Glycated Hemoglobin, Prediabetes, and the Links to Cardiovascular Disease: Data From UK Biobank

Diabetes Care 2020;43:440–445 | https://doi.org/10.2337/dc19-1683

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OBJECTIVE

HbA_{1c} levels are increasingly measured in screening for diabetes; we investigated whether HbA_{1c} may simultaneously improve cardiovascular disease (CVD) risk assessment, using QRISK3, American College of Cardiology/American Heart Association (ACC/AHA), and Systematic COronary Risk Evaluation (SCORE) scoring systems.

RESEARCH DESIGN AND METHODS

UK Biobank participants without baseline CVD or known diabetes (n = 357,833) 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 16,596 participants with known baseline diabetes.

RESULTS

Incident fatal or nonfatal CVD, as defined in the QRISK3 prediction model, occurred in 12,877 participants over 8.9 years. Of participants, 3.3% (n = 11,665) had prediabetes (42.0–47.9 mmol/mol [6.0–6.4%]) and 0.7% (n = 2,573) had undiagnosed diabetes (≥48.0 mmol/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: hazard ratio (HR) 1.83 (95% CI 1.69–1.97) and 2.26 (95% CI 1.96–2.60), 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 HbA_{1c} to the QRISK3 CVD risk prediction model (C-index 0.7392) yielded a small improvement in discrimination (C-index increase of 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.

CONCLUSIONS

The near twofold higher unadjusted risk for CVD in people with prediabetes is driven mainly by abnormal levels of conventional CVD risk factors. While HbA_{1c} adds minimally to cardiovascular risk prediction, those with prediabetes should have their conventional cardiovascular risk factors appropriately measured and managed.

Circulating hemoglobin A_{1c} (HbA_{1c}) indicates average blood glucose concentrations over the preceding 3 months. The absence of the need for patients to fast for HbA_{1c} assessment is a major advantage of measuring HbA_{1c} for screening for dysglycemia, including diabetes and prediabetes, and has been endorsed for such screening by society recommendations (1). Whether screening HbA_{1c} values incrementally

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Received 21 August 2019 and accepted 27 October 2019

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contributes 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 HbA_{1c} (2).

The European Systematic COronary Risk Evaluation (SCORE) CVD risk score (3), QRISK3 risk score (4), and the American College of Cardiology/American Heart Association (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 HbA_{1c} 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 interstudy 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. This topic requires better evidence to inform clinical care.

Capitalizing on the availability of data in the UK Biobank comprising several hundred thousand participants including baseline HbA_{1c} measures and capture of longitudinal clinical outcomes, we examined the prognostic utility of HbA_{1c} for CVD in participants without prevalent diabetes.

RESEARCH DESIGN AND METHODS

The UK Biobank recruited 502,536 participants (age 37–73 years) from 22 assessment centers across the U.K. between April 2007 and December 2010. Baseline biological measurements were recorded and touch screen questionnaires were administered as previously described (9,10). The UK Biobank received ethics approval from the North West Multicenter Research Ethics Committee (reference number 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 (SBP) and diastolic (DBP) blood pressure was taken as the first baseline measurement, preferentially using an automated measurement. Smoking status was categorized 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 previously been described and validated (11). Biochemistry measures were performed at a dedicated central laboratory on ~480,000 samples between 2014 and 2017. These included serum total cholesterol and HDL cholesterol (HDL-C) (AU5400; Beckman Coulter) and plasma glycated hemoglobin (HbA_{1c}) (VARIANT II TURBO Hemoglobin Testing System; Bio-Rad). Data were adjusted by UK Biobank centrally before release to adjust for preanalytical 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 self-reported use of insulin. Statin and blood pressure medication use was also recorded from self-report. Baseline CVD was defined as self-reported prior myocardial infarction, stroke, and transient ischemic attack as well as hospital diagnoses including ICD-10 codes I20–24, I63–64, and 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. Hospital admissions were identified via linkage to Health Episode Statistics, the Patient Episode Database, and the Scottish Morbidity Records. The main outcome of interest in the current study reflected the outcome used in the QRISK3 risk score (4), namely, fatal or nonfatal coronary heart disease, ischemic stroke, or transient ischemic attack (ICD-10 G45, I20–24, and I63–64) (hereafter QRISK3 CVD events). There were two additional outcomes of interest in the current study: *1*) a composite of fatal and nonfatal CVD that reflects the ACC/AHA guideline prediction score including death from CVD (ICD-10 I20–25 and I60–64) or hospitalization for CVD (ICD-10 I21, I22, and I60–64) (5) (hereafter ACC/AHA CVD events) and *2*) fatal CVD as defined by primary cause of death from events included in the European SCORE clinical guidelines (I10–15, I44–51, I20–25, and I61–73) (12) (hereafter SCORE CVD events).

