**Variability in glycated hemoglobin and risk of poor outcomes among people with type 2 diabetes in a large primary care cohort study**

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***Abstract***

***Introduction***

Diabetes guidelines focus on target glycated hemoglobin (HbA1c) levels. Long-term variability in HbA1c may be predictive of hospitalization or mortality, but its importance at different average levels or trajectories is unclear.

***Research Design and Methods***

Using English primary care data, 58,832 Type 2 diabetes mellitus patients had HbA1c average (mean of annual means), variability (coefficient of variation, CoV) and trajectory (annual regression slope) estimated during 2006-9. Hazard Ratios (HRs) for all-cause mortality and emergency hospitalization during 2010-5 adjusting for age, sex, smoking, Body Mass Index, duration of diabetes and deprivation were estimated using Cox regression. The simultaneous impact of HbA1c average, variability and trajectory was estimated using percentiles.

***Results***

In mutually adjusted models, HbA1c variability showed a consistent dose-response relationship with mortality, while average level was only important among individuals in the highest or lowest 10% of the distribution, trajectory had no independent effect. Individuals with the most unstable HbA1c (top 10%) were almost twice as likely to die (HR=1.93, 95% CI 1.72-2.16) than the most stable (bottom 10%); an association attenuated but not explained by hypoglycemia. For emergency hospitalizations, similar trends were seen except for coronary artery disease (CAD) and ischemic stroke (IS), where increasing average rather than variability was predictive.

***Conclusions***:

HbA1c variability was strongly associated with overall mortality and emergency hospitalization, and not explained by average HbA1c, or hypoglycemic episodes. Only for CAD and IS hospitalizations was no association found, with average HbA1c strongly predictive. Targets should focus on both stability and absolute level of HbA1c.

**Introduction**

There is substantial evidence that increases in chronic levels of average hyperglycaemia (as generally measured by glycated hemoglobin, HbA1c) are associated with higher risk of various diabetes complications including microvascular and macrovascular events[1](#_ENREF_1)[2](#_ENREF_2), particularly when these are substantially elevated (for example, above 8% HbA1c [64 mmol/mol])[3](#_ENREF_3). Randomized controlled trials (RCTs) showed that lower HbA1c is associated with significant reductions in risk of microvascular complications[3](#_ENREF_3)[4](#_ENREF_4), though less convincingly or consistently in risk of all-cause mortality or cardiovascular disease[5](#_ENREF_5) [6](#_ENREF_6) [7](#_ENREF_7)[8](#_ENREF_8). Average HbA1c does not explain all the variation is risk observed though; including variability in HbA1c improved prediction of microvascular events in secondary analyses of the Diabetes Control and Complications Trial[9](#_ENREF_9). Recent studies using latent growth modelling have also demonstrated that type 2 diabetes mellitus (T2DM) patients with “low and stable” patterns of HbA1c over time have lower risks than those with upward, downward, or more variable patterns[10](#_ENREF_10)[11](#_ENREF_11). It has thus been hypothesized that longer-term variability in serial HbA1c measurements may also be important[12](#_ENREF_12)[13](#_ENREF_13).

Existing studies of HbA1c variability have provided somewhat conflicting evidence. A systematic review of observational studies published in 2015 found some evidence of higher risk associated with HbA1c variability for both type 1 and T2DM[12](#_ENREF_12). Among the 43,000 T2DM patients across 13 studies, higher variability resulted in increased risks of Cardiovascular Disease (CVD) and all-cause mortality, as well as certain microvascular outcomes (particularly retinopathy and neuropathy)[12](#_ENREF_12). However, most of the included studies had limitations such as little adjustment for key confounders[12](#_ENREF_12). Almost all included studies were based solely on secondary care patients, whilst globally most diabetes patients are managed in the community or primary care. Also, there were high levels of heterogeneity between studies which could not be explained, possibly related to different definitions and measurements of variability, follow-up durations, diabetes durations, or losses to follow-up. Not all recent studies have shown substantially increased risks associated with variability (after adjusting for mean HbA1c)[12](#_ENREF_12)[14](#_ENREF_14); a recent overview concluded that variability in HbA1c was “not yet established” as an independent risk factor for diabetes complications[13](#_ENREF_13).

Whilst randomized data might be ideal, individual RCTs lack statistical power for teasing out the relative impact of variability, after accounting for inter-related HbA1c parameters such as trajectory (direction and gradient of any trend in HbA1c over time; whether up or down) and average HbA1c. Larger registry or database analyses are therefore critical, but relatively few have been published[15](#_ENREF_15)[16](#_ENREF_16), and all had limitations. In particular few previously published registry or observational studies adjusted for hypoglycemic episodes. These are known to increase mortality risk[17](#_ENREF_17)[18](#_ENREF_18) and are not strongly correlated with average HbA1c[19](#_ENREF_19)[20](#_ENREF_20). Given the continued uncertainty, we assessed the importance of HbA1c variability in predicting key outcomes (all-cause mortality, CVD mortality, Coronary Artery Disease [CAD] and Ischemic Stroke [IS] mortality, and non-cardiovascular mortality, all emergency hospitalization (overall and for infections and CVD, CAD and IS) in a large representative retrospective cohort of primary care patients in England. Unlike previous studies, our large analysis included both men and women, middle aged and older age groups (ages 40-89) and better characterization of variability and average HbA1c as well as adjustment for key confounders[12](#_ENREF_12)[15](#_ENREF_15)[16](#_ENREF_16).

