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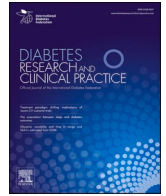
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HbA1c variability and all-cause mortality in type 1 and type 2 diabetes: A population-based cohort study using electronic health records

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ABSTRACT

Aims: To investigate associations between HbA1c variability and all-cause mortality in individuals with diabetes, accounting for average HbA1c level.

Methods: Mean HbA1c and variability score (HVS) were estimated for people aged 31–90 with diabetes (type 1 = 20,347, type 2 = 409,821) with 4+ HbA1c measurements recorded in the Clinical Practice Research Datalink in 2011–14 and alive on 1/1/2015. Cox models estimated hazard ratios (HR) for all-cause mortality, ascertained from national linked mortality data during 2015–17. HbA1c level and variability were mutually adjusted for each other and other measured confounders.

Results: Greater HbA1c variability was associated with younger age, non-white ethnicities (type 1 only), obesity, co-morbidities, and living in deprived areas. During follow-up, 1,043 (5.1%) individuals with type 1 diabetes and 40,723 (9.9%) individuals with type 2 diabetes died. In those with the most HbA1c variability compared to the least (HVS = 80–100 vs 0–20), the estimated adjusted HRs for mortality were 2.78 (95%CI 2.15, 3.60) in type 1 diabetes and 1.91 (1.83, 1.99) in type 2 diabetes.

Conclusions: Variability in HbA1c was associated with greater subsequent mortality among people living with diabetes, independent from average HbA1c. Future research should investigate whether reducing HbA1c variability over time in selected patients lowers mortality risk independent of HbA1c level improvements.

1. Introduction

Diabetes is one of the leading causes of death and disability, and in 2022 there were an estimated 828 million adults living with diabetes worldwide [1,2]. It is therefore important to understand characteristics of diabetes that may affect the burden of morbidity and mortality.

The importance of diabetes control as measured by average HbA1c is well established and is a focus of diabetes management guidelines[3–5]. There is, however, also growing evidence that not just average level but variability in HbA1c may be important for multiple micro- and macrovascular outcomes[6–20]. Associations between HbA1c variability and mortality have been found in several observational studies focusing on type 2 diabetes [8,11,15–17,21,22], but have been less well described in

type 1 diabetes[23]. Data on 9483 participants with type 2 diabetes from the ACCORD trial also found variability was a strong predictor of all-cause-mortality [24]. To our knowledge there are no papers describing type 1 and type 2 separately using a single dataset.

Assessment of HbA1c variability is not straightforward, and a range of different measures have been used including standard deviation, coefficient of variation (SD/mean), Z-scored coefficient of variation, and HbA1c variability score (HVS, proportion of significant changes in HbA1c level over time)[25]. Several studies have compared multiple measures of variability within a single dataset and have found that associations with mortality were consistent across the different measures of variability used[18,22,24,26,27]. HVS has the advantage of being a more clinically understandable measure than the more statistical

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measures.

There is a challenge in separating out variability in HbA1c from mean HbA1c level, as individuals with the highest mean levels often also have the most variability. Some studies adjust for mean HbA1c to assess the independent effect of variability, but it is also important to consider potential effect modification, whereby associations with variability may be different at different average levels. If the impact of variability changes with average level, this may have implications for monitoring and targets for HbA1c that are not currently included in guidelines.

It is not well known what the main factors that predict variability are, and whether these are the same for type 1 and type 2 diabetes. This is important to understand so that we can appropriately control for these factors in analyses looking at associations between variability and outcomes such as mortality. Understanding such factors could also identify individuals who may benefit from closer management. In this study our objectives were:

- 1) to describe and compare the characteristics of people living with type 1 and type 2 diabetes who have high HbA1c variability with those with low variability, and
- 2) to estimate associations between HbA1c variability and all-cause mortality in type 1 and type 2 diabetes, accounting for average HbA1c level and for other measured characteristics found to be associated with variability.

2. Materials and Methods

2.1. Data Resource

CPRD (Clinical Practice Research Datalink) is a primary care database in the UK jointly sponsored by the Medicines and Healthcare products Regulatory Agency and the National Institute for Health and Care Research [28]. It provides a pseudonymised longitudinal medical record for all registered patients (>99 % of the UK population are registered as a patient with a General Practitioner), with diagnoses and other clinical information recorded using Read Codes. This study used a February 2022 extract from the CPRD Aurum database, which included approximately 16 million currently registered patients from 1,447 general practices (England only). Over 90 % of contributing practices in Aurum have consented to their data being linked to external sources [29]. These data sources include the ONS (Office for National Statistics) mortality data which includes cause of death, and the Index of Multiple Deprivation (IMD), a composite small-area (approximately 1500 people) measure used in England for allocation of resources, which provides a good proxy for individual socio-economic deprivation. Study ethical approval was granted by CPRD's Research Data Governance (protocol number 21_000592).

