Glycated hemoglobin, prediabetes and the links to cardiovascular disease: data from UK Biobank

Short running title: Prediabetes, HbA1c and cardiovascular risk

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Abstract

Objective HbA1c levels are increasingly measured in screening for diabetes; we investigated whether HbA1c may simultaneously improve CVD risk assessment, using QRISK3, ACC/AHA and SCORE scoring systems.

Research Design and Methods UK Biobank participants without baseline CVD or known diabetes (n=358,275) were included. Associations of HbA1c with CVD was assessed using Cox models adjusting for classical risk factors. Predictive utility was determined by the C-index and net reclassification index (NRI). A separate analysis was conducted in 16,619 participants with known baseline diabetes.

Results Incident fatal or non-fatal CVD, as defined in the QRISK3 prediction model, occurred in 12,894 participants over 8.9 years. 3.3% (n=11,680) of participants had prediabetes (42.0-47.9mmol/mol (6.0 to 6.4%) and 0.7% (n=2579) undiagnosed diabetes (≥48.0mmol/mol;≥ 6.5%). In unadjusted models, compared with the reference group (<42.0 mmol/mol; <6.0%), those with prediabetes and undiagnosed diabetes were at higher CVD risk: HR 1.83 (95% CI 1.69-1.97) and 2.26 (95% CI 1.97-2.61), respectively. After adjustment for classical risk factors, these attenuated to HR 1.11 (95% CI 1.03-1.20) and 1.20 (1.04-1.38), respectively. Adding HbA1c to the QRISK3 CVD risk prediction model (C-index 0.7387) yielded a small improvement in discrimination (C-index +0.0004, 95% CI 0.0001, 0.0007). The NRI showed no improvement. Results were similar for models based on the ACC/AHA and SCORE risk models.

Conclusion The near two-fold higher unadjusted risk for CVD in prediabetes is driven mainly by abnormal levels of conventional CVD risk factors. Whilst HbA1c adds minimally to CV risk prediction, those with pre-diabetes should have their conventional CV risk factors appropriately measured and managed.

Funding

Introduction

Circulating hemoglobin A1c (HbA1c) indicates average blood glucose concentrations over the preceding 3 months. The absence of the need for patients to fast for HbA1c assessment is a major advantage of measuring HbA1c for screening for dysglycemia, including diabetes and pre-diabetes, and has been endorsed for such by society recommendations (1). Whether screening HbA1c values incrementally contribute to cardiovascular disease (CVD) risk assessment and prognostication beyond established risk predictors in patients without diabetes remains uncertain, with meta-analysis of observational data suggesting independent prognostic utility of HbA1c (2).

The European Systematic Coronary Risk Estimation (SCORE) CVD risk score (3), QRISK3 risk score (4), and the ACC/AHA CVD risk score (5) currently do not include any specific measure of glycemia in their risk prediction models, and include only diabetes as a categorical entity. In support of this approach, an individual participant meta-analysis of nearly 300,000 participants without diabetes or known CVD at baseline suggested that HbA1c added very modest discriminative ability to CVD risk estimation methods that use conventional risk factors (6). Moreover, some data suggest that individuals with prediabetes are at significantly elevated CVD risk due in part to their modestly raised glycemia levels (7,8). However, such work has been based on either relatively small single cohorts or multiple cohorts with considerable inter-study heterogeneity. The lack of data from a single large cohort with consistent phenotyping of exposures and events is a limitation in interpreting the existing literature on this topic. Since increasing numbers of people are being screened for

diabetes using HbA1c measurement, this question needs better evidence to inform clinical care.

Capitalizing on the availability of data in the UK Biobank comprising several hundred thousand participants including baseline HbA1c measures and capture of longitudinal clinical outcomes, the CVD prognostic utility of HbA1c was examined in participants without prevalent diabetes.

Methods

The UK Biobank recruited 502,617 participants (aged 37 to 73) from 22 assessment centres across the UK between April 2007 and December 2010. Baseline biological measurements were recorded and touch-screen questionnaires were administered, as described elsewhere (9,10). The UK Biobank received ethical approval from the North West Multi-centre Research Ethics Committee (REC reference: 11/NW/03820). All participants gave written informed consent before enrolment in the study, which was conducted in accord with the principles of the Declaration of Helsinki.