**Methods**

***Data Source***

The Clinical Practice Research Datalink (CPRD) is a large primary care database representative of the United Kingdom (UK) population[21](#_ENREF_21)[22](#_ENREF_22). This study is based on 361 general practices in England only with anonymous linkage to Hospital Episodes Statistics (HES) and Office for National Statistics (ONS) death registration data[23](#_ENREF_23). HES records clinical and administrative information on all National Health Service (NHS)-funded inpatient episodes and allows for identification on method of admission (e.g. emergency), in addition to the primary reason for the admission[24](#_ENREF_24). Linkage is also available to the Index of Multiple Deprivation (IMD), the official measure for small area deprivation in the UK, a composite ecological measure based on postcodes[25](#_ENREF_25). IMD combines data from 7 domains (income, employment, education skills and training, health and disability, crime, barriers to housing and services, and living environment), ranking local areas from the most deprived (1) to the least deprived (32,884)[25](#_ENREF_25).

***Study Design***

We carried out a further analysis of individuals with diabetes from a previously published retrospective matched cohort study[7](#_ENREF_7)[22](#_ENREF_22). Diabetes type was classified using a combination of diabetes (DM) Read codes and prescribing of anti-DM medication[22](#_ENREF_22). Read codes are a primary care clinical terminology used extensively in the UK[26](#_ENREF_26). They are structured similarly to International Classification of Disease (ICD)-9 and cross mapping tables are available**.** In this analysis, we included only patients who were identified as having T2DM by 01/01/2008 (n=82,492), and continuously registered with their practice to at least 1/1/2010 (Supplementary Figure 1). From this group, we then restricted to 58,832 (71.3%) patients with at least 1 glycated hemoglobin (HbA1c) measurement in each calendar year during the four-year baseline period (2006-9). All patients were then followed for outcomes from 1/1/2010 until the earliest date of: death, de-registration from practice, practice leaving CPRD, or 31 December 2015. Mean follow-up time for all patients was approximately 4.1 years.

***Outcomes***

We measured the following primary outcomes during follow-up: all-cause mortality and first emergency hospitalization (defined as an admission which was unpredictable and at short notice because of clinical need). In further analyses, we divided mortality into cardiovascular (CVD; any ICD-10 code beginning with “I”) and non-cardiovascular using underlying cause of death. We subsequently sub-divided CVD into those deaths related to Coronary Artery Disease – (CAD); I20-I25.9) and Ischemic Stroke (IS; I63-64) versus all other CVD codes. These causes were chosen based on a prior study demonstrating strong associations with average HbA1c[28](#_ENREF_28).

We also stratified emergency hospitalizations into infection related, CVD, and CAD + IS admissions. We included infection using previously defined codes[8](#_ENREF_8)[25](#_ENREF_25), due to strong associations with hyperglycaemia and since infections may also promote HbA1c variability[7](#_ENREF_7), [22](#_ENREF_22).

***HbA1c Summaries***

Using all recorded HbA1c measurements from 2006-9, for each patient we estimated:

1. Average HbA1c using the mean of annual means in each year;
2. Variability in HbA1c using the coefficient of variation (CoV) and
3. Trajectory in HbA1c estimated from the individual patient annual slope from a linear regression model.

Patients had a minimum of 4 recorded HbA1c measurements to be included (one per year in the main analysis; or 4 at any time in a less restrictive sensitivity analysis). We summarized the impact of average, variability and trajectory of HbA1c by creating six categories for each measure (using the 10-25-50-75-90th percentiles as cut-points – see Supplementary Figure 2). These categories are not of equal size because we wanted to be able to investigate extremes. However, by using the same percentiles for each measure this ensures a fair comparison of the importance of each of these three HbA1c summary measures. We chose reference categories according to the category with the a-priori lowest risk – for level this was the 10-25th percentiles (HbA1c >6.09 to 6.58% [43-48 mmol/mol]) due to the J-shaped distribution observed, for variability this was the most stable 10% (CoV = 0 to 3.14), and for trajectory the category with the smallest annual slope (>-0.20 to +0.01%/year).

***Confounders***

In our primary analyses, we adjusted for age, sex, practice, smoking status, Body Mass Index (BMI), duration of DM and deprivation (IMD). In secondary analyses, we further adjusted for baseline (01/01/2010) comorbidities, hypoglycemic episodes, anti-DM medications, and medications to reduce cardiovascular risk (statins, anti-hypertensives).

For co-morbidities, we searched the primary care record for any Read code denoting a history of atrial fibrillation, metastatic cancer, Chronic Obstructive Pulmonary Disease, dementia, epilepsy, heart failure, psychosis, schizophrenia or bipolar disorder, stroke or transient ischemic attack[29](#_ENREF_29). Hypoglycemic episodes were similarly identified using Read codes, and additionally ICD-10 codes on the linked hospital record. We categorized use of anti-DM medications in the baseline period (2006-2009) into 5 mutually exclusive hierarchical categories: any use of insulin; sulphonylureas (without insulin); biguanides (without insulin or sulphonylureas); other anti-DM medications (with or without biguanides); none.

***Statistical Analysis***

Cox regression was used to estimate Hazard Ratios (HRs) for all-cause mortality and time to first emergency hospitalization during follow-up, adjusting for age, sex, practice, smoking status, BMI, durations of DM and deprivation (IMD). We then compared the impact of average, variability and trajectory of HbA1c by separately fitting the comparable categories described above to the models. Subsequently, we fitted mutually adjusted models which included 2 and then all 3 of these HbA1c summaries. In sensitivity analyses, we further adjusted for additional confounders including a history of significant hypoglycemic episodes, comorbidities using a score[29](#_ENREF_29) validated for use with UK primary care data, and medication both for diabetes and for reducing cardiovascular risk (anti-hypertensives, statins), as described above.

