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RESEARCH ARTICLE

HbA_{1c} variability associated with dementia risk in people with type 2 diabetes

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Abstract

INTRODUCTION: Although poor glycemic control is associated with dementia, it is unknown if variability in glycemic control, even in those with optimal glycosylated hemoglobin A_{1c} (HbA_{1c}) levels, increases dementia risk.

METHODS: Among 171,964 people with type 2 diabetes, we evaluated the hazard of dementia association with long-term HbA_{1c} variability using five operationalizations, including standard deviation (SD), adjusting for demographics and comorbidities.

RESULTS: The mean baseline age was 61 years (48% women). Greater HbA_{1c} SD was associated with greater dementia hazard (adjusted hazard ratio = 1.15 [95% confidence interval: 1.12, 1.17]). In stratified analyses, higher HbA_{1c} SD quintiles were associated with greater dementia hazard among those with a mean HbA_{1c} < 6% ($P = 0.0004$) or 6% to 8% ($P < 0.0001$) but not among those with mean $HbA_{1c} \geq 8\%$ ($P = 0.42$).

DISCUSSION: Greater HbA_{1c} variability is associated with greater dementia risk, even among those with HbA_{1c} concentrations at ideal clinical targets. These findings add to the importance and clinical impact of recommendations to minimize glycemic variability.

KEYWORDS
dementia, diabetes, glycemic control, glycosylated hemoglobin A_{1c} variability

Highlights

- We observed a cohort of 171,964 people with type 2 diabetes (mean age 61 years).
- This cohort was based in Northern California between 1996 and 2018.
- We examined the association between glycosylated hemoglobin A_{1c} (HbA_{1c}) variability and dementia risk.
- Greater HbA_{1c} variability was associated with greater dementia hazard.
- This was most evident among those with normal–low mean HbA_{1c} concentrations.

1 | BACKGROUND

Type 2 diabetes is associated with an ≈ 2-fold increased risk of dementia.[1–3] However, the mechanisms underlying this increased risk are unclear. Glycemic control is a commonly postulated mechanism linking diabetes and dementia and is often examined with regard to mean values of glycosylated hemoglobin A_{1c} (HbA_{1c}).[4,5] However, large trials focusing on achieving strict mean glycemic control to reduce dementia risk have not provided definitive evidence of benefit.[6] Another, less studied, characteristic of glycemic control is variability, which, when considered, is often examined only in the context of dysglycemic events. Few studies have examined the possible role of visit-to-visit glycemic variability separate from dysglycemic event status[4,7–9] even though greater visit-to-visit HbA_{1c} variability has been associated with various other health outcomes (e.g., all-cause mortality, cardiovascular disease, renal disease, and peripheral neuropathy) with many of these associations independent of glycemic control.[10] A recent meta-analysis pooling the results of five studies from the UK and Asia reported that greater glycemic variability was associated with greater dementia risk.[9] However, it remains unclear whether the association between HbA_{1c} and dementia risk varies by other factors related to dementia risk such as mean HbA_{1c}, sex, race, and ethnicity.

We aimed to study the association between HbA_{1c} variability and dementia risk using multiple metrics of variability and examine whether these associations varied by mean HbA_{1c}, sex, and race and ethnicity in a large diverse sample in an integrated health care system in Northern California.

