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Effects of long-term HbA1c variability on serious infection risks in patients with type 2 diabetes and the influence of age, sex and ethnicity: A cohort study of primary care data

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ABSTRACT

Aims: Long-term HbA1c (glycated haemoglobin) variability is associated with micro- and macrovascular complications in Type 2 diabetes (T2D). We explored prospective associations between HbA1c variability and serious infections, and how these vary by HbA1c level, age, sex and ethnicity.
Methods: 411,963 T2D patients in England, aged 18–90, alive on 01/01/2015 in the Clinical Practice Research Datalink with ≥ 4 HbA1c measurements during 2011–14. Poisson regression estimated incidence rate ratios (IRRs) for infections requiring hospitalisation during 2015–19 by HbA1c variability score (HVS) and average level, adjusting for confounders, and stratified by age, sex, ethnicity and average level. Attributable risk fractions (AF) were calculated using reference categories for variability (HVS < 20) and average level (42–48 mmol/mol).
Results: An increased infection risk (IRR > 1.2) was seen with even modest variability (HVS ≥ 20, 73 % of T2D patients), but only at higher average levels (≥64 mmol/mol, 27 % patients). Estimated AFs were markedly greater for variability than average level (17.1 % vs. 4.1 %). Associations with variability were greater among older patients, and those with lower HbA1c levels, but not observed among Black ethnicities.
Conclusions: HbA1c variability between T2D patients' primary care visits appears to be associated with more serious infections than average level overall. Well-designed trials could test whether these associations are causal.

1. Introduction

There is increasing evidence that long-term glycaemic (HbA1c) variability may be a predictive marker for poor health outcomes and mortality among people with diabetes[1,2]. It is well established that maintaining lower levels of HbA1c can reduce the risk of microvascular complications and cardiovascular events in patients with Type 2 diabetes (T2D)[3]. Systematic reviews have more recently highlighted many studies which demonstrated that a risk of diabetes complications, such as renal disease, is associated with the variability in HbA1c measurements recorded over several years, and acts independently of the level of HbA1c[2,4]. Despite this, the interaction between HbA1c mean and variability has not been fully explored, and it has not been established whether the risks associated with variability differ by patient characteristics such as age, sex and ethnicity, which are already known to influence overall HbA1c level[5].

One of the challenges researchers have encountered is how best to summarise glycaemic variability, particularly in an accessible form that could be widely applicable to clinical practice; earlier research has used a variety of different parameters to assess variability[2,6]. Measures such as coefficient of variation may have statistical advantages in complex analyses, but are not easily generalisable for clinicians and patients[7]. Alternative measures such as the HbA1c variability score, which counts the number of significant changes in HbA1c level over time, have been suggested recently, are more clinically intuitive, and have been shown to provide similar findings[8]. Another issue is the

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close relationship between HbA1c variability and HbA1c level itself, as patients with higher levels tend to have more variation between measurements[6]. While some studies have adjusted for mean levels to demonstrate the independent effect of HbA1c variability, it is not clear whether the risks associated with higher HbA1c variability are similar between patients with low and high average HbA1c levels, or whether mean HbA1c might be an effect modifier.

Previously we used a large primary care database to show that HbA1c variability was positively associated with emergency hospitalisations and mortality among patients with T2D[9], with trends stronger than those observed with average HbA1c level. Among the outcomes, we also observed novel associations with infections requiring hospitalisation, which represent a substantial cause of ill health and health service use for people with T2D[10]. In this current, much larger and more recent study of people with T2D, we utilise improved ethnicity recording to further investigate the relationship between infection-related hospital admissions and visit-to-visit HbA1c variability. Specifically, we wanted to: (i) describe the associations between serious infections and variability at different average levels of HbA1c, (ii) compare these associations with variability by age, sex and ethnicity and (iii) assess which of HbA1c variability or average level were more important overall in the population of people living with T2D.

2. Subjects, materials and Methods

2.1. Data resource

The Clinical Practice Research Datalink (CPRD) 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[11]. It provides a pseudonymised longitudinal medical record for all registered patients (greater than 99 % of the UK population are registered with a General Practitioner), with diagnoses and other clinical information recorded using Read codes. By 2022, it included 16 million currently registered patients[12]. Over 90 % of contributing CPRD practices in England have consented to their data being linked to external sources; researchers have no access to geographical identifiers such as residential postcode[13]. These data sources include HES (Hospital Episodes Statistics), which records every NHS hospital admission in England[14], and the Index of Multiple Deprivation (IMD), a composite small-area (approximately 1500 people) measure used in England for allocation of resources[15]. Within CPRD, the distribution of IMD is comparable to the national distribution and provides researchers with a good proxy for individual socio-economic deprivation [16].

2.2. Study design and participants

We have previously described how we designed a cohort of 527,151 adults with T2D aged 18 to 90 alive on 1st January 2015 and actively registered for at least one year, from practices where hospitalisation linkage was available[10]. In this analysis, we restricted to 411,963 (78 %) patients who had at least four HbA1c measurements recorded in their primary care record, taken at least 30 days apart, during 2011–14 (Figure S1). In the UK, most T2D patients have on average 1–2 HbA1c measurements taken in a calendar year, however it is not routinely assessed in patients without diabetes, thus patients recently diagnosed with diabetes are less likely to fulfil these criteria. Most measurements since 2011 are recorded in mmol/mol; measurements made using older DCCT percentage units were converted by the formula (%value − 2.15) x 10.92. Infeasible values were excluded (<10 or > 200) and a mean in mmol/mol units was estimated. Categories for mean HbA1c level were chosen that map to integer values for the DCCT percentage units, with the exception of 42 (6 %) to 53 mmol/mol (7 %) which we further divided at 48 mmol/mol as this is used as a target in the UK for T2D patients managed by diet and lifestyle or by single therapy not associated with hypoglycaemia[17].

