Diabetologia (2020) 63:85–94
https://doi.org/10.1007/s00125-019-04986-8

ARTICLE

Association between visit-to-visit variability of HbA_{1c} and cognitive decline: a pooled analysis of two prospective population-based cohorts

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Received: 17 June 2019 / Accepted: 30 July 2019 / Published online: 4 September 2019

Abstract

Aims/hypothesis The aim of this study was to investigate the association between visit-to-visit variability in HbA_{1c} and cognitive function decline in the elderly population.

Methods We performed a pooled analysis of two prospective population-based cohorts (the Health Retirement Study [HRS] and the English Longitudinal Study of Ageing [ELSA]). Cognitive function, including memory and executive function, were assessed at baseline and every 2 years, while HbA_{1c} levels were assessed at baseline and every 4 years. Visit-to-visit variability (VVV) in HbA_{1c} was calculated using the CV, SD and variation independent of the mean (VIM) during the follow-up period. Linear mixed models were used to evaluate the association between HbA_{1c} variability and cognitive function decline with adjustment for demographics, mean HbA_{1c}, education, smoking, alcohol consumption, BMI, baseline hypertension, baseline diabetes status and HDL-cholesterol.

Results The study enrolled 6237 participants (58.23% women, mean age 63.38 ± 8.62 years) with at least three measurements of HbA_{1c}. The median follow-up duration was 10.56 ± 1.86 years. In the overall sample, compared with the lowest quartile of HbA_{1c} variability, participants in the highest quartile of HbA_{1c} variability had a significantly worse memory decline rate (−0.094 SD/year, 95% CI −0.185, −0.003) and executive function decline rate (−0.083 SD/year, 95% CI −0.125, −0.041), irrespective of mean HbA_{1c} values over time. Among individuals without diabetes, each 1-SD increment in HbA_{1c} CV was associated with a significantly higher rate of memory *z* score decline (−0.029, 95% CI −0.052, −0.005) and executive function *z* score decline (−0.049, 95% CI −0.079, −0.018) in the fully adjusted model.

Conclusions/interpretation We observed a significant association between long-term HbA_{1c} variability and cognitive decline among the non-diabetic population in this study. The effect of maintaining steady glucose control on the rate of cognitive decline merits further investigation.

Keywords Cognitive decline · Cognitive function · Epidemiology · Glucose variability · HbA_{1c}

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00125-019-04986-8) contains peer-reviewed but unedited supplementary material, which is available to authorised users.

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Research in context

What is already known about this subject?

- Evidence from longitudinal studies has indicated that HbA_{1c} variability is associated with the risk of mortality and cardiovascular disease among diabetic individuals
- An association between HbA_{1c} variability and cognitive decline is not well established

What is the key question?

- Is there an association between visit-to-visit HbA_{1c} variability and long-term cognitive decline in the general population?

What are the new findings?

- We observed a significant association between long-term HbA_{1c} variability and cognitive decline, irrespective of mean HbA_{1c} values, among the non-diabetic population, using data from the Health Retirement Study and the English Longitudinal Study of Ageing

How might this impact on clinical practice in the foreseeable future?

- Measuring long-term visit-to-visit variability in HbA_{1c} could be helpful for predicting the risk for cognitive decline in the non-diabetic population, and interventions targeting HbA_{1c} variability may help reduce the burden of cognitive decline

Abbreviations

CVD	Cardiovascular disease
ELSA	English Longitudinal Study of Ageing
HRS	Health and Retirement Study
MICE	Multiple imputation of chained equation
VIM	Variation independent of the mean
VVV	Visit-to-visit variability

Introduction

Dementia is one of the most common neurodegenerative diseases worldwide [1] and results in poor quality of life among the impacted individuals and a serious public health burden for society. Cognitive decline occurs over a long period prior to dementia and is important for the monitoring and early intervention of cognitive deterioration [2]. Thus, the identification of risk factors for cognitive decline could contribute to screening individuals who are at risk of dementia.

Long-term variability in HbA_{1c} has been proposed as an important risk factor related to mortality [3–6], cardiovascular disease (CVD) [7–9], nephropathy [10–12] and other complications [13–17] independent of HbA_{1c} levels. Recently, there has been considerable interest in the emerging association between glycaemic variability and decline in cognitive function [18–22]. Although the previous studies mainly focused on individuals with type 2 diabetes, evidence from the general population (especially people without diabetes) is still scarce.

The Health and Retirement Study (HRS) and the English Longitudinal Study of Ageing (ELSA) were two sister cohorts that included a large and diverse population (age ≥ 50 years), and in these studies, repeated measurements of HbA_{1c} and cognitive assessments at set time intervals were performed. In this study, we aimed to identify the relationship between visit-to-visit variability (VVV) in HbA_{1c} and the rate of cognitive decline in two elderly populations with normal cognition at baseline. We hypothesised that a higher variability in HbA_{1c} would be associated with accelerated cognitive decline in the elderly population.