2 | METHODS

2.1 | Study population

Kaiser Permanente Northern California (KPNC) is a large, integrated health-care delivery system that represents ≈ 30% of the surrounding geographic region, providing comprehensive medical care to > 4.5 million members.[11] Compared to insured adults in the KPNC service area, KPNC members were similar with regard to race, ethnicity, educational attainment, and health indicators, but were less likely to be experiencing low socioeconomic status.[12] The KPNC Diabetes Registry identifies all members with diabetes using a validated algorithm (99% sensitive) combining pharmacy and laboratory information, hospitalization records, and outpatient diagnoses.[13] Among people in the Diabetes Registry, we restricted the sample to individuals aged ≥ 50 years during the study period (January 1, 1996 to December 31, 2018) and identified individuals with type 2 diabetes (n = 494,828) using the following criteria: at least two type 2 diabetes International Classification of Diseases (ICD)-9 diagnoses or ≥ 50% of the individual's diabetes-related diagnostic codes indicating type 2 diabetes. We excluded a total of 251,750 individuals due to prevalent dementia at baseline (n = 5080), < 5 years of follow-up (n = 242,457), or the presence of a history of hospital admission for hypoglycemia or hyperglycemia at baseline (n = 4213). We further excluded 71,114 people who did not have at least one HbA_{1c} per year in the first 3 years of follow-up. Cohort entry was the first date between January 1, 1996 and December 31, 2018 that the person was ≥ 50 years old and had type 2 diabetes based on the criteria described above. People in this dynamic cohort were followed until one of the following occurred: diagnosis of dementia, KPNC membership lapse of ≥ 90 days, death, or the end of the study period (December 31, 2018). This study was approved by the KPNC Internal Review Board and deemed exempt from requiring informed consent.

2.2 | Outcome

Dementia diagnoses were identified based on electronic inpatient and outpatient records from January 1, 1996 to December 31, 2018 based on the following ICD-9/10 codes: Alzheimer's disease (331.0/G30.1, G30.1, G30.8, G30.9), non-specific dementia (290.0x, 290.1x, 290.2x, 290.3x, 294.1x, 294.2x, 294.8/ F03.90, F03.91), and vascular dementia (290.4x/F01.50, F01.51).

2.3 | Exposure

HbA_{1c} variability was estimated using all HbA_{1c} values from the KPNC laboratory database measured during the first 3 years of follow-up in people with at least one HbA1c measure per year. As there is no gold

standard for measurement of variability,[14] we examined the continuous versions of the following various characterizations of variability: (1) standard deviation (SD), (2) coefficient of variation (SD/mean), (3) *Z* scored coefficient of variation, (4) SD adjusted for number of HbA_{1c} measurements (SD/$\sqrt{}$(n/n − 1 measurements), and (5) average real variability (i.e., the average absolute difference in consecutive HbA1c measures). Each operationalization takes into consideration different limitations associated with variability measures such as accounting for mean HbA_{1c}, number of observations, influence of outliers, or the influence of consecutive measurements.[15] We focused on commonly understood metrics of HbA_{1c}: SD and coefficient of variation.[14] To examine potential non-linear associations between HbA_{1c} SD and coefficient of variation, we also operationalized SD and coefficient of variation into quintiles.

2.4 | Covariables

Demographic characteristics (age, sex, race, and ethnicity) and baseline health condition diagnoses (peripheral artery disease, nephropathy, retinopathy, neuropathy, stroke, myocardial infarction, and severe hyperosmolality and ketoacidosis events resulting in emergency room visit or hospitalization; ICD codes presented in Table S1 in supporting information) were obtained from electronic medical records from the time of cohort entry. Mean HbA_{1c} was calculated using all HbA_{1c} measures from the same 3 years used to calculate HbA_{1c} variability).

2.5 | Statistical analysis

We examined the distribution of participant demographics and comorbidities at baseline in the overall sample and by sex, and race and ethnicity. We first implemented a set of Cox proportional hazards models (age as timescale) to estimate the association between SD as a continuous measure as well as quintiles (reference = lowest quintile) and dementia hazard. The models were sequentially adjusted for covariates as follows: Model 1 adjusted for age (as timescale), sex, race, and ethnicity; Model 2 further adjusted for baseline health conditions, namely history of myocardial infarction, peripheral artery disease, neuropathy, nephropathy, stroke, retinopathy, and prior hyperosmolarity and ketoacidosis; and Model 3 additionally adjusted for the number of HbA_{1c} measures available. We repeated this approach using HbA_{1c} coefficient of variation (continuous and divided into quintiles), and average real variability (continuous and divided into above/below median). To reduce the potential of reverse causation, we enforced a 2-year lag between the end of the glycemic measurement period and commencement of period identifying dementia.

