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Abstract

Objective: HbAlc is increasingly appreciated as a risk factor for all-cause and cardiovascular disease (CVD) mortality in the non-diabetic population. In this study, we investigated the association between HbAlc and mortality with a particular focus on the impact of race–ethnicity.

Design: Cohort study.

Methods: We analyzed the association between HbAlc and all-cause and CVD mortality in 12,698 non-diabetic adults 20 years or older from the Third National Health and Nutrition Examination Survey using separate models for people of different race–ethnicity.

Results: In our stratified analyses, higher non-diabetic HbAlc levels were associated with all-cause and CVD mortality in non-Hispanic whites only. In this group, compared with HbAlc values of 5.0–5.35%, the multivariable-adjusted estimated hazard ratios (est. HR) with 95% confidence interval (CI) for all-cause mortality were 1.21 (0.92, 1.58), 1.22 (1.03, 1.45), 1.29 (1.14, 1.47), and 1.4 (1.02, 1.87) for HbAlc levels of 5.0, 5.35–5.7, 5.7–6.5, and 6.5% or greater respectively. The association did not reach significance in Mexican–Americans (est. HR (95% CI): 1.77 (1.08, 2.91), 0.81 (0.56, 1.19), 1.16 (0.86, 1.57), and 1.4 (0.83, 2.36)). No association was observed in non-Hispanic blacks: 1.13 (0.91, 1.39), 0.81 (0.61, 1.08), 0.84 (0.69, 1.03), and 0.94 (0.67, 1.33). Results were similar for CVD mortality.

Conclusions: Our data suggest limitations of HbAlc as a risk factor for all-cause and cardiovascular mortality across race–ethnic populations.

Introduction

The percentage of HbAlc reflects average plasma glucose levels over a preceding 2–3 month period and correlates well with the risk of long-term microvascular complications (1, 2). Over the past 30 years these characteristics have firmly established HbAlc as the standard measure for monitoring glucose control in patients with diabetes.

Recently, the American Diabetes Association (ADA) has recommended HbAlc as an additional marker in the diagnosis of diabetes, providing healthcare practitioners with the appealing concept of combining both diagnosing diabetes and monitoring glycemic control into one measurement (3). Compared with other measurements of hyperglycemia, HbAlc has several advantages, including its independence of food intake, lower within-person variability and little interference by short-term perturbations of glucose levels such as illness or stress (4). Furthermore, HbAlc is increasingly recognized as an independent risk factor for micro- and macrovascular complications, and all-cause mortality in patients with and without diabetes (1–3, 5–10).

However, the measured level of HbAlc can be consistently different from what would be expected based on a person’s average level of blood glucose. Influencing non-glycemic factors include the rate of erythrocyte turnover, structural hemoglobinopathies, end-stage renal disease, and vitamin C ingestion (11). Several studies have also demonstrated consistently higher HbAlc levels among non-Hispanic blacks compared with non-Hispanic whites independent of plasma glucose levels (12–16). Whether race–ethnic variability in baseline HbAlc modifies the risk of complications or mortality in non-diabetic subjects has not been evaluated. Considering the growing enthusiasm for the use of HbAlc, there is need of a thorough characterization of differences in HbAlc levels between individuals and groups and their correlation with complications. In this study, we have investigated
the association between HbA1c and mortality in the non-diabetic adult population of the Third National Health And Nutrition Examination Survey (NHANES III), with a particular focus on the impact of race–ethnicity. We have hypothesized that the association of interest is significantly different among non-Hispanic whites, Mexican–Americans, and non-Hispanic blacks.

Subjects and methods

Sample

The NHANES III was the seventh in a series of surveys conducted by the National Center of Health Statistics and was carried out between 1988 and 1994. A complex multistage sample design was applied to yield a nationally representative sample of the United States civilian non-institutionalized population. Details about sampling strategies, informed consent and recommended statistical methods are described elsewhere (17). Briefly, an oversampling strategy of children, older people, black persons, and Mexican–Americans was used to increase the precision of prevalence estimates in these groups.

In this study, we included persons with non-missing data aged 20 years and older, who specified their race–ethnicity as ‘non-Hispanic white, non-Hispanic black’ or ‘Mexican–American’ and who were not diagnosed with diabetes (n = 12,689). People were classified as diabetic if they self-reported: i) to have ever been told to have diabetes (including gestational diabetes); ii) to take anti-diabetic pills; or iii) to take anti-diabetic pills.

