HHS Public Access

Author manuscript

J Geriatr Psychiatry Neurol. Author manuscript; available in PMC 2017 May 01.

Published in final edited form as:

J Geriatr Psychiatry Neurol. 2016 May ; 29(3): 120–125. doi:10.1177/0891988715627016.

The Association Between Diabetes and Dementia Among Elderly Individuals: A Nationwide Inpatient Sample Analysis

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Abstract

Background/Aim—To date, few studies have cross-examined the relationship between diabetes mellitus (DM) and dementia nationally. There is also a lack of evidence regarding dementia subtypes and how this relationship changes among older individuals. The objective was to better delineate this relationship and influence of multiple comorbidities using a nationwide sample.

Methods—Data were obtained from the Nationwide Inpatient Sample 1998 to 2011 using appropriate *International Classification of Diseases, Ninth Version* codes. Descriptive and bivariate analysis was performed. Multivariate nominal logistic regression models adjusted for age, sex, race, and comorbidities explored the independent relationship between Alzheimer dementia (AD), non-Alzheimer dementia (VaD), and diabetes.

Results—21% of the participants were diabetic patients, 3.7% had AD, and 2.2% had VaD. Diabetes prevalence in AD, VaD, and no dementia groups were 20.6%, 24.3%, and 26.2%, respectively. In the unadjusted model, those with DM had lower odds of AD (odds ratio [OR] 0.73; 95% confidence interval [CI] 0.72–0.74) and VaD (OR 0.91, 95% CI 0.89–0.92). Adjusting for age, sex, race, and comorbidities, diabetic patients had significantly higher odds of VaD (OR = 1.10, 95% CI 1.08–1.11) and lower odds of AD (OR 0.87, 95% CI 0.86–0.88). Inclusion of interaction terms (age, race/ ethnicity, depression, stroke, and hypertension) made the relationship between diabetes and VaD not significant (OR 1.002, 95% CI 0.97–1.03), but the relationship of DM with AD remained significant (OR 0.57, 95% CI 0.56–0.58; $P < .05$).

Conclusion—Patients with a diagnosis of diabetes mellitus had lower odds of having AD. Age, race/ethnicity, depression, stroke, and hypertension modified the relationship between DM and both VaD and AD. Further exploration of the relationship between DM and AD is warranted.

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Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Keywords

dementia; vascular dementia; Alzheimer disease

Introduction

Currently, there are more than 24 million people worldwide with dementia, and the number is expected to double every 20 years, reaching 81 million by 2040.[1] Our aging society will face an epidemic of dementia; more than 13% of those over the age of 70 have a form of dementia,[2] and this percentage doubles every 5 years after 70 years of age.[3] Studies have indicated that the proclivity for all dementias, including Alzheimer dementia (AD), is influenced by other comorbidities often seen in the elderly patients such as hypercholesterolemia, hypertension, and diabetes. Diabetes mellitus (DM) in particular has been associated with decline in cognitive abilities, such as memory and executive function.[4] A recent meta-analysis revealed DM to be a strong risk factor for all types of dementia.[5] Yet only a few epidemiological studies have been performed to better elucidate the relationship between DM and specific types of dementia, with inconsistent findings. Luchsinger et al and Hassing et al who used participants aged 65 years and older and 80 years and older, respectively, both found no increased risk of AD and a greater than 2-fold increase in risk of non-Alzheimer dementia (VaD) in patients with DM.[6,7] In contrast, DM was found to increase both AD and VaD in twins aged 65 years and older in Xu et al's study.[8] Ott et al even found DM to double the risk of AD and VaD among participants aged 55 years and older.[9] In another study, merely borderline DM among those aged 75 years and older led to an increase in AD and dementia as a whole,[10] while Raffaitin et al found that DM among those aged 65 years and older but not impaired fasting glycemia was associated with VaD and dementia as a whole.[11] Several systematic reviews have found a link between the development of Alzheimer disease among patients with DM and found that some antidiabetic medications, such as the glucagon-like peptide-1 receptor agonists, may protect against dementia and AD.[12,13] The varying results between different studies highlight the need for large-scale database analysis to examine the risk of dementia in patients with DM. In this cross-sectional study, we attempted to explore the link between DM and dementia in a nationally representative database.