In stratified analyses, we examined if the association between HbA_{1c} variability and dementia varied by mean HbA_{1c}. We used quintiles of SD (reference = lowest quintile) as the exposure of interest as it does not include adjustments for mean HbA_{1c}. We examined three strata of mean HbA_{1c} based on commonly used clinical thresholds (i.e., < 42 mmol/mol [< 6%], 42–63 mmol/mol [6%–7.9%], and ≥ 64 mmol/mol [8%])[16–19] and examined the relationship between higher HbA_{1c} SD quintile relative to the lowest quintile of SD on dementia risk. Each set included three models: (1) adjusted for age (as timescale), sex, race, and ethnicity; (2) further adjusted for baseline health conditions, myocardial infarction, peripheral artery disease, neuropathy, nephropathy, stroke, retinopathy, and prior hyperosmolarity and ketoacidosis; and (3) additionally adjusted for the number of HbA_{1c} measures available.

To explore the potential for differences in the associations between glycemic variation and dementia hazard by sex or race and ethnicity, we examined the associations between glycemic SD and coefficient of variation on dementia hazard stratified by these characteristics. Finally, in a series of sensitivity analyses, we repeated our original models examining the associations between glycemic SD and coefficient of variation on dementia hazard varying the number of years during which glycemic control was measured to 5, 7, and 10 years (maintaining a 2-year lag between exposure and outcome periods). We used SAS, version 9.4, for all analyses. We used the Strengthening the Reporting of Observational Studies in Epidemiology reporting guidelines for this article.

RESEARCH IN CONTEXT

1. **Systematic review**: We reviewed the literature using traditional (e.g., PubMed) sources and meeting abstracts and presentations. Although type 2 diabetes is associated with an increased risk of dementia, the contribution of glycemic control to this increased risk is unknown. We therefore examined the association between glycosylated hemoglobin A_{1c} (HbA_{1c}) variability and dementia risk.
2. **Interpretation**: In > 170,000 people > 50 years of age with type 2 diabetes, greater HbA_{1c} variability was associated with a statistically significant elevated risk of dementia and this was most pronounced among those with the lowest mean HbA_{1c}. This suggests that HbA_{1c} variability can be a marker of dementia risk.
3. **Future directions**: More work is required to understand how glycemic variability may act as a marker for dementia risk and whether this is a modifiable factor.

3 | RESULTS

There were a total of 171,964 people in the analytic sample, of whom 15,450 (9%) developed dementia (Table 1) over a mean follow-up of 5.9 years (SD = 4.6). The mean age at study entry was 61.1 years (SD = 9.1) and 48% of participants were women. Approximately 49% of the sample were White with most of the remaining sample identifying as Asian (19%), Hispanic (15%), or Black (9%). The mean

TABLE 1 Baseline characteristics of cohort.

