Association Between Hemoglobin A1c and All-Cause Mortality: Results of the Mortality Follow-up of the German National Health Interview and Examination Survey 1998

**OBJECTIVE**
This study examined the association of HbA1c-defined glycemic status and continuous HbA1c with all-cause mortality.

**RESEARCH DESIGN AND METHODS**
The study population comprised 6,299 participants (aged 18–79 years) of the German National Health Interview and Examination Survey 1998, who were followed up for mortality for an average of 11.6 years. Glycemic status was defined as known diabetes (self-reported diagnosis or intake of antidiabetic medication) and based on HbA1c levels according to American Diabetes Association diagnostic criteria as undiagnosed diabetes (≥6.5% [≥48 mmol/mol]), prediabetes with very high (6.0–6.4% [42–46 mmol/mol]) or high diabetes risk (5.7–5.9% [39–41 mmol/mol]), and normoglycemia (<5.7% [<39 mmol/mol]). Associations between glycemic status and mortality were examined by Cox regression adjusting for age, sex, education, lifestyle factors, anthropometric measures, and history of chronic diseases (reference: normoglycemia). Spline models were fitted to investigate associations between continuous HbA1c and mortality among participants without known diabetes.

**RESULTS**
Excess mortality risk was observed for participants with known diabetes (hazard ratio 1.41 [95% CI 1.08–1.84]) and undiagnosed diabetes (1.63 [1.23–2.17]) but not for those with high (1.02 [0.80–1.30]) or very high diabetes risk (0.87 [0.67–1.13]). Spline models revealed a U-shaped association, with lowest risk at HbA1c levels 5.4–5.6% (36–38 mmol/mol) and a significantly increased risk at ≤5.0% (≤31 mmol/mol) and ≥6.4% (≥46 mmol/mol).

**CONCLUSIONS**
Unlike known and undiagnosed diabetes, HbA1c levels in the prediabetic range were not associated with an increased mortality risk. The observed U-shaped relationship adds to existing evidence that not only high but also low HbA1c levels might be associated with all-cause mortality.
Glycated hemoglobin A1c (HbA1c) reflects the individual average blood glucose concentration within the past 2–3 months and is an established biomarker for monitoring glycemic control in diabetic patients (1,2). The American Diabetes Association (ADA) and the World Health Organization (WHO) also recently recommended HbA1c (≥6.5% [≥48 mmol/mol]) for diabetes diagnosis (3,4). In addition, the ADA has recommended HbA1c for the identification of individuals at high (HbA1c 5.7–5.9% [39–41 mmol/mol]) or very high (HbA1c 6.0–6.4% [42–46 mmol/mol]) diabetes risk, also referred to as prediabetes (3,5).

There is evidence that increased HbA1c levels predict not only diabetes but also cardiovascular morbidity among people with and without diabetes (6,7). Moreover, a number of studies have analyzed the relationship between HbA1c and all-cause mortality. Most of these previous studies observed an increased risk of death from all-causes at diabetic HbA1c levels among adults without known diabetes, independent of other known cardiovascular risk factors (6–11), whereas some studies found no significant association (12–14). Whether the risk for all-cause mortality is already increased at HbA1c levels in the prediabetic range is unclear. Former studies showed contradictory results and differed in applied HbA1c cutoffs (6,9–13,15–17). So far, only one previous study assessing all-cause mortality in relation to HbA1c in the prediabetic range applied ADA recommendations. However, this study did not differentiate between HbA1c categories related to a high risk versus a very high risk for diabetes (15).

Several studies have assessed the risk of all-cause mortality independently of pre-defined cutoffs by modeling HbA1c levels continuously in adults without known diabetes. Although some studies reported a linear association between HbA1c and all-cause mortality (17–19), others observed a J-shaped relationship (6,14,16). Further, it is possible that the association between HbA1c and mortality changes with aging and thus might no longer be detectable in studies of older populations (12).

Given the wide application of diagnostic HbA1c testing in clinical practice, we investigated the association of HbA1c-defined glycemic status and continuous HbA1c with all-cause mortality in a nationwide sample of adults in Germany. In categoric analyses, we applied ADA cutoff criteria for undiagnosed diabetes and subcategories of prediabetes and also considered different reference groups to define normoglycemia. Spline models were fitted to test for nonlinearity in the relationship between HbA1c and mortality among people without known diabetes. Further, we investigated the modification of the association between HbA1c and mortality by age.