Primary variable of interest

HbA1c was measured using the Diamat Analyzer System (Bio-Rad Laboratories). As variant hemoglobins (hemoglobin C, D, and F) can interfere with this assay, samples containing hemoglobin variants or elevated hemoglobin F (HbF) were analyzed by an affinity chromatographic method. All measurements were standardized to the reference method that was used for the Diabetes Control and Complications Trial (DCCT) (1).

We classified apparently non-diabetic participants by following HbA1c categories: < 5.0, 5.0–< 5.35, 5.35–< 5.7, 5.7–< 6.5 and ≥ 6.5%. The two highest cut off points were chosen a priori according to the ADA definitions of ‘increased risk of diabetes’ (5.7 ≤ HbA1c < 6.5%) and ‘manifest diabetes’ (HbA1c ≥ 6.5%) (3). Limits of lower categories were selected to allow groups with comparable numbers of participants.

Assessment of covariates

Using interview data, we included the following variables in our analyses: race–ethnicity, age, sex, self-reported use of aspirin, smoking history, history of heart attack, hypercholesterolemia, or hypertension, and positive family history of heart attack before the age of 50. A participant was classified as former smoker if the participant had smoked at least 100 cigarettes in his/her lifetime and as current smoker if he/she currently smoked cigarettes. Blood pressure was averaged using up to five measurements (interview and examination). The mean arterial pressure was calculated with the following equation: 2/3 × diastolic blood pressure (mmHg) + 1/3 × systolic blood pressure (mmHg). We used education (less than, equal to or more than 12 years of school) and the poverty income ratio as proxies for socioeconomic status. A participant’s body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. According to the categorization proposed by the CDC four BMI groups were defined (18). We evaluated, as possible, confounding laboratory variables total serum cholesterol, high density lipoprotein (HDL) cholesterol, hemoglobin, and C reactive protein (CRP); all were analyzed as continuous variables. Serum creatinine levels were calibrated to the Cleveland Clinic Laboratory standard using the Deming regression to adjust for errors in measurement (19). We estimated the glomerular filtration rate (GFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (20). All blood analyses were done in venous blood samples and processed by standard protocol (17). Urine albumin and creatinine concentration were measured in a random spot urine sample. The urine albumin to urine creatinine ratio was calculated and sex-specific cut off values were used to define kidney damage (21).

Outcomes

To ascertain mortality status, the National Center of Health Statistics matched NHANES participants aged 17 years or older by probability matching to the National Death Index through December 31st 2006. A selected sample of death certificates was reviewed manually to validate the process. From 1986 to 1998, the underlying cause of death was coded according to the International Classification of Diseases, Ninth Revision (ICD-9), after 1998 the coding was based on ICD-10 codes. For simplification, deaths until 1998 were recoded to ICD-10 codes that were finally utilized for our analyses. We used, as outcome, all-cause mortality and death from cardiovascular diseases (CVD). CVD deaths included deaths from major CVD, essential (primary) hypertension and hypertensive renal disease, cerebrovascular disease, atherosclerosis, and from other diseases and disorders of the circulatory system (ICD-10 I00-I78).

Statistical analysis

All analyses were weighted according to NHANES methodology to account for the complex survey design and the stratified multistage cluster sample. NHANES mobile examination weights were applied to all analyses.
to adjust for differential probabilities of selection and nonresponse in the survey sample.

Demographic characteristics were reported for the whole sample and stratified by race–ethnicity. Continuous and categorical variables were presented as weighted means and frequencies with S.E.M. respectively. Crude and age-adjusted mortality rates per weighted person-months of follow-up were shown. We used Cox proportional hazard models to estimate the relationship between HbA1c categories and other covariates and mortality. The HbA1c category of 5.0–< 5.35% had the largest number of participants (3966) and was used as the reference category. For the analysis of CVD mortality, participants were censored at the time of death from other causes. Estimated hazard ratios (est. HR) and 95% confidence intervals (CI) were reported. Initially, we adjusted the association between all-cause and CVD mortality for age and sex (model 1). In a further model (model 2), we included variables if i) a variable is a known risk factor for the association between HbA1c and mortality or ii) if the inclusion or exclusion of this variable in the model changed the parameter estimate more than 15%. The assumption of hazard proportionality was examined by testing interactions of survival time and included variables in Cox models. None were found to be significant. Interactions were tested by adding a product term for HbA1c categories and each of the following covariates: race–ethnicity, sex, history of heart attack, and history of chronic heart failure. The interaction between categorized HbA1c and race–ethnicity was highly significant for all-cause and CVD mortality (P<0.0001). As a consequence, all results were presented as analyses stratified by race. There was no other significant interaction.