Variables	Overall *n* (%)	Women *n* (%)	Men *n* (%)
n	171,964	82,559	89,405
Mean age at baseline (SD) (years)	61.1 (9.1)	61.5 (9.4)	60.8 (8.9)
Race and ethnicity			
White	84,822 (49)	38,425 (47)	46,397 (52)
Black	15,823 (9)	8747 (11)	7076 (8)
Hispanic	25,828 (15)	12,811 (16)	13,017 (15)
Asian	33,705 (19)	16,580 (20)	17,125 (19)
Other	10,087 (6)	5317 (6)	4770 (5)
Missing	1699 (1)	679 (1)	1020 (1)
Diabetes complications at baseline			
Coronary heart disease	6934 (4)	3016 (4)	3918 (4)
Peripheral artery disease	7357 (4)	2946 (4)	4411 (5)
Stroke	4282 (2)	1917 (2)	2365 (3)
Neuropathy	25,842 (15)	13,548 (16)	12,294 (14)
Nephropathy	19,615 (11)	8,844 (11)	10,771 (12)
Retinopathy	20,844 (12)	9948 (12)	10,896 (12)
Reason for end of follow-up			
Death	26,026 (15)	11,152 (14)	14,874 (17)
Dementia	15,450 (9)	8,390 (10)	7060 (8)
Membership dropout	31,603 (18)	14,821 (18)	16,782 (19)
Administrative censoring	98,885 (58)	48,196 (58)	50,689 (57)
Mean age at dementia diagnosis (SD) (years)	80.8 (7.8)	81.3 (7.8)	80.2 (7.7)
Mean number of HbA_{1c} measures in first 3-year exposure period (SD)	6.2 (2.3)	6.3 (2.3)	6.2 (2.3)
Mean HbA1c in first 3-year exposure period (SD)	7.3 (1.3)	7.33 (1.3)	7.3 (1.3)

Abbreviations: HBA_{1c}, glycosylated hemoglobin A_{1c}; SD, standard deviation.

number of HbA_{1c} values available for each participant in the first 3 years was 6.2 (SD = 2.3). The mean HbA_{1c} for each participant in the first 3 years was 7.4% (SD = 1.33). Table 2 presents the sample's various operationalizations of HbA_{1c} variability and their definitions. The mean SD of HbA_{1c} for each participant was 0.86% and the mean coefficient of variation was 0.11.

3.1 | Associations between various metrics of variability measures and dementia hazard

Table 3 presents the associations of the various measures of HbA_{1c} variability and dementia risk adjusted for age, sex, and race and ethnicity. Greater HbA_{1c} variability was associated with greater hazard of dementia when measured using SD (adjusted hazard ratio [aHR] = 1.15 [95% confidence interval (CI): 1.12, 1.17]), SD adjusted for number of HbA_{1c} measurements (aHR = 1.16 [95% CI: 1.14, 1.19]), coefficient of variation (aHR = 2.56 [95% CI: 2.14, 3.06]), *z* scored coefficient of variation (aHR = 1.08 [95% CI: 1.07, 1.10]), and average real variability (aHR = 1.10 [95% CI: 1.09, 1.11]). The hazard estimates were minimally altered by the addition of baseline health conditions, including peripheral artery disease, nephropathy, neuropathy, retinopathy, stroke, myocardial infarction, and prior hyperosmolarity and ketoacidosis.

3.2 | Associations between degree of variability and dementia hazard

Table 3 presents the associations between each SD and coefficient of variation quintile and dementia hazard. The sample characteristics of participants in each of the quintiles of SD and coefficient of variation are presented in Tables S2 and S3 in supporting information, respectively. Relative to being in the lowest quintile of HbA_{1c} SD, the hazard of dementia increased as SD increased. In fully adjusted models, relative to those in the lowest SD quintile, the hazard of dementia in those in the second quintile was 1.13 (95% CI 1.07, 1.19%), 1.26 (95% CI 1.20, 1.33) for those in the third quintile, 1.37 (95% CI 1.30, 1.44) for those in the fourth quintile, and 1.46 (95% CI 1.39, 1.54) for those in the highest quintile of SD. Relative to the lowest CV quintile, those in the second, third, fourth, and fifth quintiles had greater hazard of

TABLE 2 HbA_{1c} variation during the exposure period using different operationalizations.