Our main analyses were carried out with baseline (2006-2009) HbA1c measures. We then carried out a number of sensitivity analyses. In the first we excluded all patients who died within the first 2 years after baseline to assess the impact of “reverse causality”, as it seemed plausible that control might become more variable in the last few years before death. In a second, less restrictive analysis, we included 74,339 (over 90%) of patients who had at least 4 measurements of HbA1c at any time during the baseline period (2006-2009), relaxing the requirement to have at least one measurement per year. Finally, we fitted a model with time-dependent HbA1c summaries, where we updated each of the three main parameters (average, variability, and trajectory) on an annual basis (2011 to 2015) by including the most recent year of data into the 4 year run-in period and dropping the earliest year.

We assessed whether the pattern of relationships between average, variability and trajectory of HbA1c was similar for different cause-specific outcome measures (CVD, CAD, IS and infection mortality or admissions. All analyses were performed in SAS version 9.4.

**Results**

The mean age of the 58,832 eligible patients was 67.7 years (SD=10.9) in 2008, with 55.3% men (Supplementary Table 1). Over the 4-year run-in period, eligible patients averaged 7.9 total measurements of HbA1c, with a mean level of 7.4% (SD=0.7), and a slight downward trajectory (-0.01%/year). Average level and coefficient of variation (CoV) were positively correlated (r=0.40), while trajectory was only weakly negatively correlated with variability (r=-0.12) and not at all with average (r=-0.002) (Supplementary Figure 2). Higher average levels, increasing variability, and positive or negative trajectories were all associated with younger age and obesity, while longer duration of DM was only related to increasing average level (Table 1 and Supplementary Figure 3). Type of DM treatment had a significant impact on average, variability and trajectory, with those on insulin having higher average levels, more variability and positive or negative trajectories (Supplementary Figure 4).

***HbA1c and Mortality***

In separately adjusted Cox models, both higher and very low levels of average HbA1c (below 6.09% [**43 mmol/mol]** or over 7.16% HbA1c [**55 mmol/mol]**), increasing variability, and positive or negative trajectories of HbA1c were all associated with higher all-cause mortality (Table 2). In mutually adjusted models (adjusting for variability, average and trajectory of HbA1c simultaneously) the impact of average HbA1c was now only seen in the top 10% of the HbA1c distribution (HR=1.35, 95%CI 1.24-1.47 for HbA1c >8.88% [**74 mmol/mol]** vs reference category of >6.09 to 6.58% [43 to 48 mmol/mol]), while only a small impact of negative trajectory remained. Adjusting for CoV explained virtually all the effect of trajectory (Supplementary Table 2). By contrast, a graded increase in mortality risk was seen with increasing variability, ranging from HR=1.32 (95%CI 1.21-1.44) in the 25-50th percentile group for CoV and HR=1.93 (95%CI 1.72-2.16) in the top 10th percentile category. Further adjustment for history of hypoglycemic events attenuated the impact of variability, but it still maintained a stronger and more consistent association with mortality than average (Table 2). Sensitivity analyses adjusting for comorbidities did not impact the estimates of mortality risk associated with any of the HbA1c measures, while adjustment for DM treatment category explained the greater risk associated with highest average level but not any of the associations with variability (Supplementary Table 3). Results were similar for older and younger groups (Supplementary Figure 5). Excluding patients with less than 2 years survival after baseline did not substantially change any coefficient (Supplementary Table 4). Including more patients by relaxing the inclusion criteria to 4 HbA1c measurements at any time did not significantly alter any patterns of risk (Supplementary Table 5).

The impact of variability on mortality risk was seen at both the highest and lowest levels of average HbA1c (Figure 1 and Supplementary Table 6). Among 14,703 patients (25%) with the lowest average HbA1c levels (below 6.6% [48 mmol/mol]), HR for mortality was 1.40 (95%CI 1.06-1.85) for those with the highest levels of CoV (>16.64%). For 14,737 patients with the highest average HbA1c levels (above 7.9% [63 mmol/mol), the respective HR for the highest CoV was 2.14 (95% CI 1.32-3.47). The impact of increasing average HbA1c for those patients with the highest and lowest CoV was again restricted to those in the top category; for the 25% of patients with the lowest CoV, average HbA1c of 8.88% [**74 mmol/mol]** or higher had a raised risk (HR=1.49, 95%CI 1.06-2.11) of mortality, similar to the HR of 1.31 (95%CI 1.11-1.54) for those with the same average HbA1c and the highest levels of CoV.

In time-updated Cox models, CoV became a stronger predictor of mortality risk (HR=2.97, 95%CI 2.60-3.38 for those with the highest CoV of 16.64% or above) whilst the average HbA1c was no longer statistically significant, even at the highest level of >8.88% [>**74 mmol/mol]** (HR=1.05, 95%CI 0.95-1.16). (Supplementary Table 7).

However, the pattern of variability being more strongly associated than average level was somewhat altered when the cause of death was CAD and IS (Supplementary Table 8). Here a rise in mortality was seen with any average HbA1c above 7.91% [63 mmol/mol], and there was almost a doubling in risk of death for those with the highest HbA1c levels (HbA1c above 8.88%; **74 mmol/mol**; HR = 1.88, 95% CI 1.60 to 2.21). Associations with variability were still present but slightly weaker for CAD and IS deaths (HR =1.54 95%CI 1.23 to 1.93) for the most variable patients (CoV over 16.64%).