Systolic and diastolic blood pressure was taken as the first baseline measurement, preferentially using an automated measurement. Smoking status was categorised into never or former/current smoking. Ethnicity was coded as white, black, South Asian, or mixed/other, with white as the referent group. Blood collection sampling procedures for the study have been previously described and validated (11). Biochemistry measures were performed at a dedicated central laboratory on around 480,000 samples between 2014 and 2017. These included serum total cholesterol

(TC) and HDL cholesterol (Beckman Coulter AU5400) and plasma glycated hemoglobin (HbA1c, Bio-Rad VARIANT II Turbo). Data were adjusted by UK Biobank centrally before release to adjust for pre-analytical variables. Further details of these measurements, ==and of the data adjustments,== can be found in the UK Biobank online showcase and protocol (http://www.ukbiobank.ac.uk and ==https://biobank.ndph.ox.ac.uk/showcase/showcase/docs/biomarker_issues.pdf==).

The definition of baseline diabetes included self-reported type 1 or type 2 diabetes, and those who reported using insulin. Statin and blood pressure medication use were also recorded from self-report. Baseline cardiovascular disease was defined as self-reported prior myocardial infarction, stroke, transient ischemic attack as well as hospital diagnoses including ICD10 codes I20-24, I63-64, G45.

Date and cause of death were obtained from death certificates held by the National Health Service (NHS) Information Centre for participants from England and Wales, and the NHS Central Register Scotland for participants from Scotland. The main outcome of interest in the present study reflected the outcome used in the QRISK3 risk score (4), namely fatal or non-fatal coronary heart disease, ischemic stroke or transient ischemic attack (ICD-10 G45, I20-24, I63-64) (hereafter QRISK3 CVD events). There were two additional outcomes of interest in the present study: 1) a composite of fatal and non-fatal cardiovascular disease that reflects the ACC/AHA guidelines prediction score including death from cardiovascular disease (ICD-10 I20-25, I60-64) or hospitalisation for cardiovascular disease (ICD-10 I21, I22, I60-64)(5) (hereafter ACC/AHA CVD events); 2) fatal cardiovascular disease as defined by

primary cause of death from events included in the European SCORE clinical guidelines (I10-15, I44-51, I20-25, I61-73) (12) (hereafter SCORE CVD events).

End of follow-up for each participant was recorded as the date of death or the date of end of follow-up for the assessment centre attended (31st January 2018 for participants in England or Wales, and 30th November 2016 for participants in Scotland), or the first date of CVD-related hospitalisation (for both composite fatal/non-fatal outcomes), whichever came first. The period at risk per participant began on the date of their assessment. Participants with baseline CVD were excluded from all analyses, and those with baseline diabetes were analysed separately from the main cohort.

Statistical analyses

Log transformed HbA1c was analysed as a continuous variable and was categorised using thresholds of <42.0mmol/mol (<6.0%) (normal/referent), 42.0-47.9mmol/mol (6.0-6.4%) (prediabetes), and ≥48.0mmol/mol (≥6.5%) (undiagnosed diabetes), as well as deciles of the distribution. Classical CVD risk factors were expressed as mean (standard deviation) if symmetrically distributed, median (interquartile range) if skewed, and number (%) if categorical. The prediabetes category of HbA1c was further split into the following categories to examine its relationship with CVD outcomes: 42.0-44.9mmol/mol (6.0-6.2%), and 45.0-47.9mmol/mol (6.3-6.4%). The distribution of classical CVD risk factors by categories of HbA1c was assessed using ANOVA, a Wilcoxon test for trend, or a chi-squared test, respectively. Associations between classical CVD risk factors and HbA1c with CVD outcomes of interest were also tabulated using these methods.

Univariable associations of categories of HbA1c with outcomes of interest were initially explored using Kaplan-Meier methods. Associations of continuous and categorical HbA1c with outcomes of interest were investigated using Cox-proportional hazard models for each outcome (adjusted for age, sex, ethnicity, total and HDL cholesterol, SBP, DBP, antihypertensive medications, smoking, and statin use in ACC/AHA or SCORE risk scores where for QRISK3, adjusted for age, ethnicity, Townsend deprivation index (index of deprivation based on postcode), total:HDL cholesterol, BMI, family history of CVD, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3-5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications, erectile dysfunction), and also using restricted cubic splines to explore the shape of the association (data not shown). The proportional hazard assumption was checked by inspection of Schöenfeld residuals. Tests for interaction were performed by categories of the main covariates of interest.