Measure	What it captures	Mean	Standard deviation	Range
Standard deviation	For each person, the difference between each HbA_{1c} measurement and the average HbA_{1c} measurement during the exposure period	0.86	0.77	0–8.05
Standard deviation adjusted for *N* observations	For each person, the standard deviation of HbA_{1c} adjusted for number of HbA_{1c} measurements during the exposure period	0.77	0.69	0–6.99
Coefficient of variation	For each person, the standard deviation of HbA_{1c} divided by their mean HbA_{1c} during the exposure period	0.11	0.09	0–0.86
Z scored coefficient of variation	Scales the coefficient of variation to the sample so that zero is the average coefficient of variation in the sample and a one-unit change represents one standard deviation change	0	1.00	−1.27 to 8.97
Average real variability	The average of absolute difference in consecutive HbA_{1c} measurement for individual	1.57	1.41	0–18.16

Abbreviation: HBA_{1c}, glycosylated hemoglobin A_{1c}.

TABLE 3 Associations between various metrics of HbA_{1c} variation and dementia hazard.

	HR (95% CI) adjusted for baseline age, race, ethnicity, and sex	HR (95% CI) adjusted for age, race, sex, and baseline health conditions[a]	HR (95% CI) adjusted for age, race, sex, baseline health conditions[a], and number of HbA_{1c} measurements
Standard deviation (SD)			
Continuous SD	1.15 (1.12, 1.17)	1.15 (1.12, 1.17)	1.15 (1.12, 1.17)
Quintiles of SD			
Quintile 1	Reference	Reference	Reference
Quintile 2	1.14 (1.08, 1.20)	1.13 (1.07, 1.19)	1.13 (1.07, 1.19)
Quintile 3	1.29 (1.22, 1.35)	1.26 (1.19, 1.33)	1.26 (1.20, 1.33)
Quintile 4	1.40 (1.33, 1.48)	1.37 (1.30, 1.44)	1.37 (1.30, 1.44)
Quintile 5	1.48 (1.41, 1.56)	1.46 (1.38, 1.54)	1.46 (1.39, 1.54)
Standard deviation (adjusted for n observations)	1.16 (1.14, 1.19)	1.16 (1.13, 1.19)	1.16 (1.13, 1.19)
Coefficient of variability (CV)			
Continuous CV (%)	1.009 (1.008, 1.011)	1.009 (1.008, 1.011)	1.009 (1.008, 1.011)
Continuous CV	2.56 (2.14, 3.06)	2.57 (2.14, 3.08)	2.54 (2.12, 3.05)
Quintiles of CV			
Quintile 1	Reference	Reference	Reference
Quintile 2	1.16 (1.11, 1.23)	1.15 (1.09, 1.21)	1.15 (1.09, 1.21)
Quintile 3	1.29 (1.23, 1.36)	1.26 (1.20, 1.33)	1.26 (1.20, 1.33)
Quintile 4	1.40 (1.33, 1.47)	1.36 (1.29, 1.43)	1.36 (1.29, 1.44)
Quintile 5	1.42 (1.35, 1.50)	1.40 (1.33, 1.48)	1.40 (1.33, 1.48)
Z scored CV (continuous)	1.08 (1.07, 1.10)	1.08 (1.07, 1.10)	1.08 (1.06, 1.10)
Average real variability (continuous)	1.10 (1.09, 1.11)	1.09 (1.08, 1.10)	1.10 (1.09, 1.11)

Abbreviations: HBA_{1c}, glycosylated hemoglobin A_{1c}; CI, confidence interval; HR, hazard ratio; SD, standard deviation.
[a]Each of the following baseline health conditions was adjusted for in the model: history of hyperosmolality and ketoacidosis events, myocardial infarction, peripheral artery disease, neuropathy, nephropathy, stroke, retinopathy, and prior hyperosmolarity and ketoacidosis.