RESEARCH DESIGN AND METHODS

The Mortality Follow-up of the German National Health Interview and Examination Survey 1998

The nationwide German National Health Interview and Examination Survey 1998 (GNHIES98) was conducted between October 1997 and March 1999, targeting the residential, noninstitutionalized German population aged 18–79 years. A two-stage stratified clustered sampling technique was used. First, a representative sample of communities stratified by federal state and community size was drawn. Second, a random sample of adults stratified by age and sex was selected from local population registries proportional to the age and sex structure of the German population. The overall response rate was 61.4%, equivalent to 7,124 participants (20).

Study participants were recontacted between October 2008 and October 2011 and invited to participate in the first wave of the German Health Interview and Examination Survey for Adults (DEGS1). For those who did not respond or could no longer be contacted at the most current address, vital status and the exact date of death for deceased individuals were obtained from local population registries. Follow-up for death was complete for 6,979 participants (98.0%). After excluding participants with missing information regarding known diabetes (n = 22), HbA1c level (n = 398) or covariates (n = 260) at baseline, the study population for the present analysis comprised 6,299 persons. The GNHIES98 was approved by the Federal Commissioner for the Protection of Data and Freedom of Information. All study participants provided written informed consent before participation (20).

Assessment of Glycemic Status

Known diabetes was determined as 1) self-reported history of physician-diagnosed diabetes in standardized interviews conducted by specifically trained physicians or 2) intake of antidiabetic medication within the 7 days preceding the interview documented through a detailed medication review and coding of unique product identifiers (Pharmazentralnummer [PZN]) on original drug containers. Among participants without known diabetes, normoglycemia (HbA1c <5.7% [<39 mmol/mol]), prediabetes (HbA1c 5.7–6.4% [39–46 mmol/mol]), and undiagnosed diabetes (HbA1c ≥6.5% [≥48 mmol/mol]) were defined according to recent ADA recommendations (21). Prediabetes was further categorized as prediabetes with high (HbA1c 5.7–5.9% [39–41 mmol/mol]) or very high (HbA1c 6.0–6.4% [42–46 mmol/mol]) risk for diabetes (5,21).

HbA1c was measured in fresh whole blood specimens with a Diamat high-performance liquid chromatography analyzer (Bio-Rad Laboratories, Munich, Germany) and reagents of Recipe (Recipe Chemicals and Instruments, Munich, Germany) in the Robert Koch Institute in Germany) in the Robert Koch Institute Central Epidemiological Laboratory (20). The interassay coefficients of variation were 2.0–2.8%. The Bio-Rad HbA1c analysis system was certified by the National Glycohemoglobin Standardization Program (NGSP) ensuring standardization of HbA1c test results to the Diabetes Control and Complications Trial (22).
chronic diseases (hypertension, hyperlipidemia, myocardial infarction, stroke, cancer, hepatitis, chronic liver disease) was obtained by trained study physicians conducting standardized interviews (20). Hb was measured in EDTA-blood with a Coulter HmX Hematology Analyzer (Beckman Coulter, Krefeld, Germany) and anemia was defined by Hb <13 g/dL for men and <12 g/dL for women (25). Creatinine was measured in serum with an Architect analyzer (Abbott, Wiesbaden, Germany), and chronic kidney disease was defined by an estimated glomerular filtration rate <60 mL/min/1.73 m² (26). Trained health professionals used standardized operational procedures to obtain measures of height, weight, and waist circumference. BMI was calculated as the ratio of body weight (kg) and height squared (m²).

Statistical Analysis
Cox proportional hazards regression was performed to calculate hazard ratios (HR) and 95% confidence intervals (CI) for death during follow-up according to the glycemic status at baseline using normoglycemia as the reference category. Follow-up time, as a dependent time variable, was defined as the interval in days between the date of the baseline examination in GNHIES98 and the date of recontact during follow-up or the date of death. We verified that the proportional hazards assumption was met by including a product term of each independent variable and the log of survival time in the Cox model. Model 1 was adjusted for sex and age (years). Model 2 was further adjusted for established mortality risk factors: educational level (low, medium, high), smoking status (never, former, current), sport activity (≥2 h/week, <2 h/week), moderate alcohol consumption (yes, no), BMI (kg/m²), and waist circumference (cm). Model 3 was additionally adjusted for chronic diseases, including self-reported history of myocardial infarction, stroke, or cancer (yes, no) and hypertension or hyperlipidemia (yes, no). Sensitivity analyses were performed excluding 1) participants with <2 years of follow-up (n = 52) to account for potential influence of prevalent diseases influencing HbA₁c levels; 2) participants with a history of self-reported myocardial infarction, stroke, or cancer (n = 393); and 3) participants with baseline conditions known to affect HbA₁c, including pregnancy, anemia, chronic kidney disease, and self-reported history of hepatitis or chronic liver disease (n = 444). In an additional sensitivity analysis, the reference group was confined to HbA₁c levels of 5.0% to <5.7% (31 to <39 mmol/mol), because HbA₁c levels <5.0% (<31 mmol/mol) may be associated with increased mortality risk (15).