End of follow-up for each participant was recorded as the date of death, the date of end of follow-up for the assessment center attended (31 January 2018 for participants in England or Wales and 30 November 2016 for participants in Scotland), or the first date of CVD-related hospitalization (for both composite fatal/nonfatal 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 analyzed separately from the main cohort.

Statistical Analyses

Log-transformed HbA_{1c} was analyzed as a continuous variable and was categorized using thresholds of $<$42.0 mmol/mol ($<$6.0%) (normal/referent), 42.0–47.9 mmol/mol (6.0–6.4%) (prediabetes), and $\geq$48.0 mmol/mol ($\geq$6.5%) (undiagnosed diabetes), as well as deciles of the distribution. Classical CVD risk factors were expressed as mean (SD) if symmetrically distributed, median (interquartile range) if skewed, and number (%) if categorical. The prediabetes category of HbA_{1c} was further split into the following categories to examine its relationship with CVD outcomes: 42.0–44.9 mmol/mol (6.0–6.2%) and 45.0–47.9 mmol/mol (6.3–6.4%). The distribution of classical CVD risk factors by categories of HbA_{1c} was assessed using ANOVA, a Wilcoxon test for trend, or a χ^2 test. Associations of classical CVD risk factors and HbA_{1c} with CVD outcomes were also tabulated using these methods.

Univariable associations of categories of HbA_{1c} with outcomes of interest were initially explored using Kaplan-Meier methods. Associations of continuous and categorical HbA_{1c} with outcomes of interest were investigated using Cox proportional hazards models for each outcome, adjusted for age, sex, ethnicity, total cholesterol and HDL-C, SBP, DBP, antihypertensive medications, smoking, and statin use in ACC/AHA or SCORE risk scores and adjusted for age, sex, SBP,

smoking, ethnicity, Townsend deprivation index (index of deprivation based on postcode), total cholesterol–to–HDL-C ratio, 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, and statin use for QRISK3 (also using restricted cubic splines to explore the shape of the association [data not shown]). The proportional hazard assumption was checked by inspection of Schoenfeld residuals. Tests for interaction were performed by categories of the main covariates of interest.

The ability of HbA_{1c} 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 (with adjustments as above). Improvement in prediction was tested using Harrell C-Index for survival data, testing for increased concordance upon the addition of HbA_{1c} to the model. We used a categorical net reclassification index (NRI) to investigate changes in predicted risk classification upon addition of HbA_{1c} to the models (13). Discrimination upon addition of HbA_{1c} was also tested after exclusion of participants with HbA_{1c} >48.0 mmol/mol, i.e., undiagnosed diabetes.

All analyses were performed using STATA 14 (StataCorp) and R (3.5.1). A two-sided *P* value of 0.05 was considered statistically significant without adjustment for multiple comparisons.