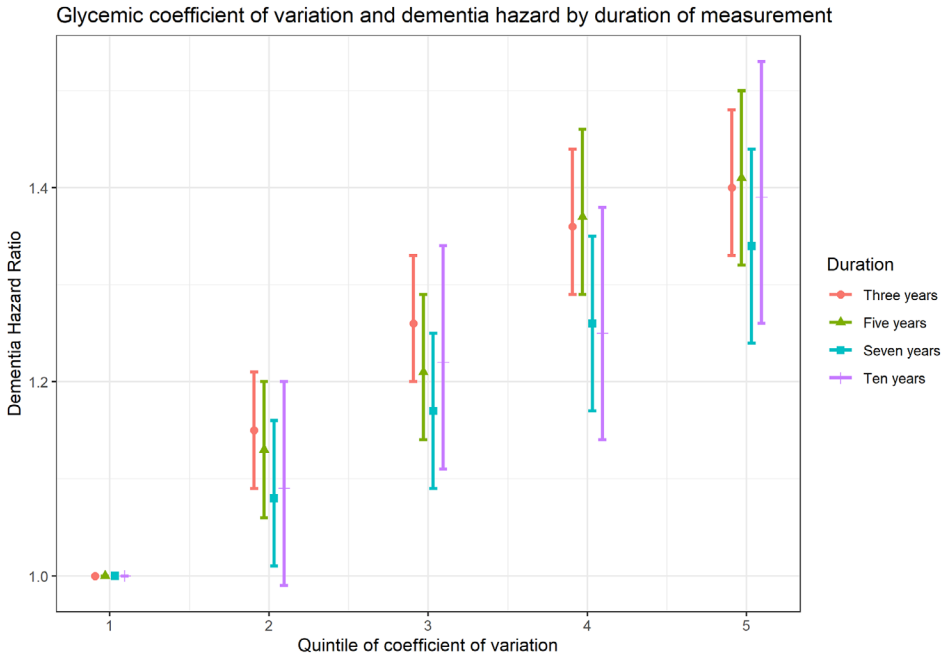

FIGURE 1 Associations between quintile standard deviation of glycosylated hemoglobin A_{1c} (HbA_{1c}) and dementia hazard by duration of exposure and follow-up.

dementia (aHR = 1.15, 1.26, 1.36, and 1.40, respectively). In sensitivity analyses varying the duration of exposure (5, 7, 10 years), we found the cohorts to have broadly similar characteristics (Table S4 in supporting information) and patterns of association between greater HbA_{1c} variability and dementia hazard (Figure 1; Table S5, Figure S1 in supporting information).

3.3 | Associations between degree of variability and dementia hazard by mean HbA_{1c}

To further understand whether the association between increased variability and increased dementia risk was modified by mean glycemic control, we examined the association between quintiles of HbA_{1c} SD and dementia hazard by tertile of mean HbA_{1c}. In the fully adjusted models (Figure 2, Table S6 in supporting information), we found that—relative to the lowest SD quintile—greater HbA_{1c} SD was broadly associated with greater hazard of dementia in the < 6% (overall $P = 0.0004$) and 6% to 8% (overall $P < 0.0001$) HbA_{1c} categories but not in those with a mean $HbA_{1c} \geq 8\%$ (overall $P = 0.42$). We identified similar patterns between greater glycemic variability and dementia hazard when stratified by sex (Table S7, Figures S2, S3 in supporting information) and race and ethnicity (Table S8, Figures S4, S5 in supporting information).

4 | DISCUSSION

In this diverse sample of > 170,000 people with type 2 diabetes, we found that greater HbA_{1c} variability was associated with greater dementia risk across sex, racial, and ethnic subgroups, regardless of the way variability was measured. Measured using either SD or coefficient of variation, people in the second to fifth quintile had 20% to 50% greater risk of dementia than those in the first quintile of HbA_{1c} variability (i.e., those with least variability). This association persisted even after accounting for age, race, ethnicity, sex, baseline health conditions, and number of HbA_{1c} measurements. Furthermore, the association between greater HbA_{1c} variability and dementia risk appeared to be modified by long-term glycemic control (mean HbA_{1c}) with the harmful associations between variability and dementia most pronounced in those with mean HbA_{1c} concentrations < 6%. These results support current clinical advice to reduce glycemic variability[20] and highlight that those with the lowest HbA_{1c} may experience the worst effects of glycemic variability.