Methods

Study population In this study, we used data from Wave 2006 to Wave 2016 of the HRS and Wave 2 (2002–2003) to Wave 8 (2014–2015) of the ELSA, two prospective and nationally representative cohorts conducted in the USA and England. Detailed descriptions of the objective, design and methods of these two cohorts have been described elsewhere [23, 24]. The time of the first HbA_{1c} measurement was considered as the baseline for all participants. A flow chart of participant selection for the present study is shown in Fig. 1. In the HRS, a total of 3314 participants had three measurements of HbA_{1c} from Wave 2006 to Wave 2016. Of these, 17 participants were excluded owing to lack of cognitive measurement at baseline, and 43 participants were excluded because of a history of dementia and/or Alzheimer's disease at baseline. In the ELSA, a total of 2993 participants had three or four measurements of HbA_{1c} from Wave 2 to Wave 8. Of these participants, ten were excluded due to lack of cognitive assessment at baseline ($n = 5$) or a history of dementia or Alzheimer's disease at baseline ($n = 5$). The remaining participants from

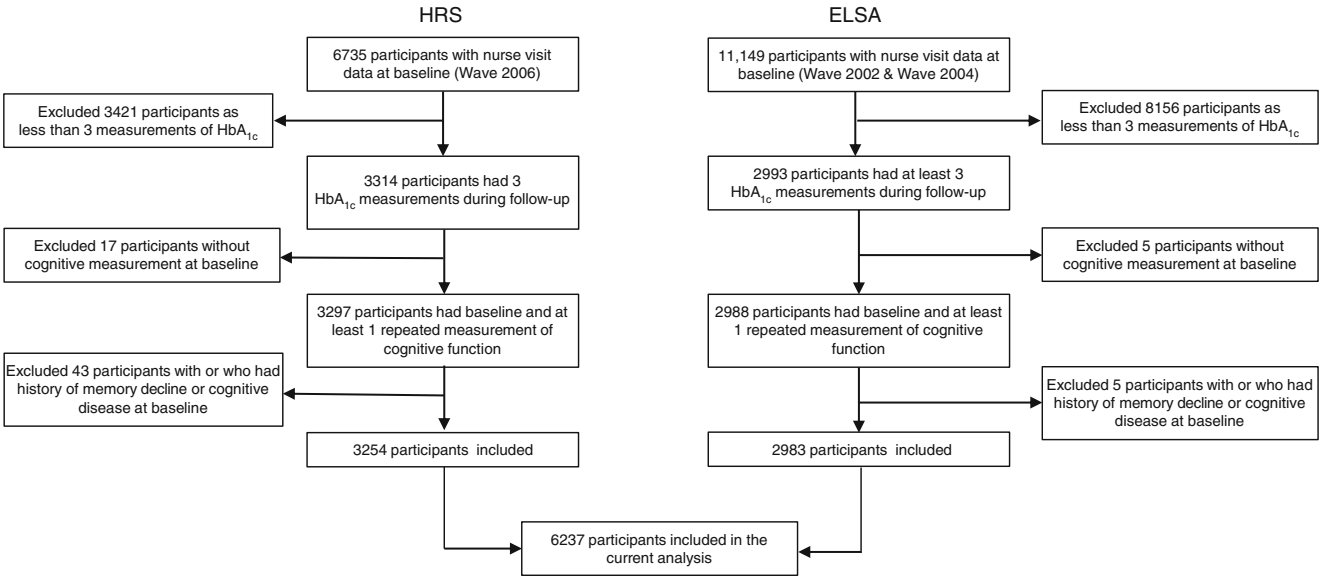

Fig. 1 Flow chart of inclusion and exclusion of the participants in the current study

the HRS ($n = 3254$) and ELSA ($n = 2983$) with complete HbA_{1c} measurements, baseline cognitive assessments and at least one reassessment of cognitive function were included in the analyses.

This study conformed to the guidelines of the Declaration of Helsinki. Institutional Review Board approval of the HRS was obtained through the University of Michigan and the National Institute on Aging. The ELSA was approved by the London Multicentre Research Ethics Committee. Informed consent was obtained from all participants in both cohorts.

Measurement of HbA_{1c} and HbA_{1c} variability Blood sample collection and measurement of HbA_{1c} in the HRS and ELSA were conducted every 4 years. Details of the process have been described elsewhere [25, 26]. National Health and Nutrition Examination Survey (NHANES)-equivalent assay values of HbA_{1c} in the HRS were used in our study as recommended [26]. In this study, HbA_{1c} was reported as the percentage of the erythrocyte haemoglobin that was glycated.

The mean HbA_{1c} value was calculated based on the mean of all visits for each participant. The VVV in HbA_{1c} was primarily defined as the intra-individual CV across visits. Due to the lack of an appropriate gold-standard measurement for HbA_{1c} VVV, we calculated two other metrics, including the SD and the variation independent of the mean (VIM). These calculation processes have been previously described [27].