Methods

Data were obtained from the Nationwide Inpatient Sample (NIS) 1998 to 2011 developed as part of the Healthcare Cost and Utilization Project, a Federal-State-Industry partnership sponsored by the Agency for Healthcare Research and Quality. Nationwide Inpatient Sample is designed to approximate a stratified 20% sample of all nonfederal, short-term, general, and specialty hospitals serving adults in the United States. All discharges from sampled hospitals for the calendar year are then selected for inclusion into NIS. It captures discharge-level information on primary and secondary diagnoses and procedures, discharge vital status, and demographics on discharges per year. To allow extrapolation for national estimates, both hospital and discharge weights are provided. Detailed information on the design of the NIS is available at http://www.hcup-us.ahrq.gov.

The population study consisted of individuals 65 years and older. Alzheimer dementia and VaD were the main outcomes of measure, while the reference group was those without dementia. To analyze DM hospitalizations, we identified Clinical Classification Software (CCS) codes of 49 and 50. AD and VaD hospitalizations were identified using the *International Classification of Diseases, Ninth Version, Clinical Modification* primary and secondary diagnosis code of 331.0 for AD and 290.X (X including 290.4, 290.40, 290.41, 290.42, 290.43) for VaD. *International Classification of Diseases, Ninth Version* codes for comorbidities such as stroke (431, 434.0, 434.1, 436, 437.0–437.7), depression (311), and hypertension (401) were also identified. Variables included as potential confounding variables were selected based on prior knowledge of being risk factors for the dementia and associated with DM.

Statistical Analysis

Descriptive statistics was utilized to depict the characteristics of total sample population as well as AD, VaD, and no dementia admissions (mean ± standard deviation for continuous variables and percentages for categorical variables). To test the statistical differences between the groups (AD, VaD, and no dementia), chi-square test for categorical variables and 2-sided *t* tests for continuous variables were used, and $P < .05$ was considered statistically significant. The independent associations between DM and dementia were assessed by multinomial logistic regression analysis with no dementia as a reference group. Crude and adjusted odds ratio (OR) for VaD versus no dementia and for AD versus no dementia with 95% confidence intervals (CI) were calculated. Variables considered as possible confounders in the multinomial regression analysis were age, sex, race, stroke, hypertension, depression, and chronic obstructive pulmonary disease (COPD).

In order to determine whether the relationship between DM and both AD and VaD is modified by the independent variables (age, race/ethnicity, stroke, hypertension, depression), we included the interaction term of the DM and these independent variables in the model. Significant interaction term indicates that the independent variable is an effect modifier.

In order to examine how each group of potential confounding variables (demographics and co-morbidities) changed the OR of having dementia comparing DM to non-DM group, 4 models were constructed, beginning with the unadjusted model. Model 1 included the DM and the demographic variables (age, gender and race/ethnicity). Model 2 included the variables in model 1 plus the comorbidity variables (stroke, hypertension, depression, and COPD). Model 3 included the variables in model 2 plus the interaction terms of DM with age and race/ethnicity; DM and stroke; DM and hypertension; and DM and depression. Data were presented as OR and 95% confidence interval, and *P* value < .05 was considered statistically significant. Data were analyzed using SAS version 9.2.

Results

The population characteristics of our sample are reported in Table 1. The mean age in years of patients with AD, VaD, and no dementia was 83.0 (standard deviation [SD] 7.8), 82.9 (SD 7.3), and 77.4 (SD 7.7), respectively. The prevalence of diabetes in AD, VaD, and no dementia groups were 20.6%, 24.3%, and 26.2%, respectively. Overall, 48.7% had

hypertension. The percentage of patients who have a history of hypertension as well as AD, VaD, or no dementia were 46.4%, 47.3%, and 48.8%, respectively. All comorbidities including hypertension, stroke, depression, and COPD were significantly different between the 3 groups ($P < .05$; Table 1).

