Hypoglycemic Episodes and Risk of Dementia in Older Patients With Type 2 Diabetes Mellitus

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Context Although acute hypoglycemia may be associated with cognitive impairment in children with type 1 diabetes, no studies to date have evaluated whether hypoglycemia is a risk factor for dementia in older patients with type 2 diabetes.

Objective To determine if hypoglycemic episodes severe enough to require hospitalization are associated with an increased risk of dementia in a population of older patients with type 2 diabetes followed up for 27 years.

Design, Setting, and Patients A longitudinal cohort study from 1980-2007 of 16,667 patients with a mean age of 65 years and type 2 diabetes who are members of an integrated health care delivery system in northern California.

Main Outcome Measure Hypoglycemic events from 1980-2002 were collected and reviewed using hospital discharge and emergency department diagnoses. Cohort members with no prior diagnoses of dementia, mild cognitive impairment, or general memory complaints as of January 1, 2003, were followed up for a dementia diagnosis through January 15, 2007. Dementia risk was examined using Cox proportional hazard regression models, adjusted for age, sex, race/ethnicity, education, body mass index, duration of diabetes, 7-year mean glycated hemoglobin, diabetes treatment, duration of insulin use, hyperlipidemia, hypertension, cardiovascular disease, stroke, transient cerebral ischemia, and end-stage renal disease.

Results At least 1 episode of hypoglycemia was diagnosed in 1465 patients (8.8%) and dementia was diagnosed in 1822 patients (11%) during follow-up; 250 patients had both dementia and at least 1 episode of hypoglycemia (16.95%). Compared with patients with no hypoglycemia, patients with single or multiple episodes had a graded increase in risk with fully adjusted hazard ratios (HRs): for 1 episode (HR, 1.26; 95% confidence interval [CI], 1.10-1.49); 2 episodes (HR, 1.80; 95% CI, 1.37-2.36); and 3 or more episodes (HR, 1.94; 95% CI, 1.42-2.64). The attributable risk of dementia between individuals with and without a history of hypoglycemia was 2.39% per year (95% CI, 1.72%-3.01%). Results were not attenuated when medical utilization rates, length of health plan membership, or time since initial diabetes diagnosis were added to the model. When examining emergency department admissions for hypoglycemia for association with risk of dementia (535 episodes), results were similar (compared with patients with 0 episodes) with fully adjusted HRs: for 1 episode (HR, 1.42; 95% CI, 1.12-1.78) and for 2 or more episodes (HR, 2.36; 95% CI, 1.57-3.55).

Conclusions Among older patients with type 2 diabetes, a history of severe hypoglycemic episodes was associated with a greater risk of dementia. Whether minor hypoglycemic episodes increase risk of dementia is unknown.

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Corresponding Author: Rachel A. Whitmer, PhD, Kaiser Permanente, Division of Research, Section of Etiology and Prevention, 2000 Broadway, Oakland, CA 94612 (raw@dp.kaiser.org).
barrier integrity. Despite these consequences, the possible effects of severe hypoglycemia on the risk of subsequent dementia have not been evaluated at a population level.

The objective of this study was to determine whether prior episodes of hypoglycemia that required hospitalization or emergency department (ED) visits are associated with an increased risk of dementia during 22 years of follow-up for hypoglycemia episodes and more than 4 years of follow-up for incident dementia in a large well-characterized cohort of older patients with type 2 diabetes.

**METHODS**

**Population**

We evaluated 16,667 older patients with type 2 diabetes who are members of the Kaiser Permanente Northern California Diabetes Registry. This is a well-characterized diabetic population that has been the basis of a wide range of genetic, epidemiologic, and health services research since 1994. Kaiser Permanente of Northern California (KPNC) is an integrated, non-profit, group practice, and prepaid health care delivery organization that provides comprehensive medical services to 3.3 million members—30% of the surrounding population. Its membership closely approximates the general population by race/ethnicity and socioeconomic status with exception for underrepresented individuals in the extreme tails of income distribution.