Measurement of cognitive function Cognitive function was assessed every 2 years in both the HRS and ELSA using a variety of tests, including self-rated memory, immediate and delayed word recall, and backward count. In this study, we used scores of memory test and executive function as outcomes, which were assessed in both the HRS and ELSA. We created a total memory recall score ranging from 0 to 20 by summing the scores of immediate and delayed recall tests. A higher score on the memory recall test indicated better memory performance. Executive function was assessed by a verbal fluency task in which participants were required to orally list as many animal names as they could in 60 s. The score of verbal fluency was calculated as the total count of words excluding repeated and non-animal words, and higher scores indicated better executive function. Both immediate and delayed word recall tests and verbal fluency tests have been shown to have good validity and consistency [28, 29].

The standardised z score for the cognitive test scores at each wave was calculated by subtracting the mean score at baseline and dividing the value by the SD of the baseline scores. Thus, a z score of 1 means the performance on the particular cognitive test was 1 SD above the mean score at baseline.

Covariates The covariates included demographic and clinical variables. The demographic variables included age, sex, educational level (college or above), BMI, living arrangement (living alone or not), current cigarette smoking, and current alcohol consumption (alcohol consumption at least 1 day per week). Clinical variables included history or presence of CVD (myocardial infarction, CHD, revascularisation, stroke and peripheral arterial disease of heart failure), hypertension, diabetes, lung disease and cancer. Depressive symptoms were measured using an 8-item version of the Center for Epidemiologic Studies Depression Scale (CES-D). Mean systolic BP across visits was also calculated for each participant. Baseline HDL, tested in both the HRS and ELSA, was also included.

Statistical analysis All participants were categorised into quartiles of CV of HbA_{1c}. Categorical variables are presented as numbers (proportions), and continuous variables are presented as the mean ± SD. We used the Cochran–Armitage trend test for categorical variables and linear regression for continuous variables to test the significance of the trends across the quartiles.

We used a multivariable linear mixed-effect model (a widely used model to address repeated measurement data) to evaluate the longitudinal association between VVV in HbA_{1c} and cognitive decline. In the current study, the intercept and slope were both fitted as random effects to address the inter-individual differences at baseline and different rates of cognitive function change during the follow-up period. A negative β value for the interaction item of time and CV of HbA_{1c} indicated that a 1-unit increment of CV of HbA_{1c} was associated with a faster rate of decline with increasing time in the study. Two models were used as follows: Model I included the CV of HbA_{1c} (the lowest quartile as the reference group), time (years from baseline), interaction item of time and CV of HbA_{1c}, mean HbA_{1c} value, interaction item of time and mean HbA_{1c} value, age (continuous variable) and sex (male or female). Model II included all covariates in Model I and was additionally adjusted for education, current smoking status (yes or no), alcohol consumption status (yes or no), BMI (continuous variable), hypertension (yes or no), diabetes (yes or no) and HDL (continuous variable). The p value for the trend was calculated by using the median value in each quartile of the HbA_{1c} CV. The effect of each SD increment in HbA_{1c} CV was also calculated by modelling HbA_{1c} CV as a continuous variable. Subgroup analysis was conducted by stratifying the participants into two groups based on their status of diabetes at baseline: diabetes and non-diabetes. The effects were calculated within each cohort separately and were pooled using a random-effects model. Heterogeneity of β values between the two cohorts was evaluated by the Cochran's Q test and I^2 statistic.

The multiple imputation of chained equations (MICEs) method was also used to impute missing data from the cognitive assessments during follow-up. Baseline characteristics, including age, sex, education, BMI, smoking status, alcohol consumption status, diabetes, hypertension and baseline cognitive scores, were used to impute the missing values. We created 20 imputed datasets and pooled the results using the R package 'MICE' for each model. The imputation quality was assessed by comparing the imputed data with the original data using density plots. Sensitivity analyses were conducted as follows: (1) modelling SD or VIM instead of CV as VVV metrics of HbA_{1c}; (2) repeating analysis with all available data without multiple imputations; (3) removing the participants with three HbA_{1c} measurements in the ELSA from the analysis.

All statistical analyses were performed using R software 3.4.1 (R Foundation, Vienna, Austria). The R package 'lme4' was used to perform the linear mixed-effect model [30]. Two-sided p values less than 0.05 were considered statistically significant.

Results

Baseline characteristics A total of 6237 participants (3254 from the HRS and 2983 from the ELSA) were included in the analysis. The mean age at baseline was 64.55 ± 9.11 years in the HRS and 62.03 ± 7.79 years in the ELSA. A total of 1974 (60.66%) participants in the HRS and 1658 (55.58%) participants in the ELSA were female. The mean follow-up times were 10.48 ± 0.63 years and 10.56 ± 1.86 years for the HRS and ELSA, respectively. A comparison of baseline characteristics between participants included and not included is shown in electronic supplementary material (ESM) Table 1.

Table 1 presents the characteristics of the included participants across quartiles of HbA_{1c} CV. Participants in the highest quartile of HbA_{1c} CV had a higher BMI, baseline HbA_{1c}, mean HbA_{1c} across visits, mean systolic BP, prevalence of hypertension and diabetes, and a lower education level and HDL in both the HRS and ELSA. Participants tended to have a lower baseline cognitive function (both total recall score and verbal fluency score) as the quartiles of HbA_{1c} CV increased (p for trend <0.001).