The ability of HbA1c to improve prediction of CVD was tested for the outcomes of interest, using the specific established risk factors for each risk score for the relevant outcomes; the ACC/AHA (adjusting as above) models for composite fatal and non-fatal CVD, and the SCORE European model for fatal CVD (adjusting as above for fatal CVD outcome). All models excluded participants with baseline CVD. Improvement in prediction was tested using Harrell's C-Index for survival data, testing for increased concordance on the addition of HbA1c to the model. We used a continuous net reclassification index (NRI) to investigate changes in predicted risk classification on addition of HbA1c to the models. The continuous NRI is based on

improvements in classification across integer % risk thresholds, thus avoiding arbitrary decisions about defining clinically relevant risk categories (13). Four sensitivity analyses were conducted. Discrimination ability after addition of HbA1c was also tested: 1) after exclusion of participants with HbA1c>48.0mmol/mol, i.e. undiagnosed diabetes; 2) after exclusion of participants on statins; and 3) after exclusion of participants with self-reported diabetes and those with HbA1c>48.0 mmol/mol. We also compared CVD risk within the prediabetes category by splitting this group into those with levels of 42-44 (6.0-6.2%) and 45-47 mmol/mol (6.3-6.4%).

All analyses were performed using STATA 14 (StataCorp LP) and R. A 2-sided p value of 0.05 was considered statistically significant without adjustment for multiple comparisons.

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The funder played no role in developing the analysis plan, conducting the analysis, or writing of the manuscript.

Results

Cross sectional associations

Of 438,548 people without baseline CVD included in the study, complete data on covariates, including HbA1c were available in 374,894 (76%) participants, and after exclusion of participants with known/self-reported diabetes (n=16, 619), the cohort for the main analyses included 358,275 participants, including those with HbA1c ≥48.0 mmol/mol (≥6.5%) without report of prior diabetes diagnosis (i.e. undiagnosed

diabetes). Median HbA1c in this cohort was 34.9mmol/mol (5.3%) (Q1-Q3 32.5-37.3mmol/mol (5.1-5.6%)).

Participants with prediabetes were slightly older, and had a poorer CVD risk profile as they were more likely to be current smokers, had higher SBP by more than 6 mmHg, higher BMI by more than 3 kg/m^2, and higher total cholesterol to HDL-C ratio driven by lower HDL-C (**Table 1**). They were also more likely to be of non-white and take blood pressure lowering medications or statins (**Table 1**). The higher prevalence of other CVD risk factors was even more marked for those with undiagnosed diabetes, particularly for BMI and SBP and HDL-C (**Table 1**).

CVD outcomes

In the main cohort without known baseline diabetes, median follow up time for the QRISK3-based fatal/non-fatal CVD outcome was 8.9 years (Q1-Q3 8.2-9.4). The fatal/non-fatal CVD outcome occurred in 12,894 participants (3.6%), ACC/AHA-based CVD outcomes occurred in 6618 participants (1.9%), and SCORE-based fatal CVD occurred in 1813 participants (0.5%). In the main cohort without known baseline diabetes, HbA1c was on average 1.2 mmol/mol higher in participants who subsequently had an incident CVD event (35.1 versus 36.2 mmol/mol in those without versus with incident CVD, a difference of 1.2 mmol/mol, 95% CI 1.1-1.3). In people with known baseline diabetes (n=16, 619), over a median of 8.7 years follow up, the QRISK-3 based CVD outcome occurred in 1475 (8.9%) of participants, and fatal CVD occurred in 308 (1.9%).

Association of HbA1c with CVD outcomes

The unadjusted risk of the composite fatal/non-fatal CVD outcome was greatest for participants with known diabetes but was also higher in those with undiagnosed baseline diabetes and in those with prediabetes (**Figure 1**). Those with prediabetes were at 1.83 (95% CI 1.69-1.97) fold higher risk of CVD compared with those with normal HbA1c, and those with undiagnosed diabetes were at 2.26 (95% CI 1.97-2.61) higher risk (**Table 2**).

Figure 2 shows the unadjusted and adjusted risks associated with HbA1c across the range from normal to pre-diabetes, undiagnosed diabetes and prevalent diabetes. The results, as also noted in **Table 2,** show that the CVD risks in the pre-diabetes range were substantially attenuated with adjustment for usual CVD risk factors such that the HRs were rather modest. Whilst adjustment also attenuates the HR in the undiagnosed and diabetes groups, adjusted relative risks remained statistically significant. The association between HbA1c and the ACC/AHA outcome was broadly similar, but adjusted hazard ratios for the association between HbA1c and fatal (SCORE) CVD were larger in the undiagnosed diabetes group (**Table 2**).