Patients were grouped into five broad ethnicity categories (White, South Asian, Black, Mixed/Other and missing) based on recorded Read codes[10]. In the UK, ethnicity is predominantly self-reported in primary care records. In our data, we were able to classify ethnicity for approximately 90 % of patients with T2D. All patients were followed up to the earliest date of: patient death or de-registration, practice leaving CPRD, or 31st December 2019.

2.3. Defining HbA1c variability

To summarise long-term HbA1c variability, we estimated a HbA1c variability score (HVS), similar to that originally suggested by Forbes[8] and used in other studies since[7,18]. 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 (Figure S2). As it has been shown to perform similarly to standard deviation or coefficient of variation, it has the potential advantage of being a more "clinically translatable" summary measure[7]. One criticism is whether an absolute visit-to-visit change of 0.5 % or 5.5 mmol/mol is equivalent for patients with very different baseline HbA1c levels, and whether the threshold for significant fluctuations should instead be based on a relative change (e.g. 10 percent or more from the previous measurement)[19]. For example, 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 (Figure S2).

For our main analyses, we present the HVS based on relative changes of +/-10 percent from the previous HbA1c; the rationale being that a percentage change might be a more important marker of variability than an absolute change in HbA1c. Additionally, by focusing on relative changes, the HVS will now be less closely related to the mean level. However, in sensitivity analysis we compare our findings with the original HVS based on an absolute change of 0.5 % (5.5 mmol/mol). We also explored estimating the HVS using annual means (2011–14) for 300,120 patients with a HbA1c recorded in each year. All HVS estimates were categorised into 4 levels (0-<20, 20-<50, 50-<80, 80–100).

2.4. Infection outcomes and covariates

We described previously how we classified and grouped infections resulting in a hospitalisation using ICD-10 codes in the linked hospital data[10]. Over a 5-year period (2015–19) we counted any new hospital episode (an admission or subsequent period of inpatient care) where an infection was the primary diagnosis. Episodes within 90 days of each other were assumed to be the same event and not counted. We also carried out an analysis by specific infection types: bone/joint, gastrointestinal, genitourinary, lower respiratory, sepsis, skin and surgical site. Following earlier concerns around ICD-10 coding on death certification data resulting in sepsis being underestimated[20], we took a conservative approach and counted sepsis, even if it was not the primary reason for the admission episode, but if it appeared within the first 5 diagnoses.

We also extracted patient information on smoking history, body mass index (BMI), co-morbidities and prescribing as of 1st January 2015. For smoking and BMI, we used the last recorded status/value, adding a missing category if no recording was available. We used 12 chronic conditions that were routinely collected as part of the Quality and Outcomes Framework (QOF), a UK wide system for performance management and payment of GPs in primary care[21]. These were 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. For anti-diabetic medication, we classified patients into the following categories based on prescriptions issued in 2014: none,

biguanides only, biguanides & other (excluding insulin), other (excluding biguanides & insulin), and insulin (only or in combination).

2.5. Statistical methods

Poisson regression compared infection rates across different categories of HbA1c variability score (HVS) and average HbA1c during follow-up with an offset fitted for total days of follow-up time in the study (Stata version 15). For average HbA1c level we used a reference category with the lowest observed risk (42 to < 48 mmol/mol). All models were adjusted for age, sex, ethnicity, socio-economic status (IMD quintile, with quintile 1 representing the most deprived 20 % small areas in England), body mass index (<25, ≥25-30, ≥30-40, ≥40), smoking (never, ex, current) and a comorbidity count. These were fitted first with average HbA1c and HVS categories separately, and then together. For each model we estimated attributable risk fractions (AF)[22], which assume the associations are causal and that all patients are shifted to the reference category (42 to < 48 mmol/mol for average HbA1c, 0 to 20 for HVS). To further explore whether HVS predicted infection risk independent of average level, we stratified the model by the categories of average level (and vice versa for average at different HVS categories). To assess the robustness of the association with HbA1c variability we carried out sensitivity analyses on subsets of patients with potentially better managed diabetes and/or lower presumed infection risk. These were: excluding patients with a history of hypoglycaemia by 2015; only including HbA1c measures if they were at least 90 days apart; excluding patients who had a prior infection hospitalisation during 2011–14; excluding patients on any anti-diabetic medication in 2014; only including patients first diagnosed in the last 5 years (2010–14); and only including patients whose HbA1c measurements during 2011–14 were all between 42 and 64 mmol/mol. We also explored whether the associations with variability differed according to the direction of the last recorded HbA1c change (either more or less than 10 % of the previous value). For stratified analyses of HVS by sex, age (<60, 60 +) and ethnicity, we simplified the categories for average level (<53, 53 to < 75, ≥75 mmol/mol).

3. Results

3.1. Summary of HbA1c measurements and variability

Among the 411,963 people with T2D eligible for the analysis, the median number of HbA1c measurements recorded during 2011–14 was 6 (IQR = 5–8), with a median gap between measurements of 198 days (IQR = 163–254). The average HbA1c level was 58.0 mmol/mol (SD = 14.0). More than 1-in-3 patients (n = 158,277, 38.3 %) had a HbA1c variability score (HVS) of 50 or greater, meaning that at least half of their measurements during 2011–14 were varying by 10 % or greater relative to the previous measurement. Estimating the HVS using a relative (10 %) versus absolute (5.5 mmol/mol) threshold produced a similar score (Table S1), though using an absolute threshold produced a score more highly correlated with mean level (r = 0.60). Using a relative threshold reduces the correlation (r = 0.40), but greater variability is still clearly observed at higher levels (Figures S3-S4).