Association of HbA_{1c} variability with cognitive decline in the overall sample As listed in Tables 2 and 3, a 1% increase in the mean HbA_{1c} value was associated with an increased rate of decline in the memory z score (−0.089 SD/year, 95% CI −0.165, −0.014) and executive function z score (−0.058 SD/year, 95% CI −0.111, −0.004) in Model I. This association was attenuated after further adjustment for covariates in Model II but remained significant for memory function (−0.041, 95% CI −0.071, −0.012).

We observed a potential dose–response relationship between the quartiles of HbA_{1c} CV and the rate of cognitive decline. Participants in the highest quartile had a significantly accelerated rate of memory z score decline (−0.100 SD/year, 95% CI −0.197, −0.001) and executive function z score decline (−0.081 SD/year, 95% CI −0.126, −0.037) compared with that of the lowest quartile of HbA_{1c} CV (p for trend <0.05). The results remained significant when further adjusted for education level, baseline BMI, smoking status, alcohol consumption status, disease status at baseline (including hypertension and diabetes) and HDL at baseline (ESM Fig. 1). When modelled as a continuous variable, a 1-SD increment in HbA_{1c} CV was associated with both a higher rate of memory z score decline (−0.032 SD/year, 95% CI −0.049, −0.015) and executive function z score decline (−0.034 SD/year, 95% CI

