

Change in HbA_{1c} over 3 years does not improve the prediction of cardiovascular disease over and above HbA_{1c} measured at a single time point

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Abstract

Aims/hypothesis HbA_{1c} is an important risk factor for cardiovascular disease (CVD), with 1% higher HbA_{1c} levels associated with a 10–20% increased risk of CVD. Little is known about the association between change in HbA_{1c} over time and cardiovascular risk in non-diabetic populations. This study examined the association between change in HbA_{1c} over time and cardiovascular risk in a non-diabetic British population.

Methods We used data on HbA_{1c} collected at baseline and at a second health examination 3 years later among a population of 5,790 non-diabetic men and women who participated in the European Prospective Investigation of Cancer (EPIC)–Norfolk. The association between change in HbA_{1c} over 3 years and incident cardiovascular events over the following 8 years was examined using multivariate Cox regression. We also examined whether information on change in HbA_{1c} over time improved prediction of cardiovascular events over a single measure of HbA_{1c} by comparing the area under the receiver operating characteristic curves (aROC) and computing the net reclassification improvement.

Results The mean change (SD) in HbA_{1c} over 3 years was 0.13% (0.52). During 44,596 person-years of follow-up, 529 cardiovascular events occurred (incidence 11.9 per 1,000 person-years). Each 0.5% rise in HbA_{1c} over 3 years was associated with a 9% increase in risk of a cardiovascular event (HR 1.09; 95% CI 1.01, 1.18) after adjustment for baseline HbA_{1c} and other major cardiovascular risk factors. However, change in HbA_{1c} was not associated with cardiovascular risk after adjustment for HbA_{1c} at follow-up. Multivariate models with and without information on change in HbA_{1c} over time showed a similar aROC of 0.78. Adding change in HbA_{1c} to the model with HbA_{1c} at follow-up did not improve risk classification.

Conclusions/interpretation Addition of information on change in HbA_{1c} over 3 years did not improve the prediction of CVD over and above information on HbA_{1c} and other major cardiovascular risk factors from a single time point.

Keywords Cardiovascular disease · Discriminatory ability · Glycated haemoglobin (HbA_{1c}) · Net reclassification improvement · Prediction · Risk factors · Temporal change

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Abbreviations

aROC	Area under the receiver operating characteristic curve
CVD	Cardiovascular disease
EPIC–Norfolk	European Prospective Investigation of Cancer–Norfolk
NRI	Net reclassification improvement

Introduction

Glycaemia is an important risk factor for cardiovascular disease (CVD), not only in those with diabetes but across

the range of blood glucose values [1, 2]. Previous studies have suggested that HbA_{1c} has a continuous and graded relationship with CVD, with 1% higher HbA_{1c} levels associated with a 20% and 26% increased risk of CHD and total mortality, respectively [3, 4]. Systematic reviews of randomised controlled trials of tight glycaemic control among patients with diabetes provide further evidence of a causal relationship between blood glucose and CVD [5, 6]. However, there are no trials of glucose-lowering therapy in people with non-diabetic hyperglycaemia that have reported a reduction in cardiovascular events [7]. Consequently, there remains uncertainty over the benefits of lowering blood glucose to prevent CVD in non-diabetic populations [2].

Previous studies examining the relationship between glycaemia and CVD were based on between-individual differences in levels of glycaemia [3, 4, 8]. Studies have tracked glycaemic control and CVD risk in individuals with diabetes, but glucose-lowering treatment contributes to change in glycaemia and other cardiovascular risk factors in these individuals. Little is known about change in glycaemia over time and its association with CVD in non-diabetic populations. If an association does exist, it is unclear whether information on change in glycaemia over time will improve prediction of cardiovascular events compared with a single measure of glycaemia and other major cardiovascular risk factors. In a large British prospective cohort, we examined: (1) the association between change in HbA_{1c} over 3 years and risk of CVD; (2) whether information on change in HbA_{1c} over time might improve prediction of CVD compared with information collected at a single time point.