2.2. Study design and participants

The study used as its source population all people aged 18 to 90 with a Read code for diabetes who were active in CPRD on 1st January 2015 and had been registered with their GP practice for at least one year (Fig. S1). We have previously described how they were classified into type 1, type 2 or unknown based on their diagnosis codes and anti-diabetes medication [30]. For this analysis of mortality, we further restricted to (i) ages 31 and above as there are comparatively few deaths at younger ages, (ii) people who had at least four HbA1c measurements recorded in their record, taken at least 30 days apart, during 2011–14. This resulted in 20,347 people with type 1 diabetes and 409,821 people with type 2 diabetes (Fig. S1).

2.3. HbA1c average level and variability

In the UK, people with diabetes have on average 1–2 HbA1c measurements recorded in their primary care records in a calendar year.

Most measurements since 2011 are recorded in mmol/mol; measurements made using older Diabetes Control and Complications Trial (DCCT) percentage units were converted by the formula (%value – 2.15) x 10.92. Infeasible values (<10 or > 200 mmol/mol) were excluded and a mean was estimated. Categories for mean HbA1c level were chosen that map to integer values for the DCCT percentage units (<42, 42–<53, 53–<64, 64–<75, 75–<86, 86– mmol/mol).

To summarise HbA1c variability, we estimated an HbA1c Variability Score (HVS), similar to that originally suggested by Forbes et al [25]. This counts how frequently HbA1c rises or decreases by a fixed threshold (pre-specified at 0.5 % or 5.5 mmol/mol) or more, across a series of successive measurements made over time and summarised as a percentage. We previously adapted the HVS so that the threshold for significant fluctuations is instead based on a relative change (10 percent or more from the previous measurement) [31], with the rationale that the HVS will now be less closely related to the mean level. Therefore, if a previous measurement was 70 mmol/mol, then a subsequent measurement ≤ 64.5 or ≥ 75.5 mmol/mol would be counted as a significant fluctuation based on an absolute threshold but would need to be ≤ 63 or ≥ 77 mmol/mol based on a relative threshold of 10 percent.

2.4. Statistical analysis

2.4.1. Predictors of high variability

To provide a summary of predictors of variability, a binary variable of an HVS score of ≥ 50 was generated. This cut off was chosen for its clinical interpretability: it tells us that at least half of an individual's HbA1c measurements vary by ± 10 % of their previous values. Using this binary outcome, modified Poisson regression, using generalised estimating equations (GEE) to account for the clustering by practice, was utilised (PROC GENMOD, SAS version 9.4). For type 1 and type 2 diabetes separately, the following factors were all first considered individually: sex, age, ethnicity, time since diagnosis, body mass index, smoking, IMD, co-morbidities (atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, dementia, epilepsy, heart failure, hypertension, peripheral vascular disease, serious mental illness and stroke) and HbA1c level. Then, subsequent analyses adjusted for: (i) age + sex, (ii) age + sex + ethnicity + BMI + smoking + IMD, (iii) age + sex + average HbA1c level.

2.4.2. Associations between variability and mortality

For the main analyses, HVS estimates were categorised into 4 levels (0–<20, 20–<50, 50–<80, 80–100), with a test for trend performed by fitting HVS as a continuous variable. Cox proportional hazards models were used to estimate hazard ratios for 3-year mortality during 2015–17 by different categories of average HbA1c and variability for type 1 and type 2 diabetes separately (PROC PHREG, SAS version 9.4). The reference categories were 42–<53 mmol/mol for average level and 0–<20 for HVS. Initial models included adjustments for only age, sex, and ethnicity, and co-adjusted for mean and variability in type 1 and type 2 diabetes separately. The main models included the following covariates: age, sex, ethnicity, deprivation (IMD), time since diagnosis, comorbidity count, smoking and BMI. Subsequent analyses then stratified by (i) mean level (<64 or ≥ 64 mmol/mol), (ii) age (<60, ≥ 60 years), (iii) type of medication prescribed in 2014 for type 2 diabetes (insulin, non-insulin only, none), with a test for an interaction between each of the stratified variables and HVS trend also carried out.

To further compare the associations of HbA1c mean and variability on mortality, population attributable fractions were calculated, whereby the proportion of deaths that could have been averted if all individuals had values of average HbA1c or variability in the reference category (average HbA1c 42–<53 mmol/mol; HVS < 20), assuming a causal relationship. Additionally, an alternative model fitted a cross-classification of mean vs. variability (20 categories), with 42–53 mmol/mol combined with an HVS = 0–20 as the reference category. All

study participants were followed up from 1st January 2015 to 31st December 2017, or their linked date of death if it occurred before then.

Two additional analyses looked at whether direction of fluctuations affected results. Firstly, the main analysis was repeated but the HVS was re-calculated in two ways, (i) only counting negative fluctuations of 10 % or more, (ii) counting only positive fluctuations of 10 % or more. Secondly, an analysis was carried out using only two measurements, the first HbA1c measurement in 2015 to assess level, and the change from the last recorded measurement made in 2014 to assess both negative and positive fluctuations. This analysis was based on 13,835 people with type 1 and 305,262 people with type 2 diabetes who fulfilled these requirements, and follow-up time started from the date of first HbA1c measurement in 2015.