The registry is an ongoing epidemiologic cohort of all KPNC members with diabetes who were identified from 5 automated databases: outpatient encounter files (diagnosis of diabetes); pharmacy prescriptions for diabetes medications; glycated hemoglobin (HbA1c) values greater than 7% in laboratory files; primary hospital discharge diagnoses of diabetes; and ED records of diabetes as the reason for visit. As of January 1, 2006, the identification method was estimated to be 99% sensitive based on capture in health plan member surveys. From a medical record review conducted between 1993 and 1994, the registry was found to contain 2.4% false-positive diabetes diagnoses.

Between 1994-1997, all members of the KPNC diabetes registry were mailed a survey to collect information regarding their sociodemographics and health behaviors, with 83% responding to the survey. In a previous study, we compared the demographic composition of the diabetes survey respondents (age, sex, and socioeconomic status) with nonrespondents and found no evidence suggesting respondent bias.

**Analytic Cohort**

We studied individuals who were members of Kaiser Permanente at the January 1, 2003, onset date of dementia follow-up; in the KPNC diabetes registry having completed a diabetes survey; aged 55 years or older when surveyed; diagnosed with type 2 diabetes; and alive and without prior diagnoses of dementia, mild cognitive impairment, and dementia not otherwise specified.

**Measurement of Hypoglycemia**

We identified all hospitalization and ED diagnoses of hypoglycemia using codes from our hospitalization and ED database using ICD-9-CM codes 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified). We did not include the following ICD-9-CM codes: 250.3 (diabetes mellitus with coma) because it does not distinguish between diabetic ketoacidosis or hypoglycemia; 250.8 (diabetes mellitus with other specified manifestations) because it does not specify hypoglycemia; 270.3 (leucine-induced hypoglycemia); 775.6 (neonatal hypoglycemia); and 775.0 (hypoglycemia in an infant born to a diabetic mother). We included hypoglycemic episodes from January 1, 1980, through December 31, 2002. Episodes occurring after the beginning of follow-up for dementia were excluded because of our inability to clearly discern the temporal sequence of dementia and hypoglycemia.

This method of case identification using ICD-9-CM codes has been shown to be comparable with medical records review. It is a more accurate source than billing claims because there is no incentive for overcoding.

**Evaluation of Dementia Cases**

Incident cases of dementia were identified from both inpatient and outpatient databases based on ICD-9-CM diagnosis codes of senile dementia uncomplicated (290.0), Alzheimer disease (331.0), vascular dementia (290.4), and dementia not otherwise specified (290.1). This ascertainment scheme has been used successfully in several recent studies of this population.

**Covariates**

A variety of comorbid conditions that could confound the association were collected from our laboratory and inpatient discharge and outpatient databases. Diagnoses of hypertension and cardiovascular diseases (ICD-9-CM codes 395-429), and stroke (ICD-9-CM codes 431-438) were collected from inpatient and outpatient diagnostic databases (1995-2007). End-stage renal disease was identified from Kaiser Permanente’s comprehensive end-stage renal disease treatment registry.

Comorbidities were combined using a simple count method and the sum was used to create a composite scale that is used in all models adjusting for comorbidities.

Patient age, education, duration of diabetes, body mass index (calculated as weight in kilograms divided by height in meters squared), and race/ethnicity were based on self-report from the survey. Race/ethnicity included 6 categories in which the patients could self-identify (white, African American, Asian, Hispanic, Native American, or other). Type of diabetes was determined using an algorithm based on self-reported clinical characteristics as well as inpatient and outpatient diagnoses. Diabetes treatment was evaluated using our pharmacy databases from 2002-2003 and classified as insulin only, oral...
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Agent only (ie, insulin secretagogues such as sulfonylureas or insulin sensiti-
zizers such as metformin and thiazoli-
dinediones), insulin and oral agent combined, or diet treatment only (ie, neither insulin nor oral agent prescrip-
tions). In addition to the diabetes treat-
ment variable, we also created an in-
sulin duration variable that consisted of
the number of years of insulin use be-
 tween 1994 and the end of the study.
Levels of HbA1c were collected from our
laboratory databases from 1995-2002
using the first and last measurements
from each year to create a single, aver-
age HbA1c value during this 7-year
period.

