HbA$_{1C}$ variability and hypoglycemia hospitalization in adults with type 1 and type 2 diabetes: A nested case-control study

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ABSTRACT

Aims: To determine association between HbA$_{1C}$ variability and hypoglycemia requiring hospitalization (HH) in adults with type 1 diabetes (T1D) and type 2 diabetes (T2D).
Methods: Using nested case-control design in electronic health record data in England, one case with first or recurrent HH was matched to one control who had not experienced HH in incident T1D and T2D adults. HbA$_{1C}$ variability was determined by standard deviation of ≥3 HbA$_{1C}$ results. Conditional logistic models were applied to determine association of HbA$_{1C}$ variability with first and recurrent HH.
Results: In T1D, every 1.0% increase in HbA$_{1C}$ variability was associated with 90% higher first HH risk (95% CI, 1.25–2.89) and 392% higher recurrent HH risk (95% CI, 1.17–20.61). In T2D, a 1.0% increase in HbA$_{1C}$ variability was associated with 556% higher first HH risk (95% CI, 3.88–11.08) and 573% higher recurrent HH risk (95% CI,1.59–28.51). In T2D for first HH, the association was the strongest in non-insulin non-sulfonylurea users ($P < 0.0001$); for recurrent HH, the association was stronger in insulin users than sulfonylurea users ($P = 0.07$). The HbA$_{1C}$ variability-HH association was stronger in more recent years in T2D ($P ≤ 0.004$).
Conclusions: HbA$_{1C}$ variability is a strong predictor for HH in T1D and T2D.

1. Introduction

As a major barrier of diabetes management,[1] severe hypoglycemia affects up to 30% of people with type 1 diabetes (T1D) annually[2] and is not uncommon in individuals with long-standing type 2 diabetes (T2D) or treated with insulin or sulfonylurea.[3,4] Severe hypoglycemia can potentially cause dire short-term consequences including coma and death,[5] and is also related to long-term harms including vascular events, dementia, and mortality.[6,7]

HbA$_{1C}$ has been associated with severe hypoglycemia, although the shape of the association remains controversial.[8–12] However, data regarding the association between HbA$_{1C}$ variability and severe hypoglycemia are limited and inconsistent. One study reported a positive association of HbA$_{1C}$ variability with severe hypoglycemia[13] while the other study found a J-shaped association.[14] All other studies focused on HbA$_{1C}$ variability and chronic vascular complications of diabetes,[15] not acute complications such as hypoglycemia. Short-term glycemic variability (calculated from blood glucose) is a strong predictor of hypoglycemia in diabetes.[16] However, HbA$_{1C}$ variability is a different measure of glycemic control, reflecting long-term glycemic variability. In fact, HbA$_{1C}$ is not meaningfully affected by short-term glycemic variability after accounting for mean blood glucose.[17]

Accordingly, the relationship between HbA$_{1C}$ variability and severe hypoglycemia is unclear. Further, it is not known if differential associations exist between diabetes types or different patient characteristics. In

addition, severe hypoglycemia is recurrent and is a strong predictor of future severe hypoglycemia.[18] However, no study has compared the association of HbA_{1C} variability between first and recurrent hypoglycemia. Using primary care data from the Clinical Practice Research Datalink (CPRD) and linked secondary care data from the Hospital Episode Statistics (HES) in the United Kingdom (UK), the current study focused on a most severe form of hypoglycemia which requires hospitalization. We designed a nested case-control study to determine the association of HbA_{1C} variability with first and recurrent hypoglycemia hospitalization in adults with T1D or T2D.

2. Participants and methods

2.1. Data sources

The CPRD is a primary care database that contains anonymous longitudinal electronic medical records from >680 practices in the UK.[19] Over 15 million patient records are collected who are broadly representative of the UK population in terms of age, gender, and ethnicity. Patient-level admitted care data are from the HES that stores every hospital admission to National Health Service hospitals in England. Clinical entries in the HES are coded using ICD-10 codes (international classification of diseases, 10th revision) while the CPRD uses Read codes, a hierarchical clinical coding system in General Practice in the UK.[20] Our study population is all patients registered with the 398 of 684 CPRD practices that agreed to be linked to the HES between April 1, 1997 and March 31, 2014. Hypoglycemia hospitalizations were extracted from the HES and the CPRD provided all other data. The study protocol (15_259RA) was approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency in the UK, and by the Institutional Review Boards at the University of North Carolina at Chapel Hill in the United States. The CPRD also had ethics approval from the National Health Service (NHS) Research Ethics Committee for observational studies.

