversely affect brain health through vascular damage and inflammatory mechanisms, it may have a more direct influence on specific Alzheimer pathologies, e.g. by interfering with amyloid-β (Aβ) metabolism in the brain, resulting in increased deposition of Aβ in plaques [5].

To date, few studies have examined the effect of fasting insulin, independent of diabetes, on cognitive decline and dementia [6, 7]. We previously reported an association between higher levels of C-peptide (a measure of insulin production) and impaired performance on a single cognitive assessment in a subset of Nurses' Health Study (NHS) participants without diabetes [8]. In the present study, we sought to assess the robustness of this relation by examining the longitudinal association between fasting plasma insulin levels and decline on 3 repeated cognitive assessments conducted over 4 years in a much larger sample of nondiabetic women in the NHS.

## Methods

*Study Population*

The Nurses' Health Study (NHS) began in 1976 and included 121,700 registered female nurses, aged 30–55 years. Participants completed biennial mailed questionnaires updating information on lifestyle and health outcomes, including whether they were diagnosed with diabetes. In addition, 21,095 women provided fasting blood samples drawn between 1989 and 1990. Health and lifestyle characteristics were very similar between the whole cohort and those who provided blood samples. The total follow-up for these women exceeds 98.0%.

Beginning in 1995, NHS participants aged 70 years and over, free of diagnosed stroke, were invited to participate in a telephone-based study of cognitive function, and 19,395 (93.3%) completed an initial cognitive assessment. Since then, 2 follow-up assessments have been performed approximately 2 years apart. Follow-up remains over 90%.

Of the women for whom fasting blood samples from the 1989–1990 collection were available, 3,915 were in the cognitive study and had completed 2 follow-up assessments. Participation rates in the cognitive study were similar in those who had and had not provided blood, suggesting little possibility for bias in examining associations in those providing blood samples [8]. We measured fasting insulin in a random sample of 1,068 women without diagnosed diabetes at blood draw. To increase power, we added another 348 nondiabetic women (all of whom were participants in the cognitive study, with 2 completed follow-up assessments) with available measures of fasting insulin obtained using blood samples from the 1989–1990 collection. Fasting insulin had been assayed when these women were selected as controls in prior nested case-control studies of diabetes (n = 75) and hypertension (n = 76), or as cases and controls (n = 197) in a previous nested case-control study of breast cancer. We included both cases and controls from the breast cancer study, rather than just controls, as breast cancer case status is not related to cognition in our data [8]. This yielded a final sample for analysis of 1,416 women.

This study was approved by the Institutional Review Board of Brigham and Women's Hospital, Boston, Mass., USA.

*Fasting Insulin Measurements*

Using fasting blood samples that had been stored at –130°C, we measured plasma insulin levels with a radioimmunoassay specific for insulin (Linco, St. Louis, Mo., USA), based on an antiserum with less than 1% cross-reactivity for proinsulin and des-31, 32-proinsulin. In blinded quality control tests, intra-assay coefficients of variation for all batches were <10%.

*Cognitive Function*

Cognitive testing included: the Telephone Interview for Cognitive Status (TICS) [9], a telephone-based test of general cognition similar to the Mini-Mental State Examination [10]; immediate and delayed recalls of the East Boston Memory Test [11] to assess verbal memory; a test of category fluency, in which women named as many different animals as possible during 1 minute; a delayed recall of the TICS 10-word list; and digit span backward, in which women repeated an increasingly long series of digits backwards, to evaluate attention and working memory.

General cognition and verbal memory were our 2 primary outcomes; in particular, verbal memory is a strong predictor of early Alzheimer disease [12, 13]. To assess general cognition, we used the TICS, as well as a global cognitive score, calculated by averaging the z scores of all 6 cognitive tests. To calculate a verbal memory score, we combined the results of the immediate and delayed recalls of both the East Boston Memory Test and the TICS 10-word list, by averaging z scores of the 4 individual tests [8]. The global score and verbal memory score were only calculated for participants who had completed all component tests.

*Data Analysis*

To examine the association of plasma insulin levels with cognitive decline, batch-specific quartiles of insulin levels were constructed; the lowest quartile was used as the reference category. We used linear mixed-effects models [14] to examine the association between fasting insulin and changes in cognitive scores across the 3 assessments. Basic models were adjusted for age at baseline cognitive interview and highest attained education. Multivariable models further adjusted for other potential confounders, determined at the time of blood draw: BMI, current smoking (yes/no), history of hypertension (yes/no), history of elevated cholesterol (yes/no), history of heart disease (yes/no), alcohol use (g/day), physical activity (metabolic equivalents per week), and postmenopausal hormone use (yes/no).