In the unadjusted model, individuals with DM had a negative association with VaD (OR = 0.91, 95% CI = 0.89–0.92) and AD (OR = 0.73, 95% CI 0.72–0.74). After adjusting for the demographic variables (age, gender, and race/ethnicity), the odds of having VaD reversed to 1.08 (95% CI 1.07–1.09) and that of AD remained negative at 0.865 for AD (95% CI 0.86–0.87). Additional adjustment for comorbidity (stroke, hypertension, depression, and COPD) did not substantially change the relationship for VaD (OR 1.10, 95% CI 1.08–1.11) or AD (OR 0.87, 95% CI 0.86–0.88). Age, stroke, and hypertension modified the relationship between DM and VaD as evidenced by significant interaction terms in the model ($P < .05$; Table 2A). Age, race/ethnicity, depression, stroke, and hypertension modified the relationship between DM and AD, where the interaction terms were statistically significant ($P < .05$; Table 2B). The inclusion of these interaction terms to the model alter the results for VaD (OR 1.002, 95% CI 0.97–1.03), which becomes not significant (Table 2A) but did not alter the results for AD (OR 0.57, 95% CI 0.56–0.58; Table 2B).

Significant predictors that had higher odds of VaD were age, race/ethnicity (black and other race compared to white), stroke, and depression ($P < .05$). Those with hypertension and COPD had lower odds of VaD ($P < .05$: Table 2A). Significant correlation with lower odds of AD were DM, hypertension, and COPD ($P < .05$) and those with higher odds of AD were age, gender (female relative to male), race/ethnicity (black and Hispanics compared to white), stroke, and depression ($P < .05$; Table 2B).

Discussion

Our results show that in this nationally representative data set, the odds of having AD is significantly lower in those with a diagnosis of DM. Of interest, this negative association migrated toward the null after adjustment for demographic variables and CCI score. The association between VaD and DM reversed from negative to positive after adjusting for age, sex, and race/ethnicity. The additional adjustment for comorbidities and the interaction terms alters this association to become not statistically significant.

Literature on the relationship between DM and different types of dementia has thus far been conflicting. Many studies have found a strong link between DM and AD.[6,14–17] In fact, in some literature, AD has even been referred to as type 3 diabetes.[18] However, a number of articles also suggest that diabetes has no effect[7,19] or has been shown to be negatively associated with AD neuropathology.[20] Our result support the inverse relationship between these 2 conditions. One possible mechanism that has been suggested is related to the use of insulin in the diabetic patients. Exogenous insulin has been postulated to protect against the pathogenic binding of β-amyloid onto neuronal synapses in the brain.[21] A recent randomized controlled trial with intranasal insulin therapy also demonstrated that insulin protected against cognitive decline in participants with AD.[22] Our data do not identify insulin use, which limits our ability to make a direct association. Another plausible

mechanism that has been proposed is related to neuritic plaques. In a postmortem study, autopsies of residents in a nursing home showed that diabetic patients had fewer neurofibrillary tangles in the cerebral cortex than nondiabetic patients, the hallmark protein that definitively diagnoses AD.[20] Similarly, early evidence suggests that diabetic patients are less likely to have β-amyloid deposits, another protein that has been associated with AD and its progression.[23] A cross-sectional study looking at brains from 385 autopsies demonstrated that an average type 2 diabetic patient had 6.0 senile plaques compared to 9.4 plaques in a nondiabetic patient.[20] A later article by Ahtiluoto et al found 86% of nondiabetic patients had β-amyloid plaques compared to 74% in diabetic patients.[23] From these studies, DM appears to be associated with a decreased level of β-amyloid plaques and neurofibrillary tangles, which may provide some insight into molecular mechanism linking DM to AD and possible pathways to treatment of AD.