RESULTS

Cross Sectional Associations

Of 472,309 people without baseline CVD included in the study, complete data on covariates, including HbA_{1c}, were available for 374,429 (79%) participants, and after exclusion of participants with known/self-reported diabetes (n = 16,596), the cohort for the main analyses included 357,833 participants, including those with HbA_{1c} ≥48.0 mmol/mol (≥6.5%) without report of prior diabetes diagnosis (i.e., undiagnosed diabetes). Median HbA_{1c} in this cohort was 34.9 mmol/mol (5.3%) (interquartile range 32.5–37.3 mmol/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 >6 mmHg, higher BMI by >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 nonwhite 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/nonfatal CVD outcome was 8.9 years (Q1–Q3 8.2–9.4). The fatal/nonfatal CVD outcome occurred in 12,877 participants (3.6%), ACC/AHA-based CVD outcomes occurred in 6,608 participants (1.9%), and SCORE-based fatal CVD occurred in 1,803 participants (0.5%). In the main cohort without known baseline diabetes, HbA_{1c} was higher in participants who subsequently had an incident CVD event (35.1 vs. 36.2 mmol/mol in those without vs. with incident CVD, a rounded difference of 1.2 mmol/mol [95% CI 1.1–1.2]). In people with known baseline diabetes (n = 16,596), over a median of 8.7 years of follow-up, the QRISK3-based CVD outcome occurred in 1,472 (8.9%) of participants and fatal CVD occurred in 306 (1.8%).

Association of HbA_{1c} with CVD Outcomes

The unadjusted risk of the composite fatal/nonfatal CVD outcome was greatest for participants with known diabetes but was also higher in those with undiagnosed baseline diabetes and in those with prediabetes (Fig. 1). Those with prediabetes were at 1.83-fold (95% CI 1.69–1.97) higher risk of CVD compared with those with normal HbA_{1c}, and those with undiagnosed diabetes were at 2.26-fold (95% CI 1.96–2.60) higher risk (Table 2).

Figure 1 shows the unadjusted and adjusted risks associated with HbA_{1c} across the range from normal to prediabetes, undiagnosed diabetes, and prevalent diabetes. The results, as in Table 2, show that the CVD risks in the prediabetes range were substantially attenuated with adjustment for usual CVD risk factors such that the adjusted hazard ratios (HRs) were rather modest. While adjustment also attenuates the HR in the participants with undiagnosed diabetes and diabetes, adjusted relative risks remained statistically significant. The association between HbA_{1c} and the ACC/AHA outcome was broadly similar, but the association between HbA_{1c} and fatal (SCORE) CVD was stronger (Table 2).

When the association between HbA_{1c} and QRISK CVD was analyzed separately in split prediabetes groups (42.0–44.9 mmol/mol [6.0–6.2%] and 45.0–47.9 mmol/mol [6.3–6.4%]), HRs were similar and had overlapping CIs (1.11 [95% CI 1.02–1.21] and 1.11 [95% CI 0.95–1.29], respectively).

HbA_{1c} 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 HbA_{1c} (C-index increase of 0.0004 [95% CI 0.0001–0.0007]). In those with a baseline HbA_{1c} <48.0 mmol/mol (<6.5%), modeling using classical CVD risk factors yielded a C-index of 0.7392 (95% CI 0.7353–0.7431), which was also modestly improved upon addition of log HbA_{1c} (C-index increase of 0.0003 [95% CI 0.0001–0.0006]).

Patterns were similar for the other outcomes of interest. In a model of ACC/AHA CVD, using classical CVD risk factors in those without diagnosed diabetes yielded a C-index of 0.7360 (95% CI 0.7304–0.7416). Addition of log HbA_{1c} to the ACC/AHA model also modestly improved discrimination (C-index increase of 0.0007 [95% CI 0.0001–0.0012]). In models of CVD based on the SCORE fatal CVD outcome, modeling using classical CVD risk factors yielded a C-index of 0.7747 (95% CI 0.7646–0.7849), and addition of log HbA_{1c} improved discrimination modestly (C-index increase of 0.0020 [95% CI 0.0005–0.0036]). For the NRI, no significant reclassification was noted upon addition of HbA_{1c} in either case subjects (i.e., those with an outcome) or noncase subjects in any model (Table 3). These results were similar when participants with HbA_{1c} ≥48 mmol/mol (≥6.5%) were excluded.