In the mixed-effects models, we included time since baseline interview (in years), age, education, fasting insulin quartile, as well as interaction terms for time and age, and time and fasting insulin quartile as fixed effects; in the multivariable mixed models, we also included the other potential confounders as fixed effects. In addition to the fixed effects, we included 2 person-specific random effects: baseline cognitive level (random intercept) and rate of change (random slope). The interaction terms for time and fasting insulin quartile from these mixed models represented the annual rate of cognitive decline associated with fasting insu-

**Table 1.** Characteristics at time of the 1989-1990 blood draw, across quartiles of insulin levels

| | 1st quartile (n = 355) | 2nd quartile (n = 353) | 3rd quartile (n = 354) | 4th quartile (n = 354) |
|---|---|---|---|---|
| Median insulin, μIU/ml | 2.1 | 2.7 | 3.9 | 6.7 |
| Mean age at blood draw, years | 64.0 | 64.1 | 64.4 | 64.3 |
| Master's or doctorate degree, % | 8.3 | 6.8 | 9.0 | 4.8 |
| Mean body mass index | 23.4 | 24.2 | 25.3 | 27.7 |
| Current smoking, % | 8.3 | 11.6 | 9.0 | 8.6 |
| History of hypertension, % | 21.1 | 24.1 | 33.2 | 46.6 |
| History of elevated cholesterol, % | 30.4 | 34.2 | 34.9 | 39.0 |
| History of heart disease, % | 1.5 | 1.0 | 1.5 | 1.5 |
| Mean alcohol use, g/day | 6.1 | 6.4 | 5.0 | 3.9 |
| Mean physical activity, metabolic equivalent-hours/week | 18.4 | 18.6 | 17.6 | 14.4 |
| Current postmenopausal hormone use, % | 36.2 | 33.7 | 29.6 | 25.2 |

**Table 2.** Baseline cognitive test scores across quartiles of fasting insulin

| Cognitive test | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile |
|---|---|---|---|---|
| TICS | 34.2 ± 2.4 | 34.2 ± 2.5 | 34.1 ± 2.4 | 34.2 ± 2.4 |
| EBMT, immediate recall | 9.6 ± 1.6 | 9.5 ± 1.7 | 9.7 ± 1.7 | 9.6 ± 1.7 |
| EBMT, delayed recall | 9.3 ± 1.9 | 9.2 ± 1.8 | 9.3 ± 1.8 | 9.3 ± 1.8 |
| Category fluency | 18.1 ± 4.8 | 17.7 ± 4.5 | 17.4 ± 4.6 | 17.3 ± 4.4 |
| 10-word list, delayed recall | 2.5 ± 1.9 | 2.5 ± 1.9 | 2.3 ± 2.0 | 2.5 ± 1.9 |
| Digit span backward | 7.2 ± 2.3 | 6.9 ± 2.4 | 6.8 ± 2.4 | 6.6 ± 2.2 |
| Global cognition z score | 0.03 ± 0.59 | –0.01 ± 0.62 | –0.01 ± 0.57 | –0.03 ± 0.57 |
| Verbal cognition z score | –0.01 ± 0.68 | –0.02 ± 0.71 | 0.00 ± 0.67 | –0.00 ± 0.67 |

Values are presented as means ± SD. EBMT = East Boston Memory Test.

lin across the 3 assessments (mean interval from first to third assessment = 4.3 years).

*Secondary Analyses*

Since depression may influence cognitive performance, we repeated the analyses adjusting for regular antidepressant use at the time of baseline cognitive assessment. Regular use of antidepressants was utilized as the depression variable, since data on depression scores were not available at the time of baseline testing.

To examine whether diabetes or stroke occurring during cognitive follow-up may be responsible for any observed associations, we conducted secondary analyses in which we excluded participants who were diagnosed with diabetes mellitus at any time after blood draw, or with stroke after the baseline cognitive assessment.

Finally, we repeated our analyses in only those 1,068 women who were in the random sample.