***HbA1c and Hospitalizations***

Both average and CoV HbA1c showed statistically positive associations with time to first emergency hospitalization, while trajectory was not related (Table 3). Overall, and for infection and all CVD hospitalizations, the magnitude of the association was more comparable between average level and variability, especially at extreme levels. For CAD and IS hospitalizations the pattern was different; a stronger graded association with average HbA1c was now seen. Risk was increased for any HbA1c above 7.16% [55 mmol/mol] and for the top 10% (above 8.88%; >**74 mmol/mol** there was over a doubling in risk of hospitalization (HR 2.13, 95% CI 1.91 to 2.37). Further, associations with rising CoV were no longer statistically significant (Table 3). Trajectory was not independently associated with hospitalization.

**Discussion**

***Key Messages***

Increasing variability and raised average level of HbA1c were both associated with higher risks of mortality. Trajectory of trend in HbA1c was not associated after adjustment for variability (see Supplementary Table 2). There appeared to be a J-shaped relationship between average HbA1c and mortality, with increased risks at very low levels of average HbA1c (<6.09%; 43 mmol/mol), and the highest level (over 8.88% [**74 mmol/mol]**, the top 10% of our distribution). A steeper and more monotonic relationship was observed between variability and mortality, with even small rises in CoV increasing risk. Associations with variability were also consistent, being present at both higher and lower levels of average HbA1c and among both younger and older people with T2DM. This was particularly evident after carrying out time-updated analyses, or adjusting for treatment category, when the highest levels of variability almost trebled the risk of mortality, and average HbA1c was no longer associated with mortality at all. The magnitude of associations with variability was attenuated slightly after adjusting for severe hypoglycemic episodes; adjustments for a comorbidity score or use of key medications had little effect on any measure

However, with CAD and IS as the key outcome, these associations were altered. For mortality, associations with average HbA1c became stronger than CoV, and for first emergency hospitalization, associations with average HbA1c were further strengthened, and the relationship with CoV was no longer statistically significant.

***Comparisons with recent literature***

Recent systematic reviews have identified a range of potential risks associated with HbA1c variability, but have had great difficulty in reaching clear conclusions about the magnitude of these risks and how they interplay with average HbA1c[12-14](#_ENREF_12). This uncertainty may be due to the lack of standard approach to summarizing HbA1c variability, or agreement about how much might be clinically significant. Many studies use a relative measure (e.g. using categories of the distribution of HbA1c variability such as quartiles) but this is hard to compare both across studies, and even within the same study (with average HbA1c, mostly defined using absolute levels).

Nevertheless, our results are broadly similar to two other recent studies; one a cohort study from Italy (RIACE)[30](#_ENREF_30), and the other an analysis of UK data from a different primary care dataset[16](#_ENREF_16). The Italian study (15,000 T2DM patients) shared many similar conclusions, particularly that HbA1c variability was a stronger predictor of all-cause mortality than mean HbA1c, and that trajectory was not associated with mortality after adjusting for variability. They also found an impact of variability at both higher and lower levels of mean HbA1c, though unlike our results they found no J-shape association between average HbA1c and risk. The large (n=54,000) UK primary care cohort study among older people (>70) in the UK found mortality risks of similar magnitude (about a 2 times increase), with average HbA1c only important at higher levels, over 9% [75 mmol/mol][16](#_ENREF_16). Unlike our study, these authors also reported independent associations between HbA1c trajectory and mortality. They defined “variability” as an absolute change in HbA1c of at least 0.5%, which might potentially classify individuals with frequent smaller changes as “stable” who would be classified as more “variable” using our CoV measurement; this might explain why trajectory seemed to have stronger associations with poor outcomes in their analysis. Our study also showed that variability is important in younger people with T2DM as well as older people.

Our results feature key areas of disagreement with other recent studies. A large cohort study of US Veterans Affairs patients (about 58,000 T2DM patients) identified increased risks of mortality, hospitalization, and MI associated with increasing variability, but they seemed lower in magnitude, with average HbA1c remaining more strongly associated[15](#_ENREF_15). This study included mostly older white men (mean age 65), not representative of broader populations, and could not adjust for some key confounders such as DM duration, strongly related to average HbA1c in our dataset, and did not use statistically comparable categories to compare average and variability in HbA1c. A very large primary care based Chinese cohort (about 90,000 T2DM patients) found linear associations between variability in HbA1c with cardiovascular and all-cause mortality, but these were only significant in younger people, under 65 years[31](#_ENREF_31). Baseline assessments of HbA1c were not clearly made before measurement of outcomes, and this potentially introduces a risk of “reverse causality” for older people where stronger associations with variability were observed. A small cohort of older people with long-standing T2DM from Rio de Janiero found that variability was a better predictor of microvascular complications than average HbA1c, but only when average levels were relatively low (<7.5%; 58.5 mmol/mol). The somewhat conflicting results of these key studies has possibly also led to some inertia in developing guidelines that more explicitly address HbA1c stability in T2DM patients.