3.2. HbA1c mean and variability by patient characteristics

Table 1 summarises how the mean average HbA1c level and HVS vary by patient demographics and baseline characteristics. Both measures fall with increasing age, but the trend was stronger with HVS, such that over half (51.2 %) of patients under age 60 had an HVS ≥ 50. Paradoxically however, those who have lived with a diabetes diagnosis for longer (> 15 years) had higher mean average HbA1c levels and HVS. Being male, of Black ethnicity, living in more deprived areas, having a higher BMI recorded and being prescribed more anti-diabetic medications and/or requiring insulin were also associated with higher mean average HbA1c levels and HVS. Although patients who had the most HbA1c measurements during 2011–4 (10 +) had higher mean average levels, the percentage of these patients with an HVS ≥ 50 was lower than those with fewer measurements.

3.3. Infections by HbA1c mean and variability

During the 5-year follow-up, 88,929 people with T2D (21.6 %) were hospitalised for an infection or had a hospital acquired infection (an annual rate 67.2 per 1,000 persons). Table 2 summarises adjusted IRRs for infections requiring hospitalisation from models that fit average HbA1c and HVS separately, and then together. While increasing HbA1c levels and variability were both separately associated with infections requiring hospitalisation, a 20 % greater risk (IRR > 1.2) was observed with modest variability (HVS ≥ 20, 73 % of T2D patients) whereas a greater risk was only seen at higher average levels (≥64 mmol/mol, 27 % of T2D patients). Attributable risk fractions (assuming a causal relationship and all patients achieve the reference category) were 19.1 % for variability and 10.0 % for average level. Mutually adjusting HbA1c average and variability for each other attenuated the IRRs in the highest category for each, but the greater risk with all categories of HVS persisted. Attributable risk fractions from this model were now 17.1 % for variability and 4.1 % for average level.

A series of sensitivity analyses for Table 2 were performed. Firstly, the analysis was restricted to different subsets of patients with potentially less severe diabetes (Table S2) and suggested that variability overall was still more influential than average level in predicting infections resulting in a hospitalisation. Then the HVS was re-calculated, first using an absolute threshold of 5.5 mmol/mol instead and produced very similar findings (Table S3). Then two further estimates of HVS using relative and absolute thresholds were calculated now using annual means during 2011–14 (new Table S4). Again, this produced the same conclusion as the original analysis.

3.4. Associations with HbA1c variability stratified by mean level

Fig. 1 summarises the IRRs for hospitalisation infections by HVS stratified by categories of average HbA1c level. The positive association between variability and infections is observed at all HbA1c levels except at the highest category (≥86 mmol/mol). At lower average HbA1c levels the association between infection risk and HVS was far stronger - for example, patients with an average level of HbA1c 42–48 mmol/mol who had an HVS ≥ 80 (n=1,500, 0.4 % of all T2D patients) were at double the risk (IRR = 1.99, 95 %CI 1.83–2.17) compared to patients with the least variability (HVS 0–<20). Moderate variability (HVS ≥ 20–50) among patients with an HbA1c average of 42–53 mmol/mol (12.9 % of all T2D patients) was associated with a 18–23 % increase in risk in hospitalisation infections. By contrast, models for average HbA1c level stratified by HVS categories (Figure S5) again show that larger increases in infection risk (IRR > 1.5) are only seen with the highest level of average HbA1c (≥86 mmol/mol). Estimated risks with HbA1c variability with infection were similar irrespective of the direction of the last recorded change i.e. whether HbA1c was rising or falling (Figure S6).

3.5. Associations with HbA1c variability stratified by sex, age and ethnicity

We explored how the risk of infection with HbA1c variability and average HbA1c level varied by sex, age (<60, 60 +) and ethnicity. First, stratified models (Tables S5-S6) suggested that the individual risks associated with HbA1c variability were more marked in women and older patients, but largely absent among the Black ethnic group. The risks with variability for each sub-group were then estimated at different average HbA1c levels (<53, 53–75, >75 mmol/mol) and are summarised in Figs. 2 and 3. The associations between HVS and infection at HbA1c levels below 75 mmol/mol are consistently observed in both men

Table 1
HbA1c average and variability scores during 2011–14, and hospitalisation for infection during follow-up (2015–19) by baseline patient characteristics.