## Results

Table 1 shows the characteristics of the study sample at the time of blood draw, across quartiles of fasting insulin levels. As expected, higher levels of fasting insulin tended to be associated with higher BMI, higher prevalence of hypertension and elevated cholesterol, and lower alcohol intake, physical activity and postmenopausal hormone use.

Unadjusted scores on baseline cognitive tests, across fasting insulin quartiles, are shown in table 2. In general, those with higher insulin levels tended to have lower mean scores on category fluency and digit span backward, and also appeared to have worse cognitive performance on the global and verbal memory scores.

When we examined cognitive decline across 3 cognitive assessments over an average of 4 years, we found sig-

**Table 3.** Mean differences in cognitive decline across quartiles of fasting insulin

| Cognitive test | 1st quartile | 2nd quartile | 3rd quartile | 4th quartile | p trend |
|---|---|---|---|---|---|
| TICS | 0.00 | −0.06 (−0.16 to 0.03) | −0.14 (−0.24 to −0.04) | −0.09 (−0.19 to 0.01) | 0.04 |
| Global score | 0.00 | −0.01 (−0.03 to 0.02) | −0.03 (−0.05 to 0.00) | −0.01 (−0.04 to 0.01) | 0.16 |
| Verbal score | 0.00 | −0.01 (−0.04 to 0.02) | −0.05 (−0.08 to −0.02) | −0.02 (−0.05 to 0.01) | 0.02 |

Values represent mean differences in the annual rate of decline on cognitive test scores compared to the first quartile over an average of 4 years, and have been adjusted for age and highest attained education. The 95% CI values are given in parentheses.

nificantly worse decline on both the TICS and the verbal score with increased fasting insulin levels (table 3). Specifically, compared to the first quartile, the annual rates of decline (with 95% CI values in parentheses) for the second, third and fourth quartiles were: TICS, −0.06 (−0.16, 0.03), −0.14 (−0.24, −0.04) and −0.09 (−0.19, 0.01) points (p trend = 0.04); verbal memory score, −0.01 (−0.04, 0.02), −0.05 (−0.08, −0.02) and −0.02 (−0.05, 0.01) standard units (p trend = 0.02). Multivariable-adjusted estimates remained similar; compared to the first quartile, the annual rates of decline for the second, third and fourth quartiles were: TICS, −0.05 (−0.15, 0.05), −0.12 (−0.22, −0.03) and −0.10 (−0.19, 0.00) points (p trend = 0.06); verbal memory score, −0.02 (−0.05, 0.01), −0.05 (−0.08, −0.02) and −0.03 (−0.06, 0.00) standard units (p trend = 0.02).

In secondary analyses, adding regular antidepressant use to the multivariable model produced nearly identical results. Similarly, further exclusion of women who reported either a diagnosis of diabetes mellitus after blood draw or stroke after the baseline cognitive assessment did not affect our estimates, e.g. compared to the first quartile, the age-and-education-adjusted annual rates of decline for the second, third and fourth quartiles were: TICS, −0.06 (−0.15, 0.04), −0.14 (−0.23, −0.04) and −0.09 (−0.19, 0.01) points (p trend = 0.05); verbal memory score, −0.01 (−0.04, 0.02), −0.05 (−0.08, −0.02) and −0.02 (−0.05, 0.01) standard units (p trend = 0.02). Finally, after restricting our analyses to only women in the random sample (n = 1,068), estimates were again unchanged.

## Discussion

In women without type 2 diabetes mellitus at blood draw, we found that higher levels of fasting insulin were associated with faster rates of cognitive decline. Associations were independent of numerous potential confounding factors and persisted after the exclusion of women who were diagnosed with diabetes mellitus or stroke after the baseline cognitive interview. Although the largest point estimates for rates of cognitive decline were found in the third and not in the fourth quartile, the p trends were significant across quartiles for the TICS and verbal memory, supporting a dose-effect relationship.