The study was approved by the in-
stitutional review board of Kaiser Per-
manente of Northern California and
consent was waived.

Statistical Analysis
All analyses were conducted using SAS
statistical software version 9.1 (SAS In-
stitute Inc, Cary, North Carolina). Co-
variates by hypoglycemic status were
compared using $\chi^2$ analyses and t tests.
Age-adjusted incidence rates of demen-
tia by hypoglycemic status were esti-
mated using the cohort as the standard.
Attributable risks (defined as absolute
risk differences for dementia between pa-
tients with a history of 1 or more hypo-
glycemic events and those with none)
and confidence intervals (CIs) were cal-
culated. Cox proportional hazards re-
gression models were used to examine
adjusted associations of hypoglycemic episodes and dementia risk for all mod-
els. Given that dementia hazard is more
a function of age than time since comple-
tion of the survey, age was chosen as the
time scale in the Cox regression mod-
els. Models were adjusted for age (as a
time scale), education, race/ethnicity, sex,
diabetes duration, body mass index, hy-
perlipidemia, hypertension, cardiovas-
cular disease, stroke, end-stage renal dis-
ease, diabetes treatment, duration of
insulin use, and HbA1c level. Assuming
an 8.8% prevalence of at least 1 hypo-
glycemic event and 1822 incident de-
mentia diagnoses, the cohort size of
16667 provides sufficient power of 80%
to detect a hazard ratio (HR) of 1.25 or
greater.

Data on hypoglycemic events were
collected retrospectively and risk of ini-
tial dementia diagnosis was evaluated
from January 1, 2003, forward. The ana-
lytic cohort included individuals who
were alive as of January 1, 2003, with
no prior diagnosis of dementia or
memory impairment. “Time in” started
in 2003 when the patients could be at
risk for dementia; moreover, we used
patient age in 2003 as the time scale,
which is the most robust method to
control for age effects. Follow-up time
commenced with patient age at start of
dementia ascertainment on January 1,
2003, to the earliest of the following
events: age at incident dementia di-
agnosis, age at termination of health plan
membership, age at death, or age at end
of the study period on January 15, 2007.
The association of hypoglycemic epi-
isodes with dementia risk was ana-
yzed in 3 ways. In each method of
analysis, patients having no hypogy-
lcemic events served as the reference
group and were compared with (1)
those having 1 or more events; (2)
those having 1, 2, or more events; and
(3) those having 1, 2, 3, or more events.

To address the possibility that re-
verse causality could explain ob-
served associations, we conducted 2 ad-
ditional sets of analyses. In the first set,
a lag of 2 years was introduced be-
 tween the end of hypoglycemic ascer-
tainment and onset of observation for
risk of incident dementia, such that we
only considered incident dementia cases
occurring from January 1, 2005, to Jan-
uary 15, 2007. In the second, we intro-
duced a longer “backward” lag of 18
years, such that we only considered the
effect of hypoglycemic episodes occur-
r ing in the first 5 years of follow-up
from 1980-1985, on dementia risk from
2003-2007. Each of these was in-
tended to reduce the possibility that
preclinical dementia was increasing the
likelihood of hypoglycemic episodes.

Since African American race/ethnici-
ty, stroke, and end-stage renal disease were highly correlated with the
likelihood of hypoglycemia, we con-
ducted subgroup analyses stratified by
these variables to determine associa-
tions of hypoglycemic episodes with
dementia risk among patients without a
stroke, those without end-stage renal
disease, and those not of African Amer-
ican race/ethnicity. We also separately
analyzed the association of dementia
with hypoglycemic events that were
from the ED only.

Finally, we performed a series of
models with additional adjustments for
length of health plan membership, time
since first diagnosis of diabetes in the
health plan, and medical utilization rate.
A P value of less than .05 was consid-
ered to be statistically significant.