***Key Strengths and Limitations***

The key strengths of our study are the large and representative dataset that was used. We included both younger and older people with prevalent T2DM, and measured variability, average and trajectory of HbA1c over a four year time period using comparable categories before assessing outcomes. This is important in assessing causality since many DM complications (e.g. infections, cardiovascular events) themselves interfere withHbA1c control and alter HbA1c levels, potentially leading to reverse causality[22](#_ENREF_22). While we designed our study to ensure that HbA1c variables were measured prior to the occurrence of any key outcome, the limitation here is that these measurements become out-of-date over the lengthy follow-up (up to 6 years). To address this, we carried out a sensitivity analysis which incorporated time-updated HbA1c values. This strengthened the importance of variability as a predictor of all-cause mortality, with average HbA1c no longer showing an effect. Whilst time-updated analyses appear more credible, they also run a greater risk of reverse causality i.e. HbA1c may become more variable in the final years before death due to functional, physical or cognitive decline. However, in an analysis of individuals with at least 2-year survival after baseline we found no evidence of reverse causality. We did not find strong evidence of an impact of trajectory (direction of trends in HbA1c) on mortality or hospitalization risks after adjusting for variability. However, our study design only measured trajectory over a 4 year time period, which may be insufficient to fully characterize this for most people. Our results were robust to adjustment for key confounders measured at baseline, and we were able to adjust for more potential confounders than previous studies. However, residual confounding remains a potential explanation for our findings. In particular, we were unable to adjust for other lifestyle factors that might be important (e.g. exercise, diet) and also for adherence to treatment. Most of our covariates are likely to be relatively stable over the study period, but medication use may vary, and therefore reported associations based on baseline usage may be attenuated. We were unable to consider newer classes of anti-DM medications (e.g. sodium-glucose co-transporter-2 or glucagon like peptides) that may be beneficial in promoting stability, as too few patients were taking these drugs during the baseline period (2006 to 2009), though this could be possible in the future. Our primary analyses excluded a significant number of patients who did not have at least one measurement of HbA1c in each year of the 4 year baseline period. This was done in order to develop a more robust measurement of variability, and to avoid biasing estimates of variability towards patients who may have had a lot of measurements taken close to a health event (e.g. infection[16](#_ENREF_16), CVD episode[32](#_ENREF_32) or medication change that might influence this parameter) but not at other times. However, in a less restrictive sensitivity analysis including any patient with at least 4 measurements (over 90% of the total eligible) at any time during the baseline period, and results were almost identical. As there was virtually no other missing data, we believe our findings are likely representative of most patients with T2DM. However, 6% of the cohort died during the baseline period, and also younger, more recently diagnosed patients were less likely to be included as they may not have had 4 serial measurements before 01/01/2010. Our definition of hypoglycemia is highly specific, and likely to have missed milder episodes that occur and are resolved by the patient or with assistance from their carers / family and are not recorded. However, more severe hypoglycemia requiring medical care would be expected to present in secondary care (either through accident and emergency attendance or hospital admission) and have been reported to primary care, so captured in our dataset, and may also be more strongly associated with poor outcomes. Most previous larger studies using HbA1c to assess variability have not been able to adjust for hypoglycemia. Finally, our manuscript is based entirely on observational data so cannot consider the extent to which any risks might be reversible if variability was reduced.

***Clinical Implications and Mechanisms***

A detailed analysis of mechanisms by which longer-term variability might increase mortality risk are beyond the scope of this study. Adjustments for severe hypoglycemia did not affect estimates of the strength of associations between poor outcomes and average HbA1c, but somewhat attenuated the magnitude of our variability estimates, though they remained statistically and clinically significant. Associations between mortality and average HbA1c were attenuated after adjustment for treatment, but this was not the case for CoV, which may suggest different mechanisms of action. Any increases in CoV raised mortality risk in our analyses, whilst higher average HbA1c had an effect only among the highest 10% of the distribution. Elevated average HbA1c was more strongly associated with CAD and IS deaths, and particularly CAD and IS hospitalizations, where the association with CoV was completely attenuated and only average levels appeared predictive. Strong associations between average HbA1c and CAD, and MI were also observed recently in the UK Biobank Data[28](#_ENREF_28) and the Veterans Affairs study[15](#_ENREF_15). Few other studies have been sufficiently powered to assess associations between HbA1c average, variability, and CVD sub-codes, but this suggests that a focus on CVD as an outcome could be incomplete. HbA1c has known associations with both pre-prandial glucose levels and atherosclerosis[33](#_ENREF_33)[34](#_ENREF_34), but is poorly correlated with post-prandial glucose[33](#_ENREF_33)[34](#_ENREF_34), and provides an incomplete measure of acute glucose excursions. Other measures including blood glucose variability may therefore be important to support diabetes management better[33](#_ENREF_33)[34](#_ENREF_34), though HbA1c measurements are the mainstay of diabetes management in primary care in the UK.

Higher levels of HbA1c variability could potentially reflect many different patient and service level factors. Our study identified that higher variability was associated with many patient characteristics that might be related to patient adherence with diabetes management, such as smoking, higher BMI, being male, younger age and higher levels of socio-economic deprivation. However, we are not aware of evidence that HbA1c variability is directly related to treatment adherence, and could not assess this. Other factors that may increase variability might include poor social support, infections and cardiovascular events[35](#_ENREF_35) and / or potentially a more severe, rapidly progressing form of diabetes[36](#_ENREF_36). Nevertheless, variability in HbA1c could be easily measured in UK primary care, and likely elsewhere, since multiple measurements of HbA1c are available in routine practice for most patients. They could thus inform decisions based on finer assessments of future risk.