Spline regression analyses excluded participants with known diabetes at baseline (n = 313). The shape of the association between continuous HbA₁c levels and mortality was modeled by restricted cubic splines in the fully adjusted model, with four knots set at the 5th, 25th, 75th, and 95th percentile. Knots were equivalent to an HbA₁c level of 4.7% (28 mmol/mol), 5.1% (32 mmol/mol), 5.8% (40 mmol/mol), and 6.3% (45 mmol/mol), respectively. The reference was set at the median HbA₁c level of 5.4% (36 mmol/mol), and the plot was truncated at the 1st and the 99th percentile. The number of deceased individuals at specific HbA₁c values was limited (e.g., 22 deceased at an HbA₁c level of 5.4% [36 mmol/mol]).

To test the robustness of results, the reference was hence set at alternate HbA₁c levels, including 5.3% (34 mmol/mol) and 5.5% (37 mmol/mol). Because HbA₁c has been shown to increase in older age in nondiabetic individuals (27,28), a test for interaction was conducted by including a product term with age (<55 vs. ≥55 years) and HbA₁c in the spline model. Interaction with sex was tested in a separate model by including a product term with sex and HbA₁c.

SAS 9.3 software (SAS Institute Inc., Cary, NC) was used for all statistical analyses. The level of statistical significance was set at P = 0.05 based on two-sided tests.

RESULTS
Baseline characteristics of the study population stratified by glycemic status are presented in Table 1. Participants with undiagnosed diabetes and with known diabetes were similar in most characteristics. However, those with known diabetes showed a higher prevalence of hypertension and were less likely current smokers. With increasing HbA₁c from normoglycemia to a high and very high risk for diabetes to undiagnosed diabetes, individuals were older and more likely to have a lower educational level and a higher BMI. Moreover, the prevalence of hypertension increased in a stepwise fashion with deteriorating glycemic status. When the normoglycemic group was subdivided into individuals with an HbA₁c level <5.0% (<31 mmol/mol) and those with an HbA₁c level of 5.0 to <5.7% (31 to <39 mmol/mol), those with a lower HbA₁c level were more likely female, younger, had a higher educational level, a lower BMI and waist circumference, and a lower prevalence of hypertension, hyperlipidemia, and myocardial infarction (data not shown).

Overall, 552 of 6,299 eligible study participants were confirmed to have died during an average follow-up of 11.6 years, amounting to 73,299 person-years. Compared with participants with normoglycemia, mortality rates were approximately two to three times higher among participants with a high and a very high diabetes risk and approximately seven times higher among subjects with known or undiagnosed diabetes (Table 2). In Cox proportional hazards models adjusting for age and sex, undiagnosed diabetes and known diabetes, but not the prediabetic states, were associated with a significantly higher mortality risk compared with normoglycemia. The risk was 87% higher among subjects with undiagnosed diabetes and 66% higher among subjects with known diabetes compared with those with normoglycemia. Further adjustment for established mortality risk factors moderately attenuated risk estimates among all groups. In the model additionally adjusted for chronic diseases at baseline, mortality risk was still significantly increased by 63% (23–117%) among individuals with undiagnosed diabetes and by 41% (8–84%) in those with known diabetes. These results were confirmed in several sensitivity analyses (Table 3). Determining the reference group as an HbA₁c level of 5.0 to <5.7% (31 to <39 mmol/mol) slightly increased risk estimates among all groups. Among subjects with an HbA₁c level <5.0% (<31 mmol/mol), mortality risk was significantly increased by 70% (16–150%). The latter finding did not change materially after exclusion of 1) individuals who died within the first 2 years of follow-up (66% [10–151%]), 2) those with a history of myocardial infarction, stroke, or cancer (yes, no), smoking status (never, former, current), sport activity (≥2 h/week, <2 h/week), moderate alcohol consumption (yes, no), BMI (kg/m²), and waist circumference (cm).
infarction, stroke, or cancer (64% [6–153%]), or 3) those with baseline conditions known to affect HbA$_{1c}$ (66% [10–152%]) (data not shown).