2.4.3. Sensitivity analyses

Several sensitivity analyses for HbA1c mean and variability were carried out. (i) Adjusting only for age, sex, and ethnicity and then including individual comorbidities (atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, dementia, epilepsy, heart failure, hypertension, peripheral vascular disease, serious mental illness and stroke) in the model rather than a simple comorbidity count. (ii) Only reporting on 1-year mortality to the end of 2015. (iii) Only using HbA1c measures made at least 90 to 730 days apart. (iv) Using the coefficient of variation instead of the HVS. (v) Removing any people who died within 6 months. (vi) Excluding individuals with any recorded history of hypoglycaemic episodes. (vii) Excluding individuals with any co-morbidities.

3. Results

3.1. Population characteristics

People with type 1 diabetes were on average 15 years younger than people with type 2 diabetes (52.9 vs. 67.5 years, Table 1). Proportion of men was similar (57 % type 1 diabetes, 56 % type 2 diabetes). While people with type 2 diabetes were more likely to come from more deprived areas, this was not true for type 1 diabetes. Mean (SD) number of HbA1c measurements during 2011–14 was 6.5 (2.1) and 6.7 (2.2) in type 1 and type 2 diabetes respectively. People with type 1 had higher average HbA1c levels during 2011–14 (68.7 vs. 58.0 mmol/mol), but variability measures were on average greater among type 2 (38 % of people with type 2 diabetes had an HVS \geq 50 compared to 33 % of type 1). The higher proportion with a HVS \geq 50 was more pronounced among those with an HbA1c average level \geq 64 mmol (63 % type 2 vs. 36 % type 1, Fig. S2). When people with type 2 diabetes were categorised by recent anti-diabetes medication, variability was highest in those on insulin, and greater than seen for all Type 1 (Fig. S3).

3.2. Predictors of high variability

HbA1c variability was inversely associated with age in both type 1 and type 2 diabetes (Table S1). Fig. 1 summarises relative risks for an HVS \geq 50 vs an HVS < 50 by a series of characteristics in type 1 diabetes and type 2 diabetes separately (95 % CIs given in Table S2) adjusted for age and other factors including average HbA1c level. Among type 2 diabetes, men were more likely to have high variability whereas there was no evidence of a difference by sex in type 1 diabetes. Non-white ethnicity predicted high variability for type 1 diabetes, particularly so in individuals with type 1 of black ethnicity (adjusted RR of high variability of 1.53 (95 % CI 1.36, 1.72)). Differences by ethnicity were smaller in the type 2 diabetes group, and were explained by adjusting for other factors. A more recent diagnosis of diabetes (within 5 years) was strongly associated with high variability in type 1, whereas in type 2 no clear trend was observed after adjusting for average HbA1c level. Body mass index and deprivation predicted high variability for both types of diabetes, as did many co-morbidities, particularly severe mental illness,

Table 1
Baseline characteristics of study population, by diabetes type.

		Type 1 diabetes (n = 20,347)	Type 2 diabetes (n = 409,821)
Sex, n(%)	Females	8662 (42.6)	181,072 (44.2)
	Males	11,685 (57.4)	228,749 (55.8)
Age (years), Mean (SD)		52.9 (13.2)	67.5 (12.2)
Ethnicity, n(%)	South Asian	444 (2.2)	41,016 (10)
	Black	316 (1.6)	16,545 (4)
	Mixed	584 (2.9)	23,066 (5.6)
	White	16,881 (83)	292,706 (71.4)
	Missing	2122 (10.4)	36,488 (8.9)
Index of Multiple Deprivation, n(%)	1 (least deprived)	4532 (22.3)	69,700 (17)
	2	4420 (21.7)	77,171 (18.8)
	3	4107 (20.2)	79,403 (19.4)
	4	3770 (18.5)	89,214 (21.8)
	5 (most deprived)	3498 (17.2)	94,047 (23)
	Missing	20 (0.1)	286 (0.1)
Body Mass Index (kg/m ²), Mean (SD)*		27.3 (5.1)	30.9 (6.3)
Smoking, n(%)	Never	8377 (41.2)	151,001 (36.9)
	Ex	8366 (41.1)	206,939 (50.5)
	Current	3602 (17.7)	51,860 (12.7)
	Not recorded	2 (0)	21 (0)
Number of co-morbidities**, n(%)	0	10,525 (51.8)	88,427 (21.6)
	1–2	8383 (41.2)	253,333 (61.8)
	>2	1439 (7.1)	68,061 (16.6)
Summary of all anti-diabetic medications prescribed in 2014, n(%)	None		68,418 (16.7)
	Biguanides only		123,903 (30.2)
	Biguanides & other ¹		130,054 (31.7)
	Other ² Insulin ³	20,347 (100)	20,126 (4.9) 67,320 (16.4)
Time Since Diagnosis (years), n(%)	0 to 5	1139 (5.6)	112,972 (27.6)
	5 to 15	4179 (20.5)	221,716 (54.1)
	>15	15,029 (73.9)	75,133 (18.3)
Distribution of average HbA1c (mmol/mol), n(%)	<42	238 (1.4)	27,505 (6.7)
	42 to < 53	2084 (10.2)	147,898 (36.1)
	53 to < 64	5990 (29.4)	126,200 (30.8)
	64 to < 75	6195 (30.5)	60,587 (14.8)
	75 to < 86	3380 (16.6)	27,760 (6.8)
	\geq 86	2415 (11.9)	19,871 (4.9)
Distribution of HbA1c Variability Score, n(%)	0 to < 20	5606 (27.6)	109,939 (26.8)
	20 to < 50	8105 (39.8)	143,201 (34.9)
	50 to < 80	5558 (27.3)	124,498 (30.4)
	80 to 100	1078 (5.3)	32,183 (7.9)