Methods

Study design and population We used data from the European Prospective Investigation of Cancer (EPIC)–Norfolk, a large population-based prospective study of men and women aged 40–79 years residing in the county of Norfolk, UK. Details of the study have been described elsewhere [9]. Between 1993 and 1997, 25,639 men and women attended a baseline health examination, which included a self-administered health and lifestyle questionnaire, medical history taking, physical examination and blood testing. Participants completed questionnaires about their personal and family history of disease, medication and lifestyle factors including smoking habits. They were asked whether a physician had ever told them that they had any of the conditions in a list that included diabetes, heart attack and stroke. Anthropometric and blood pressure measurements and non-fasting blood samples were also taken at the health assessment.

Information on HbA_{1c} at baseline was available for around half of all participants, as funding for the test only

became available in 1995. HbA_{1c} was measured on fresh EDTA blood samples using high-performance liquid chromatography (Diamat Automated Glycated Hemoglobin Analyzer; Bio-Rad Laboratories, Hemel Hemstead, UK), which was standardised to the Diabetes Control and Complications Trial (DCCT) assay.

The study was approved by the Norwich District Health Authority Ethics Committee. All participants gave written informed consent. EPIC–Norfolk is similar to a nationally representative sample for anthropometric indices, blood pressure and serum lipids, albeit with a lower prevalence of cigarette smoking [9].

Participants were invited to attend a second health assessment after 3 years (1998–2001), at which identical measurements were taken, and 15,028 participants (59%) attended. Results from the health examinations on risk factors such as total cholesterol, blood pressure and HbA_{1c} were reported to the participants' general practitioners so that they could assume responsibility for follow-up, confirmation of the diagnosis and organisation of care.

We limited our analysis to individuals with complete data for HbA_{1c} at the baseline and second health examinations ($n=6,372$). Those with complete data on HbA_{1c} were healthier than those without with regard to risk factors at baseline (electronic supplementary material [ESM] Table 1). We further excluded individuals with clinically diagnosed diabetes (self-reported physician-diagnosed diabetes, diabetes medication or diet modification due to diabetes, diabetes identified on hospital records, diabetes registers or diabetes coded on death certificates) [10] at both health examinations ($n=245$). We then excluded those with prior CVD at the baseline examination and those who developed a first CVD event up to the second health examination ($n=337$), leaving 5,790 individuals for our main analyses. We calculated the change in HbA_{1c} for each individual, the main exposure in this study, by subtracting baseline HbA_{1c} values from values at the second health examination.

Follow-up and ascertainment of CVD We followed up participants who were free of CVD at the time of their second health examination for the development of a first CVD event or death. We report results for follow-up from the second health examination to 31 March 2008, a median of 8.1 years (interquartile range 7.7–8.4). Incident CVD was defined as a composite of fatal or non-fatal CVD, including hospitalisation from CHD and stroke; or death from CHD, stroke or peripheral vascular disease. Vital status for all EPIC–Norfolk participants was obtained via death certification at the Office for National Statistics. Participants admitted to a hospital were identified by their National Health Service number. Hospitals were linked to the East Norfolk Health Authority database, which identifies all hospital contacts throughout England and Wales for Norfolk residents. Hospital record data and vital

status information were complete for 95% and 99% of participants, respectively. Previous validation studies in this prospective cohort indicated high validity of such case ascertainment [11].

Statistical analyses Baseline characteristics and change in HbA_{1c} over 3 years were summarised by CVD outcome, using percentages, means (SD) and medians (interquartile ranges). We tested for differences between groups using χ^2 tests for categorical variables, and *t* tests or Kruskal–Wallis tests for normally or non-normally distributed continuous variables.

The distribution of HbA_{1c} at baseline and the second health examination and change in HbA_{1c} was approximately normal. We calculated the mean values of the three measures and tested whether the change in HbA_{1c} over time was different from zero.