RESULTS
A total of 1822 patients (11%) had a di-
agnosis of dementia during a mean fol-
low-up (starting in 2003) of 3.8 years
and median of 4.8 years. The mean age
of our cohort was 64.9 years at the time
of the survey and 1465 patients (8.8%)
had at least 1 episode of hypoglycemia
from 1980-2002. Ten of the hypogy-
lcemic episodes were hypoglycemic comba
( ICD-9-CM code 251.0) and 535
episodes (36.5%) were from ED diag-
noses. The number of hypoglycemic
episodes increased sharply in 2000-
2002, with almost 700 events during
this period. Compared with patients
without hypoglycemia, those with hy-
poglycemia were more likely to be
older, African American, treated with
insulin, and to have hypertension,
stroke, and end-stage renal disease
(TABLE 1). Those with at least 1 hypogly-
cemic event were also more likely to
be diagnosed with dementia (TABLE 2).

Of the 1465 patients with hypogly-
cemia, 68.5% had 1 episode, 18% had
2 episodes, and 13.5% had 3 or more
episodes. Age-adjusted incidence rates
of dementia by frequency of hypogly-
lcemic episodes were significantly ele-
vated for patients with at least 1 epi-
isode (566.82 cases; 95% CI, 496.52-
637.48 per 10 000 person-years vs 327.6
cases; 95% CI, 311.02-343.18 per
10 000 person-years) compared with
patients with no episodes (Table 2). The
attributable risk of dementia for pa-
tients with 1 or more hypoglycemic episodes compared with those with no episodes was 2.39% per year (95% CI, 1.72-3.01; Table 2).

In the Cox proportional hazard models adjusted for age, body mass index, race/ethnicity, education, sex, and diabetes duration (Table 3), patients with at least 1 episode of hypoglycemia had an increased risk of dementia compared with those with no episodes (HR, 1.68; 95% CI, 1.47-1.93). Patients with 2 or more episodes appeared to be at somewhat greater risk with an HR of 2.15 (95% CI, 1.64-2.81), as did patients with 3 or more episodes (HR, 2.60; 95% CI 1.78-3.79). Further adjustment for diabetes-related comorbidities, HbA1c level, diabetes treatment, and years of insulin use (Table 3) modestly attenuated the effect, although it remained statistically significant and clinically relevant (1 episode [HR, 1.26; 95% CI, 1.10-1.49], 2 episodes [HR, 1.33; 95% CI, 1.12-1.51] vs no episodes).

When examining risk of dementia using the 2-year lagged model (ie, only considering incident dementia cases that occurred between January 1, 2005, and January 15, 2007), trends were similar. In a model fully adjusted for demographics, comorbidities, HbA1c levels, diabetes treatment, and years of insulin use, patients with 1 hypoglycemic episode had an HR of 1.15 (95% CI, 0.89-1.48), 2 episodes (HR, 1.65; 95% CI, 1.10-2.48), and 3 or more episodes (HR, 2.06; 95% CI, 1.32-3.24) vs patients with no hypoglycemic episodes.

Backward lag models that examined only hypoglycemic events that occurred from 1980 through 1985 on risk of dementia were also performed. Although there were fewer hypoglycemic events, hypoglycemia was associated with risk of dementia (1 or more episodes vs no episodes: HR, 1.32; 95% CI, 1.02-1.3) adjusted for age, education, race/ethnicity, body mass index, comorbidities, diabetes duration, diabetes mellitus treatment, years of insulin use, and HbA1c levels.