To test the robustness of the association, we excluded in additional analyses patients without self-reported diabetes but with HbA1c or blood glucose levels above the thresholds that are used for the diagnosis of diabetes according to the ADA (3). Furthermore, patients with a self-reported history of diabetes were included in the regression model (controlled for the history of diabetes). For all analyses, a P<0.05 for a two-tailed test was considered significant. Analyses were performed by SUDAAN Statistical Software (release 10.0; Research Triangle Institute, Research Triangle Park, NC, USA).

Results

Final sample

There were 17 030 NHANES participants aged 20 years and older of whom 14 37 had self-reported diabetes. Of the non-diabetic adult sample, 585 classified their race as ‘other’ than non-Hispanic white, non-Hispanic black, or Mexican–American, ten had no available mortality status and a further 2300 had at least one missing covariate. Thus, our final sample included 12 698 subjects.

Baseline characteristics and mortality frequencies

The overall weighted mean time of observation was 169 months (~14 years). In total, 2746 all-cause deaths (21.63%) and 1197 CVD deaths (9.43%) occurred in a total of 1 71 508 years of observation. The mean age of the whole sample was close to 44 years. Black subjects had significant higher mean HbA1c values than whites and Mexican–Americans (all pairwise comparisons P<0.0001). Apart from history of chronic heart failure, all covariates differed significantly between people of different race–ethnicity (Table 1).

Compared with white subjects, the distribution between HbA1c categories was shifted toward higher HbA1c values in Mexican–American and black participants (P<0.001 for all pairwise comparisons between ethnic subgroups; Fig. 1). Non-black subjects had most often HbA1c values between 5 and 5.3%. However, most black participants had a HbA1c level between 5.7 and 6.5%.

Multivariable-adjusted Cox proportional hazard regressions

In age- and sex-adjusted Cox proportional hazard models (model 1), we observed in non-Hispanic whites a statistically significant positive association between increasing HbA1c categories and increasing risk of death from all causes compared with a HbA1c level between 5 and 5.3% (Table 2). In Mexican–Americans, the association between HbA1c and all-cause mortality was similar to that of non-Hispanic white subjects without reaching significance. No statistically significant association was found in non-Hispanic blacks.

After further adjustment for GFR, albuminuria, CRP, total cholesterol, positive family history, BMI, education, mean arterial pressure, history of heart attack, history of chronic heart failure, and smoking status, the association between increasing HbA1c categories and all-cause mortality was attenuated but remained statistically significant for non-Hispanic whites. The risk of dying increased significantly with increasing HbA1c levels above the reference category. On the contrary, non-Hispanic blacks had a 19, 16, and 6% risk decrease for HbA1c levels of 5.35–5.7, 5.67–6.5, and ≥6.5%, respectively. However, these estimates did not reach significance. In Mexican–Americans, we observed a statistically significant risk increase (est. HR 1.77, P=0.02) in the lowest HbA1c category. Furthermore, although not statistically significant, the estimates suggested higher hazards in the higher HbA1c categories.

CVD mortality

In model 1, the associations regarding CVD mortality were similar to that observed for all-cause mortality (Table 2). Statistically significant associations were
observed in non-Hispanic whites. After controlling for additional confounding factors as listed before, in white subjects the positive association between increasing levels of HbAlc and CVD mortality was attenuated but remained significant for HbAlc levels between 5.35–5.7 and 5.7–6.5% (estimated risk increase 31 and 34% respectively). Black subjects did not show any association between HbAlc and CVD mortality. As for all-cause mortality, the association in Mexican–Americans seemed to be positive in higher HbAlc categories, but did not reach significance.