When the CVD association between HbA1c and CVD was analysed separately in the split pre-diabetes groups (42.0-44.9 mmol/mol (6.0-6.2%) and 45.0-47.9 mmol/mol (6.3-6.4%), hazard ratios were similar and had overlapping confidence intervals (1.11, 95% CI 1.02-1.21, and 1.11, 95% CI 0.95-1.29, respectively).

HbA1c and prediction of CVD outcomes in addition to classical risk factors

Using models accounting for classical CVD risk factors, individuals with normal glycemia had a median 10-year CVD risk of 2.7% for QRISK3 CVD, 1.4% for ACC/AHA CVD, and 0.4% for fatal SCORE CVD.

In a model of CVD prediction based on the QRISK3 CVD outcome among participants without self-reported diabetes at baseline, classical CVD risk factors yielded a C-index of 0.7392 (95% CI 0.7353-0.7431), which was slightly increased upon addition of log HbA1c (C-index change +0.0004, 95% CI 0.0001-0.0007). In those with a baseline HbA1c<48.0mmol/mol (<6.5%), modelling using classical CVD risk factors yielded a C-index of 0.7391 (95% CI 0.7352-0.741), which was also modestly improved upon addition of log HbA1c (C-index change +0.0003, 95% CI 0.0001-0.0006).

Patterns were similar for the other outcomes of interest. In a model of ACC/AHA CVD, modelling using classical CVD risk factors yielded a C-index of 0.7360 (95% CI 0.7304-0.7416). Addition of log HbA1c to the ACC/AHA model also modestly improved discrimination in participants with known diabetes mellitus (C-index + 0.0007, 95% CI 0.0001-0.0012). In models of fatal CVD based on the SCORE fatal CVD outcome, modelling using classical CVD risk factors yielded a C-index of 0.7653 (95%CI 0.7548-0.7759), and addition of log HbA1c improved discrimination modestly (C-index +0.0025, 95% CI 0.0005-0.0045). For the net reclassification index, no significant reclassification was noted upon addition of HbA1c, in either cases (i.e. those with an outcome) or non-cases in any model (**Table 3**). These results were similar when participants with HbA1c ≥48mmol/mol (≥6.5%) were excluded.

Discussion

In this large cohort of over 370,000 individuals, we confirm that HbA1c is broadly linearly related to CVD risk in unadjusted analyses, but that this association is substantially attenuated with adjustment for conventional CVD risk factors. Indeed, in those with prediabetes, whilst their unadjusted HR for CVD risk was 1.83 relative to those with normal HbA1c, this fell to just 1.11 when adjusting for usual CVD risk factors. This means that whilst people with prediabetes are, on average, have around an 80% greater CVD risk compared with those with normal HbA1c levels, such risk is not largely driven by elevated HbA1c per se, but rather by differences in the prevalence or levels of other established CVD risk factors: age, blood pressure, smoking, lipid levels, and BMI. Furthermore, we show that addition of HbA1c when the conventional risk factors are already accounted for does not meaningfully improve CVD risk prediction, as shown by no gain in the NRI, a measure of risk improvement. In contrast, the risk of CVD was meaningfully higher in those with known or undiagnosed baseline diabetes, supporting the diagnostic cut-off for HbA1c as it relates to CVD risk.

Our results add to existing literature by validating prior results published by the ERFC that demonstrated that whilst HbA1c levels better predicted incident CVD events than fasting and post prandial glucose levels in those without prior diabetes or CVD, the added predictive gain from inclusion of HbA1c in risk prediction was modest. The importance of repeating this work cannot be underestimated for several reasons. First, ERFC data used individual HbA1c data from multiple cohorts with a wide variety of HbA1c measurement techniques. Second, assays for HbA1c have

improved since the early 2000s with better reproducibility and our results are based on one assay used in the entire cohort, thereby limiting inter-assay variation. Finally, we were able to compare results in those categorised using a modern definition of prediabetes, as accepted by the National Institute for Health and Care Excellence (NICE) and criteria used in other European countries, and as such inform clinical practice. Splitting this category into lower and higher HbA1c (42-44mmol/mol (6.0-6.2%), or 45-47 mmol/mol (6.3-6.4%)) revealed near identical point estimates and overlapping confidence intervals between the two groups. Therefore, despite the breadth of HbA1c values observed and potential differential risk categories, it appears appropriate to retain the present boundaries in particular for diabetes diagnosis at 6.5% (or 48 mmol/mol), at least on the basis of CVD risk. Of course, the glycemia thresholds to diagnose diabetes have been determined on the basis of risk for retinopathy, but it is interesting that they seem appropriate for macrovascular disease.