2.2. Definition of incident T1D and T2D and follow-up window

We used previously published algorithm for T1D and T2D from the CPRD.[21] Among patients with at least one diabetes-related Read code, we defined T1D as having any one of those: (i) ≥1 T1D code and insulin use only; (ii) ≥1 T1D code and insulin use only on the diagnosis date and non-insulin glucose-lowering drug (NIGLD), if any, was introduced 6 months later; (iii) ≥2 insulin prescriptions only. T2D was defined as one of the following: (i) ≥2 T2D codes and 0 T1D code, regardless of GLD use; (ii) ≥1 T2D code and 0 T1D code and NIGLD use only; (iii) ≥1 T2D code and 0 T1D code and on both NIGLD and insulin with insulin prescribed later; (iv) ≥2 classes of NIGLD; (v) ≥2 prescriptions of a non-insulin non-metformin GLD. NIGLD included metformin, sulfonylurea, glinide, thiazolidinediones, inhibitors of dipeptidyl peptidase-4 (DPP-4), inhibitors of sodium-glucose co-transporter 2 (SGLT-2), glucagon-like peptide-1 (GLP-1) receptor agonists, and acarbose. Patients were excluded if they had a record of secondary diabetes, maturity onset diabetes of young, latent autoimmune diabetes in adults, and malnutrition related diabetes. Also excluded were patients with unacceptable data quality determined by the CPRD team.

The first diabetes visit date was either the earliest date of a diabetes related code or a GLD prescription, whichever was earlier. Incident T1D and T2D cases were those with the first diabetes visit > 365 days after registration.[22] The follow-up started at the maximum date of the following: April 1, 1997, first diabetes visit, patient registration, Up To Standard (UTS) date,[19] or 18 years old. Follow-up ended at the minimum date of the following: March 31, 2014, death, transfer out, last data collection for the practice, and hospital admission for hypoglycemia.

2.3. Hypoglycemia hospitalization and HbA_{1C} variability

Hypoglycemia (E16.0, E16.1 and E16.2) as primary diagnosis for hospitalization was identified. We recorded both the first and second hypoglycemia hospitalization during follow-up. Individuals having ≥3 HbA_{1C} test results prior to the first hypoglycemia hospitalization were included. HbA_{1C} variability was measured by standard deviation (SD) of the available HbA_{1C} results, accounting for the number of HbA_{1C} measurements. HbA_{1C} results recorded with different units were converted to % using equations found here: http://www.ngsp.org/ifccngsp.asp.

2.4. Nested case-control design

A nested case-control design was chosen to use electronic health data efficiently, to ensure the time comparability for computing HbA1c variability due to its time-varying nature, and to improve statistical efficiency.[23,24] Diabetes duration in days was used as the time scale for selecting 1 control for each case using incidence density sampling method.[25] Thus, controls who had not experienced hypoglycemia hospitalization had the same number of days with diabetes as matched cases. For T1D, cases and controls were additionally matched on age ± 5 years, gender, weight status (normal/underweight, overweight, and obese), Charlson comorbidity score (≤2, 3–4, and ≥5), and having ≥3 HbA_{1C} results. For T2D, cases and controls were also matched on age ± 5 years, gender, weight status (normal/underweight, overweight, and obese), Charlson comorbidity score (≤3, 4–5, and ≥6), current use (yes/no) of insulin, sulfonylurea, metformin, DPP-4 inhibitor, thiazolidinedione, and acarbose, and having ≥3 HbA_{1C} results. No cases with hypoglycemia hospitalization used GLP-1 receptor agonist, glinide or SGLT-2 inhibitor. Charlson score containing 17 comorbidities was calculated according to Khan et al.'s approach.[26] All codes are available on a web repository at www.ClinicalCodes.org.[27]

2.5. Statistical analysis

We studied T1D and T2D, and first and recurrent hypoglycemia hospitalization, separately and respectively. The differences in demographic and clinical characteristics between cases and controls were tested using Student's t, χ^2, or Fisher's exact tests. Non-linearity of the association between HbA_{1C} variability and first or recurrent hypoglycemia hospitalization was explored by the Proc Gam procedure in SAS (version 9.4, SAS Institute Inc.) and was displayed graphically using polynomial terms in the fully adjusted conditional logistic regression model. If the association was linear, HbA_{1C} SD in its continuous form was used as the exposure. If the association was not linear, a quadratic and a cubic term of HbA_{1C} SD were added to capture the non-linearity. The models were adjusted for matching variables specified above and the number of HbA_{1C} tests, but age, BMI, and Charlson score were added as continuous variables to control for residual confounding, as they were matched by broad categories. Other covariates were also adjusted for including years of registration, current smoking, current alcohol drinking, current prescription of antihypertensive drugs (including alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates), and specific diseases that may cause hypoglycemia (including chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, and adrenal insufficiency). Finally, the average of all available HbA_{1C} results prior to the first hypoglycemia hospitalization and its quadratic term were additionally included as covariates, since a U-shaped HbA_{1C}–severe hypoglycemia association was reported.[10] Adjusting for the HbA_{1C} result closest but prior to the first hypoglycemia hospitalization only minimally affected the results.

The interaction of HbA_{1C} variability with age, gender, BMI, Charlson comorbidity score, current use of GLD, and calendar year was tested. If P value was <0.05, stratified analyses were performed. A sensitivity analysis was conducted to evaluate whether the potential misclassification

of diabetes type may influence obtained results. Previous analyses found that the criteria ii and iii for T1D and criterion iii for T2D may misclassify approximately 11.8% and 0.33% of T1D and T2D cases, respectively.[21] We re-analyzed the HbA$_{1C}$ variability-hypoglycemia association by deleting these patients. Another sensitivity analysis was conducted to restrict recurrent hypoglycemia hospitalization within 3 months or 1 year rather than including recurrent hypoglycemia hospitalization at any time in T2D. The sample size in T1D did not allow this restriction. Odds ratios (ORs) and 95% confidence intervals (CIs) were estimated. Statistical significance was indicated by a two-tailed P value < 0.05.

