Education, glucose control, and mortality risks among U.S. older adults with diabetes

Matthew E. Dupre a,b,c, Mina Silberberg b, Janese M. Willis b, Mark N. Feinglos d

a Duke Clinical Research Institute, Duke University, Durham, NC, USA
b Department of Community and Family Medicine, Division of Community Health, Duke University, Durham, NC, USA
c Department of Sociology, Duke University, Durham, NC, USA
d Department of Medicine, Division of Endocrinology, Metabolism, and Nutrition, Duke University, Durham, NC, USA

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A B S T R A C T

Aim: Studies have shown that diabetes mellitus disproportionately affects persons of low socioeconomic status and that the burden of disease is greatest among the disadvantaged. However, our understanding of educational differences in the control of diabetes and its impact on survival is limited. This study investigated the associations among education, hemoglobin A1C (HbA1C), and subsequent mortality in adults with diabetes.

Methods: Prospective cohort data from the 2006, 2008, and 2010 Health and Retirement Study were linked with biomarker data for U.S. older adults with diabetes (n = 3312). Weighted distributions were estimated for all subjects at baseline and by the American Diabetes Association’s general guidelines for HbA1C control (<7.0% [53 mmol/mol] vs. ≥7.0% [53 mmol/mol]). Proportional hazard models were used to estimate educational differences in all-cause mortality by HbA1C level with sequential adjustments for contributing risk factors.

Results: Mortality risks associated with HbA1C ≥ 7.0% [53 mmol/mol] were significantly greater in lower-educated adults than higher-educated adults (P < 0.001). We found that the hazard ratios (HR) associated with HbA1C ≥ 7.0% [53 mmol/mol] were highest among low-educated adults (HR = 2.18, 95% CI: 1.62, 2.94) and that a combination of socioeconomic, psychosocial, and behavioral factors accounted for most, but not all, of the associations.

Conclusions: Educational differences in HbA1C control have significant implications for mortality and efforts to reduce these disparities should involve more vigilant screening and monitoring of lower-educated adults with diabetes.

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1. Introduction

Diabetes mellitus and its complications are major causes of excess morbidity and mortality in the United States [1,2].

1 Corresponding author at: Duke Clinical Research Institute, Duke University Medical Center, PO Box 17569, Durham, NC 27715, USA.
Tel.: +1 9196816811; fax: +1 9196605623.
E-mail addresses: matthew.dupre@dm.duke.edu (M.E. Dupre)
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Nearly 20 million adults in this country have been diagnosed with diabetes and millions more are believed to be undiagnosed or exhibit prediabetes [3]. Effective medical care and disease management are critical for glycemic control and the prevention of poor outcomes from complications [4-7]. Yet,
there remain cumulative shortfalls in the numbers of diabetic adults who are diagnosed, properly treated, and achieve recommended control, which have enormous human and financial costs [8–10]. Furthermore, those who are socioeconomic disadvantaged may be most susceptible to this cascade of inadequate care and control [10].

Studies have shown that diabetes disproportionately affects individuals of low socioeconomic status (SES) [11,12] and that the burden of disease is greatest among those with low education [13,14] and income [15–17]. Although the association between low education and mortality has been documented in adults with diabetes [18–21], evidence is limited in how hemoglobin A1c (HbA1c) contributes to educational differences in mortality. For adults with low education, adherence to the American Diabetes Association’s (ADA) recommended guidelines for the treatment of diabetes is often difficult to achieve because of limited financial assets, reduced access to health care, inadequate psychosocial resources and support, and poor health behaviors [8,14,22]. Consequently, adults with diabetes and low education are at high risk for cardiovascular complications, kidney disease, and an overall shortened lifespan [15,22,23]. However, it remains unclear to what extent glycemic control is contributing to survival differences and the potential factors underlying these disparities.

This study is the first nationally representative examination of educational differences in ADA’s recommended glycemic levels and the factors contributing to survival differences in U.S. older adults with diabetes. Using prospective cohort data that were linked to biomarker data, we first examined educational differences in levels of HbA1c and then described the characteristics of study subjects by the ADA’s recommended levels of HbA1c (within general guidelines [≤7.0% [53 mmol/mol]] vs. not within guidelines [≥7.0% [53 mmol/mol]]). We then used multivariate models to examine the direct and interactive associations among education and guideline levels for HbA1c on all-cause mortality and tested a wide range of factors that may have contributed to the associations. The implications of the findings are discussed.