Our results have practical implications for clinical practice. First, these data are broadly supportive that HbA1c should be used to diagnose prediabetes and new diabetes, but also show that it is unlikely to be meaningfully additive for CVD risk prognostication in those without known diabetes. Second, all those found to have prediabetes on the basis of HbA1c levels should have their CVD risk assessed by conventional methods, i.e. with additional measurement of lipids and blood pressure, as currently recommended (14) and it would not be appropriate to give only lifestyle advice to prevent or delay diabetes. Rather, as those with prediabetes had higher baseline CVD risk, with meaningfully higher mean SBP at just under 146 mmHg, mean BMI just over 30 kg/m^2, and higher average cholesterol to HDL-C ratios, they

need comprehensive CVD risk management. Finally, given modest numbers with prediabetes or undiagnosed diabetes (<4% of cohort in total), the value of using a non-lab based score first to identify those at highest risk for diabetes is reaffirmed such that HbA1c should be added only to those with a high non-lab based risk score, as has been proposed by NICE (15). We do, however, recognise that UK Biobank is not nationally representative but even so, the relatively modest numbers with prediabetes and undiagnosed diabetes is noteworthy.

As with any study, our work has strengths and limitations. The present study is among the largest single cohort reported to date to measure HbA1c and assess CVD risk, with standardised measurements across the cohort. The limitations stem, as noted above, from UK Biobank cohort characteristics that are somewhat healthier than the average UK population. They also arise from lack of other glycemia measures due to the non-fasting nature of the baseline measurements in many, although ERFC data have shown HbA1c is more strongly linked to CVD than fasting or 2-hour glucose. Due to limited power, we were also unable to examine whether associations of HbA1c to outcomes were different by ethnicity..

In conclusion, in this very large well phenotyped cohort with central lab assessment of HbA1c, we show that HbA1c minimally improves CVD risk prediction in patients without diabetes. The same is also true for the subset with prediabetes. The near two-fold higher unadjusted risk for CVD in prediabetes is driven mainly by abnormal levels of conventional CVD risk factors. As such, and as recommended (14), this group would benefit from lifestyle advice to prevent diabetes, *and* from all conventional CVD risk factors being assessed and, where relevant, treated.

Contributors

NS and PW were involved in the design of the study. CW and PW wrote the first draft of the report, which was edited by NS. All authors were involved in data analysis and interpretation, and in drafting and critically revising the report. All authors had access to study results and the first author and corresponding author take responsibility for the integrity of the data and accuracy of the data reported. All authors reviewed and approved the final version of the report for submission. NS had full access to all the data and had final responsibility for the decision to submit for publication. NS is guarantor, and takes responsibility for the contents of the article.

Declaration of interests

NS has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Napp, Novo Nordisk, and Sanofi, and received grant support from Boehringer Ingelheim outside the submitted work. All other authors declare no competing interests.

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Table 1. Distribution of classical cardiovascular disease risk factors across categories of HbA1c in those *without known diabetes*.

	HbA1c category			
	<42.0mmol/mol (<6.0%) Normal	42.0-47.9mmol/mol (6.0-6.4%) Prediabetes	≥48mmol/mol (≥6.5%) Undiagnosed diabetes	P-value
N, percent	(n=344,016, 96.0%)	(n=11,680, 3.3%)	(n=2579, 0.7%)	
Age (years)	55.94 (8.10)	59.65 (6.94)	57.91 (7.47)	<0.001
Sex (%)				
Women	192435 (55.9%)	6395 (54.8%)	1060 (41.1%)	<0.001
Men	151581 (44.1%)	5285 (45.2%)	1519 (58.9%)	
Ethnicity (%)				
White	329593 (95.8%)	10108 (86.5%)	2143 (83.1%)	<0.001
Black	3795 (1.1%)	586 (5.0%)	134 (5.2%)	
South Asian	4058 (1.2%)	463 (4.0%)	172 (6.7%)	
Other	6570 (1.9%)	523 (4.5%)	130 (5.0%)	
Smoker				
No	309000 (89.8%)	9792 (83.8%)	2205 (85.5%)	<0.001
Yes	35016 (10.2%)	1888 (16.2%)	374 (14.5%)	
Systolic blood pressure (mmHg)	139.31 (19.63)	145.92 (19.61)	149.50 (19.40)	<0.001
Diastolic blood pressure (mmHg)	82.35 (10.66)	84.89 (10.62)	88.14 (10.74)	<0.001
BMI (kg/m^2)	26.99 (4.47)	30.17 (5.57)	32.01 (5.72)	<0.001
BP medication (%)	52909 (15.4%)	3724 (31.9%)	722 (28.0%)	<0.001
Statins (%)	32229 (9.4%)	2774 (23.8%)	494 (19.2%)	<0.001
Total cholesterol	5.82 (1.08)	5.81 (1.18)	5.89 (1.24)	0.007
HDL cholesterol	1.48 (0.38)	1.33 (0.33)	1.20 (0.29)	<0.001
Total : HDL cholesterol	4.14 (1.11)	4.57 (1.20)	5.08 (1.25)	<0.001