Sensitivity analysis

The exclusion of participants who did not self-report having diabetes but who had a diabetes according to ADA guidelines (fasting glucose ≥ 126 mg/dl, random non-fasting glucose ≥ 200 mg/dl, 2 h post-challenge glucose > 200 mg/dl or HbAlc > 6.5%) as well as the inclusion of diabetic patients resulted in fundamentally similar findings (Supplementary Tables 1 and 2, see section on supplementary data given at the end of this article).

Discussion

The recommendation from the ADA to include HbAlc in the diagnosis of diabetes has focused growing attention on HbAlc levels in patients without known diabetes (3). Furthermore, HbAlc is increasingly appreciated as a risk factor for all-cause and CVD mortality in the non-diabetic population (6–9, 22). In this study, we have analyzed the relationship between HbAlc levels, mortality and race–ethnicity in the non-diabetic adult population of the nationally representative sample of the NHANES III. Consistent with other studies, we have found a significant association of normal to high
non-diabetic HbAlc levels with increased risk of all-cause and cardiovascular mortality in non-Hispanic whites. However, the relationship in Mexican–Americans did not reach significance, and in non-Hispanic blacks we did not observe any association between HbAlc and mortality. Our data suggest limitations of HbAlc as a risk factor for cardiovascular and all-cause mortality across race–ethnic groups and warrant further research in non-diabetic subgroups with known variation in HbAlc.

In patients with diabetes, increased HbAlc levels are an important risk factor for both micro- and macrovascular complications as well as all-cause mortality (1, 2, 7, 10). Moreover, a growing number of studies have demonstrated a relationship between HbAlc categories and mortality in the non-Hispanic white population. However, whether this association holds true among other race–ethnic subgroups is not clear, since few data exist on clinical outcomes in non-Hispanic blacks or Mexican–Americans. In our sample, race–ethnicity was a significant effect modifier of the association between HbAlc categories and mortality. Despite higher baseline HbAlc levels in non-Hispanic black participants we did not observe any association with either all-cause or cardiovascular mortality in this group. In Mexican–Americans, we observed increased hazard ratios in the lowest and the two highest categories of HbAlc, although not statistically significant, our data suggest an association in Mexican–Americans between worse clinical outcomes and HbAlc levels below the threshold for diabetes.

Race–ethnic variability in HbAlc levels has been reported in multiple previous studies (12–16) and might provide a rationale for the observed differences in outcome. In several studies, African–Americans had consistently higher HbAlc levels than non-Hispanic whites (12, 13, 15). The most recent observation was reported by Ziemer et al. (12) who analyzed data from the Screening for Impaired Glucose Tolerance (SIGT) study and the NHANES III. In this cross-sectional analysis, the significant difference between black and white participants persisted across the full spectrum of glycemia even after adjustment for plasma glucose levels and other characteristics known to correlate with HbAlc levels. Several studies have also compared HbAlc mortality and HbAlc below the recently defined threshold for the diagnosis of diabetes of 6.5% (3, 5, 6, 8, 9). Consistent with these studies, we have found a significant association between HbAlc and all-cause and cardiovascular mortality in the non-Hispanic white population. However, whether this association holds true among other race–ethnic subgroups is not clear, since few data exist on clinical outcomes in non-Hispanic blacks or Mexican–Americans. In our sample, race–ethnicity was a significant effect modifier of the association between HbAlc categories and mortality. Despite higher baseline HbAlc levels in non-Hispanic black participants we did not observe any association with either all-cause or cardiovascular mortality in this group. In Mexican–Americans, we observed increased hazard ratios in the lowest and the two highest categories of HbAlc. Although not statistically significant, our data suggest an association in Mexican–Americans between worse clinical outcomes and HbAlc levels below the threshold for diabetes.

**Table 2** Estimated hazard ratios of HbAlc categories for all-cause and CVD mortality with 95% CI, stratified by race–ethnicity.