Although there are very few studies of insulin levels and cognition in nondiabetics, our findings are consistent with previous studies linking higher fasting insulin levels to cognitive impairment [15], dementia [6] and cognitive decline [6] in healthy subjects. For example, among 386 nondiabetic men, those in the highest quartile of fasting insulin level had 25% more errors on the Mini-Mental State Examination compared with those in the lowest quartile [15]. Luchsinger et al. [6] reported an association between higher insulin and an increased risk of dementia in persons without diabetes (hazard ratio = 2.3, 95% CI = 1.5–3.6); an association between insulin and decline in memory-related cognitive scores was also found. Though not directly examining fasting insulin levels, other studies support the hypothesis of a role of insulin in the development of cognitive impairment. Yaffe et al. [16] showed an elevated risk of developing cognitive impairment in women with impaired fasting glucose but without diabetes (fasting glucose level >6.1 mmol/l but <7.0 mmol/l), compared to women with a normal fasting glucose. Recently, higher glycosylated hemoglobin levels were associated with an increased risk of mild cognitive impairment and dementia in 1,983 women; these associations remained after the exclusion of women with diagnosed diabetes [17].

In this NHS cohort, we previously reported an association between higher levels of C-peptide (a measure of insulin production) and cognitive impairment among 718 women [8]; we found similar results for C-peptide among 367 men in the Physicians' Health Study [18]. However, in these 2 studies, complete information from cognitive testing was only available from a single exami-

nation. Thus, the current study adds substantively to the literature by showing a significant relation between higher fasting insulin levels and increased rates of decline over time on repeated assessments of cognition – in particular, a decline in verbal memory, a key predictor of dementia [12, 13].

In addition, growing biologic evidence supports a role of insulin in cognitive decline and dementia [19]. It has been shown that peripheral insulin is actively transported across the blood-brain barrier [20], and insulin receptors have been found throughout the brain, in particular in the hippocampus and cortex [21]. Moreover, it has been suggested that high insulin levels in the brain may directly interfere with Aβ metabolism by inhibiting degradation of Aβ by insulin-degrading enzyme, resulting in increased deposition of Aβ in plaques [5]. Thus, insulin may directly affect specific Alzheimer pathologies. Additionally, it is likely that part of the relation of insulin to cognition and dementia is mediated by vascular disease, although, in our study and in others, adjustment for known major vascular factors did not affect the association between insulin and cognitive decline. However, it is difficult to accurately measure the presence of subclinical vascular disease. Indeed, it seems plausible that a combination of both direct (e.g. increased brain Aβ) and indirect effects (e.g. inflammation or vascular endothelial damage) of elevated insulin may underlie the observed association with cognitive decline.

The strengths of this study include the high rate of follow-up and the breadth of information on potential confounding factors, updated every 2 years. In addition, fasting insulin levels were measured in blood collected in mid-life; since cognitive impairment appears to take many years to develop, risk factors at these younger ages may be the most important assessment.

Potential limitations of our study should be considered. First, information on cognitive decline was gathered through telephone-based testing rather than through in-person testing. However, the high validity of our telephone method has been established [8]; furthermore, the telephone testing yields high participation and follow-up rates, enhancing the validity of results. Second, we only had a single measurement of insulin, which may have increased random measurement error; however, this would have led to an underestimation of the association between insulin and cognitive decline. Third, this is a select population of largely healthy Caucasian nurses, and the absolute levels of fasting insulin were somewhat lower than those recently reported in nondiabetic, community-dwelling women of comparable age [22, 23]. However, a slightly narrower distribution of fasting insulin levels would lead, if anything, to underestimating the relation between insulin and cognitive decline in the general population; indeed, the significant association we found between insulin and cognitive decline in these healthy women with relatively low levels of insulin emphasizes the potential importance of even modestly elevated insulin. Fourth, since we relied on self-reports of diabetes status to exclude diabetic women, our study sample may have included women with undiagnosed diabetes mellitus; hence, our findings may partly be explained by the association between diabetes and cognitive decline. However, as noted earlier, insulin levels in this sample were not very high, indicating a low prevalence of insulin resistance, and our results remained similar when we excluded women who were diagnosed with diabetes mellitus during follow-up, likely eliminating any women with undiagnosed diabetes mellitus at the time of blood draw. Moreover, as health professionals, virtually all our participants have access to health care, making undiagnosed diabetes mellitus less likely; indeed, in a random sample of 200 NHS participants who never reported diabetes, we found only 1 had a plasma fasting glucose or fructosamine level in the diabetic range [8]. Finally, although we were able to adjust for many potential confounders, residual confounding should be considered, as in any observational study. The relative homogeneity of our cohort, however, reduces the potential effect of many unmeasured confounders, such as health knowledge and access.