* BMI means based on those with valid BMI recording only (missing in 94 (0.5%) people with type 1 diabetes and 1668 (0.4%) people with type 2 diabetes).

** Count of the following: Atrial fibrillation, cancer, chronic obstructive pulmonary disease, coronary heart disease, chronic kidney disease, dementia, epilepsy, heart failure, hypertension, peripheral vascular disease, serious mental illness (e.g. psychosis, schizophrenia & bipolar affective disorder), stroke/TIA. 1 – Excluding insulin, 2 – Excluding biguanides & insulin, 3 – Only or in combination

	Type 1 Diabetes (n=20,347)				Type 2 Diabetes (n=409,821)			
	Unadjusted	Age + sex	Age + sex + ethnicity + BMI + smoking + IMD	Age + sex + average HbA1c level	Unadjusted	Age + sex	Age + sex + ethnicity + BMI + smoking + IMD	Age + sex + average HbA1c level
Sex								
- Male vs. Female	-4%	-4%	-4%	-2%	15%	13%	14%	12%
Age (years)								
- Decrease of 10	8%	8%	7%	7%	18%	18%	16%	10%
Ethnicity								
- South Asian vs. White	25%	20%	21%	18%	9%	-4%	2%	-6%
- Black vs. White	64%	60%	54%	53%	18%	9%	12%	3%
- Mixed vs. White	28%	23%	21%	22%	9%	-1%	3%	-3%
Years since diagnosed								
- 0-5 vs. 5-15	56%	55%	55%	58%	2%	-6%	-6%	7%
- 15+ vs. 5-15	-16%	-13%	-10%	-11%	11%	21%	20%	4%
BMI (kg/m²)								
- 25-30 vs. 18-25	-7%	-6%	-4%	-5%	9%	4%	4%	4%
- 30-40 vs. 18-25	0%	1%	3%	1%	28%	17%	18%	13%
- 40- vs. 18-25	21%	21%	23%	22%	46%	28%	28%	22%
Smoking								
- Current vs. Never	29%	27%	24%	20%	14%	5%	6%	2%
- Ex vs. Never	7%	11%	11%	10%	2%	5%	4%	5%
IMD Quintile								
- 2 vs. 1 (least)	5%	4%	4%	3%	5%	4%	3%	2%
- 3 vs. 1 (least)	12%	11%	9%	9%	10%	7%	6%	4%
- 4 vs. 1 (least)	20%	18%	13%	14%	15%	11%	9%	5%
- 5 vs. 1 (least)	39%	36%	27%	28%	22%	16%	13%	7%
Co-morbidities (yes vs. no)								
- Atrial fibrillation	11%	28%	27%	27%	-4%	12%	10%	11%
- Cancer (since 2003)	-3%	7%	7%	7%	-3%	9%	9%	10%
- Coronary heart disease	11%	26%	22%	23%	-3%	8%	7%	3%
- Chronic kidney disease	14%	28%	24%	25%	-8%	14%	13%	11%
- COPD	7%	20%	10%	17%	3%	14%	11%	13%
- Dementia	36%	65%	60%	58%	6%	37%	38%	30%
- Epilepsy	11%	9%	7%	8%	11%	8%	7%	9%
- Heart failure	31%	50%	43%	47%	13%	30%	26%	20%
- Hypertension	-7%	2%	0%	2%	-12%	0%	-3%	1%
- Peripheral artery disease	5%	16%	10%	13%	3%	15%	14%	7%
- Serious mental illness	40%	37%	27%	33%	18%	8%	7%	11%
- Stroke & TIA	14%	26%	21%	24%	1%	15%	14%	11%
Average HbA1c (mmol/mol)								
- Increase of 11	11%	10%	8%	10%	29%	26%	26%	26%

Fig. 1. Relative risks for a HbA1c variability score (HVS) of 50 or more vs. HVS < 50 by selected characteristics Note: relative risks are from a Poisson model for a **HVS of 50 or more** vs HVS < 50 Shading indicates strength of association, with red shading indicating higher risk and green shading lower risk IMD = Index of Multiple Deprivation. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

dementia, and heart failure.