Table 1 Baseline characteristics of the HRS and ELSA

Baseline characteristics	Total	Quartiles of visit-to-visit variability in HbA_{1c}				*p* for trend
		Quartile 1	Quartile 2	Quartile 3	Quartile 4	
HRS						
Range of HbA_{1c} CV, %	0.05–51.15	<3.36	≥3.36 & <5.48	≥5.48 & <8.42	≥8.42	–
No. of participants	3254	814	812	814	814	–
Mean follow-up time, years	10.48 ± 0.63	10.49 ± 0.64	10.46 ± 0.63	10.54 ± 0.64	10.41 ± 0.61	0.548
Female, %	1974 (60.66)	501 (61.55)	505 (62.19)	488 (59.95)	480 (58.97)	0.529
Age, years	64.55 ± 9.11	64.80 ± 8.76	64.50 ± 9.12	65.50 ± 9.09	64.50 ± 9.01	0.922
BMI, kg/m^2	29.68 ± 7.67	28.91 ± 7.12	28.95 ± 5.65	29.53 ± 9.37	31.52 ± 8.29	<0.001
Education, %	978 (30.06)	277 (34.03)	272 (33.50)	245 (30.10)	184 (22.60)	<0.001
Current smoker, %	401 (12.32)	106 (13.02)	78 (9.61)	105 (12.90)	112 (13.76)	0.199
Current alcohol consumer, %	1814 (55.75)	482 (59.21)	471 (58.00)	464 (57.00)	397 (48.77)	<0.001
Living alone, %	1110 (34.11)	294 (36.12)	283 (34.85)	271 (33.29)	262 (32.19)	0.117
Hypertension, %	2094 (64.35)	494 (60.69)	466 (57.39)	531 (65.23)	603 (74.08)	<0.001
Diabetes, %	651 (20.01)	58 (7.13)	59 (7.27)	136 (16.71)	398 (48.89)	<0.001
CVD, %	603 (18.53)	132 (16.22)	132 (16.26)	152 (18.67)	187 (22.97)	<0.001
Lung disease, %	253 (7.78)	67 (8.23)	57 (7.02)	69 (8.48)	60 (7.37)	0.654
Cancer, %	358 (11.00)	80 (9.83)	94 (11.58)	99 (12.16)	85 (10.44)	0.424
SBP, mmHg	129.82 ± 19.45	128.64 ± 19.29	127.93 ± 18.37	129.74 ± 19.73	132.99 ± 20.00	<0.001
Depressive symptoms, %	436 (13.40)	108 (13.27)	94 (11.58)	106 (13.02)	128 (15.72)	0.382
HDL, mmol/l	1.44 ± 0.42	1.47 ± 0.43	1.48 ± 0.42	1.46 ± 0.42	1.35 ± 0.41	<0.001
Baseline HbA_{1c}, mmol/mol	40.0 ± 9.5	38.0 ± 5.2	37.6 ± 5.9	38.5 ± 7.1	44.4 ± 14.7	<0.001
Baseline $HbA_{1c,}$ %	5.77 ± 0.87	5.56 ± 0.44	5.54 ± 0.48	5.68 ± 0.62	6.32 ± 1.33	<0.001
Mean HbA_{1c}, mmol/mol	40.8 ± 8.7	38.0 ± 5.1	38.1 ± 5.2	39.7 ± 6.5	47.4 ± 12.1	<0.001
Mean HbA_{1c}, %	5.88 ± 0.79	5.57 ± 0.42	5.59 ± 0.40	5.76 ± 0.53	6.60 ± 1.08	<0.001
Baseline total recall score	10.66 ± 3.02	11.00 ± 3.09	10.81 ± 2.98	10.58 ± 2.94	10.25 ± 2.97	<0.001
Baseline verbal fluency score	18.27 ± 8.13	18.37 ± 6.92	18.74 ± 8.22	18.71 ± 9.18	17.32 ± 7.98	<0.001
ELSA						
Range of HbA_{1c} CV, %	0.01–43.56	<2.05	≥2.05 & <3.14	≥3.14 & <4.15	≥4.15	–
No. of participants	2983	746	740	751	746	–
Mean follow-up time, years	10.56 ± 1.86	10.05 ± 1.96	10.67 ± 1.81	10.70 ± 1.80	10.76 ± 1.80	<0.001
Female, %	1658 (55.58)	427 (57.24)	393 (53.11)	435 (57.92)	403 (54.02)	0.552
Age, years	62.03 ± 7.79	60.23 ± 7.57	62.11 ± 7.79	62.55 ± 7.74	63.22 ± 7.76	<0.001
Education, %	758 (25.41)	224 (30.03)	202 (27.30)	188 (25.03)	144 (19.30)	<0.001
BMI, kg/m^2	27.78 ± 4.71	27.29 ± 4.44	27.32 ± 4.50	27.53 ± 4.42	28.97 ± 5.24	<0.001
Current smoker, %	383 (12.84)	94 (12.60)	96 (12.97)	99 (13.18)	94 (12.60)	0.983
Current alcohol consumer, %	2255 (75.60)	575 (77.08)	562 (75.95)	585 (77.90)	533 (71.45)	0.051
Living alone, %	1003 (33.62)	262 (35.12)	244 (32.97)	238 (31.69)	259 (34.72)	0.328
Hypertension, %	1471 (49.31)	310 (41.55)	325 (43.92)	374 (49.80)	462 (61.93)	<0.001
Diabetes, %	189 (6.34)	9 (1.21)	10 (1.35)	19 (2.53)	151 (20.2)	<0.001
CVD, %	442 (14.82)	95 (12.73)	104 (14.05)	120 (15.98)	123 (16.49)	0.906
Lung disease, %	131 (4.39)	23 (3.08)	42 (5.68)	33 (4.39)	33 (4.42)	0.117
Cancer, %	160 (5.36)	49 (6.57)	29 (3.92)	40 (5.33)	42 (5.63)	0.275
SBP, mmHg	132.50 ± 17.35	130.75 ± 16.71	131.01 ± 17.10	132.32 ± 17.03	135.95 ± 18.08	<0.001
Depressive symptoms, %	348 (11.67)	92 (12.33)	94 (12.70)	72 (9.59)	90 (12.06)	0.518
HDL, mmol/l	1.55 ± 0.39	1.58 ± 0.40	1.57 ± 0.38	1.59 ± 0.39	1.48 ± 0.38	<0.001
Baseline HbA_{1c}, mmol/mol	37.3 ± 7.0	37.9 ± 3.9	36.7 ± 4.7	35.6 ± 4.4	39.2 ± 11.6	<0.001
Baseline HbA_{1c}, %	5.56 ± 0.64	5.57 ± 0.35	5.48 ± 0.37	5.40 ± 0.43	5.79 ± 1.06	<0.001
Mean HbA_{1c}, mmol/mol	39.8 ± 6.7	38.3 ± 3.8	38.4 ± 4.4	38.5 ± 4.1	43.9 ± 10.4	<0.001
Mean HbA_{1c}, %	5.79 ± 0.61	5.62 ± 0.33	5.63 ± 0.33	5.67 ± 0.40	6.22 ± 0.93	<0.001
Baseline total recall score	11.14 ± 3.10	11.30 ± 3.21	11.12 ± 3.06	11.12 ± 3.13	10.57 ± 2.92	<0.001
Baseline verbal fluency score	21.70 ± 6.27	22.08 ± 5.89	21.82 ± 6.20	21.67 ± 6.49	21.23 ± 6.47	0.009

Values are mean ± SD for continuous variables and number (%) for categorical variables. *P* values for trend were derived using univariate linear regression for continuous variables and Cochran–Armitage trend test for categorical variables

−0.084, −0.010) in the fully adjusted models. We did not observe the effect modification by sex in the current study (ESM Fig. 2).