<table>
<thead>
<tr>
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<th>&lt;5%</th>
<th>5–5.35%</th>
<th>5.35–5.7%</th>
<th>5.7–6.5%</th>
<th>≥6.5%</th>
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</thead>
<tbody>
<tr>
<td><strong>All-cause mortality</strong></td>
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<tr>
<td><strong>Model 1</strong></td>
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<tr>
<td>Non-Hispanic whites</td>
<td>1.13 (0.87, 1.47)</td>
<td>1.26 (1.05, 1.5)*</td>
<td>1.41 (1.23, 1.62)*</td>
<td>1.91 (1.46, 2.49)*</td>
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<tr>
<td>Non-Hispanic blacks</td>
<td>1.15 (0.94, 1.41)</td>
<td>0.89 (0.66, 1.19)</td>
<td>0.88 (0.71, 1.08)</td>
<td>1.02 (0.71, 1.45)</td>
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<tr>
<td>Mexican–Americans</td>
<td>1.6 (1.0, 2.56)*</td>
<td>0.82 (0.58, 1.18)</td>
<td>1.14 (0.86, 1.51)</td>
<td>1.55 (0.95, 2.51)</td>
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<tr>
<td><strong>Model 2</strong></td>
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<tr>
<td>Non-Hispanic whites</td>
<td>1.21 (0.92, 1.58)</td>
<td>1.22 (1.03, 1.45)*</td>
<td>1.29 (1.14, 1.47)*</td>
<td>1.4 (1.04, 1.87)*</td>
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<tr>
<td>Non-Hispanic blacks</td>
<td>1.13 (0.91, 1.39)</td>
<td>0.81 (0.61, 1.08)</td>
<td>0.84 (0.69, 1.03)</td>
<td>0.94 (0.67, 1.33)</td>
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<tr>
<td>Mexican–Americans</td>
<td>1.77 (1.08, 2.91)*</td>
<td>0.81 (0.56, 1.19)</td>
<td>1.16 (0.86, 1.57)</td>
<td>1.4 (0.83, 2.36)</td>
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<td><strong>CVD mortality</strong></td>
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<td><strong>Model 1</strong></td>
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<tr>
<td>Non-Hispanic whites</td>
<td>1.08 (0.77, 1.51)</td>
<td>1.37 (1.09, 1.72)*</td>
<td>1.45 (1.11, 1.89)*</td>
<td>1.79 (1.2, 2.67)*</td>
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<tr>
<td>Non-Hispanic blacks</td>
<td>0.98 (0.55, 1.74)</td>
<td>0.79 (0.45, 1.38)</td>
<td>1.03 (0.69, 1.55)</td>
<td>1.23 (0.6, 2.52)</td>
<td></td>
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<tr>
<td>Mexican–Americans</td>
<td>1.12 (0.55, 2.3)</td>
<td>0.78 (0.5, 1.21)</td>
<td>1.35 (0.85, 2.14)</td>
<td>1.68 (0.76, 3.71)</td>
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<tr>
<td><strong>Model 2</strong></td>
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<tr>
<td>Non-Hispanic whites</td>
<td>1.19 (0.83, 1.69)</td>
<td>1.31 (1.06, 1.61)*</td>
<td>1.34 (1.04, 1.71)*</td>
<td>1.2 (0.81, 1.79)</td>
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<tr>
<td>Non-Hispanic blacks</td>
<td>0.91 (0.49, 1.68)</td>
<td>0.68 (0.37, 1.24)</td>
<td>0.94 (0.6, 1.47)</td>
<td>0.95 (0.43, 2.09)</td>
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<tr>
<td>Mexican–Americans</td>
<td>1.35 (0.65, 2.83)</td>
<td>0.67 (0.44, 1.03)</td>
<td>1.3 (0.81, 2.09)</td>
<td>1.35 (0.61, 3.0)</td>
<td></td>
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</table>

*Indicates P<0.05.

aModel 1 adjusted for age and sex.

bModel 2 adjusted for age, sex, GFR, kidney damage, CRP, total cholesterol, positive family history, BMI, education, mean arterial pressure, history of heart attack, history of chronic heart failure, and smoking status.
levels in non-Hispanic whites and Mexican–Americans with the majority reporting higher HbAlc levels in Mexican–Americans (14, 16). Consistent with the literature, both race–ethnic subgroups studied in our analyses had higher mean HbAlc values than non-Hispanic whites.