2. Methods

2.1. Study population

This study used nationally representative data from the Health and Retirement Study (HRS) for analysis. The HRS is an ongoing prospective cohort study of U.S. older adults sponsored by the National Institute on Aging. The original HRS cohort included 9624 respondents born between 1931 and 1941 who have been interviewed biennially since 1992. The initial participation rate was 82% and re-interview rates have been approximately 94% through 2010, with low rates of attrition due to nonresponse and lost tracking. Since 1998, the HRS has been supplemented with selective birth cohorts to replenish the nationally representative sample of older adults. Further details of the multisite sampling design, implementation, and response rates have been documented elsewhere [24].

In 2006 and 2008, HRS respondents were randomly selected to receive enhanced interviews that included physical measurements and a blood-spot sample to collect biomarker data. A random half-sample of respondents was selected in 2006 (n = 6735) and the other half-sample was selected in 2008 (n = 6392). Informed consent was obtained and blood samples were collected using standardized protocols for storage and shipment of specimens [25]. Assays were conducted for HbA1c, serum cholesterol, and cystatin C. Assays for HbA1c were performed using the Roche Unimate immunoassay and the Cobas Integra Analyzer, which were certified by the National Glycohemoglobin Standardization Program (NGSP). The Bio-Rad Variant high-performance liquid chromatography (HPLC) method, utilizing ion exchange HPLC to separate HbA1c, was also NGSP certified [25]. The biomarker subsample included 12,418 adults aged 45 to 90 who provided consent and HbA1c data for analysis. Subjects identified as having diabetes (n = 3312) were followed through 2010. The data were obtained through approval of a Restricted Data Use Agreement from HRS and the study protocol was deemed exempt from the Duke University institutional review board because the data were de-identified.

2.2. Measures

The classification for having diabetes was defined according to ADA’s guidelines and as reported by the Centers for Disease Control and Prevention as HbA1c ≥ 6.5% (48 mmol/mol) or a reported diagnosis by a physician [8,26]. Comparisons with national rates of physician-diagnosed and undiagnosed diabetes (HbA1c ≥ 6.5% [48 mmol/mol]) from the National Center for Health Statistics (NCHS) are consistent with the rates obtained from our nationally representative sample of older adults for this time period (NCHS: 28.5% vs. HRS: 28.9%) [26]. Preliminary analyses showed that almost all of the subjects with diabetes had been diagnosed (90%) and that median HbA1c levels were only slightly higher in the undiagnosed group than the diagnosed group (HbA1c = 6.8% [51 mmol/mol] vs. 6.5% [48 mmol/mol], P < 0.05). There were no significant differences in education level between the undiagnosed and diagnosed groups. The recommended level of HbA1c was defined as ≤7.0% (53 mmol/mol) (within guidelines) and ≥7.0% (53 mmol/mol) (not within guidelines) according to ADA’s Standards of Medical Care for most people with diabetes [8].

The primary measure for educational attainment was categorized as less than high school education or high school education or more. Preliminary analyses considered alternative measures of education and showed that years of education were not normally distributed (with significant skewness and kurtosis) and that additional categorizations of education did not improve model fit or change the substantive findings.

Demographic characteristics included age, sex, and race/ethnicity (Hispanic, non-Hispanic white, non-Hispanic black, or non-Hispanic other race). We also included covariates for several clinical factors to account for potential differences in underlying physiology. Clinical characteristics included time since diagnosis (years), insulin use (yes or no), obesity (calculated as weight in kilograms divided by height in meters squared ≥30.0; yes or no), blood pressure (<130/80 mmHg; yes or no), and non-HDL cholesterol (<130 mg/dL; yes or no) [8]. Because blood-spot samples were obtained from HRS participants who had not been fasting, LDL cholesterol levels could
not be used to determine recommended LDL levels (<100 mg/dl). Therefore, we used non-HDL cholesterol criteria as previously demonstrated in patients with diabetes [27,28]. We also included measures for cardiovascular comorbidity (yes or no; if ever diagnosed with angina, congestive heart failure, myocardial infarction, or stroke) and cystatin C (≤1.25 mg/L or >1.25 mg/L) as a clinical proxy for general kidney function [29,30].

