

High and Low HbA1c Values Associated with Increased Risk of Alzheimer's Disease in Diabetic Patients

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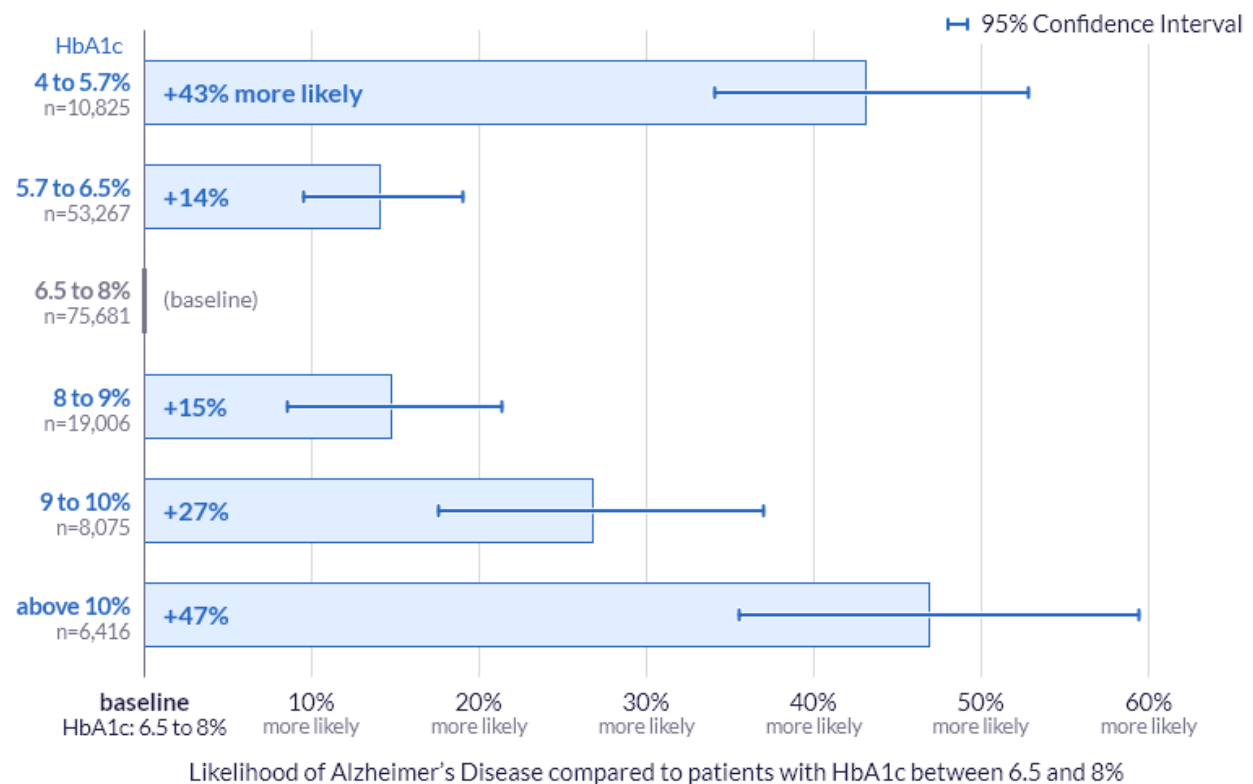
Key Findings:

- Diabetic patients diagnosed with Alzheimer's disease are more likely to have average HbA1c values less than 6.5% or more than 8% in the five years prior to their Alzheimer's diagnoses than diabetic patients not diagnosed with Alzheimer's.

Some studies have suggested that insulin resistance might be correlated with neurodegeneration leading to Alzheimer's disease.^{1,2} To better understand how diabetic control might be linked to Alzheimer's disease, we studied 173,270 diabetic patients aged 65–75 with at least three HbA1c readings. HbA1c measures blood glucose over time. We compared the average HbA1c values over a five-year period for patients who were diagnosed with Alzheimer's disease to those not diagnosed.

We adjusted for patient sex, Social Vulnerability Index (SVI), race and ethnicity, comorbid conditions, and whether the patient was prescribed insulin. We found that patients with average HbA1c values less than 6.5% or greater than 8% were at an increased risk of developing Alzheimer's disease. Patients with average HbA1c values greater than 10% were 47% more likely to have Alzheimer's disease, while patients with values less than 5.7% were 43% more likely.

Likelihood of Alzheimer's Disease in Diabetic Patients



N = 173,270 patients

"Likelihood of Alzheimer's Disease in Diabetic Patients," 2024. EpicResearch.org

Figure 1. The likelihood of diabetic patients to be diagnosed with Alzheimer's disease stratified by average HbA1c.

Additionally, we found that patients who required insulin to help manage their diabetes were 45% more likely to be diagnosed with Alzheimer's disease. Diabetic males were 23% less likely than diabetic females to be diagnosed with Alzheimer's disease. We found no difference in likelihood of Alzheimer's disease between patients in any of the social vulnerability index quartiles.

These data come from Cosmos, a dataset created in collaboration with a community of Epic health systems representing more than 270 million patient records from 1,568 hospitals and more than 35,000 clinics from all 50 states, Lebanon, and Saudi Arabia. This study was completed by two teams that worked independently, each composed of a clinician and research scientists. The two teams came to similar conclusions. Graphics by Brian Olson.

References

1. Nguyen T.T., Ta Q.T.H., Nguyen T.T.D., Le T.T., Vo V.G. Role of Insulin Resistance in the Alzheimer's Disease Progression. *Neurochem. Res.* 2020 doi: 10.1007/s11064-020-03031-0.
2. Caberlotto L., Nguyen T.P., Lauria M., Priami C., Rimondini R., Maioli S., Cedazo-Minguez A., Sita G., Morroni F., Corsi M., et al. Cross-disease analysis of Alzheimer's disease and type-2 Diabetes highlights the role of autophagy in the pathophysiology of two highly comorbid diseases. *Sci. Rep.* 2019;9:3965. doi: 10.1038/s41598-019-39828-5.