3. Results

3.1. Characteristics of cases and matched controls

In T1D adults, 193 cases of first hypoglycemia hospitalization and 41 cases of recurrent hypoglycemia hospitalization were matched (Table 1). Cases with first hypoglycemia hospitalization had higher HbA$_{1C}$ SD than controls (mean ± SD: 1.13 ± 0.72 versus 0.92 ± 0.51, $P = 0.0009$) and higher mean HbA$_{1C}$ ($P = 0.04$). No difference between cases and controls was found in terms of age, gender, diabetes duration, BMI, Charlson score, years of registration, current smoking, current drinking, antihypertensive drug use, and having diseases that may induce hypoglycemia. Cases with recurrent hypoglycemia hospitalization had higher HbA$_{1C}$ SD than controls ($P = 0.054$) and higher mean HbA$_{1C}$ ($P = 0.02$) and no other difference was seen. The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.75 ± 2.43 years.

In T2D adults, 1361 cases of first hypoglycemia hospitalization and 178 cases of recurrent hypoglycemia hospitalization were matched (Table 2). Compared to controls, cases with first hypoglycemia hospitalization had higher HbA$_{1C}$ SD (mean ± SD: 1.23 ± 0.61 versus 1.01 ± 0.59, $P < 0.0001$), higher mean HbA$_{1C}$ ($P < 0.0001$), and were less likely to drink alcohol currently ($P = 0.0006$). Cases with recurrent hypoglycemia hospitalization had higher HbA$_{1C}$ SD than controls ($P < 0.0001$),

higher mean HbA$_{1C}$ ($P < 0.0001$) and were more likely to have disease that may induce hypoglycemia ($P = 0.03$). The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.28 ± 1.27 years.

3.2. HbA$_{1C}$ variability and hypoglycemia hospitalization

In T1D adults, the association between HbA$_{1C}$ variability and first or recurrent hypoglycemia hospitalization was linear (Fig. 1A and B). Every 1.0% increase in HbA$_{1C}$ variability was associated with 90% higher risk of first hypoglycemia hospitalization (OR, 1.90; 95% CI, 1.25 to 2.89; $P = 0.003$) and 392% higher of recurrent hypoglycemia (OR, 4.92; 95% CI, 1.17 to 20.61; $P = 0.03$). Adjusting for mean HbA$_{1C}$ attenuated the association for first (OR, 1.77; 95% CI, 1.15 to 2.73; $P = 0.01$) and recurrent hypoglycemia hospitalization (OR, 2.75; 95% CI, 0.59 to 12.71; $P = 0.20$). No effect modification by age, gender, BMI, Charlson score or calendar year was found.

In T2D adults, higher HbA$_{1C}$ variability was associated with higher risk of first or recurrent hypoglycemia hospitalization ($P < 0.0001$), but the association was not linear and the increase in the association reached a plateau or slowed down when HbA$_{1C}$ variability was >1.5% (Fig. 2A and B). A 1.0% increase in HbA$_{1C}$ variability was associated with 556% higher risk of first hypoglycemia hospitalization (OR, 6.56; 95% CI, 3.88 to 11.08; $P < 0.0001$) and 573% higher of recurrent hypoglycemia (OR, 6.73; 95% CI, 1.59 to 28.51; $P = 0.01$). Adjusting for mean HbA$_{1C}$ attenuated the association for first (OR, 4.48; 95% CI, 2.54 to 7.88; $P < 0.0001$) and recurrent hypoglycemia hospitalization (OR, 2.94; 95% CI, 0.60 to 14.49; $P = 0.18$).

In T2D adults, the association between HbA$_{1C}$ variability and first hypoglycemia hospitalization was stronger in non-insulin non-sulfonylurea users and in more recent years ($P < 0.0001$, Fig. 3A and B). However, the association was similar between current insulin users and sulfonylurea users. For recurrent hypoglycemia hospitalization, the association was stronger in current insulin users than sulfonylurea users ($P = 0.07$, Fig. 3C); the estimate for non-insulin non-sulfonylurea users was not available due to the small sample size. Still,

Table 1
Characteristics of cases with hypoglycemia hospitalization and matched controls in adults with type 1 diabetes.