Restricted cubic spline regression modeled for subjects without known diabetes revealed a U-shaped association (Fig. 1A). Risk for all-cause mortality was lowest at HbA$_{1c}$ levels of 5.4–5.6% (36–38 mmol/mol), whereas HbA$_{1c}$ levels ≤5.0% (≤31 mmol/mol) and ≥6.4% (≥46 mmol/mol) were both associated with a significantly increased risk. In sensitivity analyses with the reference set at HbA$_{1c}$ levels 5.3% (34 mmol/mol) or 5.5% (37 mmol/mol) instead of 5.4% (36 mmol/mol), the overall shape of the curve remained essentially the same, and the HbA$_{1c}$ range related to the lowest mortality risk was comparable (5.3–5.6% [34–38 mmol/mol] or 5.4–5.6% [36–38 mmol/mol], respectively; data not shown). However, the spline reacted slightly flexible before the first and after the last knot, with an increased mortality risk at HbA$_{1c}$ levels ≥5.1% (≥32 mmol/mol) and ≥6.6% (≥49 mmol/mol) for the reference of 5.3% (34 mmol/mol) or ≤4.9% (≤30 mmol/mol) and ≤6.3% (≤45 mmol/mol) for the reference of 5.5% (37 mmol/mol), respectively. Spline regression stratified by age group indicated a steeper increase in mortality risk in both the low and high range of HbA$_{1c}$ among participants aged <55 years compared with those aged at least 55 years (Fig. 1B and C), although a test for interaction between age group and HbA$_{1c}$ was not significant (P = 0.51). There was also no evidence for a significant interaction between HbA$_{1c}$ and sex (P = 0.24).

**CONCLUSIONS**

In the current study, known diabetes and HbA$_{1c}$-defined undiagnosed diabetes (HbA$_{1c}$ ≥6.5% [≥48 mmol/mol]), but not prediabetes, in the high or the very high diabetes risk category (HbA$_{1c}$ 5.7–6.4% [39–46 mmol/mol]), were significantly associated with an increased risk of all-cause mortality compared with normoglycemia (HbA$_{1c}$ <5.7% [<39 mmol/mol]). Results persisted in various sensitivity analyses, excluding individuals with preexisting chronic diseases or conditions with a possible effect on HbA$_{1c}$ and resetting the normoglycemic reference category to HbA$_{1c}$ levels of 5.0 to <5.7% [31 to <39 mmol/mol]. A U-shaped association was found between continuous HbA$_{1c}$ and all-cause mortality, with the lowest risk at HbA$_{1c}$ levels of 5.4–5.6% (36–38 mmol/mol) and a significantly increased risk at HbA$_{1c}$ levels ≤5.0% (≤31 mmol/mol) and ≥6.4% (≥46 mmol/mol). In accordance with evidence from previous studies, we observed an excess mortality risk among participants with known diabetes and HbA$_{1c}$-defined undiagnosed diabetes compared with normoglycemic individuals (6,9,10,29,30). In the main and sensitivity analyses, the risk for all-cause mortality was

### Table 1—Baseline characteristics for participants of the mortality follow-up of the GNHIES98 according to categories of glycemic status (n = 6,299)