We also performed models in which we added other variables that could be indicative of diabetes severity to the fully adjusted model (Table 3). These 3 additional models adjusted for length of health plan membership (1 episode [HR, 1.29; 95% CI, 1.10-1.53], 2 episodes [HR, 1.88; 95% CI, 1.39-2.39], and 3 episodes or more [HR, 1.76; 95% CI, 1.29-2.40] vs no episodes), time since initial diabetes diagnosis (1 episode [HR, 1.33; 95% CI, 1.12-1.51], 2 episodes [HR, 1.94; 95% CI, 1.48-2.54], 3 episodes or more [HR, 1.70; 95% CI, 1.24-2.31] vs no episodes), and medical utilization rate (1 episode [HR, 1.24; 95% CI, 1.10-1.45], 2 episodes [HR, 1.63; 95% CI, 1.20-2.18], and 3 episodes or more [HR, 1.63; 95% CI, 1.17-2.27] vs those with no episodes). These models all had results similar to the main models (Table 3), although there was some mild attenuation for those with 3 episodes or more.

### Table 1. Population Characteristics by Hospital or Emergency Department−Associated Hypoglycemia

<table>
<thead>
<tr>
<th>No. (%)</th>
<th>Hypoglycemia (n = 1465)</th>
<th>Nonhypoglycemia (n = 15202)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at survey, mean (SD), y</td>
<td>66.32 (7.54)</td>
<td>64.78 (7.0)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education</td>
<td>108 (7.4)</td>
<td>1004 (6.6)</td>
<td>.09</td>
</tr>
<tr>
<td>High/trade/business school</td>
<td>607 (41.4)</td>
<td>5997 (39.3)</td>
<td></td>
</tr>
<tr>
<td>College/higher degree</td>
<td>750 (51.2)</td>
<td>8222 (54.1)</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>804 (54.9)</td>
<td>8289 (54.5)</td>
<td>.79</td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td>877 (59.8)</td>
<td>9588 (63.1)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Asian</td>
<td>125 (8.5)</td>
<td>1917 (12.6)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>159 (10.8)</td>
<td>1667 (10.9)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>261 (17.8)</td>
<td>1626 (10.7)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>877 (59.8)</td>
<td>9588 (63.1)</td>
<td></td>
</tr>
<tr>
<td>Duration of diabetes from self-report in 1994, mean (SD), y</td>
<td>13.72 (9.2)</td>
<td>9.15 (7.9)</td>
<td></td>
</tr>
<tr>
<td>Duration of Kaiser Permanente membership, mean (SD), y</td>
<td>22.66 (5.32)</td>
<td>22.98 (5.34)</td>
<td>.03</td>
</tr>
<tr>
<td>Medical utilization rate 2003-2004, mean (SD), y</td>
<td>20.12 (16.60)</td>
<td>15.2 (12.71)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Time since first diabetes diagnosis in Kaiser Permanente system, mean (SD), y</td>
<td>15.24 (3.59)</td>
<td>14.52 (2.89)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>1224 (83.5)</td>
<td>9368 (61.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1298 (88.6)</td>
<td>13488 (88.6)</td>
<td>.98</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1429 (97.5)</td>
<td>14557 (95.8)</td>
<td>.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>645 (43.0)</td>
<td>4389 (28.9)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>End-stage renal disease</td>
<td>167 (11.4)</td>
<td>416 (2.74)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Diabetes mellitus treatment type 2002-2003</td>
<td>553 (37.75)</td>
<td>2157 (14.19)</td>
<td></td>
</tr>
<tr>
<td>Oral only</td>
<td>446 (30.44)</td>
<td>8615 (56.67)</td>
<td></td>
</tr>
<tr>
<td>Insulin only</td>
<td>352 (24.03)</td>
<td>2794 (18.38)</td>
<td></td>
</tr>
<tr>
<td>HbA1c, 1995-2002, mean (SD), %</td>
<td>8.22 (1.29)</td>
<td>8.08 (1.30)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Years of insulin use from 1994 to censored date, mean (SD), No.</td>
<td>7.23 (2.8)</td>
<td>6.52 (2.94)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

Abbreviation: HbA1c, glycated hemoglobin.

- All data are presented as No. (%) except when indicated otherwise.
- P-values were calculated using the χ² test.
- Continuous variables.
- Denotes N and column percents for categorical variables.
- Based on pharmacy data collected between January 1, 2002, and December 31, 2002.
Stratified analyses conducted among patients without stroke, without end-stage renal disease, or not of African American race/ethnicity demonstrated similar degrees of association between hypoglycemia and dementia (TABLE 4). Although history of hypoglycemia was associated with end-stage renal disease, stroke, and African American race/ethnicity, the association between hypoglycemia and dementia was not limited to these factors.