	First occurrence			Re-occurrence[a]		
	Cases (N = 193)	Controls (N = 193)	P	Cases (N = 41)	Controls (N = 41)	P
HbA$_{1C}$ standard deviation, %	1.13 ± 0.72	0.92 ± 0.51	0.0009	1.23 ± 0.75	0.94 ± 0.57	0.054
Number of HbA$_{1C}$ test	12.82 ± 9.99	12.94 ± 9.22	0.90	14.66 ± 11.85	12.85 ± 7.24	0.41
Mean HbA$_{1C}$[b], %	8.74 ± 1.61	8.40 ± 1.62	0.04	8.87 ± 1.68	8.10 ± 1.15	0.02
Mean HbA$_{1C}$[b], mmol/mol	72.06 ± 17.55	68.28 ± 17.75	0.04	73.40 ± 18.33	65.03 ± 12.52	0.02
Matching variables						
Age	52.17 ± 20.84	52.06 ± 21.02	0.96	54.61 ± 20.47	54.59 ± 20.22	0.99
Male	56.48	56.48	1.00	53.66	53.66	
Duration of diabetes, years	16.49 ± 9.63	16.49 ± 9.63	1.00	16.93 ± 8.96	16.93 ± 8.96	
Weight status			1.00			1.00
Normal/underweight	52.85	52.85		39.02	39.02	
Overweight	33.68	33.68		56.1	56.1	
Obese	13.47	13.47		4.88	4.88	
Comorbidities			1.00			1.00
Charlson score ≤ 2	51.30	51.30		41.46	41.46	
Charlson score = 3 or 4	32.64	32.64		36.59	36.59	
Charlson score ≥ 5	16.06	16.06		21.95	21.95	
Other variables						
Years of registration	31.04 ± 14.23	30.67 ± 14.83	0.80	30.01 ± 13.11	33.03 ± 16.72	0.37
BMI	25.30 ± 4.93	25.48 ± 4.19	0.70	25.21 ± 3.99	25.69 ± 3.97	0.59
Charlson comorbidity score	2.78 ± 1.93	2.65 ± 1.73	0.47	3.07 ± 1.75	3.02 ± 1.78	0.90
Current smoker	25.39	23.32	0.64	24.39	12.2	0.15
Current alcohol drinker	19.69	25.91	0.15	21.95	31.71	0.32
Use of antihypertensive drugs[c]	52.85	49.74	0.54	63.41	58.54	0.65
Diseases that may induce hypoglycemia[d]	5.18	3.11	0.31	7.32	4.88	0.64

Data were given as the mean ± SD or %. P value from chi-square test, Fisher's exact-test, or Student's t-test, as appropriate.
[a] The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.75 ± 2.43 years.
[b] Average of all previous HbA$_{1C}$ results.
[c] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics and nitrates.
[d] Included chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, and adrenal insufficiency.

Table 2
Characteristics of cases with hypoglycemia hospitalization and matched controls in adults with type 2 diabetes.

	First occurrence			Re-occurrence[a]		
	Cases ($N = 1361$)	Control ($N = 1361$)	P	Cases ($N = 178$)	Control ($N = 178$)	P
HbA_{1C} standard deviation, %	1.23 ± 0.61	1.01 ± 0.59	<0.0001	1.33 ± 0.69	1.06 ± 0.60	<0.0001
Number of HbA_{1C} test	19.38 ± 11.68	18.65 ± 11.12	0.09	19.26 ± 11.30	19.60 ± 12.52	0.79
Mean HbA_{1C}[b], %	8.06 ± 1.25	7.65 ± 1.23	<0.0001	8.43 ± 1.37	7.81 ± 1.26	<0.0001
Mean HbA_{1C}[b], mmol/mol	64.57 ± 13.69	60.09 ± 13.43	<0.0001	68.66 ± 14.98	61.83 ± 13.79	<0.0001
Matching variables						
Age	75.97 ± 10.60	75.64 ± 10.35	0.41	77.04 ± 10.44	76.87 ± 10.22	0.88
Male	52.31	52.31	1.00	54.49	54.49	1.00
Duration of diabetes, years	11.72 ± 6.22	11.72 ± 6.22	1.00	12.06 ± 6.18	12.06 ± 6.18	1.00
Weight status			1.00			1.00
Normal/underweight	32.84	32.84		38.20	38.20	
Overweight	33.65	33.65		33.15	33.15	
Obese	33.50	33.50		28.65	28.65	
Comorbidities			1.00			1.00
Charlson score ≤ 3	37.91	37.91		37.08	37.08	
Charlson score = 4 or 5	30.20	30.20		34.83	34.83	
Charlson score ≥ 6	31.89	31.89		28.09	28.09	
Current insulin use	39.60	39.60	1.00	58.43	58.43	1.00
Current sulfonylurea use	40.48	40.48	1.00	39.33	39.33	1.00
Current metformin use	41.07	41.07	1.00	34.83	34.83	1.00
Current DPP-4 inhibitor use	1.10	1.10	1.00	0.56	0.56	1.00
Current thiazolidinedione use	4.19	4.19	1.00	3.37	3.37	1.00
Current acarbose use	0.37	0.37	1.00	0.56	0.56	1.00
Other variables						
Years of registration	30.87 ± 17.03	31.20 ± 16.46	0.60	32.63 ± 18.86	31.51 ± 16.50	0.55
BMI	28.51 ± 7.79	28.51 ± 6.52	0.99	27.34 ± 6.01	27.83 ± 6.25	0.45
Charlson comorbidity score	4.49 ± 2.28	4.34 ± 2.30	0.09	4.46 ± 2.26	4.31 ± 2.23	0.56
Current smoker	11.17	9.04	0.07	13.48	7.87	0.09
Current alcohol drinker	22.78	28.51	0.0006	19.66	27.53	0.08
Use of antihypertensive drugs[c]	89.49	87.14	0.06	89.33	84.27	0.16
Diseases that may induce hypoglycemia[d]	1.98	1.18	0.09	5.06	1.12	0.03

DPP-4, dipeptidyl peptidase-4. Data were given as the mean ± SD or %. P value from chi-square test, Fisher's exact test, or Student's t test, as appropriate.