<table>
<thead>
<tr>
<th>Glycemic Status</th>
<th>Normoglycemia (HbA$_{1c}$ &lt;5.7% [≤39 mmol/mol])</th>
<th>Prediabetes (HbA$_{1c}$ 5.7–5.9% [39–41 mmol/mol])</th>
<th>Very high diabetes risk (HbA$_{1c}$ 6.0–6.4% [42–46 mmol/mol])</th>
<th>Undiagnosed diabetes (HbA$_{1c}$ ≥6.5% [≥48 mmol/mol])</th>
<th>Known diabetes (HbA$_{1c}$ ≥6.5% [≥48 mmol/mol])</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_{1c}$ (%)</td>
<td>5.2 (0.3)</td>
<td>5.8 (0.1)</td>
<td>6.1 (0.1)</td>
<td>7.1 (1.1)</td>
<td>7.7 (1.7)</td>
</tr>
<tr>
<td>HbA$_{1c}$ (mmol/mol)</td>
<td>33 (3.3)</td>
<td>40 (1.1)</td>
<td>43 (1.1)</td>
<td>54 (12.0)</td>
<td>61 (18.6)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>40.6 (14.4)</td>
<td>49.6 (14.5)</td>
<td>55.6 (13.1)</td>
<td>60.1 (13.1)</td>
<td>61.4 (11.4)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>46.4</td>
<td>54.4</td>
<td>52.5</td>
<td>58.0</td>
<td>50.5</td>
</tr>
<tr>
<td>Educational level (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>37.2</td>
<td>46.6</td>
<td>59.1</td>
<td>68.9</td>
<td>69.7</td>
</tr>
<tr>
<td>Medium</td>
<td>48.0</td>
<td>37.9</td>
<td>29.8</td>
<td>22.3</td>
<td>21.7</td>
</tr>
<tr>
<td>High</td>
<td>14.8</td>
<td>15.5</td>
<td>11.1</td>
<td>8.8</td>
<td>8.6</td>
</tr>
<tr>
<td>BMI (kg/m$^2$)</td>
<td>25.7 (4.2)</td>
<td>27.4 (4.4)</td>
<td>28.7 (4.8)</td>
<td>30.5 (5.7)</td>
<td>29.6 (5.1)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>81.2 (11.4)</td>
<td>88.4 (12.9)</td>
<td>93.9 (12.7)</td>
<td>96.9 (12.8)</td>
<td>96.5 (12.3)</td>
</tr>
<tr>
<td>Men</td>
<td>94.3 (10.6)</td>
<td>97.8 (11.7)</td>
<td>99.7 (10.7)</td>
<td>105.8 (13.6)</td>
<td>103.8 (11.7)</td>
</tr>
<tr>
<td>History of known diseases (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>16.1</td>
<td>25.7</td>
<td>35.8</td>
<td>50.0</td>
<td>62.3</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>15.8</td>
<td>25.4</td>
<td>37.4</td>
<td>41.6</td>
<td>42.5</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.1</td>
<td>1.5</td>
<td>3.3</td>
<td>8.8</td>
<td>9.0</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.4</td>
<td>1.3</td>
<td>2.3</td>
<td>3.4</td>
<td>6.7</td>
</tr>
<tr>
<td>Cancer</td>
<td>2.7</td>
<td>3.9</td>
<td>4.5</td>
<td>3.4</td>
<td>6.4</td>
</tr>
<tr>
<td>Sport activity (≥2 h/week) (%)</td>
<td>21.8</td>
<td>16.8</td>
<td>14.0</td>
<td>8.0</td>
<td>8.0</td>
</tr>
<tr>
<td>Moderate alcohol consumption (%)</td>
<td>63.9</td>
<td>61.6</td>
<td>64.0</td>
<td>59.2</td>
<td>57.8</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>46.2</td>
<td>41.7</td>
<td>43.9</td>
<td>42.4</td>
<td>52.4</td>
</tr>
<tr>
<td>Former</td>
<td>20.4</td>
<td>24.4</td>
<td>20.4</td>
<td>27.7</td>
<td>27.2</td>
</tr>
<tr>
<td>Current</td>
<td>33.4</td>
<td>33.9</td>
<td>35.7</td>
<td>29.8</td>
<td>20.5</td>
</tr>
</tbody>
</table>

Information is given as arithmetic mean (SD) or percentage. Differences in proportions and means between groups of glycemic status were assessed by χ$^2$ test and ANOVA (Scheffé test).
CI 1.23
also re
due to diabetes treatment and might
with undiagnosed diabetes. This might
with known diabetes than among those
consistently slightly lower among people
and the diabetes duration was probably
longer in the latter group, this observa-
tion might at least partially be due to di-
babetes treatment. In individuals with
known diabetes but without antidiabetic
medication, mortality risk was not in-
creased (n = 93; HR 0.85 [95% CI 0.50–
1.42]). According to their mean baseline
HbA1c value (6.7% [50 mmol/mol]), these
individuals were at a less progressed
stage of diabetes development.

With respect to a lack of an increased
mortality risk among participants without
diabetes but at high (HbA1c 5.7–5.9%
[39–41 mmol/mol]) or very high di-
babetes risk (HbA1c 6.0–6.4% [42–46
mmol/mol]), our results are in line
with findings from the German Cooper-
ative Health Research in the Region of
Augsburg (KORA) Survey. This study
showed no association between HbA1c
levels of 5.8–6.0% (40–42 mmol/mol)
and all-cause mortality (reference: HbA1c
5.4–5.5% [36–37 mmol/mol]) (11). Nei-
ther did the Cardiovascular Health Study
(HbA1c 5.61–6.20% [38–44 mmol/mol],
reference: =5.60% [=38 mmol/mol])

Table 2—Mortality rate and risk for all-cause mortality (HR [95% CI]) according to categories of glycemic status

<table>
<thead>
<tr>
<th>Prediabetes</th>
<th>High diabetes risk</th>
<th>Very high diabetes risk</th>
<th>Undiagnosed diabetes</th>
<th>Known diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 5.7% (39–41 mmol/mol)</td>
<td>1.00 (0.82–1.32)</td>
<td>0.95 (0.73–1.22)</td>
<td>1.87 (1.41–2.47)</td>
<td>1.66 (1.29–2.16)</td>
</tr>
<tr>
<td>HbA1c 5.7–5.9% (42–46 mmol/mol)</td>
<td>1.00 (0.94–1.09)</td>
<td>0.87 (0.64–1.13)</td>
<td>1.63 (1.26–2.17)</td>
<td>1.41 (1.08–1.84)</td>
</tr>
<tr>
<td>HbA1c 6.0% (≥48 mmol/mol)</td>
<td>1.00 (0.77–1.25)</td>
<td>0.75 (0.66–1.11)</td>
<td>1.37 (1.29–2.47)</td>
<td>1.25 (1.15–1.94)</td>
</tr>
<tr>
<td>Deaths, n (%)</td>
<td>195 (4.9)</td>
<td>105 (9.9)</td>
<td>89 (12.9)</td>
<td>72 (30.3)</td>
</tr>
<tr>
<td>Follow-up (PY)</td>
<td>47,456.4</td>
<td>12,191.5</td>
<td>7,888.1</td>
<td>2,445.5</td>
</tr>
<tr>
<td>Mortality rate (per 1,000 PY)</td>
<td>4.1</td>
<td>8.6</td>
<td>11.3</td>
<td>29.4</td>
</tr>
</tbody>
</table>