We calculated cardiovascular event rates by levels of baseline HbA_{1c} (<5%, 5.0–5.4%, 5.5–5.9% and $\geq 6.0\%$ [<30 , 31–36, 37–41 and ≥ 42 mmol/mol, respectively]) and change in HbA_{1c} over time (increased and unchanged or decreased). We computed Kaplan–Meier curves for groups characterised by different levels of baseline HbA_{1c}, and for individuals with high and low values of baseline HbA_{1c} (according to the median value in this population) and changes in HbA_{1c} over time (increased vs decreased or unchanged). We also computed Kaplan–Meier curves using different cut-off points to define high/low values of baseline HbA_{1c} (HbA_{1c} values of 5.7% and 6.0% [39 and 42 mmol/mol] instead of the median value). The differences between groups with different baseline HbA_{1c} and changes in HbA_{1c} were tested using the logrank test.

To examine the independent association of HbA_{1c} at baseline and HbA_{1c} at follow-up and change in HbA_{1c} over 3 years with CVD risk, we fitted five multivariate Cox proportional hazards models which included different variables as follows: (1) Model 1: HbA_{1c} at baseline and change in HbA_{1c} over 3 years; (2) Model 2: HbA_{1c} at baseline, age, sex, smoking, a family history of CVD, systolic blood pressure and serum total cholesterol; (3) Model 3: HbA_{1c} at baseline, change in HbA_{1c} over 3 years, age, sex, smoking, a family history of CVD, systolic blood pressure and serum total cholesterol; (4) Model 4: HbA_{1c} at follow-up, age, sex, smoking, a family history of CVD, systolic blood pressure and serum total cholesterol; (5) Model 5: HbA_{1c} at follow-up, change in HbA_{1c} over 3 years, age, sex, smoking, a family history of CVD, systolic blood pressure and serum total cholesterol.

To determine whether information on change in HbA_{1c} over 3 years improved risk prediction of the model which included HbA_{1c} measured at baseline or follow-up, we compared the area under the receiver operating characteristic curve (aROC) for the models with and without information on change in HbA_{1c}, using a non-parametric method [12].

To account for concurrent changes in other risk factors, we adjusted for changes in systolic blood pressure, total cholesterol and BMI. According to the new diagnostic criteria for diabetes, we performed sensitivity analyses to check if the main results would be altered when excluding those with an HbA_{1c} $\geq 6.5\%$ and $\geq 7.0\%$ (≥ 48 and ≥ 53 mmol/mol).

For each model, we calculated the probability of CVD events over 8 years for each individual using methods previously described by D’Agostino et al [13], and then stratified participants into four risk categories (<5.0%, 5.0–9.9%, 10.0–19.9% and $\geq 20\%$). To demonstrate the benefits of using information on change in HbA_{1c} over time for prediction of CVD in clinical practice, we calculated the net reclassification improvement (NRI) to determine whether information on change in HbA_{1c} over time helped improve risk classification by the models with HbA_{1c} at baseline or follow-up (Model 3 vs Model 2, and Model 5 vs Model 4) [14].

Results

Baseline characteristics of study population The baseline characteristics of the study population are summarised in Table 1. The mean age of participants at baseline was 57.2 (SD 9.3) years, and 2,451 (42.3%) were male. Individuals who developed CVD were, on average, 8 years older than those who remained free of CVD. They were more likely to be male, current smokers, to have a family history of CVD, and be prescribed antihypertensive and lipid-lowering drugs, compared with those who did not develop CVD. Those who developed CVD also had higher baseline levels of BMI, systolic blood pressure, total cholesterol, triacylglycerol and HbA_{1c}, and lower HDL-cholesterol values. There was no difference in social class between the two groups.

Change in HbA_{1c} over time Mean HbA_{1c} values (SD) at baseline and the second health examination were 5.19% (33 mmol/mol) (0.58%) and 5.32% (35 mmol/mol) (0.47%), respectively. The mean difference between the two measures of HbA_{1c} was 0.13% (0.52%) ($p < 0.001$).