Our data suggest that for T2DM patients with lower or moderately raised average HbA1c (below 9% in our cohort), mortality risk might be reduced more by promoting stability than reductions in chronic levels, and even at higher average levels stability remains important. There was already evidence, guidelines and analyses supporting more relaxed targets for average HbA1c among older people[37](#_ENREF_37), and also for people with significant comorbidity or frailty[16](#_ENREF_16)[38-40](#_ENREF_38). Our results may suggest this could also be appropriate for younger people, but this requires confirmation in RCTs. We included mainly prevalent cases of DM, some of whom had already been diagnosed with DM for many years, and considered only mortality and unplanned hospital admissions over a relatively short term. Importantly, smaller elevations in average HbA1c increased the risk of CAD and IS hospitalizations and mortality in our data, and only average was predictive of first hospitalization for CAD and IS. High quality randomized evidence has also found evidence of benefits from much tighter control (to below 7% HbA1c; 53 mmol/mol) among individuals with newly diagnosed diabetes, particularly for microvascular outcomes[3](#_ENREF_3), though benefits for cardiovascular outcomes and all-cause mortality has been less clear-cut5,6. These findings also strongly support a focus on average chronic levels. Our study highlights the need for individualized targets, but suggest a need to focus on stability as well as a lower target level for many people living with T2DM.

**Conclusion**

Variability in HbA1c was more important than average level in predicting mortality among people with prevalent T2DM in UK primary care. Average level remained important though, particularly at higher levels of HbA1c (e.g. over 9%; 75 mmol/mol), and both high average and linearly increasing variability were important for predicting first unplanned hospital admission and cardiovascular mortality. Current guidelines promote both lower levels of HbA1c and stability of HbA1c, but tend to prioritize the former, whilst our analyses generally suggest more importance should be given to stability for many patients. Measurements of variability could be incorporated into primary care consultations to guide risk assessment also.

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**Author contributions:**

Conceptualization: JAC, DGC

Acquisition of Data: IMC

Clinical input: TH, SDeW

Methodology: DGC, JAC, IMC

Statistical Analysis: IMC

Interpretation of Results, drafting manuscript and approving final version: All authors

Guarantor: IMC 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

**Competing Interest**: All authors declare that no competing interests exist.

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**Figure Legend and Title for Figure 1**

Figure Title for Figure 1: Stratified analyses demonstrating the effect of HbA1c variability at high and low values of average HbA1c, and average HbA1c at high and low levels of variability

Figure Legend: Figure 1a) shows the effects of HbA1c variability on the risk of all-cause mortality stratified by high and low average HbA1c, and b) the effects of HbA1c average on the risk of all-cause mortality stratified by high and low variability. “High” and “low” are defined as the top 25% and bottom 25% of the distributions of HbA1c average and variability. HbA1c of 6.58% converts to 48.4 mmol/mol and 7.91% to 63.0 mmol/mol.

**Table 1:** Summary of HbA1c average, trajectory and variability by baseline patient characteristics

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **HbA1c Summary** | **Category** | **N** | **Age** (Mean, SD) | **Sex** (% Men) | **BMI** (Mean, SD) | **Duration** (Mean, SD) | **No of HbA1c measure-ments**(Mean, SD) | **On any insulin**(%) | **On biguanides only** (%) | **History of hypo-glycaemia** (%) |
|  |  |  |  |  |  |  |  |  |  |  |
| **All Patients** |  | 58,832 | 67.7 (10.9) | 55.3% | 30.6 (6.2) | 7.8 (6.2) | 7.9 (2.6) | 20.2 | 23.2 | 3.3 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Average\*** | 3.63 to 6.09% | 5,891 | 69.9 (10.8) | 53.9% | 29.1 (6.0) | 6.0 (5.5) | 6.6 (2.1) | 2.7 | 23.4 | 1.6 |
|  | >6.09 to 6.58% | 8,812 | 70.3 (10.4) | 51.9% | 29.8 (6.1) | 6.3 (5.2) | 7.0 (2.2) | 4.3 | 32.8 | 1.9 |
|  | >6.58 to 7.16% | 14,746 | 69.1 (10.2) | 54.4% | 30.2 (5.9) | 7.1 (5.7) | 7.7 (2.3) | 7.4 | 37.1 | 2.5 |
|  | >7.16 to 7.91% | 14,646 | 67.5 (10.5) | 57.0% | 30.8 (6.1) | 8.1 (6.2) | 8.4 (2.5) | 19.4 | 21.0 | 3.7 |
|  | >7.91 to 8.88% | 8,894 | 65.5 (11.0) | 57.6% | 31.7 (6.4) | 9.5 (7.0) | 8.8 (2.8) | 43.2 | 7.3 | 5.3 |
|  | >8.88% | 5,843 | 62.2 (11.4) | 56.5% | 32.6 (6.8) | 10.0 (6.6) | 8.6 (2.8) | 61.0 | 2.7 | 5.3 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Trajectory**† | ≤-0.48%/y | 5,897 | 65.4 (11.1) | 56.0% | 31.8 (6.8) | 7.9 (6.5) | 8.3 (2.6) | 32.6 | 16.4 | 4.9 |
|  | >-0.48 to -0.20%/y | 8,827 | 68.0 (10.8) | 55.7% | 30.7 (6.3) | 8.5 (6.7) | 8.2 (2.6) | 24.3 | 21.8 | 3.7 |
|  | >-0.20 to 0.01%/y | 14,699 | 69.3 (10.4) | 53.7% | 29.9 (6.1) | 7.8 (6.2) | 7.8 (2.6) | 16.1 | 26.1 | 2.8 |
|  | >0.01 to 0.19%/y | 14,697 | 68.7 (10.5) | 55.5% | 30.0 (5.9) | 7.3 (5.7) | 7.6 (2.5) | 13.7 | 26.1 | 2.6 |
|  | >0.19 to 0.43%/y | 8,832 | 66.9 (10.9) | 55.9% | 31.1 (6.1) | 7.6 (6.0) | 7.9 (2.6) | 19.0 | 24.4 | 3.4 |
|  | > 0.43%/y | 5,880 | 64.6 (11.8) | 56.9% | 32.2 (6.5) | 7.9 (6.1) | 8.0 (2.6) | 29.8 | 15.6 | 4.1 |
|  |  |  |  |  |  |  |  |  |  |  |
| **CoV**‡ | 0 to 3.14 | 5,879 | 71.3 (9.8) | 50.1% | 28.8 (5.5) | 6.6 (5.3) | 6.7 (2.1) | 4.8 | 28.6 | 1.1 |
|  | >3.14 to 4.71 | 8,827 | 70.1 (10.1) | 52.5% | 29.5 (5.8) | 7.4 (6.1) | 7.4 (2.4) | 10.0 | 30.4 | 1.7 |
|  | >4.71 to 7.33 | 14,710 | 68.6 (10.4) | 54.7% | 30.2 (6.0) | 8.0 (6.2) | 8.0 (2.5) | 17.2 | 27.1 | 3.0 |
|  | >7.33 to 11.40 | 14,709 | 66.6 (10.9) | 57.0% | 31.1 (6.2) | 8.4 (6.4) | 8.3 (2.6) | 25.3 | 20.3 | 3.8 |
|  | >11.40 to 16.64 | 8,824 | 65.4 (11.2) | 58.8% | 31.9 (6.5) | 8.2 (6.4) | 8.4 (2.7) | 30.2 | 15.5 | 5.0 |
|  | >16.64 | 5,883 | 64.8 (11.6) | 56.9% | 32.3 (7.0) | 7.0 (5.9) | 8.2 (2.6) | 30.5 | 15.8 | 5.2 |
|  |  |  |  |  |  |  |  |  |  |  |