PY: person-years. Model 1: Adjusted for age at baseline (years) and sex. Model 2: Further adjusted for educational level (low, medium, high), smoking status at baseline (never, former, current), sport activity (<2 vs ≥2 h/week), moderate alcohol consumption (men: >0 and ≤20 g/d, women: >0 and ≤10 g/d), BMI (kg/m²), and waist circumference (cm). Model 3: Further adjusted for history of myocardial infarction, stroke, or cancer at baseline (yes, no), and history of hypertension or hyperlipidemia at baseline (yes, no).

Table 3—Sensitivity analyses for risk for all-cause mortality (HR [95% CI]) according to categories of glycemic status

<table>
<thead>
<tr>
<th>Prediabetes</th>
<th>High diabetes risk</th>
<th>Very high diabetes risk</th>
<th>Undiagnosed diabetes</th>
<th>Known diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c &lt; 5.7% (39–41 mmol/mol)</td>
<td>1.00 (0.82–1.36)</td>
<td>0.84 (0.64–1.11)</td>
<td>1.59 (1.18–2.16)</td>
<td>1.41 (1.06–1.86)</td>
</tr>
<tr>
<td>HbA1c 5.7–5.9% (42–46 mmol/mol)</td>
<td>1.00 (0.82–1.40)</td>
<td>0.89 (0.66–1.20)</td>
<td>1.78 (1.29–2.47)</td>
<td>1.37 (0.99–1.89)</td>
</tr>
<tr>
<td>HbA1c 6.0% (≥48 mmol/mol)</td>
<td>1.00 (0.80–1.30)</td>
<td>0.87 (0.67–1.13)</td>
<td>1.63 (1.23–2.17)</td>
<td>1.44 (1.08–1.84)</td>
</tr>
</tbody>
</table>

Exclusions of persons with <2 years of follow-up (n = 52)*
| History of myocardial infarction, stroke, or cancer (n = 393)† | 1.00 (0.82–1.36) | 0.84 (0.64–1.11) | 1.59 (1.18–2.16) | 1.41 (1.06–1.86) |
| Baseline conditions known to affect HbA1c (n = 444)‡ | 1.00 (0.82–1.36) | 0.84 (0.64–1.11) | 1.59 (1.18–2.16) | 1.41 (1.06–1.86) |

Reference set at HbA1c 5.0 to <5.7% (31 to <39 mmol/mol)*
| HbA1c < 5.0% (<31 mmol/mol) | 1.70 (1.16–2.50) | 1.00 (0.85–1.39) | 0.92 (0.71–1.20) | 1.72 (1.29–2.30) |
| HbA1c 5.0 to <5.7% (31 to <39 mmol/mol) | 1.00 (0.82–1.36) | 0.84 (0.64–1.11) | 1.59 (1.18–2.16) | 1.41 (1.06–1.86) |

Number (%) of deceased for HbA1c < 5.0% (<31 mmol/mol): 32 (3.7%); for HbA1c 5.0 to <5.7% (31–<39 mmol/mol): 163 (5.2%). *Model is adjusted for the same variables as model 3 of Table 2. †Model is adjusted for the same variables as model 3 of Table 2 except for history of myocardial infarction, stroke, and cancer at baseline. ‡Baseline conditions known to affect HbA1c were pregnancy, anemia, chronic kidney disease, hepatitis, or chronic liver disease.
The Atherosclerosis Risk in Communities (ARIC) study, in contrast, used the same cutoff criteria to define prediabetes (HbA1c 5.7–6.4% [39–46 mmol/mol]) as applied in the current study but observed a significant association between prediabetes and all-cause mortality (reference: 5.0 to <5.7% [31 to <39 mmol/mol]) (15). An increased mortality risk was also found in the National Health and Nutrition Examination Survey (NHANES) III and the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study in relation to HbA1c levels of 5.5–5.9% (37–41 mmol/mol) and 6.0–6.4% (42–47 mmol/mol) compared with HbA1c levels of 5.0–5.4% (31–36 mmol/mol) as a reference (9,16). HbA1c levels of 6.0–6.4% (42–47 mmol/mol) were also predictive of an increased mortality risk in a study of the Japanese general adult population; in that study, the reference group was set at HbA1c levels of <5.0% (<31 mmol/mol) (10).