The reasons for differences in the distribution of HbAlc levels across race–ethnic groups are poorly understood. However, several factors have been speculated to contribute to the observed differences. In patients with type 2 diabetes, socioeconomic factors and access to and quality of care have been suggested to drive differences in HbAlc among race–ethnic populations (15, 16). However, the differences in HbAlc levels continued to exist in studies conducted in managed care settings, where all subjects were insured (23). Furthermore, studies in non-diabetic patients reported race–ethnic differences after comprehensive adjustment for socioeconomic factors, access to and quality of healthcare (13, 24). Other factors that have been suggested to influence HbAlc levels include hemoglobinopathies, iron deficiency, erythrocyte survival, differences in glycation, kidney disease and vitamin C and E ingestion (11). Except for hemoglobinopathies that are more common in black subjects, the influence of these factors in the race–ethnic variability of HbAlc levels remains to be elucidated.

Interestingly, non-Hispanic whites and Mexican–Americans revealed a risk increase in the lowest HbAlc category. A similar J-shaped association has previously been reported in the literature (6, 7, 9). However, in our population this risk increase in the lowest HbAlc category was statistically significant only in Mexican–Americans with an adjusted hazard ratio of 1.77 (95% CI 1.09, 2.78). Comorbidities such as malnutrition, malignant diseases, and dementia are risk factors for hypoglycemia and might be associated with low levels of HbAlc (25). Thus, these factors could mediate the association between excess mortality in people with low values of HbAlc. The finding that this risk increase might be more pronounced in Mexican–Americans than in non-Hispanic whites needs further exploration.

While our findings suggest limitations of HbAlc as a marker for cardiovascular and all-cause mortality across race–ethnic subgroups, others have found conflicting results. Selvin et al. (9) have recently reported that race–ethnicity did not modify the associations between HbAlc and cardiovascular outcomes and death in non-diabetic participants of the ARIC study despite significant differences between black and white subjects in baseline HbAlc. The ARIC study is a community-based prospective cohort of subjects without history of CVD with a mean age that is higher than that in our NHANES sample. These differences in participant selection might partly explain discrepancies with our results.

There are several limitations of this study. First, lack of multiple HbAlc measurements increases the risk of misclassification of HbAlc status. However, this potential misclassification would probably be non-differential between cases and survivors and also non-differential between subjects of different race–ethnicity. Secondly, without follow-up data besides mortality we cannot judge whether any risk increase associated with higher HbAlc levels might be mediated by a later diagnosis of diabetes. However, it has been reported that the risk increase with higher HbAlc levels was independent from a later diagnosis of diabetes (9). Thirdly, all but the laboratory variables are derived from self-report and our sample is based on the self-reported diagnosis of diabetes mellitus. Therefore, recall and selection bias is a major concern in our study. To attenuate this risk of selection bias, we confirmed our results in samples where i) patients with any blood result that met the diagnosis of diabetes according to the ADA were excluded and ii) all subjects independent of a self-reported history of diabetes were included. These sensitivity analyses resulted in fundamentally similar findings, supporting the validity or our results. Finally, although we have adjusted for known confounders, residual confounding may still have influenced our results.

However, our study has several strengths. First, this is the first study comparing the influence of HbAlc on mortality in subjects of different race–ethnic subgroups who are representative for the US adult population. Secondly, the survey design with its oversampling strategy of race–ethnic subgroups makes these data particularly appropriate to evaluate our research question. Thirdly, we have included a large number of potential confounding variables. Finally, the NHANES data and the available linked mortality file allowed a mortality follow-up of about 14 years and loss to follow-up was very low (＜0.01%).

In conclusion, race–ethnicity is a significant effect modifier of the association between HbAlc levels and all-cause and cardiovascular mortality in non-diabetic participants of the NHANES III. While non-Hispanic whites showed a significant relationship between HbAlc and mortality, this association was attenuated in Mexican–Americans and completely missing in non-Hispanic blacks. Our data suggest limitations of HbAlc as a risk factor for cardiovascular and all-cause mortality across race–ethnic populations. Therefore, further studies investigating the mechanisms behind the race–ethnic variability of HbAlc and assessing their clinical implications are needed.

**Supplementary data**

This is linked to the online version of the paper at [http://dx.doi.org/10.1530/EJE-11-0171](http://dx.doi.org/10.1530/EJE-11-0171).

**Declaration of interest**

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.
Race–ethnicity modifies effect of HbA1c on mortality

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