BMI body mass index; BP blood pressure; HDL high-density lipoprotein; SD standard deviation.

Table 2. Association of different glycemia categories with risk of composite fatal/non-fatal CVD outcomes in unadjusted and adjusted models based on all three risk scoring systems, using a complete case analysis.

	QRISK3		ACC/AHA		SCORE	
N participants **(n CVD events)**	**357833** **(12894)**		**357833** **(6618)**		**357833** **(1813)**	
	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR	Unadjusted HR	Adjusted HR
HbA1c categories						
Referent - normal <42.0mmol/mol (<6.0%)	1	1	1	1	1	1
Prediabetes 42.0-47.9mmol/mol (6.0 to 6.4%)	1.83 (1.69-1.97)	1.11 (1.03-1.20)	1.81 (1.63-2.01)	1.19 (1.07-1.32)	2.49 (2.09-2.96)	1.10 (1.09-1.10)
Undiagnosed diabetes ≥48.0mmol/mol (≥6.5%)	2.26 (1.97 – 2.61)	1.20 (1.04-1.38)	2.42 (2.00-2.92)	1.42 (1.17-1.72)	2.89 (2.07-4.04)	2.37 (2.13-2.65)

Models adjusted according to outcome (see text for covariate lists).

Table 3. Improvement in net classification (net reclassification index) across a binary 10-year risk threshold upon addition of HbA1c to a range of CVD outcomes in 357833 participants without known baseline diabetes and with complete data for all covariates.

Model	Comparator	Addition	Binary risk threshold for high/low 10 year risk	Overall NRI (95% CI)	Case NRI (95%CI)	Non-case NRI (95% CI)
QRISK3	QRISK3 classical CVD risk factors *	+HbA1C	10%	0.01% (-0.01, 0.03)	0.01% (0.00, 0.04%)	-0.01% (-0.01, 0.00)
ACC/AHA**	ACC/AHA classical CVD risk factors**	+HbA1C	7.5%	-0.11% (-0.49, 0.22%)	-0.09% (-0.47, 0.24%)	-0.02% (-0.04, 0.00%)
SCORE	SCORE classical CVD risk factors***	+HbA1C	5%	0.28% (-0.33, 0.87%)	0.29% (-0.32, 0.88%)	-0.01% (-0.02, 0.00%)

*QRISK3 outcomes and broad risk factors (age, sex, nine category ethnicity, Townsend deprivation index, total:HDL cholesterol, SBP, BMI, family history of CVD, diabetes, hypertension, rheumatoid arthritis, atrial fibrillation, chronic kidney disease stages 3-5, migraine, steroid use, systemic lupus erythematosus, atypical antipsychotic medication use, serious psychological disorders, antihypertensive medications, erectile dysfunction, smoking and statin use).

** ACC/AHA outcomes and broad risk factors (age, sex, four category ethnicity, total cholesterol, HDL cholesterol, systolic and diastolic blood pressure, blood pressure medication, smoking, statin use).

*** SCORE outcomes and broad risk factors (age, sex, total cholesterol, HDL cholesterol, systolic blood pressure, smoking).

Figure 1. Unadjusted and adjusted (for QRISK3 risk factors) hazard ratios of composite fatal/non-fatal CVD by deciles of baseline HbA1c in those without baseline diabetes (n=355,696) and in participants with undiagnosed diabetes (n=2579) or known baseline diabetes (n= 16,619). For simplicity, categories are depicted only as mmol/mol. The dashed line represents ≥ 48 mmol/mol (6.5%).