Several categories of mechanisms were also examined as possible factors that may explain how educational differences in HbA1c were related to mortality [31–33]. Socioeconomic resources included household income from all sources in thousands of dollars (logarithmic scale) and health insurance coverage. Health insurance was operationalized as having medical insurance from any source that provided any level of coverage for doctor visits and prescription drugs (yes or no). Alternative categorizations of insurance status (e.g., having any, private, and type of plan) were also assessed and did not alter the findings. Employment status was not included because the majority of older adults in the sample were retired and preliminary analyses showed that the results were not significant. Psychosocial resources included marital status (married or not married) and validated measures of social support (12-item, range 0–36), sense of control over one’s health (one-item, range 0–10), and number of depressive symptoms measured by the eight-item Center for Epidemiologic Studies Depression Scale (CES-D, range 0–8) [34]. Behavioral characteristics included current smoking status (yes or no), alcohol consumption (≥three drinks per day; yes or no), vigorous physical exercise (<three or ≥three times per week), and regular doctor visits (<three or ≥three visits per year, excluding visits due to hospitalization).

Preliminary analyses also included variables to adjust for the subjects’ baseline interview year, birth cohort, geographic region, occupation, and overweight status (BMI 25.0–29.9); however, results were not significant and the variables were dropped from the analyses. The coding of study measures was facilitated by using HRS data files provided by the RAND Center for the Study of Aging and funded by the National Institute on Aging and the Social Security Administration [35].

2.3. Study outcome

Mortality from all causes was the main outcome for analysis. Participants who died during the study were identified from the HRS tracking file and the National Death Index [24]. Time of death was calculated in months for each of the deceased from their baseline interview date and recorded date of death. Subjects who were not identified as deceased and survived through 2010 were considered censored observations. Age (in months) at death or censoring was used to estimate age-specific mortality and to account for the staggered time exposure in 2006 and 2008 samples. On average, study participants were observed for more than three years and a total of 386 deaths (9%) were recorded.

2.4. Statistical analysis

Weighted distributions of HbA1c levels were calculated by educational group and t-tests were used to estimate significant differences. Descriptive characteristics were computed at baseline for all participants with diabetes and by HbA1c level. Comparisons between adults within guidelines and not within guidelines were calculated with χ² tests for categorical variables and t-tests for continuous variables. Kaplan–Meier plots and log-rank tests were used to assess educational differences in survival in adults with diabetes according to guideline-levels of HbA1c.

Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of all-cause mortality from baseline to 2010. The first set of multivariate models estimated the HRs for the direct associations for education and not meeting ADA criteria for HbA1c control while adjusting for age, sex, race, and ethnicity. Models were then estimated for an interaction between education and HbA1c level. The second set of multivariate models examined a series of adjusted HRs associated with levels of HbA1c and education. Models included control variables for demographic background and clinical status (Model 1) and additional models further included socioeconomic (Model 1a), psychosocial (Model 1b), and behavioral (Model 1c) covariates to examine how these factors may be contributing to the associations. A final model adjusted for all covariates (Model 1d).

All analyses adjusted for the complex HRS survey design to produce weighted and unbiased estimates of the nationally representative cohort of older adults. Tests of Schoenfeld residuals using robust variance-covariance matrix estimation indicated that the proportional hazard assumption for the Cox models was not violated. Variance inflation factors, tolerance levels, and condition values were also used to confirm the absence of multicollinearity among variables in the fitted models [36,37]. All analyses were performed using Stata version 12.1 [38].

3. Results

Fig. 1 illustrates the weighted distributions of HbA1c values by education level. The overall distribution of HbA1c levels was similar between educational groups; however, glycemic

![Fig. 1](image-url)
values were significantly higher in those with less than H.S. education compared with those with H.S. education or more (P < 0.001). Table 1 presents the characteristics of study participants with diabetes by recommended glycemic level. Adults with HbA1c values not within ADA guidelines (≥7.0% [53 mmol/mol]) were more likely to be younger, male, Hispanic, non-white, low educated, and lacking adequate health insurance compared with diabetes with guidelines (P < 0.05). Hemoglobin A1c ≥ 7.0% (53 mmol/mol) also was more common in adults who were not married, physically inactive, had low social support, inadequate doctor visits, had been diagnosed for a longer period, and used insulin compared to adults within ADA guidelines (P < 0.05).