In conclusion, data from our study suggest a role of insulin, independent of diabetes mellitus, in the development of cognitive decline. This association clearly needs further research since modulation of insulin levels may represent an effective target for prevention of cognitive decline and Alzheimer disease.

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## References


1 Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM: Diabetes mellitus and the risk of dementia. The Rotterdam Study. Neurology 1999;53:1937–1942.

2 Coker LH, Shumaker SA: Type 2 diabetes mellitus and cognition: an understudied issue in women's health. J Psychosom Res 2003;54:129–139.

3 Gregg EW, Yaffe K, Cauley JA, Rolka DB, Blackwell TL, Narayan KM, Cummings SR: Is diabetes associated with cognitive impairment and cognitive decline among older women? Study of Osteoporotic Fractures Research Group. Arch Intern Med 2000;160:174–180.

4 Biessels GJ, Staekenborg S, Brunner E, Brayne C, Scheltens P: Risk of dementia in diabetes mellitus: a systematic review. Lancet Neurol 2006;5:64–74.

5 Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, Guenette S: Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. Proc Natl Acad Sci USA 2003;100:4162–4167.

6 Luchsinger JA, Tang MX, Shea S, Mayeux R: Hyperinsulinemia and risk of Alzheimer disease. Neurology 2004;63:1187–1192.

7 Peila R, Rodriguez BL, White LR, Launer LJ: Fasting insulin and incident dementia in an elderly population of Japanese-American men. Neurology 2004;63:228–233.

8 Okereke O, Hankinson SE, Hu FB, Grodstein F: Plasma C peptide level and cognitive function among older women without diabetes mellitus. Arch Intern Med 2005;165:1651–1656.

9 Brandt J, Spencer M, Folstein MF: The telephone interview for cognitive status. Neuropsychiatry Neuropsychol Behav Neurol 1988;1:111–117.

10 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state': a practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.

11 Albert M, Smith LA, Scherr PA, Taylor JO, Evans DA, Funkenstein HH: Use of brief cognitive tests to identify individuals in the community with clinically diagnosed Alzheimer's disease. Int J Neurosci 1991;57:167–178.

12 Chen P, Ratcliff G, Belle SH, Cauley JA, DeKosky ST, Ganguli M: Patterns of cognitive decline in presymptomatic Alzheimer disease: a prospective community study. Arch Gen Psychiatry 2001;58:853–858.

13 Small BJ, Fratiglioni L, Viitanen M, Winblad B, Backman L: The course of cognitive impairment in preclinical Alzheimer disease: three- and 6-year follow-up of a population-based sample. Arch Neurol 2000;57:839–844.

14 Laird NM, Ware JH: Random-effects models for longitudinal data. Biometrics 1982;38:963–974.

15 Kalmijn S, Feskens EJ, Launer LJ, Stijnen T, Kromhout D: Glucose intolerance, hyperinsulinaemia and cognitive function in a general population of elderly men. Diabetologia 1995;38:1096–1102.

16 Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K: Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. Neurology 2004;63:658–663.

17 Yaffe K, Blackwell T, Whitmer RA, Krueger K, Barrett Connor E: Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. J Nutr Health Aging 2006;10:293–295.

18 Okereke O, Kang JH, Gaziano JM, Ma J, Stampfer MJ, Grodstein F: Plasma C-peptide and cognitive performance in older men without diabetes. Am J Geriatr Psychiatry 2006;14:1041–1050.

19 Biessels GJ, Kappelle LJ: Increased risk of Alzheimer's disease in type II diabetes: insulin resistance of the brain or insulin-induced amyloid pathology? Biochem Soc Trans 2005;33:1041–1044.

20 Banks WA: The source of cerebral insulin. Eur J Pharmacol 2004;490:5–12.

21 Park CR: Cognitive effects of insulin in the central nervous system. Neurosci Biobehav Rev 2001;25:311–323.

22 Song Y, Manson JE, Tinker L, Howard BV, Kuller LH, Nathan L, Rifai N, Liu S: Insulin sensitivity and insulin secretion determined by homeostasis model assessment and risk of diabetes in a multiethnic cohort of women: the Women's Health Initiative Observational Study. Diabetes Care 2007;30:1747–1752.

23 Lawlor DA, Fraser A, Ebrahim S, Smith GD: Independent associations of fasting insulin, glucose, and glycated haemoglobin with stroke and coronary heart disease in older women. PLoS Med 2007;4:e263.