Rates of cardiovascular events During 44,596 person-years of follow-up, there were 529 first CVD events, a cardiovascular event rate of 11.9 per 1,000 person-years. Figure 1 shows cardiovascular event rates in individuals with different levels of baseline HbA_{1c} by change in HbA_{1c} from baseline to the second health examination. Individuals whose HbA_{1c} values increased over time were more likely to experience a cardiovascular event compared with those whose HbA_{1c} values decreased or were unchanged, except

Table 1 Baseline characteristics of EPIC–Norfolk participants by CVD outcome ($n=5,790$)

Characteristic	Total ($n=5,790$)	Individuals who did not develop CVD ($n=5,261$)	Individuals who developed CVD ($n=529$)	p value ^a
Age, mean (SD), years	57.2 (9.3)	56.5 (9.2)	64.5 (7.7)	<0.001
Male sex, n (%)	2,451 (42.3)	2,138 (40.6)	313 (59.2)	<0.001
Social class I–IIIa ^b , n (%)	3,689 (64.6)	3,366 (64.8)	323 (62.6)	0.320
Smoking status ^b , n (%)				
Current smoker	534 (9.2)	477 (9.1)	57 (10.8)	<0.001
Former smoker	2,298 (40.0)	2,040 (39.1)	258 (49.1)	
Non-smokers	2,918 (50.8)	2,707 (51.8)	211 (40.1)	
Family history of CVD, n (%)	3,019 (52.1)	2,699 (51.3)	320 (60.5)	<0.001
BMI, mean (SD), kg/m ²	25.9 (3.7)	25.8 (3.8)	26.6 (3.8)	<0.001
Systolic blood pressure, mean (SD), mmHg	133.5 (17.5)	132.7 (17.2)	141.8 (18.8)	<0.001
Total cholesterol, mean (SD), mmol/l	6.1 (1.1)	6.1 (1.1)	6.4 (1.2)	<0.001
HDL-cholesterol, mean (SD), mmol/l	1.5 (0.4)	1.5 (0.4)	1.4 (0.4)	<0.001
Triacylglycerol, median (interquartile range), mmol/l	1.4 (1.0–2.1)	1.4 (1.0–2.1)	1.7 (1.2–2.3)	<0.001
HbA _{1c}				
DCCT units: mean (SD), %	5.2 (0.6)	5.2 (0.6)	5.4 (0.6)	<0.001
IFCC units, mmol/mol	33	33	36	
Change in HbA _{1c} , mean (SD), %	0.13 (0.52)	0.13 (0.51)	0.09 (0.55)	0.114
Use of antihypertensive drugs, n (%)	727 (12.6)	586 (11.1)	141 (26.7)	<0.001
Use of lipid-lowering drugs, n (%)	54 (0.9)	42 (0.8)	12 (2.3)	<0.001

^a p values represent the difference between individuals who developed CVD and those who did not develop CVD using t tests or Kruskal–Wallis tests for normally or non-normally distributed continuous variables and χ^2 tests for categorical variables

^b Registrar General's Social Class: class I, professional occupations; class II, managerial and technical occupations; class IIIa, skilled occupations (non-manual); class IIIb, skilled occupations (manual); class IV, partly skilled occupations; class V, unskilled occupations; the numbers do not add up to the total due to 79 and 50 individuals with missing data for social class and smoking status respectively

for those with a baseline HbA_{1c} <5.0% (<30 mmol/mol). Kaplan–Meier curves for individuals categorised by

different levels of baseline HbA_{1c} (Fig. 2) showed that levels of baseline HbA_{1c} differed significantly with regard

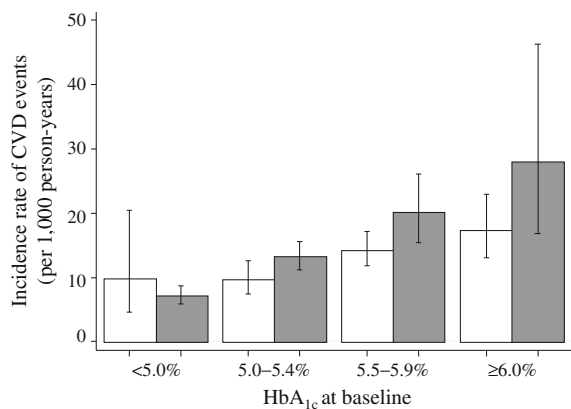


Fig. 1 Rates of first cardiovascular events over 8 years in individuals with different levels of baseline HbA_{1c} by change in HbA_{1c} between baseline and the second health examination. White bar, decreased or stable HbA_{1c} over time; grey bar, increased HbA_{1c} over time. A significant difference in cardiovascular event rates was observed in individuals with a baseline HbA_{1c} 5.0–5.4% and 5.5–5.9% ($p<0.05$). To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