The plots shown in Fig. 2 demonstrate significant educational differences in survival probabilities by guideline levels for HbA1c. Low-educated adults with diabetes had consistently lower survival during follow up than their higher-educated counterparts; with the lowest rates among those not within guideline levels (P < 0.001). Table 2 reports the demographic adjusted HRs for the direct and interaction associations for education and diabetes control. As previously shown, results indicated that having low education and not meeting general guideline levels for HbA1c control was significantly associated with increased mortality. We found that risks were greatest among the lowest educated with HbA1c ≥ 7.0% (53 mmol/mol) [HR = 2.18, 95% CI: 1.63, 2.94] compared with their higher-educated counterparts who maintained ADA levels of control. Tests for significant interactions indicated that low education and HbA1c ≥ 7.0% (53 mmol/mol) had a multiplicative effect (P = 0.031) with subsequent mortality.

Table 3 presents the adjusted HRs for mortality by levels of education and HbA1c. The significant mortality risks associated with HbA1c ≥ 7.0% (53 mmol/mol) among adults with low education were largely eliminated with the inclusion of psychosocial factors and only partly attenuated with the inclusion of socioeconomic and behavioral factors. However, the elevated HRs in low-educated adults with HbA1c ≥ 7.0% (53 mmol/mol) (Model 1d) remained significant despite accounting for all contributing factors in the study.

<table>
<thead>
<tr>
<th>Table 1 - Characteristics of participants at baseline by guideline levels for HbA1c control (n = 3312).</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
</tr>
<tr>
<td>Sample size</td>
</tr>
<tr>
<td>Demographic characteristics</td>
</tr>
<tr>
<td>Age</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Hispanic</td>
</tr>
<tr>
<td>Non-Hispanic black</td>
</tr>
<tr>
<td>Non-Hispanic other race</td>
</tr>
<tr>
<td>Education and other socioeconomic factors</td>
</tr>
<tr>
<td>Education, less than high school</td>
</tr>
<tr>
<td>Household income in thousands</td>
</tr>
<tr>
<td>Inadequate health insurance</td>
</tr>
<tr>
<td>Psychosocial resources</td>
</tr>
<tr>
<td>Not married</td>
</tr>
<tr>
<td>Social support</td>
</tr>
<tr>
<td>Sense of control over health</td>
</tr>
<tr>
<td>Depressive symptoms</td>
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<tr>
<td>Behavioral characteristics</td>
</tr>
<tr>
<td>Current smoker</td>
</tr>
<tr>
<td>Excess alcohol consumption</td>
</tr>
<tr>
<td>No vigorous exercise</td>
</tr>
<tr>
<td>Inadequate doctor visits</td>
</tr>
<tr>
<td>Clinical characteristics</td>
</tr>
<tr>
<td>HbA1c in NGSP units</td>
</tr>
<tr>
<td>HbA1c in IFCC units</td>
</tr>
<tr>
<td>Time since diagnosis, years</td>
</tr>
<tr>
<td>Insulin use</td>
</tr>
<tr>
<td>BMI ≥ 30.0</td>
</tr>
<tr>
<td>CVD mortality</td>
</tr>
<tr>
<td>Elevated BP, ≥130/80 mmHg</td>
</tr>
<tr>
<td>Elevated non-HDL, &gt;130 mg/dL</td>
</tr>
<tr>
<td>Elevated cystatin C, ≥1.25 mg/L</td>
</tr>
</tbody>
</table>

Abbreviations: HbA1c, Hemoglobin A1c; BMI, body mass index; CVD, cardiovascular disease; NGSP, National Glycohemoglobin Standardization Program; IFCC, International Federation of Clinical Chemistry; BP, blood pressure; HDL, high-density lipoprotein.

Note: Values reported as weighted percentages or means (standard error).
4. Discussion

This study is the first examination of educational differences in HbA1c levels and subsequent mortality in a nationally representative sample of U.S. older adults with diabetes. Results showed that low-educated adults had significantly higher levels of HbA1c and that mortality risks associated with not achieving ADA’s guidelines for recommended control were significantly higher among lower-educated adults than higher-educated adults. We also found no significant mortality difference between well-educated adults with poor glycemic control compared with well-educated adults within ADA’s recommended levels of HbA1c. Our study also considered the widest array of factors contributing to the educational differences in survival related to HbA1c level and found that a combination of factors accounted for only some of the associations.