3.3. 3-year mortality and HbA1c summary measures

There were 1,043 deaths (5.1 %) in the type 1 group and 40,723 (9.9 %) deaths in the type 2 group during 2015–17 (Fig. S1, Table S3). In models that mutually adjusted for average level and variability (Fig. 2), similar trends with all-cause mortality were seen among type 1 diabetes and type 2 diabetes, but the HRs were greater for type 1 diabetes. For example, in the highest HVS category versus the lowest (≥ 80 vs. < 20) HR = 2.78 (95 %CI 2.15–3.60) for type 1 diabetes and HR = 1.91 (95 % CI 1.83–1.99) for type 2 diabetes. In both groups, “any” variability (HVS 20 or more, approximately three-quarters of people) was significantly associated with mortality, whereas this was only observed with the highest average levels (≥ 75 mmol/mol, 28 % of type 1 diabetes; ≥ 64 mmol/l, 27 % of type 2 diabetes). This was reflected in the population attributable risks for 3-year mortality which, for average level (outside of 42 to 53 mmol/mol) were 16.9 % and 4.4 % for type 1 and type 2 diabetes respectively, and for variability (HVS 20 or more) were 26.2 %

and 23.2 % for type 1 and type 2 diabetes respectively (Table S4).

When the analysis was stratified by average level (< 64 or ≥ 64 mmol/mol, Fig. 3), the association between 3-year mortality and increasing HbA1c variability was consistently observed for type 1 and type 2 diabetes but tended to be greater among people with lower average levels (< 64 mmol/mol). For example, the HRs within the highest variability category compared to the least were now HR = 3.39 (95 %CI 2.16–5.33) and HR = 2.07 (95 %CI 1.86–2.18) for type 1 and type 2 diabetes respectively. Stratifying by age (≤ 60 or > 60 , Fig. S4) showed a consistent effect of HbA1c variability at both young and old ages for both type 1 and 2 diabetes, and stratifying by type of diabetes medication showed a consistent effect of HbA1c variability in all categories of medication type (Fig. S5).

Cross-classifying HbA1c average and variability (Table S5) directly in the Cox model produced similar findings to the main analysis, emphasising that both average and variability are independently associated with mortality risk. The U-shape for increasing risk with HbA1c level away from 42–53 mmol/mol is apparent at all HVS categories. At each category of HbA1c level, there are consistent gradients of