Table 1—Distribution of classical CVD risk factors across categories of HbA_{1c} in those without known diabetes

	HbA_{1c} category			
	Normal: <42.0 mmol/mol (<6.0%)	Prediabetes: 42.0–47.9 mmol/mol (6.0–6.4%)	Undiagnosed diabetes: ≥48 mmol/mol (≥6.5%)	*P*
n (%)	343,595 (96.0)	11,665 (3.3)	2,573 (0.7)	
Age (years)	56.0 (8.1)	59.7 (6.9)	57.9 (7.5)	<0.001
Sex, *n* (%)				<0.001
Women	192,214 (55.9)	6,384 (54.7)	1,058 (41.1)	
Men	151,381 (44.1)	5,281 (45.3)	1,515 (58.9)	
Ethnicity, *n* (%)				<0.001
White	329,201 (95.8)	10,094 (86.5)	2,138 (83.1)	
Black	3,787 (1.1)	586 (5.0)	134 (5.2)	
South Asian	4,054 (1.2)	463 (4.0)	172 (6.7)	
Other	6,553 (1.9)	522 (4.5)	129 (5.0)	
Smoker, *n* (%)				<0.001
No	308,623 (89.8)	9,779 (83.8)	2,202 (85.6)	
Yes	34,972 (10.2)	1,886 (16.2)	371 (14.4)	
SBP (mmHg)	139.3 (19.6)	145.9 (19.6)	149.5 (19.4)	<0.001
DBP (mmHg)	82.4 (10.7)	84.9 (10.6)	88.2 (10.7)	<0.001
BMI (kg/m^2)	27.0 (4.5)	30.2 (5.6)	32.0 (5.7)	<0.001
BP medication, *n* (%)	52,843 (15.4)	3,720 (31.9)	719 (27.9)	<0.001
Statins, *n* (%)	32,190 (9.4)	2,774 (23.8)	492 (19.1)	<0.001
TC (mmol/L)	5.82 (1.08)	5.81 (1.18)	5.89 (1.25)	0.007
HDL-C (mmol/L)	1.48 (0.38)	1.33 (0.33)	1.20 (0.29)	<0.001
TC–to–HDL-C ratio	4.14 (1.11)	4.57 (1.20)	5.08 (1.25)	<0.001

Data are mean (SD) unless otherwise indicated. BP, blood pressure; TC, total cholesterol.

CONCLUSIONS

In this large cohort of >370,000 individuals, we confirm that HbA_{1c} 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, while their unadjusted HR for CVD risk was 1.83 relative to those with normal HbA_{1c}, this fell to just 1.11 with adjustment for usual CVD risk factors. This means that while people with prediabetes on average have an ~80% greater CVD risk compared with those with normal HbA_{1c} levels, such risk is largely driven not by elevated HbA_{1c} 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 HbA_{1c} when the conventional risk factors are already accounted for does not meaningfully improve CVD risk prediction, as shown by no gain in the NRI. In contrast, the risk of CVD was meaningfully higher in those with diagnosed or undiagnosed baseline diabetes, supporting the diagnostic cutoff for HbA_{1c} as it relates to CVD risk.

Our results add to existing literature by validating prior results published by the Emerging Risk Factors Collaboration (ERFC) that demonstrated that while HbA_{1c} levels better predicted incident CVD events than fasting and postprandial glucose levels in those without prior diabetes or CVD, the added predictive gain from inclusion of HbA_{1c} in risk prediction was modest. The importance of