HbA_{1c} variability and cognitive decline among participants with diabetes For diabetic participants (Fig. 2), each 1-SD increment in the CV of HbA_{1c} was not associated with an increased rate of memory *z* score decline (−0.028 SD/year, 95% CI −0.065, 0.008) or executive function *z* score decline (0.018 SD/year, 95% CI −0.029, 0.064) (Model II). When modelled as a categorical variable (ESM Table 2), the highest quartile of

Table 2 Association between mean HbA_{1c} level, visit-to-visit variability in HbA_{1c} and memory decline using linear mixed models

	Mean HbA_{1c}	Visit-to-visit variability in HbA_{1c}				*p* for trend	β per SD increment in HbA_{1c} variability
		Quartile 1	Quartile 2	Quartile 3	Quartile 4		
HRS							
Model I[a]	−0.128 (−0.154, −0.101)	0.000 (Ref)	−0.073 (−0.111, 0.005)	−0.092 (−0.166, −0.049)	−0.150 (−0.205, −0.072)	<0.001	−0.042 (−0.063, −0.021)
Model II[b]	−0.059 (−0.098, −0.020)	0.000 (Ref)	−0.092 (−0.155, −0.030)	−0.093 (−0.159, −0.025)	−0.143 (−0.209, −0.078)	0.002	−0.043 (−0.068, −0.018)
ELSA							
Model I[a]	−0.050 (−0.082, −0.018)	0.000 (Ref)	0.041 (−0.006, 0.258)	0.018 (−0.026, 0.062)	−0.050 (−0.098, −0.001)	0.030	−0.005 (−0.033, 0.023)
Model II[b]	−0.016 (−0.062, 0.030)	0.000 (Ref)	0.002 (−0.047, 0.051)	−0.019 (−0.073, 0.036)	−0.050 (−0.100, −0.001)	0.018	−0.025 (−0.044, −0.006)
Pooled results[c]							
Model I[a]	−0.089 (−0.165, −0.014)	0.000 (Ref)	−0.015 (−0.127, 0.096)	−0.031 (−0.064, 0.002)	−0.100 (−0.197, −0.001)	0.067	−0.028 (−0.011, 0.001)
Model II[b]	−0.041 (−0.071, −0.012)	0.000 (Ref)	−0.042 (−0.134, 0.050)	−0.054 (−0.127, 0.189)	−0.094 (−0.185, −0.003)	0.019	−0.032 (−0.049, −0.015)

[a] Model I adjusted for age, sex and years from baseline

[b] Model II adjusted for covariates in Model I plus education, baseline BMI, smoking, alcohol consumption, baseline hypertension, baseline diabetes and HDL

[c] Results from two cohorts were pooled using the random-effects model

Table 3 Association between mean HbA_{1c} level, visit-to-visit variability in HbA_{1c} and executive function decline using linear mixed models

	Mean HbA_{1c}	Visit-to-visit variability in HbA_{1c}				*p* for trend	β per SD increment in HbA_{1c} variability
		Quartile 1	Quartile 2	Quartile 3	Quartile 4		
HRS							
Model I[a]	−0.083 (−0.115, −0.051)	0 (reference)	0.040 (−0.026, 0.106)	0.023 (−0.044, 0.091)	−0.076 (−0.147, −0.005)	0.028	−0.016 (−0.045, 0.014)
Model II[b]	−0.050 (−0.099, −0.002)	0 (reference)	0.017 (−0.059, 0.093)	−0.001 (−0.076, 0.075)	−0.112 (−0.193, −0.031)	0.026	−0.008 (−0.042, 0.027)
ELSA							
Model I[a]	−0.028 (−0.071, 0.015)	0 (reference)	−0.020 (−0.068, 0.028)	−0.013 (−0.061, 0.035)	−0.084 (−0.136, −0.031)	0.087	−0.071 (−0.101, −0.040)
Model II[b]	−0.003 (−0.039, 0.034)	0 (reference)	−0.008 (−0.059, 0.042)	−0.019 (−0.070, 0.032)	−0.068 (−0.121, −0.014)	0.042	−0.059 (−0.093, −0.026)
Pooled results[c]							
Model I[a]	−0.058 (−0.111, −0.004)	0 (reference)	0.005 (−0.053, 0.064)	−0.001 (−0.040, 0.039)	−0.081 (−0.126, −0.037)	0.021	−0.043 (−0.097, −0.021)
Model II[b]	−0.024 (−0.070, 0.022)	0 (reference)	−0.001 (−0.043, 0.042)	−0.013 (−0.056, 0.029)	−0.083 (−0.125, −0.041)	0.049	−0.034 (−0.084, −0.010)

[a] Model I adjusted for age, sex and years from baseline

[b] Model II adjusted for covariates in Model I plus education, baseline BMI, smoking, alcohol consumption, baseline hypertension, baseline diabetes and HDL