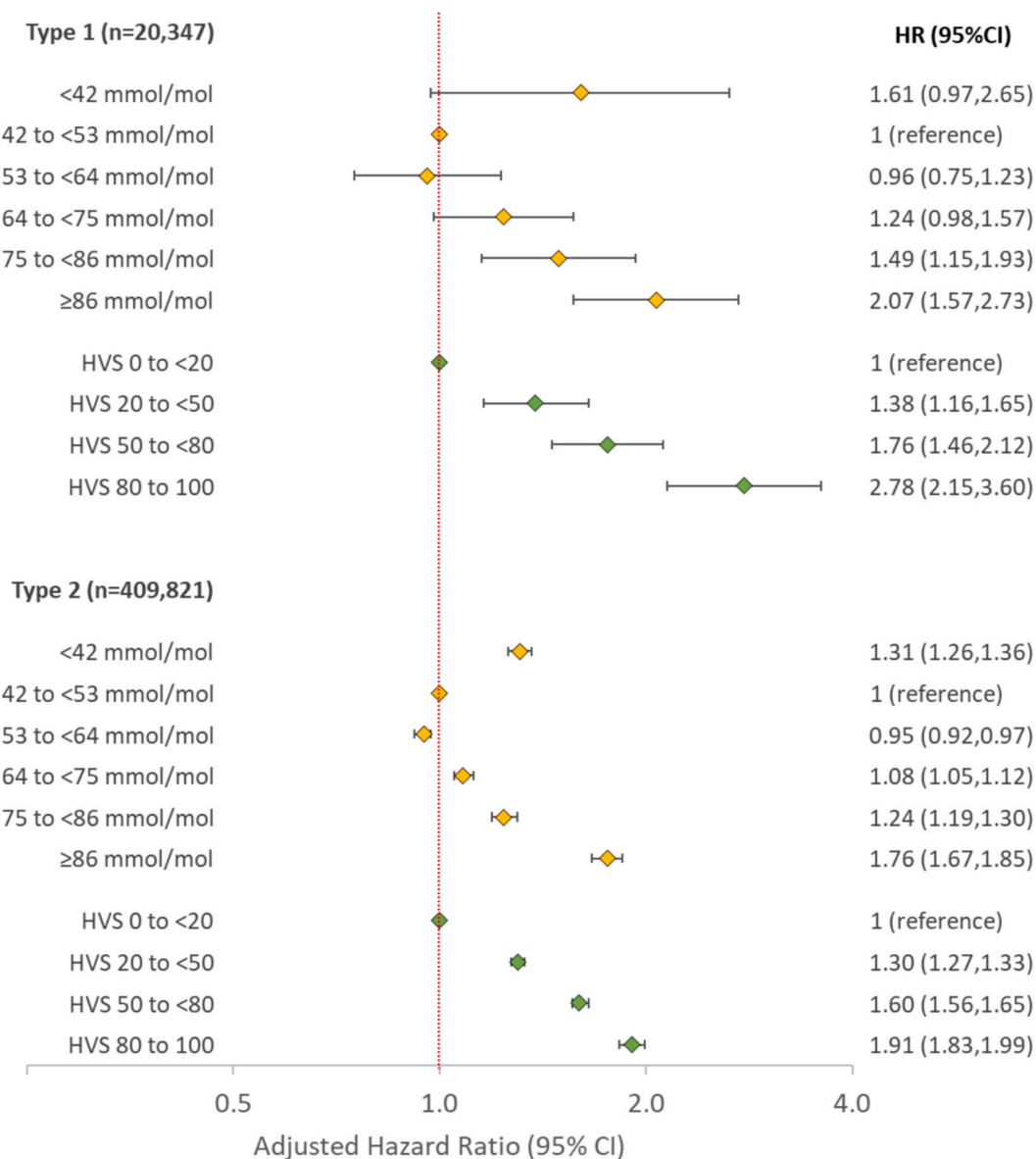


Fig. 2. Adjusted hazard ratios for all-cause mortality during 2015–17 by average HbA1c and HbA1c variability score (HVS) estimated in 2011–14, in type 1 and type 2 diabetes Hazard Ratios (HR) adjusted for age, sex, ethnicity, deprivation (IMD), time since diagnosis, co-morbidity count, smoking, BMI and HbA1c mean/variability. Tests for HVS trend were $p < 0.001$ (type 1) and $p < 0.001$ (type 2).