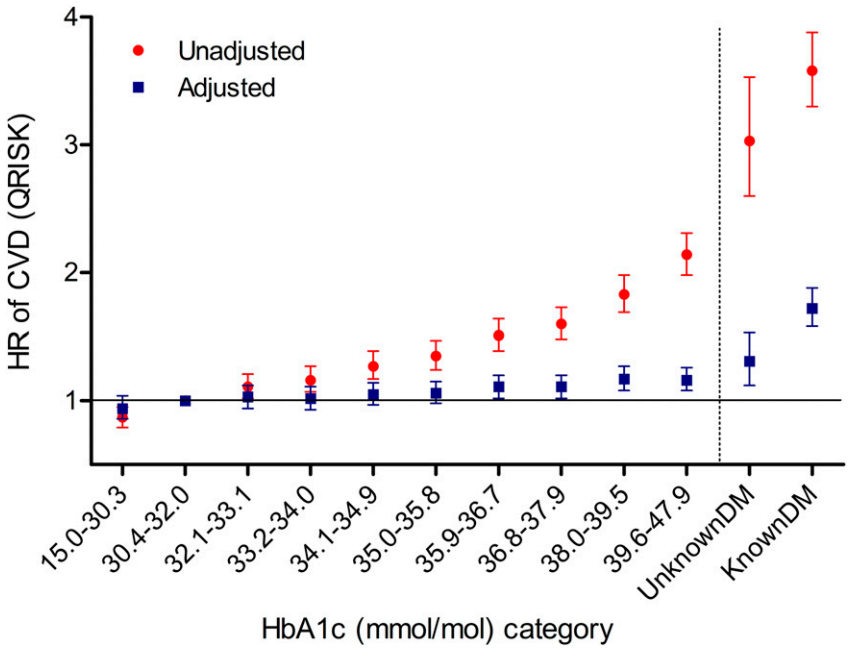

Figure 1—Unadjusted and adjusted (for QRISK3 risk factors) HRs of composite fatal/nonfatal CVD by deciles of baseline HbA_{1c} in those without baseline diabetes (n = 355,260) and in participants with undiagnosed diabetes (n = 2,573) or diagnosed diabetes (n = 16,596). For simplicity, categories are depicted only as mmol/mol. The dashed line represents ≥48 mmol/mol (6.5%). Please note all results referent to decile 2 (30.4–32.0 mmol/mol).

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

	QRISK3: N = 357,833 participants (n = 12,877 CVD events)		ACC/AHA: N = 357,833 participants (n = 6,608 CVD events)		SCORE: N = 357,833 participants (n = 1,803 CVD events)	
HbA_{1c} categories	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)	Unadjusted HR (95% CI)	Adjusted HR (95% CI)
Referent, normal: <42.0 mmol/mol (<6.0%)	1	1	1	1	1	1
Prediabetes: 42.0–47.9 mmol/mol (6.0%–6.4%)	1.83 (1.69–1.97)	1.11 (1.03–1.20)	1.81 (1.63–2.01)	1.18 (1.06–1.32)	2.50 (2.10–2.98)	1.55 (1.29–1.85)
Undiagnosed diabetes: ≥48.0 mmol/mol (≥6.5%)	2.26 (1.96–2.60)	1.20 (1.04–1.38)	2.43 (2.01–2.93)	1.43 (1.18–1.73)	2.91 (2.08–4.07)	1.75 (1.25–2.45)

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

repeating this work cannot be underestimated for several reasons. First, ERFC data used individual HbA_{1c} data from multiple cohorts with a wide variety of HbA_{1c} measurement techniques. Second, assays for HbA_{1c} have improved since the early 2000s with better reproducibility and our results are based on one assay used in the entire cohort, thereby limiting interassay variation. Finally, we were able to compare results in those categorized using a modern definition of prediabetes, as accepted by the National Institute for Health and Care Excellence and as used in other European countries, and as such inform clinical practice. Splitting participants with prediabetes into lower and higher HbA_{1c} (42.0–44.9 mmol/mol [6.0–6.2%] or 45.0–47.9 mmol/mol [6.3–6.4%]) revealed near identical point estimates and overlapping CIs between the two groups. Therefore, despite the breadth of HbA_{1c} values observed and potential differential risk categories, it appears to be 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 important that they appear valid for macrovascular disease.