Inconclusive results regarding the relationship between prediabetic HbA1c levels and mortality are likely to result from varying definitions of prediabetes and reference categories as well as differences in main characteristics of the study population, such as age range and inclusion or exclusion of individuals with prevalent cardiovascular disease or undiagnosed diabetes according to glucose criteria. In sensitivity analyses, we therefore redefined our reference category according to the ARIC study (HbA1c 5.0 to <5.7% [31 to <39 mmol/mol]). However, there was still no association between a high or very high risk for diabetes and mortality. Notably, the ARIC analysis was based on an age range other than in the current study, included different ethnicities, and did not exclude or consider in adjusted models individuals with a history of myocardial infarction, stroke, or cancer. Despite the finding of no association between prediabetes and all-cause mortality in the current study, prediabetes might still be relevant for other clinical outcomes. HbA1c levels in the prediabetic range have been shown to be associated with an increased risk for coronary heart disease and stroke in some but not all studies (6,7,31).

Similar to the current study, some other studies determined nonlinear relationships between HbA1c and all-cause mortality (6,9,16). J-shaped associations were found among adults without known diabetes in a study based on NHANES III data (16) and in the ARIC study (6). Consistent with our findings, mortality risk in both studies was significantly increased at low and high HbA1c levels. For example, the risk in NHANES III was significantly increased at HbA1c levels >4.1% (≥21 mmol/mol) and ≥6.1% (≥43 mmol/mol) (16). Further, results of Cox models showed a significantly increased mortality risk in the ARIC study at HbA1c levels <5.0% (<31 mmol/mol) compared with HbA1c levels of 5.0–5.5% (31–37 mmol/mol) (6) or 5.0 to <5.7% (31 to <39 mmol/mol) (15), respectively, and in NHANES III at HbA1c levels <4.0% (<20 mmol/mol) compared with HbA1c levels of 5.0–5.4% (31–36 mmol/mol) (16). These findings are in concordance with results from our sensitivity analysis of an increased mortality risk at HbA1c levels <5.0% (<31 mmol/mol) compared with HbA1c levels of 5.0 to <5.7% (31 to <39 mmol/mol). In contrast, the EPIC-Norfolk study did not detect an increased mortality risk in the lower HbA1c range; risk was similar for HbA1c values <5.5% (<37 mmol/mol) and significantly increased afterward (9). Some other studies also tested for nonlinearity of the association between HbA1c levels and all-cause mortality but confirmed linear relationships (17–19).

Therefore, whether low HbA1c levels are a predictor of increased mortality risk remains controversial. Low HbA1c has been considered as a general marker of disease and a correlate of impaired red blood cell indices, unfavorable measures of iron storage, and increased liver function indices (15,16,32). These factors, in turn, were shown to correlate with inflammatory processes and increased morbidity and mortality (33–35). However, in our main and sensitivity analyses considering several comorbid conditions, the increased mortality risk in the lower HbA1c range persisted, which is also in accordance with a study based on NHANES III data (16). Residual confounding (36) and reliance on self-report for most chronic diseases have to be considered for discussing this observation but are unlikely to entirely explain the robust result. Therefore, future studies with a large number of individuals with low HbA1c levels and detailed assessment of morbid conditions would be important to

Figure 1—Risk for all-cause mortality (HR [95% CI]) according to restricted cubic spline regression among participants without known diabetes. Knots were set at the 5th, 25th, 50th, and 95th percentile. Reference was set at the median HbA1c level. Plot is truncated at the 1st and 99th percentile. Total population (N = 5,986 including 461 deaths) (A), population aged <55 years (n = 4,146 including 92 deaths) (B), and population aged ≥55 years (n = 1,840 including 369 deaths) (C). HRs (95% CIs) are shown on a natural log scale.

(12) or the Hoorn Study (HbA1c 5.6–5.9% [38–41 mmol/mol], reference: ≤5.1% [≤32 mmol/mol]) (13) find an association with all-cause mortality. However, these previous studies included participants within a limited age range (11–13) and applied criteria to define reference and risk categories that were different from ADA recommendations.
further investigate mechanisms underlying the increased mortality risk in the lower HbA\textsubscript{1c} range (16).