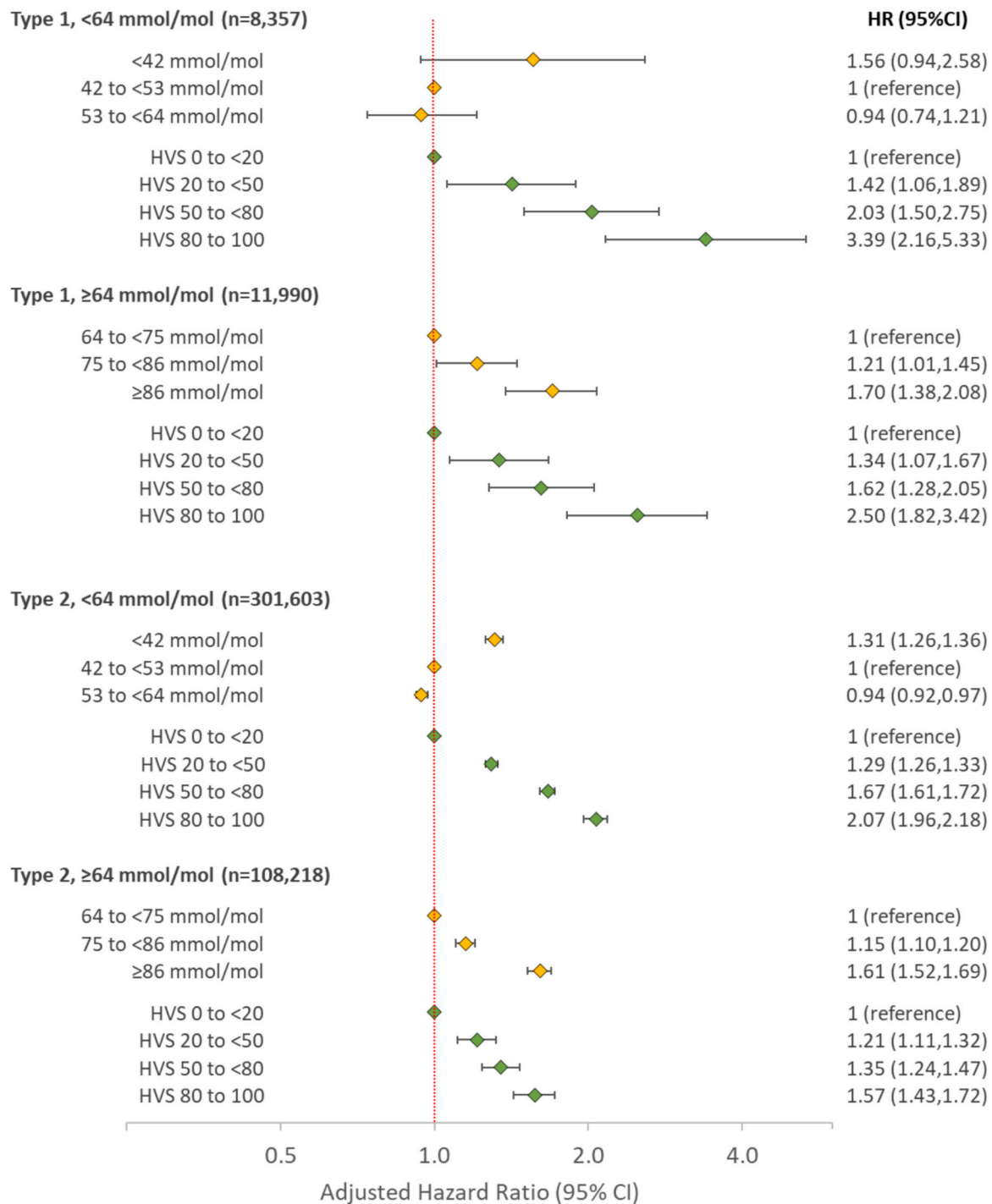


Fig. 3. Adjusted hazard ratios for all-cause mortality during 2015–17 by average HbA1c and HbA1c variability score (HVS) estimated in 2011–14, in type 1 and type 2 diabetes stratified by average HbA1c level HRs adjusted for age, sex, ethnicity, deprivation (IMD), time since diagnosis, co-morbidity count, smoking, BMI and HbA1c mean/variability. Tests for HVS trend were $p < 0.001$ (Type 1, <64), $p < 0.001$ (Type 1 ≥ 64), $p < 0.001$ (Type 2, <64), $p < 0.001$ (Type 2 ≥ 64). Tests for interaction between HVS trend and average level (<64 or ≥ 64) were $p = 0.10$ (Type 1) and $p < 0.001$ (Type 2).

increasing risk with HVS.

Two further analyses looked at the direction of fluctuation in HbA1c (increasing or declining). One found that both negative and positive fluctuations were separately associated with 3-year mortality for type 1 diabetes and type 2 diabetes (Table S6). Another analysis looked at the first recorded change in HbA1c measurement in 2015 from the last measurement made in 2014, and still found that both negative and positive changes were associated with mortality to the end of 2017 for type 1 and type 2 diabetes, independent of the 2015 HbA1c level

(Table S7).

3.4. Sensitivity analyses

There was minimal attenuation of the association between variability and mortality when all comorbidities were included in the model as individual variables instead of a simple comorbidity count (Table S4). An analysis that only considered follow-up to the end of 2015, produced the same conclusion that the observed associations with HbA1c

variability were stronger than for average level (Table S8). Similarly, restricting to HbA1c measures 90 to 730 days apart (Table S9) or using the coefficient of variation instead of the HVS (Table S10), did not change this finding. Analyses that excluded individuals who died early in follow-up, or were at higher risk (with any recorded history of hypoglycaemia or with any comorbidity), did not markedly attenuate the hazard ratios or attributable fractions (Tables S11-12).

4. Discussion

4.1. Key findings

Despite higher HbA1c levels, people with type 1 diabetes had similar patterns of HbA1c variability to type 2 diabetes. For both types of diabetes, variability was associated with younger age, obesity, comorbidities and living in deprived areas, while people of non-white ethnicities had more variability among type 1 diabetes only. While among type 1 diabetes those more recently diagnosed had more variability, the opposite was true in type 2 diabetes.

Variability in HbA1c measurements assessed over a 4-year period was associated with subsequent 3-year mortality among people with both type 1 and type 2 diabetes, independent from average HbA1c. While mean HbA1c was also important, this was less so than for variability, demonstrated by the higher population attributable fractions for mortality for variability than for average HbA1c, seen in both type 1 and type 2 diabetes. The higher attributable fractions suggests that more deaths may be statistically attributable to variability levels than optimal average HbA1c levels (although this assumes a causal relationship, which is not proven).

4.2. Strengths and limitations

A major strength of our study was the large size of the cohort, including over 400,000 patients with type 2 diabetes and over 20,000 with type 1 diabetes[30]. The CPRD is broadly representative of the UK population with respect to age, gender, and ethnicity[28,32]. By focusing on mortality over a 3-year period, it afforded us the statistical power to be able to look at the association of variability stratifying by average level and other factors such as age and sex. Thus, we were able to include people with type 1 diabetes in the same analyses, and importantly produce novel comparisons with estimated associations with HbA1c variability for people with type 2 diabetes.

As an observational study it is not possible to establish causality, but the associations seen between variability and mortality were strong, showed a dose–response pattern, were consistent at different levels of HbA1c, in both type 1 and 2 diabetes, and in both younger and older people. Additionally, the associations between mortality and variability were still observed even when the analysis excluded early deaths or was restricted to people with a lower risk of dying (no history of hypoglycaemic episodes, no co-morbidity). The HVS is a crude summary of variability over time, but is arguably easier to interpret than coefficient of variation, and sensitivity analyses using the latter produced similar findings. Our results were robust to adjustment for key measured confounders. However, it is possible that residual confounding remains, and that variability is a marker of unmeasured variables such as diet, physical activity, treatment adherence, or more detailed comorbidity phenotypes (e.g. considering ejection fraction in heart failure, or radiological findings in dementia – which we do not have sufficient information on in this dataset).

A limitation is that we only included people with diabetes with sufficient HbA1c measures (4 or more) collected in primary care during 2011–14, approximately 80 % of all eligible people with diabetes. Individuals with type 1 diabetes likely have more measurements stored in hospital records and not in the primary care results list available in this dataset. Most patients in UK primary care have their HbA1c measured once or twice a year, but some may have it measured more frequently. A

concern is that patients with diabetes measured more frequently will likely differ from other diabetes patients. However, one advantage of the HVS as a summary measure is that it is largely independent of how often patients were measured in our study, unlike other measures such as the standard deviation. [31]. Despite the potential limitations around the recording of HbA1c measurements, and exclusion of some patients, all our analyses consistently found associations to be stronger with variability measures than with average HbA1c level.