[a] The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.28 ± 1.27 years.

[b] Average of all previous HbA_{1C} results.

[c] Included alpha-blockers, beta-blockers, calcium channel blockers, angiotensin II receptor blockers, angiotensin-converting enzyme inhibitors, renin inhibitors, diuretics, and nitrates.

[d] Included chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism, and adrenal insufficiency.

stronger association between HbA_{1C} variability and recurrent hypoglycemia hospitalization was seen in recent years than earlier years ($P = 0.004$, Fig. 3D).

3.3. Sensitivity analysis

None of our cases was identified by the criteria ii and iii for T1D and criterion iii for T2D described above that may be most likely to misclassify diabetes type from clinical perspectives. Also, restricting of recurrent hypoglycemia hospitalization within 3 months or 1 year for T2D minimally affected the association (data not shown).

4. Discussion

We found that higher HbA_{1C} variability was associated with higher first or recurrent hypoglycemia hospitalization in both T1D and T2D. The association was linear in T1D but not linear in T2D. In T1D, the association between HbA_{1C} variability and recurrent hypoglycemia hospitalization was stronger than that for first hypoglycemia hospitalization. In T2D, the association of HbA_{1C} variability between first and recurrent hypoglycemia hospitalization was similar, but both stronger than in T1D. In T2D, the association between HbA_{1C} variability and first hypoglycemia hospitalization was stronger in non-insulin non-sulfonylurea users than insulin or sulfonylurea users, and in more recent years than earlier years. For recurrent hypoglycemia hospitalization, the association was stronger in insulin users than sulfonylurea users and in more recent years than earlier years.