Results for patients with ED events only were similar to the results for patients with any events. Compared with patients with no ED-derived hypoglycemic episodes, as determined from outpatient records, patients with 1 hypoglycemic episode resulting in an ED visit had an HR of 1.42 (95% CI, 1.12-1.78), and those with 2 or more episodes had an HR of 2.36 (95% CI, 1.78), and those with 2 or more episodes had an HR of 2.36 (95% CI, 1.78). To determine whether hypoglycemic episodes severe enough to require hospitalization or an ED visit are associated with increased risk of dementia, particularly for patients who have a history of multiple episodes. Specifically, we observed a 2.39% increase in absolute risk of dementia per year of follow-up for patients with history of hypoglycemia, compared with patients without a history. Although this 1-year absolute risk difference is modest, the cumulative effects would be sizeable. Moreover, our findings were independent of glycemic control as assessed by level of HbA1c, type of diabetes treatment, and diabetes comorbidities.

There are several possible mechanisms by which hypoglycemia could increase risk of subsequent dementia in older patients. Severe hypoglycemia can result in permanent neurological sequelae including neuronal cell death, which may accelerate the process of dementia. Hypoglycemia also increases platelet aggregation and fibrinogen formation, and this may accelerate vascular compromise in the brain. Animal studies have illustrated that hypoglycemic coma causes damage to neuronal receptors in the ca-1, subiculum dentate, and granule cell areas of the hippocampus, regions critical for learning and memory. Repeated episodes of hypoglycemia could affect cognition through damage to these regions, particularly in brains that may be vulnerable due to old age.

Table 2. Frequency of Hypoglycemic Episodes by Dementia Status

<table>
<thead>
<tr>
<th>No. of Hypoglycemic Episodes</th>
<th>Dementia (n = 1822)</th>
<th>Nondementia (n = 14 845)</th>
<th>Age-Adjusted Incidence Rates per 10 000 Person-Years (95% CI)</th>
<th>Excess Attributable Risk per Year, % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>1572 (10.34)</td>
<td>13 630 (89.66)</td>
<td>327.60 (311.02-343.18)</td>
<td>3.17 (1.73-5.22)</td>
</tr>
<tr>
<td>Yes</td>
<td>250 (16.95)</td>
<td>1215 (83.05)</td>
<td>566.82 (496.52-637.48)</td>
<td>4.28 (3.16-6.32)</td>
</tr>
<tr>
<td>No of episodes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1572 (10.34)</td>
<td>13 630 (89.66)</td>
<td>327.60 (311.02-343.18)</td>
<td>3.17 (1.73-5.22)</td>
</tr>
<tr>
<td>1</td>
<td>150 (14.84)</td>
<td>852 (85.16)</td>
<td>491.73 (412.60-570.80)</td>
<td>1.64 (0.91-2.36)</td>
</tr>
<tr>
<td>2</td>
<td>57 (22.26)</td>
<td>201 (77.74)</td>
<td>761.75 (561.24-962.27)</td>
<td>4.34 (2.36-6.32)</td>
</tr>
<tr>
<td>3 or more</td>
<td>43 (20.40)</td>
<td>162 (79.60)</td>
<td>755.46 (526.46-984.46)</td>
<td>4.28 (2.10-6.44)</td>
</tr>
</tbody>
</table>

Abbreviation: CI, confidence interval.

a Attributable risk calculated as difference between rate in group and rate in reference group (0 hypoglycemic events).
A P values were less than .001 and were calculated using the χ² test.