		Total	Average HbA1c (mmol/mol) in 2011–14	HbA1c Variability Score (%) in 2011–14		Hospitalised for infection in 2015–19
		N	Mean (SD)	Mean (SD)	% with HVS ≥ 50	%
All		411,963	58.0 (14.0)	37.8 (27.5)	38.3	21.6
Sex	Females	181,891	57.6 (14.1)	35.8 (27.3)	35.4	22.5
	Males	230,062	58.3 (13.9)	39.4 (27.6)	40.5	20.9
Age (years)	18 to 40	8,361	64.2 (18.0)	51.5 (27.8)	58.4	12.0
	41 to 50	32,718	63.6 (16.9)	47.7 (27.4)	53.0	11.8
	51 to 60	76.253	62.0 (16.0)	44.3 (27.5)	47.8	13.4
	61 to 70	113,710	58.1 (13.6)	38.1 (27.2)	38.7	17.3
	71 to 80	116,903	55.5 (11.7)	33.2 (26.4)	31.5	26.0
	81 to 90	64,008	54.1 (11.2)	31.0 (26.3)	28.4	37.0
Ethnicity	South Asian	42,199	60.6 (14.4)	40.6 (27.5)	42.2	16.6
	Black	16,663	60.8 (16.4)	43.6 (28.8)	47.6	14.4
	Mixed	23,219	59.8 (14.9)	38.1 (27.6)	42.7	25.4
	White	293,279	57.3 (13.6)	40.8 (27.8)	36.8	16.0
	Missing	36,593	58.2 (14.1)	36.8 (27.3)	39.0	22.7
Time Since Diagnosis (years)	0 to 5	113,787	54.7 (12.2)	37.2 (28.8)	37.9	16.6
	5 to 15	222,587	58.1 (14.1)	37.1 (27.3)	37.3	21.4
	>15	75,579	62.9 (14.8)	40.7 (25.9)	41.7	29.7
Index of Multiple Deprivation	1 (least deprived)	69,914	56.7 (12.6)	35.2 (27.0)	34.4	19.9
	2	77,448	57.1 (13.1)	36.2 (27.3)	35.8	20.6
	3	79,789	57.8 (13.6)	37.2 (27.5)	37.4	21.2
	4	89,770	58.7 (14.4)	39.2 (27.6)	40.3	22.0
	5 (most deprived)	94,744	59.4 (15.4)	40.2 (27.8)	42.0	23.7
Body Mass Index (kg/m^2)	<25	63,144	55.7 (13.8)	33.7 (27.4)	32.4	23.4
	25 to < 30	140,058	57.0 (13.3)	35.8 (27.3)	35.3	20.1
	30 to < 40	173,130	59.2 (14.2)	39.8 (27.4)	41.1	21.3
	≥40	35,020	60.8 (15.1)	43.6 (27.3)	46.9	25.7
Smoking	Never	152,155	58.2 (14.1)	40.7 (28.3)	37.9	17.7
	Ex	207,611	57.3 (13.4)	37.3 (27.2)	37.5	23.9
	Current	52,165	60.1 (15.8)	37.5 (27.6)	42.7	23.9
Number of co-morbidities	0	89,359	60.6 (15.1)	41.4 (28.1)	43.3	13.0
	1–2	254,255	57.5 (13.7)	36.7 (27.4)	36.7	20.1
	>2	68,339	56.8 (13.3)	37.3 (26.9)	37.6	38.4
Number of HbA1c measures	4–6	212,156	56.1 (14.2)	38.0 (30.1)	39.4	20.5
	7–9	156,577	58.8 (13.3)	36.9 (25.2)	37.5	22.1
	10+	43,220	64.8 (12.9)	40.0 (21.4)	35.7	24.9
Anti-diabetic medications in 2014	None	68,655	46.3 (6.9)	21.1 (24.0)	16.2	20.5
	Biguanides only	124,521	52.4 (8.6)	32.8 (26.9)	30.7	18.1
	Biguanides & other[1]	130,748	62.7 (12.6)	46.1 (26.1)	49.9	19.2
	Other[2]	20,253	56.7 (11.7)	40.4 (26.8)	41.2	30.8
	Insulin[3]	67,776	71.5 (15.4)	47.3 (24.7)	51.5	30.9
Hospitalised for infection in 2011–14	No	364,535	57.8 (13.8)	37.1 (27.5)	37.2	18.6
	Yes	47,418	59.8 (15.7)	43.7 (27.2)	46.7	44.6

1 - Excluding insulin, 2 - Excluding biguanides & insulin, 3 - Only or in combination

and women, but for age the trends with HVS appear stronger among older patients with T2D (Fig. 2). Generally, all ethnicities show positive associations with HVS at HbA1c levels below 75 mmol/mol except for Black ethnicity, where there is an absence of a consistent positive association with variability (Fig. 3).

3.6. Associations with specific infection types

Finally, we investigated fitting adjusted models for HVS and average HbA1c level by specific infection types (Table S7). HVS was positively associated with all infection types, with all outcomes showing significant risks with just moderate variability (HVS ≥ 20). The largest association was with sepsis, where 1-in-5 (AF = 20.9 %) infections could be attributed to an HVS ≥ 20; similar strong associations were seen for bone and joint, genitourinary and lower respiratory tract infections. High average HbA1c level contributed most to bone and joint infection (AF = 12.9 %). For each infection type, attributable risk fractions for variability were higher than those estimated for average levels.

4. Discussion

4.1. Principal findings

In this large cohort study of adults with T2D, we have demonstrated that visit-to-visit variability in HbA1c measurements in primary care over several years is associated with the future risk of serious infections. Importantly, we have shown that this relationship is observed with only modest amounts of variability and is most pronounced at lower levels of mean HbA1c level. This was observed in men and women at all ages, but not among people of Black ethnicity.

4.2. Strengths and limitations

The major strength of our study is the overall size (over 400,000 patients with T2D), which provided substantial statistical power to investigate associations with variability in novel ways – by cross-classifying it with average level, or by looking within specific patient sub-groups such as by age group and ethnicity. The electronic patient

Table 2
Adjusted incidence rate ratios for average HbA1c level and HbA1c variability score for hospitalisation infections.

	No. of patients	Average only	Variability only	Average and variability
	N (%)	IRR* (95 % CI)	IRR* (95 % CI)	IRR* (95 % CI)
Average HbA1c				
- <42	27,364 (6.7 %)	1.11 (1.08–1.13)	_	1.12 (1.09–1.15)
42 to < 48	70,320 (17.1 %)	1 (Reference)	_	1 (Reference)
48 to < 53	78,215 (19.0 %)	1.00 (0.98–1.02)	_	0.97 (0.95–0.99)
53 to < 64	126,809 (30.8 %)	1.05 (1.04–1.07)	_	0.97 (0.95–0.98)
64 to < 75	60,922 (14.8 %)	1.26 (1.23–1.29)	_	1.10 (1.07–1.12)
75 to < 86	27,973 (6.8 %)	1.50 (1.46–1.53)	_	1.28 (1.25–1.32)
≥86	20,080 (4.9 %)	2.10 (2.04–2.16)	_	1.82 (1.77–1.87)
Attributable Fraction to average (%)*		10.0 %	_	4.1 %
HbA1c Variability Score				
0 to <20	110,318 (26.8 %)	_	1 (Reference)	1 (Reference)
20 to <50	143,898 (34.9 %)	_	1.22 (1.21–1.24)	1.21 (1.19–1.23)
50 to <80	125,284 (30.4 %)	_	1.45 (1.43–1.48)	1.38 (1.36–1.41)
≥80	32,453 (7.9 %)	_	1.67 (1.63–1.70)	1.53 (1.49–1.56)
Attributable Fraction to variability (%)*		_	19.1 %	17.1 %