We are not aware of any study that has investigated the relationship between HbA_{1C} variability and severe hypoglycemia specifically in T1D adults. Our analyses provided initial evidence that HbA_{1C} variability was a strong risk factor for hypoglycemia hospitalization in T1D adults. The stronger association with recurrent than first hypoglycemia hospitalization may be related to the interplay among HbA_{1C} variability, insulin use, and previous hypoglycemia hospitalization. Insulin use is a major cause of severe hypoglycemia in diabetes and severe hypoglycemia itself is a strong predictor for future severe hypoglycemia.[3,18,28] Together with greater variability in glycemic control, the higher risk of recurrent hypoglycemia hospitalization is not unexpected in insulin users who experienced hypoglycemia hospitalization before.
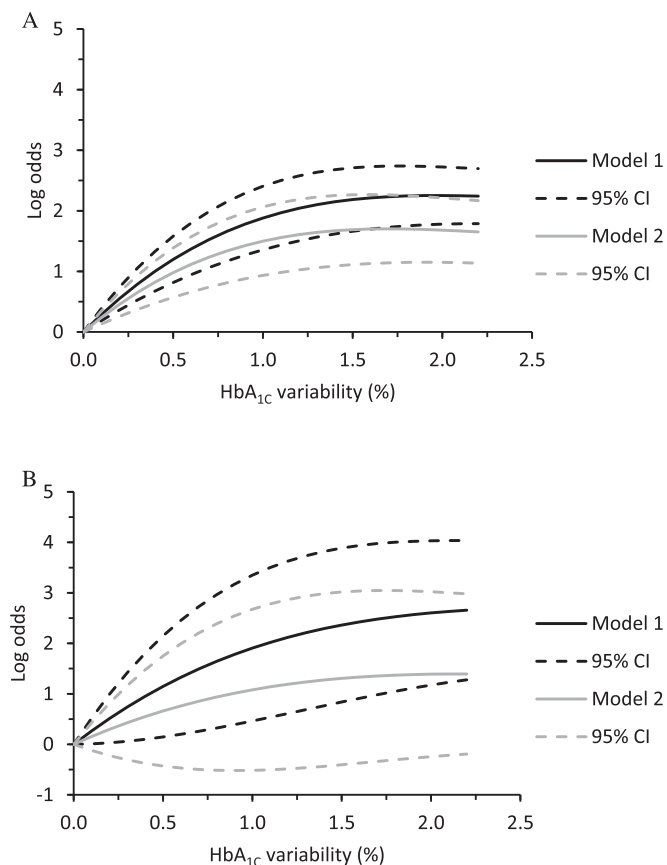
The strong positive association between HbA_{1C} variability and hypoglycemia hospitalization in T2D adults from our data was consistent with Williams et al.'s study conducted in diabetic hemodialysis patients.[13] Williams et al. did not directly explain the association, but stated that the positive association between higher baseline HbA_{1C} and higher risk of hypoglycemia hospitalization was driven by higher HbA_{1C} variability rather than higher HbA_{1C} per se. We found that adjusting for mean HbA_{1C} level attenuated the association between HbA_{1C} variability and hypoglycemia hospitalization, but HbA_{1C} variability was still a strong predictor of hypoglycemia hospitalization in T2D adults. A different shape of the association between HbA_{1C} variability and hypoglycemia requiring medical attention was reported from a large German T2D cohort who were newly transitioned to insulin therapy, but HbA_{1C} variability was calculated differently.[14] Bonke et al. defined HbA_{1C} variability as the average difference between successive HbA_{1C} values per quarter year rather than HbA_{1C} SD, because their patients were required to have an HbA_{1C} measure every quarter or half year. Bonke et al. found that the risk of hypoglycemia requiring medical attention was the lowest when HbA_{1C} change was 0.5% per quarter year. Smaller and greater change increased risk of hypoglycemia, but the latter was more dramatic. However, when using HbA_{1C} SD, both Willams et al. and our study did not identify a nadir in the association.
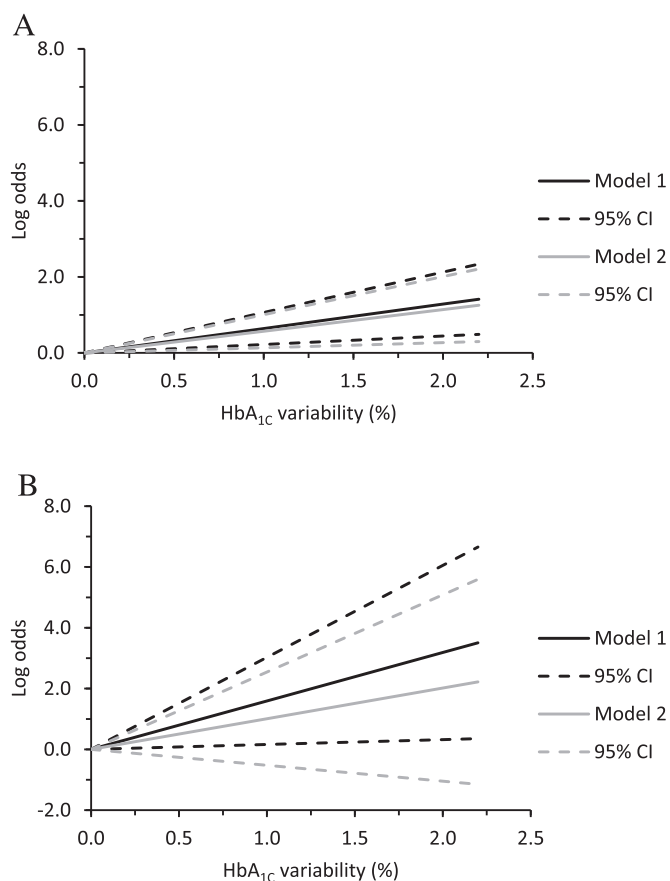
Fig. 1. A. HbA$_{1C}$ variability and first hypoglycemia hospitalization in type 1 diabetes B. HbA$_{1C}$ variability and recurrent hypoglycemia hospitalization in type 1 diabetes The association between HbA$_{1C}$ variability and hypoglycemia hospitalization was linear. Model 1 included HbA$_{1C}$ SD, number of HbA$_{1C}$ measurements, age, BMI, Charlson comorbidity score, years of registration, current smoking, current alcohol drinking, current use of antihypertensive drug, and having diseases that may induce hypoglycemia (chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism and adrenal insufficiency). Gender and duration of diabetes were identically matched. Model 2 included mean HbA$_{1C}$ and its quadratic term. The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.75 ± 2.43 years. The graph did not display the highest five percentile of HbA$_{1C}$ SD because the results were not stable due to the big range of HbA$_{1C}$ SD and small sample.

Fig. 2. A. HbA$_{1C}$ variability and first hypoglycemia hospitalization in type 2 diabetes B. HbA$_{1C}$ variability and recurrent hypoglycemia hospitalization in type 2 diabetes The association between HbA$_{1C}$ variability and hypoglycemia hospitalization was not linear. Model 1 included HbA$_{1C}$ SD and its quadratic and cubic terms, number of HbA$_{1C}$ measurements, age, BMI, Charlson comorbidity score, years of registration, current smoking, current alcohol drinking, current use of antihypertensive drug, and having diseases that may induce hypoglycemia (chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism and adrenal insufficiency). Other confounding variables were identically matched, including gender, duration of diabetes, current use of insulin, sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, and acarbose. Model 2 included mean HbA$_{1C}$ and its quadratic term. The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.28 ± 1.27 years. The graph did not display the highest five percentile of HbA$_{1C}$ SD because the results were not stable due to the big range of HbA$_{1C}$ SD and small sample.