Data Definitions

Term	Definition
Study period	January 1, 2020 – May 23, 2024
Study population	Patients with type 2 diabetes aged 65 to 75 with both of the following: - At least three HbA1c results prior to their index date - At least one outpatient face-to-face encounter at least one year following their index date Index date: first diagnosis of Alzheimer's disease for case patients, control patients use 1/1 of every year
HbA1c	A lab with LOINC code 17856-6, 17855-8, 4548-4, or 4549-2 Patients' time-weighted averages over the five years prior to the index date were categorized into: 4 - 5.7 5.7 - 6.5 6.5 - 8.0 8.0 - 9.0 9.0 - 10 - Above 10
Type 2 diabetes	Patients with any of: - An encounter diagnosis or problem list problem with SNOMED CT code 44054006 - An HbA1c value greater than or equal to 6.5% - An administration of or prescription for Alpha-Glucosidase Inhibitors, Amylin Analogs, Antidiabetic Agents, Antidiabetic Combinations, General Insulin, General Meglitinides, General Sulfonylureas, or Thiazolidinediones
Alzheimer's disease	A diagnosis with ICD-10-CM code G30*
Head Injury	A diagnosis prior to the HbA1c reading year with ICD-10-CM code S01*-S09*
Cardiovascular Disease	A diagnosis prior to the HbA1c reading year with ICD-10-CM code I20*-I26*, I30*-I39*, I40*-I49*, I51*, or I70*-I79*
Stroke	A diagnosis prior to the HbA1c reading year with ICD-10-CM code I60*-I63*, I69.3*, Z86.73 or G45.9
Hypertension	A diagnosis prior to the HbA1c reading year with ICD-10-CM code I10*
Hyperlipidemia	A diagnosis prior to the HbA1c reading year with ICD-10-CM code E78.2*-E78.5*
Hypoglycemia event	A diagnosis in an emergency department encounter or admission prior to the HbA1c reading year with ICD-10-CM code E16.0-E16.2
Insulin	An inpatient or prescription for a medication with a simple generic name of INSULIN ASPART, INSULIN DETEMIR, INSULIN, GLARGINE, HUM.REC.ANLOG, INSULIN GLULISINE, INSULIN ISOPHANE NPH, BF-PK, INSULIN ISOPHANE, PORK PURE, INSULIN LISPRO, INSULIN LISPRO PROTAMIN/LISPRO, INSULIN REGULAR, HUMAN, INSULIN REGULAR, BEEF-PORK, INSULIN REGULAR, HUMAN BUFFERED, INSULIN REGULAR, HUMAN&REL.UNT, INSULIN ZINC EXTEND HUMAN REC, INSULIN ZINC HUMAN RECOMBINANT, INSULIN ZINC, BEEF-PORK, INSULIN ZINC, PORK PURIFIED, INSULIN, PORK PURIFIED, INSULIN NPH

	HUM/REG INSULIN HM, INSULIN NPH HUMAN ISOPHANE, or INSULIN ASPART PROT/INSULIN ASP
Race and Ethnicity	Patients were classified based on any documentation of a Hispanic ethnicity as well as any Black race. Patients could be included in both categories. Patients of other races were included and classified as not being Black or Hispanic.
Model Specifications	Logistic regression was performed over the cases and controls, adjusting for the patient's HbA1c average category, sex, Social Vulnerability Index, race and ethnicity, cardiovascular disease, head injury, hyperlipidemia, hypertension, hypoglycemia, stroke , and receipt of insulin.
Stratifications	The analysis was repeated for each single patient's age in years between 65-75.

Table 1: Likelihood of Alzheimer's Disease in Diabetic Patients

	Odds Ratio	Lower CI	Upper CI	N
HbA1c Over 10	1.47	1.35	1.59	6,416
HbA1c 9 to 10	1.27	1.18	1.37	8,075
HbA1c 8 to 9	1.15	1.09	1.21	19,006
HbA1c 6.5 to 8	1.00	1.00	1.00	75,681
HbA1c 5.7 to 6.5	1.14	1.09	1.19	53,267
HbA1c Under 5.7	1.43	1.34	1.53	10,825

Table 2: Likelihood of Alzheimer's Disease in Diabetic Patients Additional Factors

	Odds Ratio	Lower CI	Upper CI
66 Years Old	1.16	1.03	1.31
67 Years Old	1.52	1.35	1.71
68 Years Old	1.86	1.65	2.09
69 Years Old	2.19	1.95	2.45
70 Years Old	2.54	2.27	2.84
71 Years Old	3.12	2.80	3.49
72 Years Old	3.57	3.21	3.98
73 Years Old	3.72	3.34	4.14
74 Years Old	4.00	3.60	4.44
75 Years Old	3.12	2.81	3.46
CVD	1.18	1.13	1.23
Hispanic	1.18	1.11	1.26
Head Injury	1.94	1.87	2.02
Hyperlipidemia	1.25	1.18	1.33
Hypertension	0.97	0.90	1.03

Hypoglycemia	1.68	1.56	1.80
Insulin Usage	1.45	1.39	1.51
Black Race	1.15	1.10	1.20
Male Sex	0.77	0.75	0.80
Stroke	2.07	1.99	2.15
SVI 2 nd Quartile	1.00	0.95	1.05
SVI 3 rd Quartile	1.06	1.01	1.11
SVI 4 th Quartile	1.03	0.98	1.08