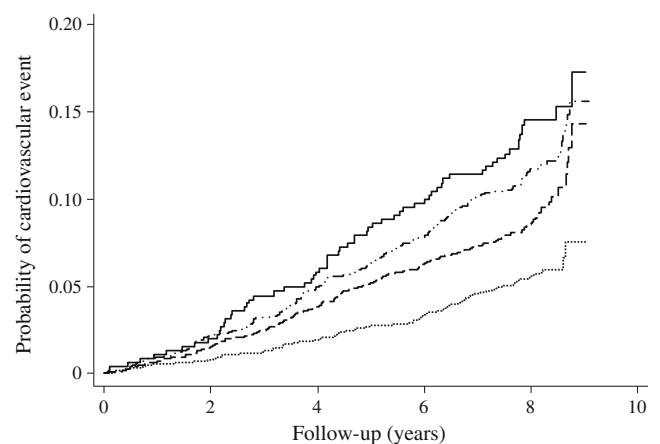


Fig. 2 Kaplan–Meier curves for development of cardiovascular events in individuals with different levels of baseline HbA_{1c}, with significant difference across groups ($p<0.001$). Dotted line, HbA_{1c} <5.0%; dashed line, HbA_{1c} 5.0–5.4%; dashed–dotted line, HbA_{1c} 5.5–5.9%; solid line, HbA_{1c} ≥6.0%. To convert values for HbA_{1c} in % into mmol/mol, subtract 2.15 and multiply by 10.929

to development of a cardiovascular event over the follow-up period (logrank test, $p < 0.001$). Figure 3 shows Kaplan–Meier curves for individuals with high and low values of baseline HbA_{1c} (according to the median value of 5.2% [33 mmol/mol] in this population) and changes in HbA_{1c} over time (increased vs unchanged or decreased). Individuals with a high baseline HbA_{1c} value and whose HbA_{1c} values increased over time were more likely to develop a cardiovascular event than were those with a similar baseline HbA_{1c} but with unchanged or decreased HbA_{1c} values over time and those with a low baseline HbA_{1c} value ($p < 0.001$). However, in those with a low baseline HbA_{1c}, change in HbA_{1c} over time was not associated with the development of a cardiovascular event (Fig. 3). Similar findings were observed when HbA_{1c} cut-off points of 5.7% and 6.0% (39 and 42 mmol/mol) were used instead of the median value.

Relative risk of cardiovascular events Table 2 shows the risk of a first cardiovascular event (HR) for change in HbA_{1c} over 3 years and other major cardiovascular risk factors including age, sex, smoking status, family history of CVD, systolic blood pressure, total cholesterol and use of lipid-lowering drugs. Change in HbA_{1c} was significantly associated with cardiovascular risk. Each 0.5% increase in HbA_{1c} over 3 years was associated with a 9% higher risk of CVD (HR 1.09; 95% CI 1.01, 1.18) after adjustment for baseline HbA_{1c} and other major cardiovascular risk factors (Model 3). A 1% higher value of baseline HbA_{1c} was associated with a 19% higher risk of CVD (HR 1.19; 95% CI 1.01, 1.39). These HRs remained unchanged after adjustment for temporal