Our results have practical implications for clinical practice. First, these data are broadly supportive that HbA_{1c} 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 HbA_{1c} 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 total 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 importance of using a non–laboratory test-based score first to identify those at highest risk for diabetes is reaffirmed. This means HbA_{1c} should only be measured in those with a high diabetes risk score, as has been proposed by the National Institute for Health and Care Excellence (15). We do, however, recognize that UK Biobank is not nationally representative, but even so, it is worth noting the relatively modest numbers with prediabetes and undiagnosed diabetes.

As with any study, our work has strengths and limitations. The current study is the largest single cohort reported to date to measure HbA_{1c} and assess CVD risk, with standardized measurements across the cohort. The limitations stem, as noted above, from UK Biobank cohort characteristics—a cohort somewhat healthier

Table 3—Improvement in NRI across a binary 10-year risk threshold upon addition of HbA_{1c} to a range of CVD outcomes in 357,833 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)	Noncase NRI (95% CI)
QRISK3	QRISK3 classical CVD risk factors*	+HbA_{1c}	10%	0.00% (−0.03 to 0.03%)	0.01% (−0.03 to 0.04%)	−0.01% (−0.01 to 0.00%)
ACC/AHA	ACC/AHA classical CVD risk factors**	+HbA_{1c}	7.5%	−0.10% (−0.43 to 0.28%)	−0.08% (−0.41 to 0.28%)	−0.02% (−0.04 to 0.00%)
SCORE	SCORE classical CVD risk factors***	+HbA_{1c}	5%	0.24% (−0.32 to 0.83%)	0.25% (−0.32 to 0.84%)	−0.01% (−0.03 to 0.00%)

*QRISK3 outcomes and broad risk factors (age, sex, nine category ethnicity, Townsend deprivation index, total cholesterol–to–HDL-C ratio, SBP, 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, smoking, and statin use. **ACC/AHA outcomes and broad risk factors (age, sex, four category ethnicity, total cholesterol, HDL-C, SBP and DBP, blood pressure medication, and smoking). ***SCORE outcomes and broad risk factors (age, sex, total cholesterol, HDL-C, SBP, and smoking).

than the average U.K. population. The limitations also arise from lack of other glycemia measures, although ERFC data have shown that HbA_{1c} is more strongly linked to CVD than is fasting glucose or 2-h glucose. Due to limited power, we were also unable to examine whether associations of HbA_{1c} with outcomes were different by ethnicity.

In conclusion, in this very large well-phenotyped cohort with central laboratory assessment of HbA_{1c}, we show that HbA_{1c} minimally improves CVD risk prediction in patients without diabetes. The same is also true for the subset with prediabetes. The near twofold 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 having all conventional CVD risk factors assessed and, where relevant, treated.

Acknowledgments. This research was conducted using the UK Biobank resource. The authors thank the participants of the UK Biobank. The work was performed under UK Biobank project number 9310. The authors thank Liz Coyle (University of Glasgow) for her excellent assistance in the preparation of this article.

Funding. The work in this study was supported by a grant from Chest, Heart and Stroke Association Scotland (Res16/A165) and by the British Heart Foundation Research Excellence Award (RE/18/6/34217).

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

Duality of Interest. D.K.M. reports personal fees from Boehringer Ingelheim, Janssen Research and Development LLC, Sanofi US, Merck Sharp and Dohme Corp., Merck & Co, Eli Lilly and Company, Novo Nordisk, GlaxoSmithKline, AstraZeneca, Lexicon, Eisai Inc., Esperion, Metavant, Pfizer, Afimmune, and Applied Therapeutics. N.S. has consulted for Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, Janssen, Napp, Novo Nordisk, Pfizer, and Sanofi and received grant support from Boehringer Ingelheim outside the submitted work. No other potential conflicts of interest relevant to this article were reported.

Author Contributions. C.W. and P.W. wrote the first draft of the manuscript, which was edited by N.S. All authors were involved in data analysis and interpretation and in drafting and critically revising the manuscript, had access to study results, and reviewed and approved the final version of the manuscript for submission. P.W. and N.S. were involved in the design of the study. N.S. had final responsibility for the decision to submit for publication. N.S. is the guarantor of this work and, as such, 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.

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