Benchmarks for effective diabetes management, in terms of disease diagnoses, adequate health insurance, routine doctor visits, and achieving recommended control of blood glucose, blood pressure, and cholesterol, often fall short of targeted levels in the United States [3,2,46]. Our study corroborates these patterns in older adults and provides additional evidence of the impact of educational differences in achieving ADA’s general recommendations for HbA1c values. Most consequential, however, was that the survival implications of suboptimal glycemic levels were greatest for adults with low educational attainment. Older adults with less than a high school education were at significantly higher risk of mortality.

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**Table 3 – Adjusted hazard ratios for all-cause mortality in U.S. Older adults with diabetes by education and HbA1c levels (n = 3312).**

<table>
<thead>
<tr>
<th>Hazard ratio (95% confidence interval)</th>
<th>HbA1c &lt; 7.0% (53 mmol/mol)</th>
<th>HbA1c ≥ 7.0% (53 mmol/mol)</th>
<th>P value for interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>High school or more education</td>
<td>(Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than high school education</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1a: adjusts for demographic and clinical characteristics</td>
<td>1.03 (0.73-1.45)</td>
<td>1.02 (0.76-1.37)</td>
<td>1.52 (1.13-2.00)</td>
</tr>
<tr>
<td>Model 1a: + socioeconomic factors</td>
<td>(Reference)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1b: + psychosocial factors</td>
<td>(Reference)</td>
<td>1.01 (0.71-1.42)</td>
<td>0.97 (0.72-1.30)</td>
</tr>
<tr>
<td>Model 1c: + behavioral factors</td>
<td>(Reference)</td>
<td>0.97 (0.69-1.42)</td>
<td>0.95 (0.70-1.39)</td>
</tr>
<tr>
<td>Model 1d: + all covariates</td>
<td>(Reference)</td>
<td>0.99 (0.69-1.41)</td>
<td>0.95 (0.71-1.39)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.91 (0.61-1.33)</td>
<td>0.89 (0.65-1.21)</td>
</tr>
</tbody>
</table>

**Abbreviations:** HbA1c, Hemoglobin A1c

**Model 1 controls for age, sex, race, ethnicity, time since diagnosis, insulin use, BMI, CVD comorbidity, blood pressure, non-HDL cholesterol, and eGFR.**

Model 1a includes Model 1 + income, employment status, and health insurance.

Model 1b includes Model 1 + marital status, social support, sense of control over health, and depressive symptoms.

Model 1c includes Model 1 + smoking, alcohol use, physical exercise, and doctor visits.

Model 1d includes Model 1 + all covariates.

* Test for significant interaction between education × HbA1c level.
related to HbA1c levels that were above guideline goals (HR = 2.18) compared with those within guideline goals. In contrast, there were no significant differences in mortality risks in higher-educated adults within and not within guideline levels.

The findings from this study are consistent with the literature demonstrating the importance of education for improved health outcomes among those with diabetes [13, 18-21]. A recent article in Science showed that an early education program for disadvantaged children resulted in significant risk reduction for metabolic disease at later ages [39]. By age 30, approximately a quarter of males in the study who did not receive the early education intervention showed evidence of metabolic syndrome; whereas none of those who received the education program exhibited evidence of the disease. Although differences in HbA1c were not significant—presumably because of the relatively young age of subjects to observe the emergence of prediabetes or Type 2 diabetes—results from this study and the current analysis underscore the importance of education for the development and treatment of diabetes.

We recognize that the duration of diabetes is an important factor associated with potential mortality. In adults with Type 2 diabetes (the majority of those with diabetes), longer duration is associated with decreased endogenous insulin secretory capacity and thus increased difficulty in controlling blood glucose. Not surprisingly, we found that the duration of diabetes was significantly longer in adults with HbA1c values ≥7.0% (53 mmol/mol) than in adults with HbA1c values <7.0% (53 mmol/mol)—approximately 11 years vs. 7 years, respectively. However, preliminary analyses showed that the duration of diabetes was not significantly different between educational groups for those with HbA1c ≥7.0% (53 mmol/mol) and that controlling for disease duration did not change the mortality estimates. Similarly, levels of HbA1c were not significantly different between those with less than H.S. education (mean HbA1c = 8.6% [70 mmol/mol]) compared with those with H.S. education or more (mean HbA1c = 8.4% [58 mmol/mol]) in adults with glycemic levels above recommended goals. Therefore, we are confident that differences in diabetes duration and HbA1c levels do not explain the present findings.