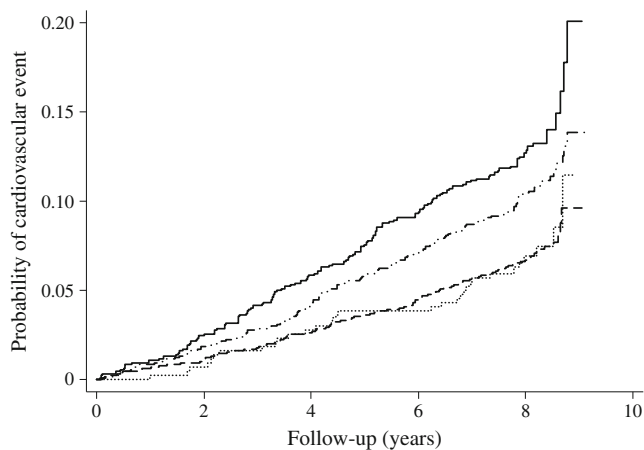


Fig. 3 Kaplan–Meier curves for development of cardiovascular events in individuals with high and low values of baseline HbA_{1c} (according to the median value of 5.2% or 33 mmol/mol in this population) and change in HbA_{1c} over time (increased, +ve; decreased, -ve), with significant difference across groups ($p < 0.001$). Dotted line, low baseline HbA_{1c} and -ve change; dashed line, low baseline HbA_{1c} and +ve change; dashed-dotted line, high baseline HbA_{1c} and -ve change; solid line, high baseline HbA_{1c} and +ve change

changes in levels of systolic blood pressure, total cholesterol and BMI. When we further adjusted Model 3 for HDL-cholesterol and use of antihypertensive drugs, the association between change in HbA_{1c} and CVD events was attenuated (HR 1.06; 95% CI 0.97, 1.15). Models with and without information on change in HbA_{1c} over time showed similar discriminatory ability (aROC 0.78 [95% CI 0.76, 0.80] for both Models 2 and 3; $p = 0.70$). When adjusting for HbA_{1c} at follow-up and other major risk factors, change in HbA_{1c} over time was not associated with risk of CVD in the following 8 years (Model 5). As shown in Table 2, adding information on change in HbA_{1c} over time did not improve predictive ability over information on HbA_{1c} at follow-up (aROC 0.78 [95% CI 0.76, 0.80] for both Models 4 and 5; $p = 0.99$). We found similar results for every SD change in HbA_{1c} (ESM Table 2). The main results were not altered when excluding individuals with HbA_{1c} $\geq 6.5\%$ and $\geq 7.0\%$ (≥ 48 and ≥ 53 mmol/mol). The inclusion of information on change in HbA_{1c} over time did not improve risk classification of the models with HbA_{1c} at baseline or follow-up (Model 3 vs Model 2: NRI 0.30%, $p = 0.71$; Model 5 vs Model 4: NRI 0%, $p = 0.50$).

Discussion

We have shown that individuals whose HbA_{1c} values increased over a period of 3 years had higher rates of cardiovascular events compared with those whose HbA_{1c} values were unchanged or reduced over time. In multivariate regression models, change in HbA_{1c} over time was associated with the risk of developing a CVD event independently of baseline HbA_{1c} and other major cardiovascular risk factors. However, the association was not significant after adjustment for HbA_{1c} at follow-up. Adding information on change in HbA_{1c} over time to a model that included baseline HbA_{1c} (or most recent HbA_{1c}) and other major risk factors did not improve the prediction of CVD events with regard to discriminatory ability and risk classification.

Comparison with previous studies Although previous studies reported that HbA_{1c} is an important risk factor for CVD, little evidence exists regarding the association between change in measures of glycaemia over time and cardiovascular risk in general populations. Although some previous studies found no association between HbA_{1c} and CVD risk [15, 16], data from a recent meta-analysis suggest that 1% higher HbA_{1c} levels are associated with a 10–20% increased risk of CVD [3, 4], which is consistent with our results. Our finding that change in HbA_{1c} values over time is independently associated with risk of CVD events, particularly in non-diabetic individuals with moderate-to-high baseline HbA_{1c} values, adds to the evidence of a causal link.