[c] Results from the two cohorts were pooled using the random-effects model

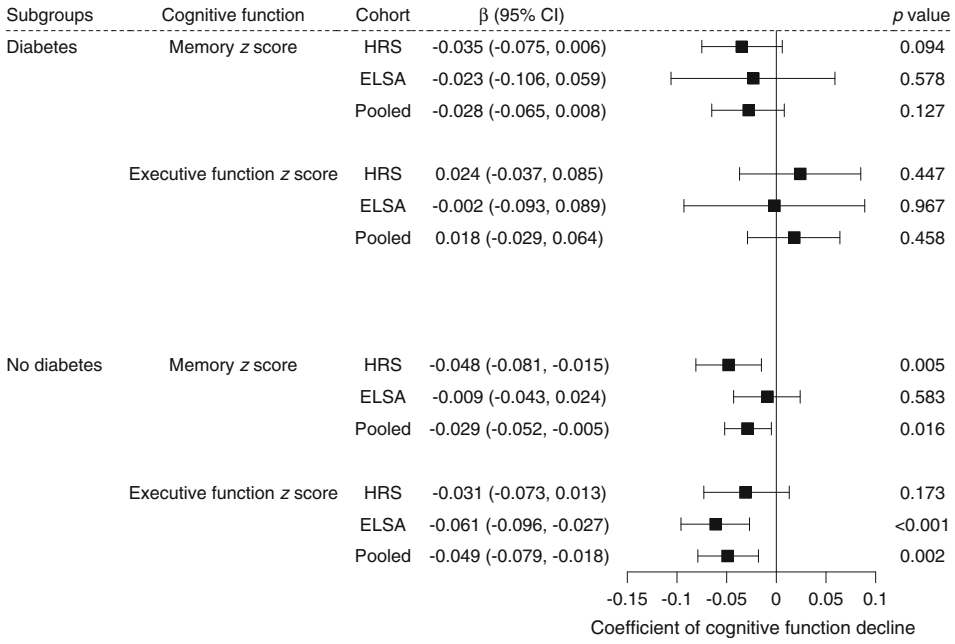

Fig. 2 Subgroup analysis of the association between each SD increment in HbA_{1c} variability and cognitive decline, stratified by baseline diabetes status

HbA_{1c} CV was associated with neither memory function (−0.023 SD/year, 95% CI −0.129, 0.082) nor executive function (0.064 SD/year, 95% CI −0.142, 0.270) in the fully adjusted model compared with the lowest quartile.

HbA_{1c} variability and cognitive decline among participants without diabetes For non-diabetic participants at baseline, each 1-SD increment in HbA_{1c} CV was associated with a significantly higher rate of memory *z* score decline (−0.029 SD/year, 95% CI −0.052, −0.005) and executive function *z* score decline (−0.049 SD/year, 95% CI −0.079, −0.018) in the fully adjusted model. When the CV of HbA_{1c} was modelled as a categorical variable, compared with the lowest quartile, the highest quartile of the CV of HbA_{1c} was associated with a higher rate of memory decline (−0.055 SD/year, 95% CI −0.096, −0.013) and executive function decline (−0.088 SD/year, 95% CI −0.197, −0.022) in the fully adjusted model (ESM Table 2).

Sensitivity analysis A similar pattern except for the significance of trend across quartiles of HbA_{1c} CV was observed in a sensitivity analysis by excluding participants with missing values of cognitive assessment (ESM Table 3). ESM Fig. 3 shows that the distribution of the imputed data is generally similar to that of the original data. Sensitivity analyses by using the SD and VIM as indices of HbA_{1c} variability did not substantially alter our findings (ESM Tables 4 and 5), but *p* values for the trend were not consistent with the main analysis. When we restricted the participants to those with four HbA_{1c} measurements in the ELSA, a positive association between HbA_{1c} variability and memory and executive function was still observed (ESM Table 6).

Discussion

In these two large population-based prospective cohorts (the HRS and ELSA) with a mean follow-up period of 10.48 years, we examined the association between HbA_{1c} variability and cognitive decline. Overall, we observed that greater HbA_{1c} variability was associated with steeper decline in cognitive function independent of mean HbA_{1c} values among individuals without diabetes but not among individuals with diabetes. Sensitivity analyses did not materially change our results. Our findings could provide evidence of the detrimental effect of HbA_{1c} variability and highlight the significance of steady glycaemic control.

To the best of our knowledge, this is the first study of the association between long-term HbA_{1c} variability and cognitive decline that analyses data from more than three cognitive function measurements over time. Moreover, prior epidemiological and clinical studies on this topic were mainly focused on individuals with type 2 diabetes mellitus [21, 22, 31, 32]. Two cross-sectional studies, both conducted among individuals with type 2 diabetes, reported significantly worse cognitive performance among participants with a greater degree of visit-to-visit glucose variability. Our study further extended the findings of a significant association between HbA_{1c} VVV and cognitive decline among a non-diabetic population. Using data from two large prospective cohorts with biennial repeated cognitive measurements and a 10-year period of total follow-up, we were able to calculate the long-term glycaemic variability and trajectory of cognitive decline and investigate the association. Prior mechanics studies [33–35] also suggested a possible deleterious effect of glycaemic variability among individuals without diabetes, which was confirmed by our findings. Bancks et al found that higher intra-

individual fasting glucose variability during young adulthood was associated with worse cognitive performances in midlife, and this association was stronger among individuals without diabetes [36]. These findings were consistent with the present result, although the cognitive tests used were different from those used in the current study. Positive associations were also observed between long-term glycaemic variability and mortality, CVD and type 2 diabetes [7, 37–39] among the non-diabetic population, which aligns with our findings.