Limitations

A major strength of this study is that it utilizes a large nationally representative sample. However, using such a database has unavoidable limitations as well. Coding errors may either over-or underestimate the true numbers. The inability to code for significant confounders such as education, with decreased educational background having been previously shown to have a positive relationship with dementia, would alter the relationship between DM and dementia.[24] Inconsistent diagnoses are also likely more common due to the sheer number of health care providers with vast skill differences in detecting DM and dementia. Selection bias is also found in this type of observational database. As an inpatient sample, NIS does not include nonhospitalized diabetic patients or patients with dementia, and the population studied in the hospital setting may be distinctly different from those in the general population. When compared to the outpatient setting, inpatients are more commonly treated by diabetic medications such as insulin, which has been recently shown improve memory in adults with mild cognitive impairment or Alzheimer disease. This increased use could therefore rationalize the negative relationship between DM and AD. In addition, we were unable to determine the age of onset of diabetes in our population. There is a stronger risk of development of AD when DM occurs in mid-life (onset age <65 years) than in late life (onset age development).[25] Therefore, a greater number of participants with late-life DM could also account for the negative relationship between DM and AD. Also, the timing and the method of diabetes assessment can affect risk estimates of dementia in people with diabetes. In a systemic review of diabetes and dementia, the methods used to identify previously undiagnosed cases of diabetes varied across studies.[26] In the elderly patients, diabetes is undiagnosed about 30% of the time, which can lead to misclassification of patients in the nondiabetic group. This too may have lead to the negative relationship that was found between DM and AD. The size of this effect should be modest compared to the large proportion of true nondiabetic patients in the group. Furthermore, DM is a systemic disease that affects a number of other mechanisms such as blood pressure, lipid metabolism, and coagulopathy that may confound the relationship between DM and AD. Finally, the design of the NIS database limits our study to a cross-sectional analysis. Therefore, the association between DM and dementia cannot be assumed to be a causal one. However, NIS represents a unique source with a large number of cases, representing 20% of US nationwide

in-hospital treatments. Therefore, our findings provide greater insight into this relationship and paves the way for future prospective studies, despite the limitations.

Conclusion

In this cross-sectional analysis of a large nationwide inpatient database, we were able to demonstrate a strong negative relationship between DM and AD. Although we cannot make a causal inference, our findings highlight the importance of further exploring the relationship of DM and its treatment with AD.

Acknowledgments

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: Dr Bazargan was supported by: (1) the CDU/UCLA Cancer Center Partnership to Eliminate Cancer Health Disparities, Grant U54-CA-143931 from NIH/NCI; (2) the AXIS (Accelerating Excellence in Translational Science) NIMHD/NIH grant U54MD007598; and (3) the Research Centers in Minority Institutions (RCMI) Translational Research Network (RTRN) grant U54MD008149 from NIMHD/NIH. Dr Shaheen was supported in part by NIH grants U54-MD007598, UL1TR000124, and S21-MD-000103.

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Table 1

Baseline Characteristics by AD and VaD Among 26 926 896 Participants.