Table 2 Relative risk (HR) estimated from multivariate Cox regression for the association between risk factors and development of a first cardiovascular event over 8 years

Risk factor	HR (95% CI)				
	Model 1 ^a	Model 2 ^a	Model 3 ^a	Model 4 ^a	Model 5 ^a
Change in HbA _{1c} over 3 years (every 0.5% change)	1.13 (1.06, 1.21)*	–	1.09 (1.01, 1.18)*	–	1.00 (0.92, 1.09)
Baseline HbA _{1c} (every 1.0% higher)	1.71 (1.51, 1.95)*	1.08 (0.94, 1.24)	1.19 (1.01, 1.39)*	–	–
HbA _{1c} at second health examination (every 1.0% higher)	–	–	–	1.19 (1.04, 1.36)*	1.19 (1.01, 1.39)*
Female sex	–	0.48 (0.40, 0.58)*	0.48 (0.40, 0.58)*	0.48 (0.40, 0.58)*	0.48 (0.40, 0.58)*
Age (every 1 year older)	–	1.09 (1.08, 1.10)*	1.09 (1.08, 1.10)*	1.09 (1.08, 1.10)*	1.09 (1.08, 1.10)*
Current smokers	–	1.55 (1.17, 2.06)*	1.55 (1.17, 2.06)*	1.55 (1.17, 2.06)*	1.55 (1.17, 2.06)*
Total cholesterol (every 1 mmol/l higher)	–	1.11 (1.03, 1.20)*	1.11 (1.03, 1.20)*	1.11 (1.03, 1.20)*	1.11 (1.03, 1.20)*
Systolic blood pressure (every 1 mmHg higher)	–	1.01 (1.00, 1.01)*	1.01 (1.00, 1.01)*	1.01 (1.00, 1.01)*	1.01 (1.00, 1.01)*
Family history of CVD	–	1.20 (1.01, 1.44)*	1.20 (1.01, 1.44)*	1.20 (1.01, 1.44)*	1.20 (1.01, 1.44)*
Use of lipid-lowering drugs	–	2.25 (1.62, 3.12)*	2.25 (1.62, 3.12)*	2.25 (1.62, 3.12)*	2.25 (1.62, 3.12)*
aROC (95% CI) ^b	0.60 (0.58, 0.63)	0.78 (0.76, 0.80)	0.78 (0.76, 0.80)	0.78 (0.76, 0.80)	0.78 (0.76, 0.80)

^aHRs for variables in each model were adjusted for all other covariates whose HR values were presented in the table and the results were not changed after adjustment for BMI at baseline, changes in systolic blood pressure, total cholesterol, HDL-cholesterol and BMI over time

^b*p* values for comparing aROC: *p*<0.001 Model 1 vs Model 3; *p*=0.702 Model 2 vs Model 3; *p*=0.987 Model 4 vs Model 5

**p*<0.05

Trial evidence to date suggests that cardiovascular risk may be reduced through tight glycaemic control in individuals with diabetes [5, 6]. However, there is still uncertainty about the effects of glucose-lowering approaches on cardiovascular risk in individuals with a lesser degree of dysglycaemia. The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) trial, which aimed to reduce CVD risk by means of a glucose-lowering drug among individuals with impaired glucose tolerance, was not able to show the beneficial effect as the trial did not meet its glycaemic control target [7]. In fact, while a small reduction in fasting plasma glucose levels was observed, 2 h postchallenge glucose was elevated in the intervention group compared with the control group. Similarly, the recently reported Outcome Reduction with Initial Glargine Intervention (ORIGIN) trial found no difference in cardiovascular outcomes over 6 years between those receiving basal insulin to target normal fasting plasma glucose level and those receiving standard care [17].

Implications There is evidence to suggest that measuring glycaemia might contribute to the estimation of CVD risk in addition to other major cardiovascular risk factors. One example is the UK Prospective Diabetes Study (UKPDS) risk engine, which incorporates HbA_{1c} and other risk factors to estimate cardiovascular risk in people with diabetes [18]. The only cardiovascular risk score developed in the general population that includes measures of glycaemia (fasting plasma glucose and 2 h

plasma glucose) is the Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) risk score [19]. We have previously shown that the addition of HbA_{1c} to the standard Framingham risk equation modestly improved its predictive ability in British men, but did not improve risk classification [20]. The present analysis suggests that, although information on change in HbA_{1c} over 3 years was associated with cardiovascular risk independently of baseline HbA_{1c} and other major risk factors, the potential contribution to risk prediction models appears limited.