IRR = Incidence rate ratio adjusts for age, sex, ethnicity (White, South Asian, Black, Mixed/Other, not recorded), deprivation (IMD quintile), co-morbidity count (0, 1, 2 or more), smoking (never, ex, current, not recorded) and body mass index (<25, ≥25-30, ≥30-40, ≥40, not recorded).
*Attributable fractions estimates assume a casual association under which all patients are moved to reference category.

records in CPRD permit adjustment for a range of other factors, which are associated with diabetes progression and likely increase infection risk, such as co-morbidities and socio-economic status. We also carried out sensitivity analyses limiting to T2D patients at presumably lower risk (e.g., no recent history of being hospitalised for infection, not currently prescribed anti-diabetic medication) and the results still suggested that HbA1c variability was playing a significant role in identifying patients at higher risk of future infections. Another advantage in our study design was to collate outcomes from a separate, but linked, database of hospital admissions from a non-overlapping period after we defined baseline exposure variables from CPRD including HbA1c variability. This helps reduce a potential bias that may have resulted from using the primary care data for infection outcomes, where patients being seen more often may be more likely to have infections recorded.

The main limitation concerns the nature of how the HbA1c measurements are collected in UK primary care. On average, most patients with T2D have their HbA1c measured once or twice per year, but not all, and some have more frequent measurements due to certain clinical requirements. Therefore, the time between measurements is not the same for all patients, and those who are measured more frequently are also likely to be seen in primary care more often, possibly related to ill-health. However, while patients with more measurements had higher HbA1c average levels, variability assessed by the HVS was largely independent of number of HbA1c measurements in our study. An obvious limitation of the HVS is that it does not account for time between measures, but then again, neither do more statistically intuitive measures such as the standard deviation[23]. Two of the sensitivity analysis we carried out addressed this issue (further excluding any measurements made within 31–90 days of each other, estimating the HVS based on 4 annual means rather than the individual measurements) and both produced similar findings, suggesting that the time discrepancy between measurements was unlikely to be an explanation for the observed associations.

Our analysis utilised attributable risks as a novel method to compare the overall burden of infections potentially attributable to HbA1c variability versus average HbA1c level. These assume our model estimates are causal which our study cannot assess. However, it would seem reasonable that any residual confounding or bias present in the models would affect both HbA1c measures (mean and variability) and is unlikely to change our finding of a greater overall impact for variability. Even so, the attributable risks are influenced by our arbitrary choice of categories for each measure, in particular the hypothetical reference category, which may not be a fair comparison. For example, for HbA1c level the reference category of 42–48 mmol/mol may be too narrow, plus adjusted infection risks were lower for average values just above this range. However, widening the reference category to 42–53 mmol/mol had only a minimal impact of the estimated attributable risk for average level (it increases from 4.1 % to 5.5 %) and would not alter our conclusion.

4.3. Comparison with other studies.

Systematic reviews and/or *meta*-analyses[1,2,4] have reported on the consistent finding from many observational studies that long-term glycaemic variability among patients with T2D is associated with both micro- and macrovascular complications from diabetes as well as all-cause mortality. By contrast the evidence from trials is more limited, but the greater risk of vascular events[24,25] and mortality[24,26] has been demonstrated with long-term glycaemic variability as well as with visit-to-visit fasting blood glucose[24,25,27]. We are not aware of any studies that have reported on the association in relation to a broad range of infections, besides our earlier study[9]. However, in two cohort studies that also included a range of microvascular T2D complications, the largest adjusted hazard ratios were seen for diabetic foot ulcers [7,28], where infection can be a common complication[29]. Our choice of a composite outcome of all serious infections, which were common in our patient group, may provide a proximal way to assess the effect of long-term HbA1c variations on poor outcomes more generally.