Variables	Total population	AD	VaD	No Dementia	*P* Value
N	26 926 896	997 207	597 737	25 331 952	
Diabetes, %	26.0	20.6	24.3	26.2	<.001
Age, %	77.7 (7.8)	83.0 (6.7)	82.9 (7.3)	77.4 (7.7)	<.001
Sex, %,					<.001
Male	42.4	34.2	38.1	42.9	
Female	57.6	65.8	61.9	57.1	
Primary payer, %,					<.001
Medicare	89.5	92.8	92.5	89.3	
Medicaid	1.5	1.1	1.7	1.5	
Private	7.6	4.9	4.7	7.8	
Other[a]	1.4	1.2	1.1	1.4	
Race/ethnicity, %,					<.001
White	80.9	79.4	78.9	81.0	
African American	8.9	10.5	11.4	8.7	
Hispanic	6.1	6.4	5.3	6.1	
[a] Other	4.1	3.5	4.4	4.2	
[b] Median household income, %					.013
US$1–US$24999	6.1	6.1	6.1	6.1	
US$25 000–US$34 999	27.8	28.0	28.3	27.7	
US$35 000–US$44 999	27.6	26.6	26.4	27.6	
US$45 000 or more	38.5	39.3	39.2	38.5	
Total in-hospital charge, mean (SD)	US$25 632 (39.1)	US$19 834 (25.4)	US$20 928 (28.2)	US$26 036 (39.7)	<.001
Length of stay	5.7 (6.8)	6.2 (7.0)	7.0 (8.5)	5.7 (6.8)	<.001
Comorbidity index score	1.8 (1.9)	1.3 (1.5)	1.6 (1.5)	1.8 (1.9)	<.001
Comorbidities, %					
Hypertension	48.7	46.4	47.3	48.8	<.001
Stroke	2.3	3.0	23.6	1.8	<.001
Depression	5.0	8.3	7.8	4.8	<.001

Variables	Total population	AD	VaD	No Dementia	*P* Value
COPD	21.2	15.5	17.6	21.6	<.001
Hospital type, %					<.001
Rural	17.4	20.0	19.0	17.3	
Urban nonteaching	44.7	46.9	46.1	44.5	
Urban teaching	37.9	33.1	34.8	38.2	
Hospital bed size, %					<.001
Large	13.3	14.6	15.8	13.2	
Medium	25.5	27.3	27.2	25.4	
Small	61.2	58.1	57.0	61.4	
Hospital region, %					<.001
Northeast	21.2	21.5	26.9	21.0	
Midwest	24.3	23.5	22.3	24.4	
South	37.8	40.7	33.1	37.8	
West	16.7	14.3	17.7	16.8	
Discharge disposition, %					<.001
Routine	52.0	24.8	22.3	53.7	
Short-term hospital	3.0	1.9	2.3	3.1	
Another type of facility home health	40.0	67.3	69.6	38.2	
Against medical advice	0.4	0.2	0.2	0.4	
Died	4.6	5.6	5.5	4.5	

Abbreviations: AD, Alzheimer dementia; VaD, Non-Alzheimer dementia; SD, standard deviation.

[a]Other includes Native American, Pacific Islanders, and Asians.

[b]Median household income is from 1999 to 2002.

Table 2A

Unadjusted and Adjusted Odds Ratios and 95% Confidence Interval of the Association Between Non-Alzheimer Dementia and Diabetes Mellitus.[a,b,c]

	Non-Alzheimer Dementia			
Variables	**Unadjusted OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
DM	0.91 (0.89–0.92)[d]	1.08 (1.07–1.09)[d]	1.10 (1.08–1.11)[d]	1.00 (0.97–1.03)
Age		1.10 (1.09–1.10)[d]	1.10 (1.09–1.10)[d]	1.10 (1.09–1.10)[d]
Gender				
Male		Ref	Ref	Ref
Female		1.01 (1.00–1.02)[d]	1.00 (0.99–1.01)	1.00 (0.99–1.01)
Race				
White		Ref	Ref	Ref
Black		1.54 (1.46–1.63)[d]	1.52 (1.43–1.62)[d]	1.52 (1.43–1.62)[d]
Hispanic		1.04 (0.95–1.14)	1.06 (0.97–1.16)	1.04 (0.95–1.14)
Other		1.16 (1.06–1.28)[d]	1.16 (1.06–1.28)[d]	1.15 (1.04–1.27)[d]
Stroke			16.14 (15.21–17.12)[d]	14.68 (13.85–15.54)[d]
Depression			1.69 (1.64–1.74)[d]	1.70 (1.65–1.75)[d]
Hypertension			0.87 (0.86–0.89)[d]	0.88 (0.86–0.89)[d]
Chronic obstructive pulmonary disease (COPD)			0.92 (0.90–0.93)[d]	0.92 (0.90–0.94)[d]
Interaction of DM and age				1.04 (1.02–1.06)[d]
Interaction of DM and race				
DM–black				1.00 (0.98–1.04)
DM–Hispanic				1.05 (1.00–1.11)
DM–other				1.05 (1.00–1.10)
Interaction of DM and depression				0.98 (0.95–1.01)
Interaction of DM and stroke				1.45 (1.41–1.49)[d]
Interaction of DM and hypertension				0.98 (0.96–1.00)[d]