The biomarker-linked HRS data allowed us to assess a wide array of possible mechanisms contributing to the associations. However, the excess mortality risks in low-educated adults with HbA1c ≥7.0% (53 mmol/mol) could not be fully explained by socioeconomic, psychosocial, behavioral, or clinical factors—not differences in the duration of disease. It is possible that other unmeasured factors (e.g., health literacy, symptom awareness) may have played a role and warrant further investigation. In particular, we suspect that the quality and level of care may be important factors underlying educational differences in diabetes treatment and management. Overall, we found that psychosocial attributes accounted for the largest reductions in mortality risks, relative to other socioeconomic and behavioral factors among low-educated adults with diabetes. Therefore, in addition to recognizing disease severity, comorbidity, and adherence to medication and behavioral regimens, clinicians should screen for depressive symptoms, inadequate social support, and/or low sense of control that may precipitate disease complications and poor outcomes in patients with diabetes, particularly in those with low educational attainment.

Contrary to expectations, behavioral factors such as doctor visits, exercise, smoking, and alcohol use had the least impact on educational differences in mortality related to guideline levels of HbA1c. Although direct comparisons of model fit could not be calculated across the non-nested weighted models, supplementary analyses on unweighted data produced the same pattern of findings and indicated that behavioral factors had the least explanatory power relative to other covariates according to Bayesian information criterion [41]. It is possible that much of the impact of health behaviors operated directly on mortality, as previously shown [42]. However, it also is possible that measurement may have played a role. For example, study respondents were not asked whether doctor visits were for routine care or to see specialists (e.g., endocrinologist, nephrologist); likewise, the nature of reported exercise could not be determined (e.g., aerobic vs. anaerobic activity) and information on diet and eating patterns also was not available.

Several other limitations should be acknowledged. Although the prospective HRS data provided a unique combination of socioeconomic, psychosocial, behavioral, and physiological measures, we were unable to assess changes in HbA1c or other covariates during the mortality follow-up period. Therefore, we caution against making causal inferences from the findings until longitudinal data are available to better address the temporal associations. We also recognize that we could not confirm whether all HRS participants in the study had diabetes without information from their medical records. However, we found that rates of physician-diagnosed and undiagnosed diabetes (HbA1c ≥6.5% [48 mmol/mol]) in this study were nearly identical with national estimates [26]. Supplementation analyses also excluded adults with HbA1c <7% (53 mmol/mol) who had not been diagnosed by a physician (n = 213; approximately 6% of the sample) and the results were highly consistent with the original findings—with only marginal changes in the point estimates and p values. Therefore, although we are confident that measurement bias is minimal, we encourage additional studies to further validate these findings.

We also acknowledge that universal guidelines for HbA1c may be unrealistic for individual patients in clinical practice—e.g., newer guidelines would recommend <5.7% (38 mmol/mol) as a goal for some adults over age 65 and/or those with heart disease or other comorbidities [8]. Likewise, although we do not account for recent guidelines that recommend less stringent control (e.g., systolic blood pressure), supplementary analyses produced the same results with blood pressure <130/80 mmHg vs. <140/80 mmHg. Finally, greater exploration of the potential role of race/ethnic differences in educational attainment, HbA1c levels, and associated risks were limited by sample size and are an important avenue for future research.

In sum, the results of this study demonstrate that education inequalities in the United States pose unique challenges for adults with diabetes. Public health programs and clinical efforts should be aligned in processes of care that recognize the excess burden of disease among those with low education and that inadequate glucose control (measured by HbA1c) has a significantly greater impact on survival among
lower-educated adults than higher-educated adults. Although educational attainment is not a readily modifiable risk factor, our findings identify opportunities for early interventions through greater awareness of socioeconomic risks and the potential factors contributing to poor outcomes. Additional studies are needed to further understand the mechanisms suggested by our findings.

Conflict of interest statement

None declared.

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Role of the sponsor

The Bristol-Myers Squibb Foundation had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Disclaimer

The views expressed in this article are those of the authors and do not necessarily reflect those of Duke University.

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Author contributions: M.E.D. had full access to the data in the study and takes responsibility for the accuracy of the data analysis.

Study concept and design: M.E.D., M.S.

Acquisition of data: M.E.D.

Analysis and interpretation of data: M.E.D.

Drafting of the manuscript: M.E.D., M.S., J.M.W., M.N.F.

Critical revision of the manuscript for important intellectual content: M.E.D., M.N.F.

Statistical analysis: M.E.D.

Administrative, technical, or material support: M.E.D.

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