Interpreting the association between HbA$_{1C}$ variability and hypoglycemia hospitalization needs to consider both the strength of the association and the background incidence of hypoglycemia hospitalization. Even a small increase in the association among patients with high hypoglycemia risk (e.g., insulin or sulfonylurea users) would substantially contribute to hypoglycemia burden.[21] The stronger HbA$_{1C}$ variability-hypoglycemia hospitalization association in T2D than T1D was largely driven by T2D adults who were not currently taking insulin or sulfonylurea, although they were at low risk of hypoglycemia hospitalization. The increased HbA$_{1C}$ variability in non-insulin non-sulfonylurea users may indicate poor adherence to glucose-lowering therapy and/or lifestyle management.[29] Also, since they were not currently taking insulin or sulfonylurea, two major hypoglycemia-causing drugs,[3] patients may pay less attention to or had not been well educated with preventing hypoglycemia. These may be possible reasons associated with the stronger HbA$_{1C}$ variability-hypoglycemia hospitalization association in non-insulin non-sulfonylurea users. Similar to T1D adults, T2D adults on insulin with previous hospitalization for hypoglycemia were also at higher risk of developing recurrent hypoglycemia hospitalization compared to non-insulin users. Thus, preventing first hypoglycemia hospitalization is particularly important for reducing risk of future

hypoglycemia hospitalization in insulin users who have the highest hypoglycemia risk.[21]

Using year 2008 as the cutoff was determined arbitrarily by splitting cases with hypoglycemia hospitalization approximately into halves. In fact, dichotomizing at an earlier or later year did not change the results (data not shown). We do not know if this may be partly related to the introduction of the Quality and Outcomes Framework (QOF) financial incentive scheme in 2004 in the UK,[30] because the data completeness in the CPRD has been improved post-QOF period. Also, from 2003, practices within the CPRD began to use automated approaches to request tests and receive results from laboratories. Laboratory data from this time are likely to be more complete than earlier years when paper-based systems were widely used. However, since the temporal variation in the association of HbA$_{1C}$ variability with hypoglycemia hospitalization was only found in T2D, not in T1D, we hypothesize that two other reasons may be more plausible: i) Diabetes management strategies have been recently shifted from emphasizing hyperglycemia control to recommending individualized glycemic targets,[31,32] particularly after the three milestone cardiovascular trials in T2D[33–35]; ii) New drugs have become available for treating T2D such as dipeptidyl
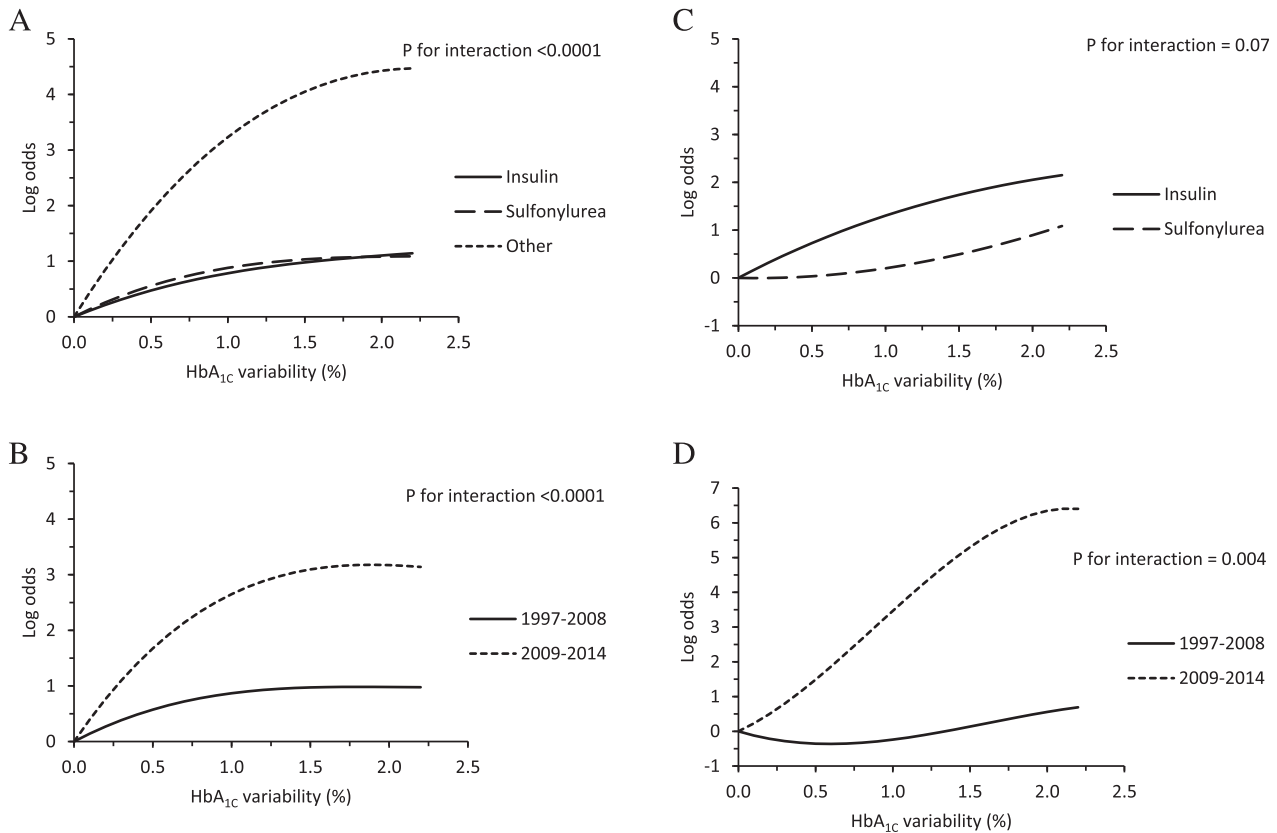
Fig. 3. A. HbA$_{1C}$ variability and first hypoglycemia hospitalization in type 2 diabetes by current use of glucose-lowering drugs B. HbA$_{1C}$ variability and first hypoglycemia hospitalization in type 2 diabetes by calendar years C. HbA$_{1C}$ variability and recurrent hypoglycemia hospitalization in type 2 diabetes by current use of glucose-lowering drugs D. HbA$_{1C}$ variability and recurrent hypoglycemia hospitalization in type 2 diabetes by calendar years The model included HbA$_{1C}$ SD and its quadratic and cubic terms, number of HbA$_{1C}$ measurements, age, BMI, Charlson comorbidity score, years of registration, current smoking, current alcohol drinking, current use of antihypertensive drug, and having diseases that may induce hypoglycemia (chronic pancreatitis, pancreatic adenoma, pituitary adenoma, cystic fibrosis, hypopituitarism and adrenal insufficiency). Gender and duration of diabetes were identically matched along with current use of insulin, sulfonylurea, metformin, thiazolidinedione, dipeptidyl peptidase-4 inhibitor, and acarbose. For Fig. 3C, the association for non-insulin and non-sulfonylurea users could not be estimated due to too few cases. The median and interquartile range of the time between the first and second hypoglycemia hospitalization was 0.28 ± 1.27 years. The graph did not display the highest five percentile of HbA$_{1C}$ SD because the results were not stable due to the big range of HbA$_{1C}$ SD and small sample.