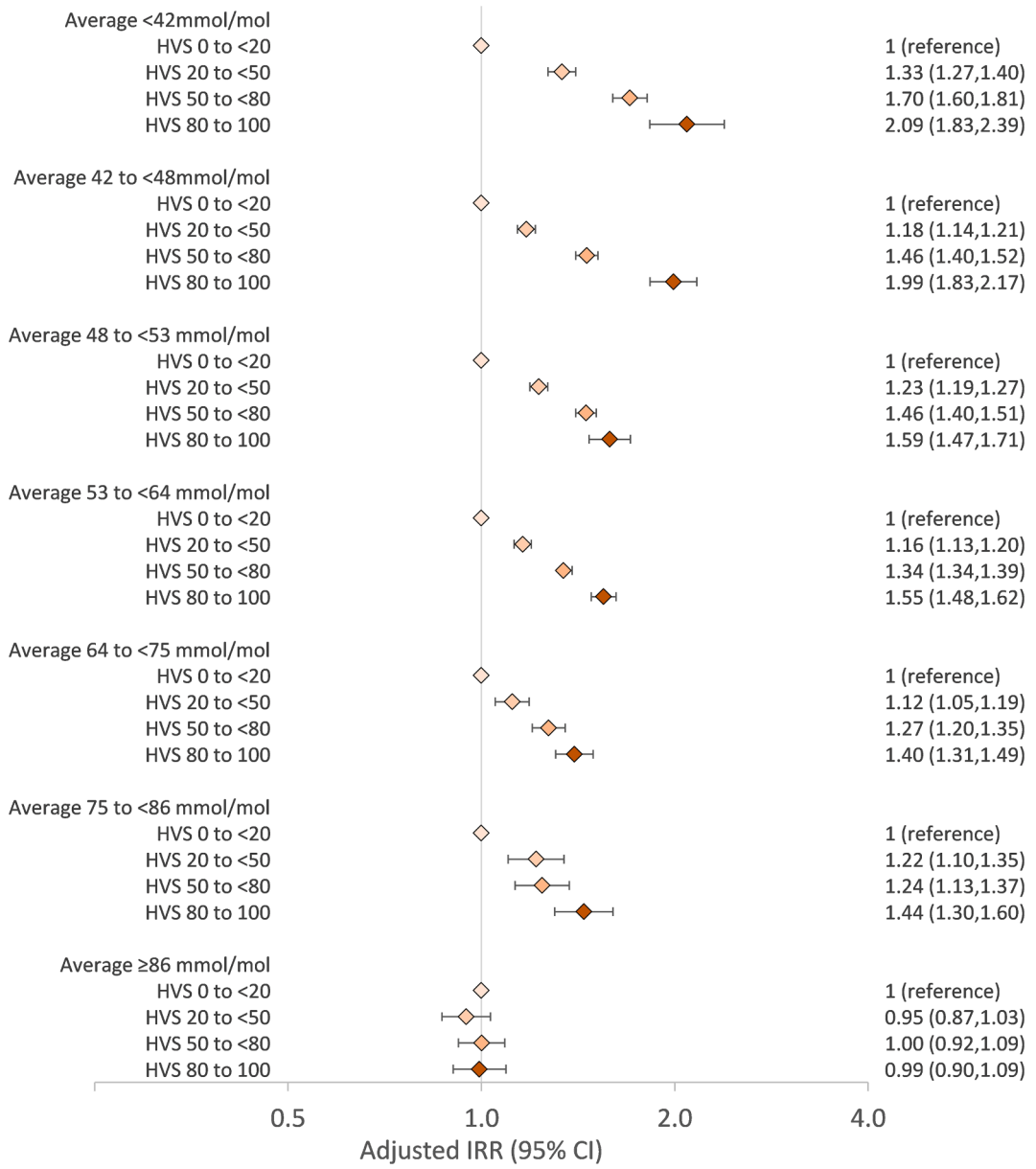

Fig. 1. Adjusted incidence rate ratios for hospitalisation infections by HbA1c variability score (HVS) at different categories of average HbA1c Note: 95% confidence intervals shown for incidence rate ratios. The distribution of HVS by average HbA1c level is given in Supplementary Figure S3.

The associations we observed between HbA1c variability and infection were present among both young and older patients living with T2D, but more pronounced among patients aged 60 and over. By contrast, a large Scottish cohort study of newly diagnosed T2D, found associations between HbA1c variability and outcomes including diabetic foot, were greater in patients under 65 years[7]. No previous research we were aware of has looked at the impact of HbA1c variability by ethnicity. HbA1c has been shown to be higher among people of Black African and Black Caribbean ethnicity, among those with and without diabetes, relative to underlying blood glucose levels[30]. Additionally, sickle cell and G6PD genetic traits are common and may result in some underestimation of HbA1c[31]. The lack of an association between serious infections and HbA1c variability among people of Black ethnicity is novel, but unclear and requires further explanation. It could also be related to inequalities around health care use, and different patterns of hospital admissions by ethnic group in the UK[32]. Of note, in the same dataset, we had previously observed lower rates of hospitalisation for infections among people of Black ethnicity and a lack of an association with prediabetes for this outcome among people of Black ethnicity only [10].

4.4. *Implications.*

Our analyses suggest that despite the increased risk of future infections in individuals with very high HbA1c levels, more infections in T2D patients overall might be statistically attributable to HbA1c variability, as a result of this phenomenon being observed in a greater proportion of patients (almost 4-in-10 had a HVS of $\geq$ 50). This would concur with a recent *meta*-analysis that suggested that "HbA1c variability can have a greater impact on the development of complications than the HbA1c level per se"[1]. Additionally, we showed that the direction of the variability (on the last recorded measure) did not seem to matter in terms of the observed risk. This may seem surprising and poses the question as to whether the variability is simply a marker of some other factors in these patients. Despite the strong positive relationship between HbA1c level and variability, we showed the effect of HVS was