There is evidence that older age is associated with higher HbA\textsubscript{1c} levels independent of fasting plasma glucose and glucose measured 2 h after an oral glucose tolerance test (27,28). Studies investigating the association between increased HbA\textsubscript{1c} levels and mortality among elderly individuals showed diverging results (11–13,37). Our results indicate that the mortality risk associated with increased HbA\textsubscript{1c} levels might be more pronounced among younger than older persons without known diabetes, although the test for interaction between HbA\textsubscript{1c} and age was not significant. However, this might be due to the relatively small number of deceased individuals aged <55 years (n = 92) and low statistical power. Future studies with a larger sample size should focus on potential differences in risk among younger and older individuals.

The current study was based on a nationwide sample of the noninstitutional, residential population covering a wide age range from 18–79 years. Information on a large number of confounding variables was available. Besides, our study is among the few studies that have defined categories of glycemic status according to recently recommended HbA\textsubscript{1c} cutoffs following ADA diagnostic criteria for diabetes and prediabetes. However, HbA\textsubscript{1c} measurements may be influenced by a number of physiological and pathophysiological conditions affecting red cell and iron metabolism, such as pregnancy, iron deficiency, chronic liver disease, alcoholism, chronic renal failure, and intake of large doses of aspirin (4,5). Nevertheless, results remained materially unchanged in sensitivity analyses that considered with increased HbA\textsubscript{1c} levels might be more pronounced among younger than older persons without known diabetes, although the test for interaction between HbA\textsubscript{1c} and age was not significant. However, this might be due to the relatively small number of deceased individuals aged <55 years (n = 92) and low statistical power. Future studies with a larger sample size should focus on potential differences in risk among younger and older individuals.

The current study was based on a nationwide sample of the noninstitutional, residential population covering a wide age range from 18–79 years. Information on a large number of confounding variables was available. Besides, our study is among the few studies that have defined categories of glycemic status according to recently recommended HbA\textsubscript{1c} cutoffs following ADA diagnostic criteria for diabetes and prediabetes. However, HbA\textsubscript{1c} measurements may be influenced by a number of physiological and pathophysiological conditions affecting red cell and iron metabolism, such as pregnancy, iron deficiency, chronic liver disease, alcoholism, chronic renal failure, and intake of large doses of aspirin (4,5). Nevertheless, results remained materially unchanged in sensitivity analyses that considered with increased HbA\textsubscript{1c} levels might be more pronounced among younger than older persons without known diabetes, although the test for interaction between HbA\textsubscript{1c} and age was not significant. However, this might be due to the relatively small number of deceased individuals aged <55 years (n = 92) and low statistical power. Future studies with a larger sample size should focus on potential differences in risk among younger and older individuals.

The current study was based on a nationwide sample of the noninstitutional, residential population covering a wide age range from 18–79 years. Information on a large number of confounding variables was available. Besides, our study is among the few studies that have defined categories of glycemic status according to recently recommended HbA\textsubscript{1c} cutoffs following ADA diagnostic criteria for diabetes and prediabetes. However, HbA\textsubscript{1c} measurements may be influenced by a number of physiological and pathophysiological conditions affecting red cell and iron metabolism, such as pregnancy, iron deficiency, chronic liver disease, alcoholism, chronic renal failure, and intake of large doses of aspirin (4,5). Nevertheless, results remained materially unchanged in sensitivity analyses that considered with increased HbA\textsubscript{1c} levels might be more pronounced among younger than older persons without known diabetes, although the test for interaction between HbA\textsubscript{1c} and age was not significant. However, this might be due to the relatively small number of deceased individuals aged <55 years (n = 92) and low statistical power. Future studies with a larger sample size should focus on potential differences in risk among younger and older individuals.

Acknowledgments. The authors thank Ingrid Katharina Wolf and Michael Lange for conducting the Mortality Follow-Up, Julia Truthmann for assistance with data management, Daniel Grams for support with figure formatting, and Wulf Thierfelder for overseeing the laboratory analyses and quality assurance of HbA\textsubscript{1c} measurements (all affiliated to the Robert Koch Institute).

Funding. The Mortality Follow-Up was supported by research grants of the Federal Ministry of Health. R.P. was supported by research grants from the Federal Ministry of Health (FKZ IIAS-2513-FSB-736). Y.D. was supported by research grants from the Kompetenzzentrum Diabetes mellitus (Competence Network Diabetes mellitus) funded by the Federal Ministry of Education and Research (FKZ 01GI1110F).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. R.P. performed the statistical analyses and drafted the manuscript. A.S.R., M.A.B., Y.D., S.T., C.S.-N., and C.H. critically revised the manuscript for important intellectual content. A.S.R. and C.H. supported statistical modeling. C.S.-N. and C.H. conceptualized the study. All authors read and approved the final version of the manuscript. R.P. 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.


References

15. Aggarwal V, Schneider AL, Selvin E. Low hemoglobin A1c in nondiabetic adults: an