**\*** – Average of the previous 4 annual means (2006, 2007, 2008, 2009). Categories correspond to the following mmol/mol cut-points: 16-43, >43-48, >48-55, >55-63, >63-74, >74. † – Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡ – Coefficient of variation derived from the mean and standard deviation of all measurements in the previous 4 years. Note that all cut-offs correspond to the following percentiles: 10th, 25th, 50th, 75th and 90th.

**Table 2:** Adjusted HR’s for mortality by HbA1c average, trajectory and variability

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **HbA1c Summary** | **Category** | **Average only** | **Trajectory only** | **Variability only** | **All HbA1c Measures** | **All Hypoglycemia** |
|  |  | HR (95% CI) |  |  | HR (95% CI) | HR (95% CI) |
|  |  |  |  |  |  |  |
| **Average\*** | 3.63 to 6.09% | 1.10 (1.02-1.19) |  |  | 1.14 (1.05-1.24) | 1.12 (1.04-1.22) |
|  | >6.09 to 6.58% | 1 |  |  | 1 | 1 |
|  | >6.58 to 7.16% | 0.99 (0.93-1.06) |  |  | 0.93 (0.87-0.99) | 0.94 (0.88-1.01) |
|  | >7.16 to 7.91% | 1.10 (1.03-1.18) |  |  | 0.95 (0.88-1.02) | 0.97 (0.90-1.04) |
|  | >7.91 to 8.88% | 1.35 (1.26-1.45) |  |  | 1.06 (0.98-1.14) | 1.07 (1.00-1.16) |
|  | >8.88% | 1.82 (1.69-1.96) |  |  | 1.35 (1.24-1.47) | 1.35 (1.24-1.48) |
|  |  |  |  |  |  |  |
| **Trajectory**† | ≤-0.48%/y |  | 1.63 (1.51-1.75) |  | 1.08 (1.00-1.18) | 1.11 (1.02-1.21) |
|  | >-0.48 to -0.20%/y |  | 1.20 (1.13-1.29) |  | 0.99 (0.93-1.05) | 1.00 (0.94-1.07) |
|  | >-0.20 to 0.01%/y |  | 1 |  | 1 | 1 |
|  | >0.01 to 0.19%/y |  | 0.97 (0.92-1.03) |  | 0.99 (0.94-1.05) | 0.98 (0.92-1.04) |
|  | >0.19 to 0.43%/y |  | 1.14 (1.06-1.23) |  | 0.98 (0.91-1.06) | 0.98 (0.91-1.06) |
|  | > 0.43%/y |  | 1.52 (1.40-1.64) |  | 1.03 (0.95-1.12) | 1.04 (0.95-1.14) |
|  |  |  |  |  |  |  |
| **CoV**‡ | 0 to 3.14 |  |  | 1 | 1 | 1 |
|  | >3.14 to 4.71 |  |  | 1.01 (0.93-1.10) | 1.03 (0.95-1.12) | 1.03 (0.94-1.11) |
|  | >4.71 to 7.33 |  |  | 1.27 (1.17-1.38) | 1.32 (1.21-1.44) | 1.25 (1.15-1.37) |
|  | >7.33 to 11.40 |  |  | 1.49 (1.38-1.62) | 1.51 (1.38-1.66) | 1.39 (1.26-1.52) |
|  | >11.40 to 16.64 |  |  | 1.78 (1.62-1.95) | 1.71 (1.53-1.91) | 1.50 (1.34-1.68) |
|  | >16.64 |  |  | 2.12 (1.93-2.23) | 1.93 (1.72-2.16) | 1.67 (1.49-1.87) |
|  |  |  |  |  |  |  |
| **History of hypoglycemia§** | Yes vs. No |  |  |  |  | 1.36 (1.24-1.49) |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