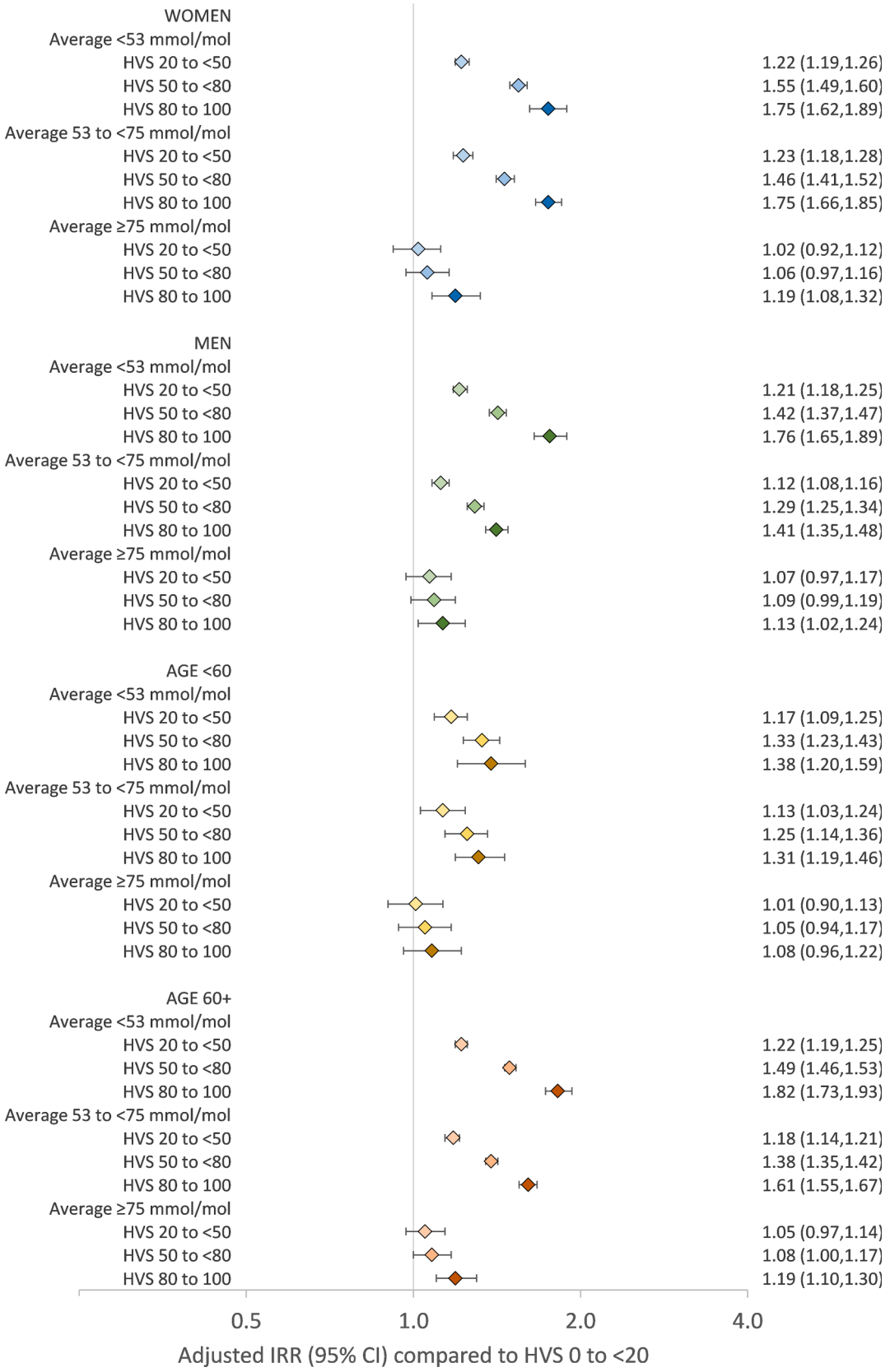

Fig. 2. Adjusted incidence rate ratios (IRR) for hospitalisation infections by HbA1c variability score (HVS) at different categories of average HbA1c, stratified by sex and age. Note: 95 % confidence intervals shown for incidence rate ratios. All comparisons are with a reference category of HVS 0 to < 20. The distribution of HVS by average HbA1c level for each sub-group is given in Figure S7 for age and sex.