Table 3. Hypoglycemia and Risk of Incident Dementia

<table>
<thead>
<tr>
<th>No. of Hypoglycemic Episodes</th>
<th>No. of Dementia Cases</th>
<th>Hazard Ratio (95% Confidence Interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Adjusted for Age (as Time Scale), BMI, Race/Ethnicity, Education, Sex, and Duration of Diabetes</td>
<td>Additionally Adjusted for Comorbidities</td>
</tr>
<tr>
<td>1 or more</td>
<td>250</td>
<td>1.69 (1.47-1.93)</td>
</tr>
<tr>
<td>1</td>
<td>150</td>
<td>1.45 (1.23-1.72)</td>
</tr>
<tr>
<td>2</td>
<td>57</td>
<td>2.15 (1.64-2.81)</td>
</tr>
<tr>
<td>3 or more</td>
<td>43</td>
<td>2.60 (1.78-3.79)</td>
</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; HbA1c, glycated hemoglobin.
a Analyses combined using Cox proportional hazard models.
b The 1 or more group was compared to 0 and 1, 2, and 3 or more groups were simultaneously compared to 0.
c Adjustment made using a comorbidity composite scale.

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Cerebrovascular disease is also a possible mechanism for the association between episodes of hypoglycemia and increased risk of dementia. Although we carefully adjusted for acute stroke, as well as transient cerebral ischemia, it was impossible in this study to adjust for subclinical cerebrovascular events. These could only be detected with brain imaging methods and this study could not determine whether one of the mechanisms between hypoglycemia and increased dementia risk is through undiagnosed cerebrovascular damage. Given evidence regarding hypoglycemia and neurological sequelae in animal models,6,16,36 cerebrovascular damage is likely one of the mechanisms.

Since hypoglycemia is a consequence of excess exogenous or endogenous insulin, the association may also reflect direct effects of long-term or recurrent hyperinsulinemia. One study found that abdominal obesity, a condition associated with hyperinsulinemia, is associated with an increased risk of dementia.39 Insulin could also affect the risk of dementia by direct action on neurons or changes in energy metabolism in the hippocampus and cortex when present in excess.40,41 Hyperinsulinemia in the periphery is associated with lower brain levels of insulin. Patients with Alzheimer disease have higher levels of insulin in the periphery and a lower level of brain-produced insulin.40-42 In animal models, insulin has also been shown to stimulate amyloid-β protein secretion and inhibit extracellular degradation of amyloid-β by competing for insulin-degrading enzyme,43-45 suggesting a direct mechanism by which hyperinsulinemia may contribute to Alzheimer disease pathology. Hypoglycemia is also a marker for diabetes severity, and the association of hypoglycemia and dementia could be related to severity or duration of diabetes. Although we adjusted for time since initial diabetes diagnosis, comorbidities that are indicative of severity, and duration of insulin use, it is still possible that diabetes severity increases risk of dementia.

Numerous studies have evaluated whether hypoglycemia interferes with cognitive function, and some of these studies suggest that hypoglycemia affects certain cognitive domains,8,10,46-50 while others found no effect.15 These studies have mainly been conducted in children and young adults with type 1 diabetes. Research in adults without diabetes using functional magnetic resonance imaging techniques has shown that induced hypoglycemia is associated with impaired brain function,51 and other studies in adults with type 1 diabetes suggest an association between hypoglycemia and greater cortical atrophy, altered cerebral blood, or both.52

By contrast, epidemiologic findings from the Diabetes Control and Complications Trial11 suggest that in young adults with type 1 diabetes, hypoglycemic episodes are not associated with higher risk of subsequent cognitive impairment during 18 years of follow-up (mean age 45 years at follow-up). The discrepancy between these findings11,15 and those of the present study could be related to the young age of patients in the Diabetes Control and Complications Trial,11 who therefore were less vulnerable to risks of dementia.