The negative effects of glycemic variability on symptoms, mortality, and conventional micro- and macrovascular complications have been well established.[10,20] Increased HbA_{1c} variability has been associated with poorer performance on cognitive tests[21–23] but only recently have studies begun to focus on the associations between glycemic variability and dementia.[4,7] Two recent studies, using electronic medical records in Taiwan[7] ($n = 16{,}706$, mean age ≈ 70 years) and the United Kingdom[4] ($n = 457{,}902$, mean age ≈ 65) have been consistent in their finding that those with the greatest HbA_{1c} variability had the greatest dementia risk. However, we are unaware of previous work reporting that the association between glycemic variability and dementia risk is dependent upon overall glycemic control.

Our finding that greater HbA_{1c} variability was associated with elevated dementia risk among those with the lowest mean HbA_{1c} appears counterintuitive. Understanding the reasons underlying this association is challenging. Those with very low HbA_{1c} are extremely

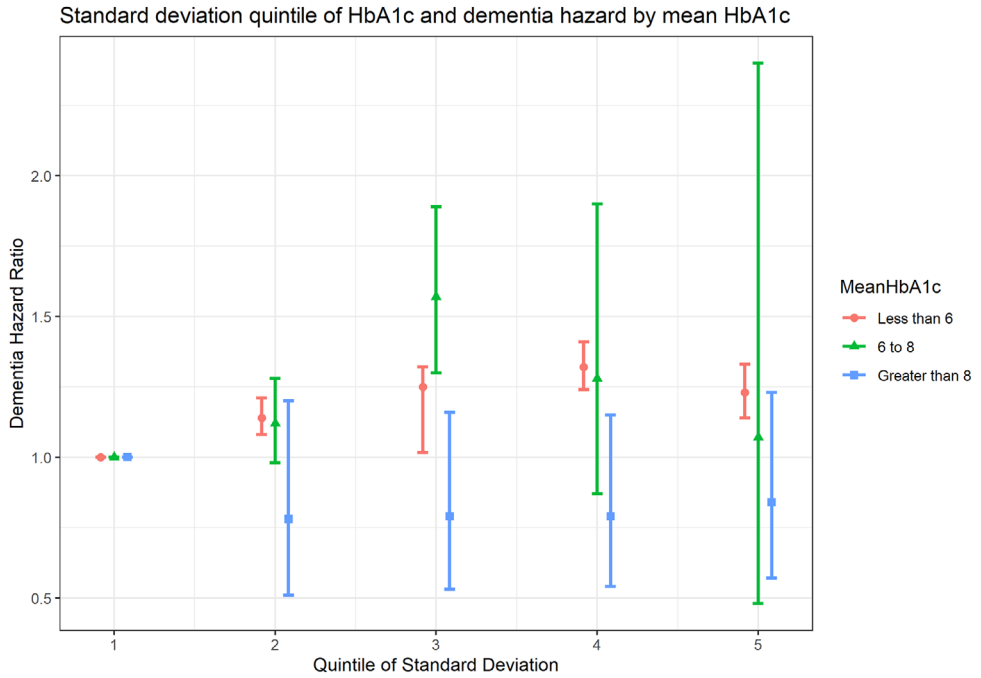

FIGURE 2 Associations between quintile standard deviation of glycosylated hemoglobin A_{1c} (HbA_{1c}) and dementia hazard by mean HbA_{1c}.

heterogenous and can include people newly diagnosed with type 2 diabetes as well as people with longstanding type 2 diabetes that have other dementia risk factors such as frailty or malnourishment.[24] In previous work, those with the extremes (lowest and highest) of HbA_{1c} had the highest risk of severe self-reported hypoglycemia.[24] Although we attempted to remove the influence of severe hypoglycemic events (requiring hospital admission) from our analyses, it remains likely that those with low HbA_{1c} concentrations frequently entered less severe hypoglycemic ranges that did not require hospital admission. As hypoglycemia is a well-established risk factor for dementia,[25,26] it is possible that frequent excursions into hypoglycemia contribute to the greater risk of dementia we see in those with low mean HbA_{1c} but greater variability. Conversely, greater HbA_{1c} variability was not associated with increased dementia risk in those with the highest mean HbA_{1c} concentrations. In this group, it is likely that greater variability included glycemic excursions into normoglycemic ranges, which we have demonstrated in previous work using this sample to be associated with lower dementia risk.[27] It is therefore likely that some of the dementia risk associated with greater glycemic variability is offset by benefits of being in normoglycemic ranges.