Abbreviations: Ref, reference category; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus.

[a] Model 1: DM and demographics (age, gender, and race/ethnicity).

[b] Model 2: DM and demographics (age, gender, and race/ethnicity), and comorbidities (stroke, depression, hypertension, and COPD).

[c] Model 3: DM and demographics (age, gender, and race/ethnicity), comorbidities (stroke, depression, hypertension, and COPD), and interaction terms.

[d] $P < .05$.

Table 2B

Unadjusted and Adjusted Odds Ratios and 95% Confidence Interval of the Association Between Alzheimer Dementia and Diabetes Mellitus.[a,b,c]

	Alzheimer Dementia			
Variables	**Unadjusted OR (95% CI)**	**Model 1 OR (95% CI)**	**Model 2 OR (95% CI)**	**Model 3 OR (95% CI)**
DM	0.73 (0.72–0.74)[d]	0.87 (0.86–0.87)[d]	0.87 (0.86–0.88)[d]	0.57 (0.56–0.58)[d]
Age		1.09 (1.09–1.09)[d]	1.09 (1.09–1.09)[d]	1.09 (1.09–1.09)[d]
Gender				
Male		Ref	Ref	Ref
Female		1.19 (1.18–1.20)[d]	1.17 (1.16–1.17)[d]	1.17 (1.16–1.18)[d]
Race				
White		Ref	Ref	Ref
Black		1.44 (1.38–1.51)[d]	1.45 (1.39–1.51)[d]	1.49 (1.43–1.55)[d]
Hispanic		1.27 (1.19–1.36)[d]	1.27 (1.19–1.36)[d]	1.27 (1.18–1.36)[d]
Other		1.00 (0.94–1.08)[d]	1.00 (0.94–1.07)	1.01 (0.94–1.08)
Stroke			1.59 (1.54–1.65)[d]	1.56 (1.50–1.61)[d]
Depression			1.79 (1.76–1.83)[d]	1.83 (1.80–1.87)[d]
Hypertension			0.89 (0.88–0.90)[d]	0.87 (0.86–0.88)[d]
Chronic obstructive pulmonary disease (COPD)			0.73 (0.71–0.74)[d]	0.73 (0.71–0.74)[d]
Interaction of DM and age				1.61 (1.58–1.64)[d]
Interaction of DM and race				
DM–Black				0.94 (0.92–0.96)[d]
DM–Hispanic				1.01 (0.98–1.05)
DM–other				1.00 (0.96–1.04)
Interaction of DM and depression				0.90 (0.88–0.92)[d]
Interaction of DM and stroke				1.09 (1.05–1.14)[d]
Interaction of DM and hypertension				1.09 (1.08–1.11)[d]

Abbreviations: Ref, reference category; OR, odds ratio; CI, confidence interval; DM, diabetes mellitus.

[a]Model 1: DM and demographics (age, gender, and race/ethnicity).

[b]Model 2: DM and demographics (age, gender, and race/ethnicity), and comorbidities (stroke, depression, hypertension, and COPD).

[c]Model 3: DM and demographics (age, gender, and race/ethnicity), comorbidities (stroke, depression, hypertension, and COPD), and interaction terms.

[d]$P < .05$.