peptidase-4 inhibitors and glucagon-like peptide-1 receptor agonists that are related to very low risk of hypoglycemia.[36,37] Nonetheless, how these may play a role in the association between HbA$_{1C}$ variability and hypoglycemia hospitalization needs further investigation.

Factors associated with HbA$_{1C}$ variability have not been well studied. More intensive glucose-lowering treatment, younger age, male gender, lower high-density lipoprotein cholesterol, higher BMI, longer duration of diabetes, having coronary artery disease, and multiple concurrent medications have been associated with greater HbA$_{1C}$ variability.[38–40] Future studies are encouraged to replicate these findings and also propose feasible algorithms for identifying people at high risk of greater HbA$_{1C}$ variability, which may be used to guide hypoglycemia prevention.

Our study determined the association between long term glycemic variability and risk of first and recurrent hypoglycemia hospitalization in adults by diabetes type and identified critical interactions. Our work contributed data to expand the current knowledge that HbA$_{1C}$ variability is not only a critical variable for predicting chronic complications and mortality as previously reported,[15] but predicts hypoglycemia hospitalization, as a severe acute complication of diabetes. Limitations should be noted. Firstly, although HbA$_{1C}$ SD is the most commonly used measure for HbA$_{1C}$ variability, it has flaws, particularly, when the number of HbA$_{1C}$ measurements is limited and the measurements are widely spaced.[14] However, the average number of HbA$_{1C}$ measurements was fairly large in our study with about 13 and 19 measurements in T1D and T2D adults, respectively. Secondly, 37.9% and 21.7% of cases with

hypoglycemia hospitalization from T1D and T2D were excluded due to missing data or not having three or more HbA$_{1C}$ results (Supplemental Tables 1 and 2). Thus, our results may not be generalized to all patients with diabetes in the CPRD, because the included cases differed from the excluded cases. Thirdly, diabetes type may have been incorrectly classified. However, none of the cases with hypoglycemia hospitalization was captured by "likely-to-misclassify" criteria according to the sensitivity analysis. Fourthly, residual confounding is likely. For example, we were unable to account for severe hypoglycemia without leading to hospitalization or hypoglycemia hospitalization that occurred before April 1, 1997 when relevant HES data were not available. Fifthly, we only studied hypoglycemia resulting in hospitalization. Applying our findings to other forms of hypoglycemia should be cautious. Sixthly, we were not able to account for the potential differences that may be created by different HbA$_{1C}$ determination methods. Lastly, due to the nature of the study design, the causality of the association between HbA$_{1C}$ variability and hypoglycemia hospitalization could not be established.

In conclusion, HbA$_{1C}$ variability may be an important target for hypoglycemia prevention and management in T1D and T2D, in addition to HbA$_{1C}$. Preventing first hypoglycemia hospitalization is important because the association between HbA$_{1C}$ variability and hypoglycemia hospitalization was strengthened among those with previous hospitalization for hypoglycemia, particularly in insulin users regardless of diabetes type. Further research is needed to confirm our findings, to explain why HbA$_{1C}$ variability-hypoglycemia hospitalization association is

stronger in more recent years in T2D, and to elucidate the relevant mechanisms linking HbA1c variability and hypoglycemia risk in diabetes.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2017.10.008.

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