Older individuals are thought to have less brain reserve or brain plasticity,33-35 and therefore may be unable to recover from neurological insult as well as younger individuals. It is plausible that hypoglycemia could cause neurological changes that render an older patient more susceptible to dementia, but have no discernable effect on cognitive function in younger patients in whom dementia processes have not commenced. Thus, hypoglycemia may not cause large adverse effects on cognitive performance in adults younger than 60 years, but could have a greater effect on neurocognition in older individuals.36

Our study is the first, to our knowledge, to focus on patients with type 2 diabetes; previous research has focused primarily on hypoglycemia and neurocognition in patients with type 1 diabetes. Thus far, there has been little research on predictors of neurocognition and dementia among patients with type 2 diabetes.3

### Strengths and Weaknesses

There are several strengths of the present study. This is a large well-characterized cohort of patients with...
type 2 diabetes that has detailed information on comorbidities, HbA1c levels, and diabetes treatment. The stability of membership in the KPNC health plan allowed us to observe the cohort for incident dementia over a prolonged period and to temporally separate hypoglycemic events from initial diagnoses of dementia. Moreover, the hypoglycemic episodes in this study were obtained from outpatient records of ED admittance or reason for hospitalization, not from self-report or billing claims. Clinicians have relatively little incentive to override in this setting.

A possible weakness is that our dementia diagnoses are based on clinical diagnoses obtained from electronic medical records, rather than the results of standardized neurological assessments administered periodically to all cohort members. Another potential concern is that due to the observational nature of our cohort study, we cannot be certain of the temporality of our findings, and cognitive problems due to undiagnosed dementia may have contributed to the occurrence of hypoglycemia. However, individuals with diagnoses of dementia, mild cognitive impairment, or general memory impairment before 2003 were excluded. In addition, we designed the study to increase the temporal separation of earlier hypoglycemic episodes from later occurrences of dementia and also conducted analyses with further lags between exposure to hypoglycemia and the beginning of observation for incident dementia. These lagged-model findings demonstrated similar associations. Even when considering only hypoglycemic episodes during the first 5 years of the study, when the patients were between the ages of 52 and 57 years (when dementia is highly unlikely), there was still an association with an elevated risk of dementia more than 2 decades later. Finally, our study involves the association between severe hypoglycemic episodes and risk of dementia; implications from our study do not address the role of less severe but more frequent episodes of hypoglycemia on dementia risk. The clinical significance of minor hypoglycemic episodes on dementia risk is unknown.

Implications

Currently, 2 large multicenter clinical trials of diabetes and cardiovascular disease are under way that assess the effect of intensive blood glucose control on complications in type 2 diabetes: Action to Control Cardiovascular Risk in Diabetes Mellitus (ACCORD) and Action in Diabetes Mellitus and Vascular Disease (ADVANCE). The data and safety monitoring board and the National Heart, Lung, and Blood Institute recently stopped 1 treatment group within the ACCORD trial 18 months early because patients receiving intensive blood glucose-lowering treatment experienced increased rates of mortality.57 The ADVANCE study, which had slightly less stringent glycemic targets, has not shown a similar effect.58 Nevertheless, the ACCORD study findings raise safety concerns for diabetes care in older patients. Our data further suggest a need for caution in this group.

In addition to fatal end points, these 2 trials are collecting data on hypoglycemic events and cognitive function measures and in a few years will be able to add experimental evidence regarding the observations of this study. In addition, the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial, a study of adults with type 2 diabetes or prediabetes, also includes a cognitive function substudy and may yield important results regarding glycemic control and cognition. A large body of evidence suggests that individuals with diabetes are at an increased risk of dementia, yet exact mechanisms are not known.1,2,5,40,59,60,61,62 our study suggests a potentially modifiable mechanism. Pharmacologically induced severe hypoglycemia may be associated with neurological consequences in an older population already susceptible to dementia. More scientific studies examining hypoglycemia and cognitive performance and brain-imaging sequelae in populations of older patients with type 2 diabetes are needed.

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Study concept and design: Whitmer, Karter, Selby.

Acquisition of data: Whitmer, Karter, Selby.

Analysis and interpretation of data: Whitmer, Karter, Yaffe, Quesenberry, Selby.

Drafting of the manuscript: Whitmer.

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HYPOGLYCEMIA AND DEMENTIA IN OLDER PATIENTS WITH TYPE 2 DIABETES