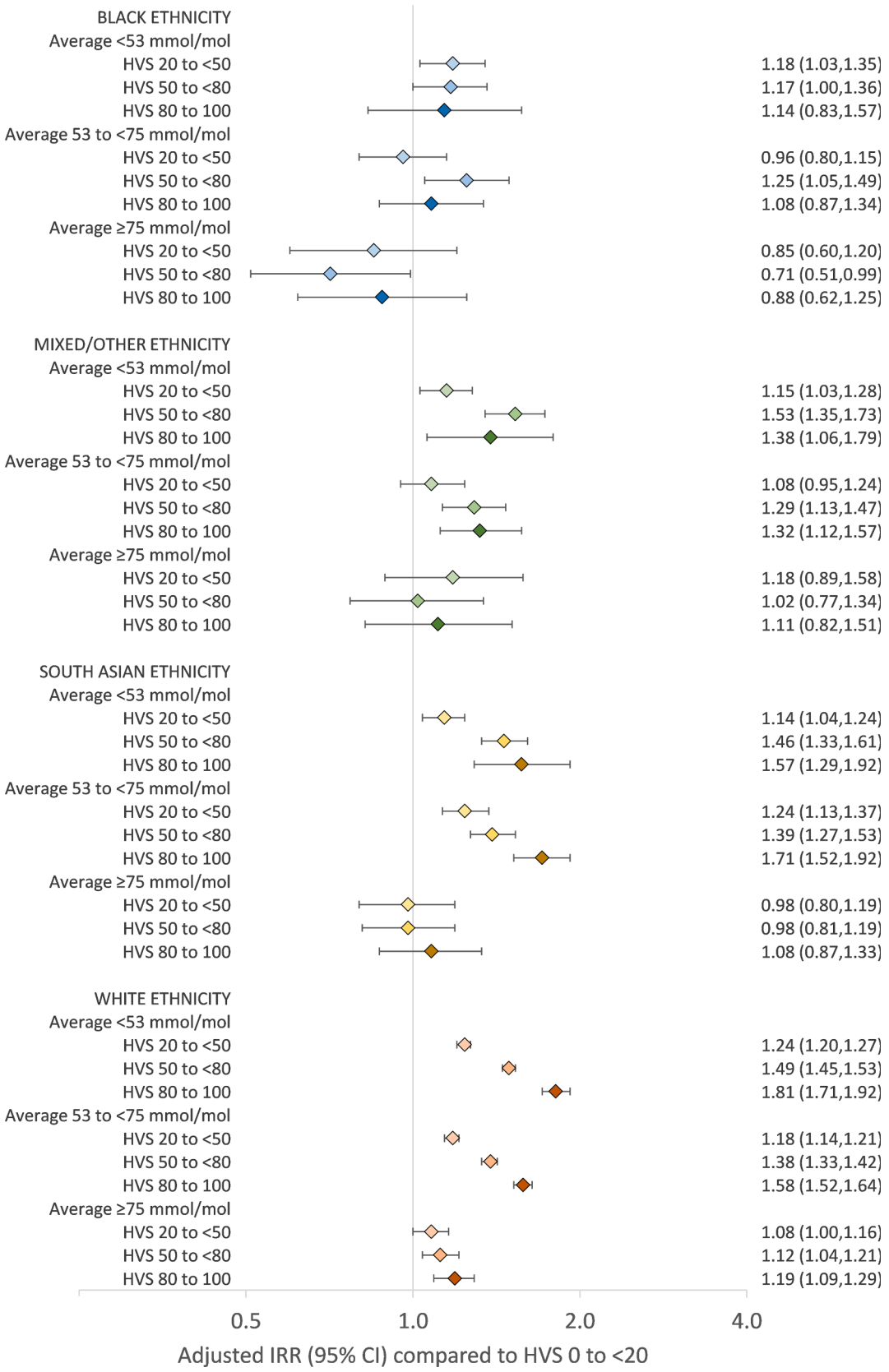

Fig. 3. Adjusted incidence rate ratios (IRR) for hospitalisation infections by HbA1c variability score (HVS) at different categories of average HbA1c, stratified by ethnicity. Note: 95 % confidence intervals shown for incidence rate ratios. All comparisons are with a reference category of HVS 0 to < 20. The distribution of HVS by average HbA1c level for each sub-group is given in Figure S8 for ethnicity.

most apparent in T2D patients with the lowest HbA1c levels raising the possibility that visit-to-visit stability may provide additional benefits for avoiding serious infections even when target levels have been achieved. The greater impact of variability in patients with lower average HbA1c levels was seen in both the VADT trial with cardiovascular disease incidence[25], and the ACCORD trial with all-cause mortality[26]. Stronger associations between HbA1c variability measures and cardiovascular outcomes in T2D patients were also observed in cohort studies in Scotland[7] and Sweden[28] when restricted to those with lower average HbA1c levels (<7% or 53 mmol/mol).

Our findings, along with those from many other studies, continue to emphasise the importance of HbA1c visit to visit variability as a potentially useful risk marker. While incorporating glycaemic variability into the prevention and management of cardiovascular disease in people living with diabetes has been argued[33], elevated HbA1c levels will always be the primary therapeutic concern[19]. Our sensitivity analyses revealed that the association with HVS was still observed in patients whose measurements stayed between 42 and 64 mmol/mol, suggesting there may be additional benefit to highlighting fluctuations in T2D patients who are within an acceptable range of glycaemic control [28]. The simplicity of the HVS could offer a straightforward way to track and monitor variability for patients and clinicians which can be easily integrated with existing computerised risk management algorithms in primary care, such as for blood pressure variability in QRISK3 for cardiovascular disease in UK primary care[34]. Whilst knowledge of HbA1c variability might improve risk stratification, what is yet to be established is whether reducing HbA1c variability in T2D patients would reduce the risk of infections or any other diabetes complications. Sodium-glucose co-transporter-2 (SGLT2s) inhibitors have been shown to lower glucose variability in both Type 1 and Type 2 diabetes patients [35,36], and in a post-hoc analysis of the EMPA-REG OUTCOME trial data, empagliflozin was shown to reduce both HbA1c variability in T2D patients and lower the risk of cardiovascular death[37]. However, the analysis was unable to directly attribute the lower mortality risk to the reductions in HbA1c variability observed during the trial. Whilst there have been calls to incorporate glycaemic variability into diabetes management[33], any such strategy ideally requires supporting intervention studies to establish causality and reversibility.

4.5. Conclusions.

Our analyses examining serious infections adds to the evidence base that people with type 2 diabetes who fluctuate significantly in their HbA1c measurements between primary care visits are at a higher risk for adverse health outcomes than patients with more stable readings over time, independent of their average HbA1c level. However, these findings are based on observational data, so it remains unknown whether reducing glycaemic variability would lower individual risks accordingly. While better awareness of HbA1c variability as a potential risk factor could be inferred[8], only a well-designed intervention can elucidate what the true long-term benefits of directly treating variability in HbA1c might be on quality of life and diabetes complications.

Tweet.

Long-term glycaemic variability in people with type 2 diabetes may account for more serious infections requiring hospitalisation overall than average HbA1c level.

Data availability

The data that support the findings of this study are available from Clinical Practice Research Datalink (CPRD) obtained under license from the UK Medicines and Healthcare Products Regulatory Agency (MHRA), but restrictions apply to the availability of these data, which were used under license for the current study and therefore are not publicly available. CPRD data governance and the license to use CPRD data does not allow distribution of patient data directly to other parties. Researchers must apply directly to CPRD for data access (https://www.cprd.com). However, code lists generated during the current study are available in the repository https://doi.org/10.24376/rd.sgul.21565557.v1.

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Authors' relationships and activities

NS has received grant and personal fees from AstraZeneca, Boehringer Ingelheim, Novartis, and Roche Diagnostics; and personal fees from Abbott Laboratories, AbbVie, Amgen, Eli Lilly, Hanmi Pharmaceuticals, Janssen, Menarini-Ricerche, Novo Nordisk, Pfizer, and Sanofi outside the submitted work.

CRediT authorship contribution statement

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

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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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2024.111641.

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