The lack of a significant association of HbA_{1c} variability with cognitive function decline among individuals with diabetes may be due to a number of factors. Bancks et al [36] assessed glucose variation before diabetes onset in the CARDIA study and observed that fasting glucose CV was more strongly associated with worse cognitive test scores among individuals without diabetes at the time of the cognitive test than among individuals with diabetes. This suggested that medication use for diabetes may disrupt the natural course of glycaemic variation and blunt the association of HbA_{1c} variability with cognitive function. The relatively small number of participants with diabetes in the present study ($n = 189$ in the ELSA and $n = 651$ in the HRS) may restrict the power to detect a positive association. Moreover, previous post hoc analysis of clinical trials showed that significant associations between long-term glycaemic variation and outcomes (CVD or mortality) were only observed in the intensive glucose-lowering arm but not in the standard glucose-lowering arm [8, 40]. The latter is somehow consistent with our results, as elderly people with diabetes are unlikely to receive intensive glucose-lowering treatment according to the recommendations of the ADA [41]. Several studies have also reported that long-term HbA_{1c} variability has a greater impact among individuals without diabetes, while short-term variability is a predictor among those with diabetes [33, 42]. Future studies are still needed to verify these observed associations.

Our findings also have implications for clinical practice. Individuals with large variability in HbA_{1c} levels, although with absolute measurement level within the normal range, may have been neglected in regard to their risk of cognitive decline. Therefore, attention should be paid to the homeostasis of HbA_{1c} levels in older adults. Measuring long-term HbA_{1c} variability might help predict cognitive decline among individuals without diabetes. However, the causal relationship warrants verification in large clinical trials, and strategies to both maintain HbA_{1c} absolute levels and reduce HbA_{1c} variability merit further investigation.

The exact mechanism of the detrimental effect of glycaemic variability on cognitive decline remains unknown. Excessive insulin secretion caused by hyperglycaemia may result in peripheral or cerebral insulin resistance associated with neuronal vulnerability, neurodegeneration and further pathological lesions [43]. Impairment of insulin receptors and signalling in the brain may affect neuronal survival, astrocyte inflammatory cytokine secretion, nitric oxide-mediated vasodilation and cerebral perfusion [43]. A number of studies have indicated that glycaemic variability may cause apoptosis of pancreatic beta cells, which could result in the deterioration of glycaemic control and subsequent diabetic complications [44, 45].

Our study has several strengths, including the large population-based sample size, the inclusion of several metrics of HbA_{1c} variability, the adoption of reliable tests of cognitive function, the appropriate statistical model and adjustment for mean HbA_{1c} values. However, our findings should be interpreted in the context of the following limitations. First, because of the observational design, only associations, not causality, can be inferred from our results. Second, large intervals between HbA_{1c} measurements (4 years) and relatively few measurements may restrict the generalisability of our findings. Third, although the HRS and ELSA were sister cohorts with a similar design, there are significant heterogeneities between the two sides of the Atlantic. Therefore, we used a meta-analysis approach with the random-effect model to combine the results from the two cohorts. Additionally, we excluded participants with less than three values of HbA_{1c} in our study, but their characteristics were different from the included participants: the excluded participants were older, included a higher percentage of smokers, and had more depressive symptoms (ESM Table 1). Therefore, some caution is still necessary when extrapolating our findings to other populations. Fourth, we were unable to examine the relationship between long-term HbA_{1c} VVV and the incidence of dementia/Alzheimer's disease due to the lack of rigorous clinical diagnoses of dementia or Alzheimer's disease during the follow-up of the HRS and ELSA. Finally, although we adjusted for several potential confounders, unmeasured variables such as genetic susceptibility, data for which were not available, may have affected our results.

Conclusion

In summary, our study provides evidence to support the association between long-term HbA_{1c} variability and cognitive decline irrespective of the effect of mean HbA_{1c} values among individuals without diabetes. Further studies are needed to determine whether decreasing glycaemic variability would benefit cognitive decline in the elderly.

Acknowledgements We thank the University of Michigan for the use of data from the HRS Waves 8–13 from 2006–2016 and the UK Data Archive for the use of data from the ELSA Waves 2–7 from 2002–2015. The original data creators, depositors or copyright holders bear no responsibility for the current analysis or interpretation.

Data availability The datasets generated and analysed during the current study are available from the corresponding author on reasonable request.

Funding The HRS data are sponsored by the National Institute on Aging (grant number U01AG009740), and the study is being conducted by the University of Michigan. The current study was funded by the Ministry of Science and Technology of the People's Republic of China (No. 2015FY111600). The funders played no role in the study design, data collection, analysis, decision to publish or preparation of the manuscript.

Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement KC is the guarantor of this work and had full access to all of the data in the study. KC and ZY conceptualised the study and designed the analysis plan. ZY performed all the statistical analyses and drafted the manuscript. JW provided supervision to ZY. All authors contributed to the acquisition, analysis or interpretation of data; provided critical revision of the manuscript for important intellectual content and approved the final version. KC is responsible for the integrity of the work as a whole.

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