Our results support the idea that approaches to lowering blood glucose might have the potential to prevent CVD among people with non-diabetic hyperglycaemia, although this needs to be confirmed by results from ongoing trials such as the Acarbose Cardiovascular Evaluation (ACE) trial (<http://clinicaltrials.gov/ct2/show/NCT00829660>, accessed 24 Jan 2013). Alongside this high-risk approach, our results also provide support for population-based prevention strategies [21]. A rise in the mean value of HbA_{1c} over 3 years observed in this study points to a shift in the distribution of glycaemia in the non-diabetic population over a relatively short time. Interventions to shift the distribution of glycaemia, and other risk factors, in the opposite direction, or to reduce the magnitude of the observed shift, are likely to be associated with a reduction in the population burden of CVD.

Strengths and limitations To our knowledge, this study is the first to examine the association between change in

HbA_{1c} and future risk of CVD. We used data from a large population-based prospective study with robust ascertainment of cardiovascular outcomes over a long follow-up. However, to address our research question, we included only participants with complete data on HbA_{1c} at baseline and the second health examination, who were generally healthier than those excluded, according to their baseline risk factor profiles (ESM Table 1). As HbA_{1c} testing became available in 1995, most participants enrolled between 1993 and 1994 were excluded (missing by design). These participants were less healthy than those included in our main analysis. This is likely to have led to underestimation of the true cardiovascular risk in the whole cohort and might therefore have influenced estimates of the association between change in HbA_{1c} and CVD risk.

As the baseline and second health examinations in EPIC–Norfolk took place in the 1990s and early 2000s, before the introduction of new HbA_{1c} diagnostic criteria [22], in our main analysis we did not exclude those with an HbA_{1c} $\geq 6.5\%$ (≥ 48 mmol/mol) at either health examination, as we assumed that they were not prescribed any glucose-lowering treatment. Furthermore, as results for HbA_{1c} were sent to participants' general practitioners, those with an HbA_{1c} $\geq 7.0\%$ (≥ 53 mmol/mol) at the time were assumed to have been followed up and a diagnosis of diabetes confirmed and recorded in diabetes registers and clinical records. These participants would therefore be captured by our methods of diabetes ascertainment using multiple sources of information. In fact, a previous capture–recapture analysis in this cohort showed that this method of ascertainment identified 99% of all clinically incident cases of diabetes, when compared with diagnostic information from a comprehensive review of clinical records [23]. Moreover, in our sensitivity analyses the exclusion of individuals with an HbA_{1c} $\geq 6.5\%$ or $\geq 7.0\%$ (≥ 48 or ≥ 53 mmol/mol) did not alter the main results.

It is possible that regression to the mean in HbA_{1c} may have altered the result of the association between change in HbA_{1c} and CVD risk. For example, individuals with a larger increase in HbA_{1c} over time tended to be those with a lower baseline HbA_{1c}, who were actually at lower risk of CVD. This might have led to an underestimation of the association between change in HbA_{1c} and CVD risk. As HbA_{1c} increases with age, we have taken into account the possible effect of increasing age on the association between change in HbA_{1c} over time and CVD risk by adjusting the association for age and other risk factors. HbA_{1c} values are influenced by some disorders affecting the lifespan of erythrocytes, such as haemoglobinopathy [22]. However, these conditions are rare in this white population. Last, as 99% of EPIC–Norfolk participants were white, the generalisability of our findings to other ethnic groups and populations might be limited.

We conclude that the inclusion of information on change in HbA_{1c} over time did not improve prediction of CVD over

and above information on HbA_{1c} and other major cardiovascular risk factors at a single time point in this non-diabetic British population.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

Contribution statement PC had full access to all of the data in the study and takes responsibility for the accuracy of the data analysis. KTK and NJW take responsibility for the integrity of the data. PC, as the corresponding author, has the right to grant on behalf of all authors and does grant on behalf of all authors.

PC, RKS and SJG were responsible for the study concept and design and drafting of the manuscript. KTK and NJW were responsible for the acquisition of the data. PC, RKS, NJW and SJG analysed and interpreted the data. All authors were responsible for critical revision of the manuscript for important intellectual content and approved the final version.

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