As the mechanisms underlying the associations between diabetes and dementia more broadly remain unclear, the pathways linking HbA_{1c} variability and dementia risk also remain to be understood. Glycemic variability contributes to proinflammatory pathways and greater markers of oxidative stress leading to downstream vascular pathology including cardiovascular events.[28] Additionally, there is increasing interest in the contribution of glycemic variability to epigenetic changes that lead to transcriptional changes in pathways moderating inflammation, oxidative stress, and angiogenesis in people with type 2 diabetes.[29] Although the focus of this work has been on examining cardiovascular outcomes, similar pathways appear to be involved in diabetic peripheral neuropathy.[30] This may be relevant for the understanding of the pathways contributing to dementia risk in people with type 2 diabetes, with both vascular and neuropathic pathways implicated.[31–33] The results of a recent study of almost 700 people without dementia support the potential involvement of multiple pathways.[34] In this study, which included people with and without diabetes, the authors reported that greater fasting glucose variability was associated with greater burden of white matter hyperintensities and insoluble amyloid beta. Furthermore, mediation analyses suggested that these biomarkers partially mediated the associations between glycemic variability and cognition.[34] Such studies highlight the need to better understand the mechanisms linking glycemic variability and brain health.

This study has a number of strengths. We used comprehensive, high quality electronic health record data in a cohort with low turnover. This enabled us to capture multiple longitudinal HbA_{1c} measures, comorbidities, and incident dementia. Our sample also had a large proportion of non-White participants, enabling us to examine associations in different race and ethnic groups. Furthermore, we used multiple operationalizations of glycemic variability and varied our duration of follow-up to enhance confidence in our results.

This study also has some limitations. Our secondary use of electronic medical records means that we did not have information regarding age at type 2 diabetes onset or duration of disease. We also lacked information regarding other relevant dementia risk factors such as frailty, obesity/malnourishment, or smoking. We cannot rule out that underreported cognitive decline leading up to a dementia diagnosis could have reduced patients' ability to self-manage and in turn increased glycemic variability. However, we reduced the likelihood of

this by including a 2-year lag between the exposure period and the follow-up period. We were also unable to examine specific dementia subtypes due to the absence of access to neuroimaging or neuropathological data. HbA_{1c} is not an ideal marker of true glycemic variation as it may overestimate glycemia relative to mean glucose among Black patients[35] and may be a poor marker of glycemia among patients with end stage renal disease, anemia, or hemoglobinopathies.[36] However, continuous glucose monitoring was extremely uncommon in people with type 2 diabetes during the observation window for this study. As continuous glucose monitoring becomes more commonly used in clinical practice, this will be more ably incorporated into large studies such as this to better understand the contribution of glycemic control to dementia risk. A further limitation is an understanding of the contribution of glucose-lowering drugs to the associations we report. It is possible that certain agents such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors may have a more stabilizing contribution to glycemic variability than basal-bolus insulin regimens.[37] However, with the advent of very short acting insulins and technologies such as closed-loop control continuous insulin infusions, these theories require further evaluation.

In conclusion, in this large cohort of people in mid to later life, we found greater glycemic variability was associated with greater dementia risk. This association was greatest in those with mean HbA_{1c} concentrations < 6%. Our results suggest that glycemic variability may be a marker for dementia risk.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest. Author disclosures are available in the supporting information.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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