Note: All models mutually adjust for HbA1c measures (unless indicated) plus age, age2, sex, duration of diabetes, index of multiple deprivation, smoking and body mass index. **\*** – Average of the previous 4 annual means (2006, 2007, 2008, 2009). † – Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡ – Coefficient of variation derived from the mean and standard deviation of all measurements in the previous 4 years. Note that all cut-offs correspond to the following percentiles: 10th, 25th, 50th, 75th and 90th. § - History of any hypoglycemic event recorded prior to 2010.

**Table 3:** Mutually adjusted HR’s for first emergency hospital admission during 2010-5 by HbA1c average, trajectory and variability

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **HbA1c** | **Category** | **First emergency hospital admission 2010-5** | | | |
| **Summary** |  | **Any** | **Infection only** | **Cardiovascular only** | **CAD/Ischaemic Stroke only** |
|  |  | HR\* (95% CI) | HR\* (95% CI) | HR\* (95% CI) | HR\* (95% CI) |
|  |  |  |  |  |  |
| **Average\*** | 3.63 to 6.09% | 1.10 (1.04-1.15) | 1.11 (1.02-1.21) | 1.02 (0.95-1.10) | 0.99 (0.89-1.10) |
|  | >6.09 to 6.58% | 1 | 1 | 1 | 1 |
|  | >6.58 to 7.16% | 0.98 (0.94-1.02) | 1.02 (0.95-1.10) | 0.95 (0.90-1.01) | 1.06 (0.97-1.16) |
|  | >7.16 to 7.91% | 0.98 (0.94-1.02) | 1.03 (0.94-1.12) | 1.06 (0.99-1.12) | 1.26 (1.16-1.38) |
|  | >7.91 to 8.88% | 1.12 (1.07-1.18) | 1.24 (1.14-1.36) | 1.20 (1.12-1.28) | 1.46 (1.32-1.61) |
|  | >8.88% | 1.42 (1.35-1.50) | 1.63 (1.48-1.80) | 1.63 (1.51-1.75) | 2.13 (1.91-2.37) |
|  |  |  |  |  |  |
| **Trajectory**† | ≤-0.48%/y | 1.00 (0.95-1.06) | 0.97 (0.88-1.07) | 0.98 (0.91-1.07) | 0.96 (0.85-1.08) |
|  | >-0.48 to -0.20%/y | 1.01 (0.97-1.06) | 1.01 (0.93-1.10) | 1.04 (0.98-1.11) | 1.08 (0.99-1.18) |
|  | >-0.20 to 0.01%/y | 1 | 1 | 1 | 1 |
|  | >0.01 to 0.19%/y | 0.96 (0.93-1.00) | 0.99 (0.93-1.06) | 0.98 (0.93-1.04) | 1.02 (0.95-1.10) |
|  | >0.19 to 0.43%/y | 0.99 (0.95-1.03) | 1.00 (0.92-1.08) | 0.99 (0.93-1.05) | 1.04 (0.96-1.13) |
|  | > 0.43%/y | 1.03 (0.97-1.08) | 1.04 (0.95-1.14) | 1.00 (0.92-1.08) | 1.09 (0.97-1.21) |
|  |  |  |  |  |  |
| **CoV**‡ | 0 to 3.14 | 1 | 1 | 1 | 1 |
|  | >3.14 to 4.71 | 1.10 (1.04-1.15) | 1.06 (0.96-1.18) | 1.04 (0.96-1.13) | 1.03 (0.96-1.13) |
|  | >4.71 to 7.33 | 1.23 (1.17-1.29) | 1.30 (1.19-1.42) | 1.16 (1.08-1.25) | 1.12 (1.02-1.24) |
|  | >7.33 to 11.40 | 1.31 (1.23-1.38) | 1.37 (1.23-1.50) | 1.23 (1.14-1.33) | 1.14 (1.02-1.28) |
|  | >11.40 to 16.64 | 1.46 (1.38-1.55) | 1.56 (1.40-1.73) | 1.32 (1.21-1.44) | 1.12 (0.99-1.27) |
|  | >16.64 | 1.53 (1.42-1.64) | 1.70 (1.50-1.93) | 1.36 (1.22-1.51) | 1.09 (0.94-1.26) |
|  |  |  |  |  |  |

Note: All models mutually adjust for HbA1c measures plus age, age2, sex, duration of diabetes, index of multiple deprivation, smoking and body mass index. During follow-up, N=25,927 (44.1%) have any emergency hospital admission, 8,192 (13.9%) have an admission for infection, 11,798 (20.1%) have a cardiovascular admission, 6,018 (10.2%) have an admission for coronary artery disease or ischaemic stroke.**\*** – Average of the previous 4 annual means (2006, 2007, 2008, 2009). † – Mean annual slope from the linear regression of all measurements in the previous 4 years. ‡ – Coefficient of variation derived from the mean and standard deviation of all measurements in the previous 4 years. Note that all cut-offs correspond to the following percentiles: 10th, 25th, 50th, 75th and 90th.