4.3. Findings in the context of what is known

The characteristics of people with high HbA1c variability are often not reported in detail, but findings of higher variability in individuals who are younger and with more comorbidities are consistent with other studies of people with type 2 diabetes [17,33,34].

The finding of higher mortality in people with more variability in HbA1c is consistent with several other studies in people with type 2 diabetes [8,11,15,17,21,24], and with studies that have combined people with type 1 and 2 diabetes [16,22]. For example, in a large database study in Sweden of over 100,000 people with type 2 diabetes and no cardiovascular disease, Ceriello et al reported dose–response HRs for 5 –year mortality [1.14, 1.27, 1.48] with quartiles of SD/variability [17]. We are only aware of one study that looked at the association specifically in individuals with type 1 diabetes; our findings are consistent with this smaller cohort Scottish cohort of approximately 6000 people with type 1 diabetes [23].

4.4. Implications for research and clinical practice

The pathophysiology explaining any causal association between HbA1c variability and mortality or morbidity outcomes remains uncertain. It is also not clear whether long-term fluctuations in HbA1c levels are reflective of short-term fluctuations in glucose levels. Some studies have found a partially mediating effect of hypoglycaemia, although this doesn't appear to completely explain the association in other data [14,18], and our results did not show an effect of adjustment for history of hypoglycaemia. There is likely under ascertainment of episodes of hypoglycaemia in the primary care records, as only those reported to and coded in primary care will be captured, but the more severe events would be more likely to be noted.

4.5. Unanswered questions and future work

The results from this study and the associated literature suggest the potential for a greater focus on variability in HbA1c among clinicians and patients, where the emphasis currently is on average HbA1c level. There is a challenge in confirming causality of this relationship and whether reducing variability would result in a corresponding reduction in risk of mortality (and other complications) as it would be difficult to design a trial aimed at focusing solely on reducing variability. It may not be possible to reduce variability in individuals with more complex comorbidities, which we know have some of the highest levels of variability. However, there are emerging opportunities to look at the effect of reducing variability with technologies for continuous glucose measurement and closed loop systems, as well as newer anti-diabetic medications that reduce variability[35,36].

Regardless of whether variability can be reduced, given its strong effects on mortality risk, it could be incorporated into HbA1c targets or trigger enhanced monitoring and support. Pei et al in a recent post hoc analysis of the ACCORD trial looked at tailoring HbA1c target levels based on variability data, assigning higher average HbA1c targets to individuals who have more variable HbA1c measurements [37]. For any clinical use of variability data, the way in which it is summarised is important[38]. The HVS used in our analysis would be relatively straightforward to incorporate into a clinical system that has a history of laboratory results.

5. Conclusions

In this study, higher variability in HbA1c was associated with subsequent mortality among people with both type 1 and type 2 diabetes, independent from average HbA1c. Future research should investigate whether reducing HbA1c variability in selected patients lowers mortality risk independent of HbA1c level improvements.

CRedit authorship contribution statement

Liza Bowen: Writing – review & editing, Writing – original draft. **Iain M Carey:** Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Umar AR Chaudhry:** Writing – review & editing, Methodology, Conceptualization. **Stephen DeWilde:** Writing – review & editing, Methodology, Conceptualization. **Selma Audi:** Writing – review & editing. **Elizabeth S Limb:** Writing – review & editing. **Derek G Cook:** Writing – review & editing, Methodology, Conceptualization. **Arshia Panahloo:** Writing – review & editing. **Peter H Whincup:** Writing – review & editing. **Naveed Sattar:** Writing – review & editing. **Tess Harris:** Writing – review & editing, Methodology, Conceptualization. **Julia A Critchley:** Writing – review & editing, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Role of the funding source.

The study funder had no role in study design, collection, analysis, and interpretation of data; writing of the report or decision to submit the paper for publication. IC had full access to all the data in the study, and LB and IC had final responsibility for the decision to submit for publication.

Authors' relationships and activities.

NS has consulted for and/or received speaker honoraria from Abbott Laboratories, AbbVie, Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novartis, Novo Nordisk, Pfizer, Roche Diagnostics, and Sanofi; and received grant support paid to his University from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics outside the submitted work.

Author contributions.

LB and IC wrote the first draft of the manuscript with input from all co-authors. IC led the data curation and statistical analysis. IC, UC, JC, SW, DC and TH were involved in the conception and design of the study. JC led on funding acquisition. LB, IC, UC, JC, SW, EL, AP, NS, SA, DC, PW and TH were involved in the interpretation of data for the work. LB, IC, UC, JC, SW, EL, AP, NS, SA, DC, PW, and TH approved the final version for publication. IC had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. LB and IC are the guarantors of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.diabres.2025.112229>.

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