Association Between Hemoglobin A_{1c} and All-Cause Mortality: Results of the Mortality Follow-up of the German National Health Interview and Examination Survey 1998

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OBJECTIVE

This study examined the association of HbA_{1c}-defined glycemic status and continuous HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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, HbA_{1c} 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 HbA_{1c} levels might be associated with all-cause mortality.

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Glycated hemoglobin A_{1c} (HbA_{1c}) 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 HbA_{1c} (≥6.5% [≥48 mmol/mol]) for diabetes diagnosis (3,4). In addition, the ADA has recommended HbA_{1c} for the identification of individuals at high (HbA_{1c} 5.7–5.9% [39–41 mmol/mol]) or very high (HbA_{1c} 6.0–6.4% [42–46 mmol/mol]) diabetes risk, also referred to as prediabetes (3,5).

There is evidence that increased HbA_{1c} 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 HbA_{1c} and all-cause mortality. Most of these previous studies observed an increased risk of death from all-causes at diabetic HbA_{1c} 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 HbA_{1c} levels in the prediabetic range is unclear. Former studies showed contradictory results and differed in applied HbA_{1c} cutoffs (6,9–13,15–17). So far, only one previous study assessing all-cause mortality in relation to HbA_{1c} in the prediabetic range applied ADA recommendations. However, this study did not differentiate between HbA_{1c} 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 predefined cutoffs by modeling HbA_{1c} levels continuously in adults without known diabetes. Although some studies reported a linear association between HbA_{1c} and all-cause mortality (17–19), others observed a J-shaped relationship (6,14,16). Further, it is possible that the association between HbA_{1c} and mortality changes with aging and thus might no longer be detectable in studies of older populations (12).

Given the wide application of diagnostic HbA_{1c} testing in clinical practice, we investigated the association of HbA_{1c}-defined glycemic status and continuous HbA_{1c} 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 of the relationship between HbA_{1c} and mortality among people without known diabetes. Further, we investigated the modification of the association between HbA_{1c} 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), HbA_{1c} level (n = 398), or covariates (n = 260) at baseline, the study population for the present analysis comprised 6,299 people. 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 (HbA_{1c} <5.7% [<39 mmol/mol]), prediabetes (HbA_{1c} 5.7–6.4% [39–46 mmol/mol]), and undiagnosed diabetes (HbA_{1c} ≥6.5% [≥48 mmol/mol]) were defined according to recent ADA recommendations (21). Prediabetes was further categorized as prediabetes with high (HbA_{1c} 5.7–5.9% [39–41 mmol/mol]) or very high (HbA_{1c} 6.0–6.4% [42–46 mmol/mol]) risk for diabetes (5,21).

HbA_{1c} 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 Central Epidemiological Laboratory (20). The interassay coefficients of variation were 2.0–2.8%. The Bio-Rad HbA_{1c} analysis system was certified by the National Glycohemoglobin Standardization Program (NGSP) ensuring standardization of HbA_{1c} test results to the Diabetes Control and Complications Trial (22).

Assessment of Covariates

A standardized self-administered questionnaire was used to obtain information on age, sex, educational level, sport activity, and smoking status. Trained interviewers checked all completed questionnaires for plausibility and completeness (20). Educational level (low, medium, or high) was classified by the Comparative Analysis of Social Mobility in Industrial Nations (CASMIN), encompassing general as well as vocational training (23). Sport activity was assessed by five categories as no sport, <1 h/week, regularly 1–2 h/week, regularly 2–4 h/week, or regularly >4 h/week. This information was aggregated into two categories (<2 h/week or ≥2 h/week) for analyses. Smoking status was categorized as never, former, and current smoking. Alcohol intake (g/day) was obtained by a semiquantitative food frequency questionnaire (24). Moderate alcohol intake was defined as >0–20 g/day for men and >0–10 g/day for women. History of physician-diagnosed

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 m^2 (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 (m^2).

Statistical Analysis

Cox proportional hazards regression was performed to calculate hazard ratios (HRs) and 95% confidence intervals (CIs) 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/m^2), and waist circumference (cm). Model 3 was additionally adjusted for chronic diseases, including selfreported 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 HbA_{1c} 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 HbA_{1c}, 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 HbA_{1c} levels of 5.0% to <5.7% (31 to <39 mmol/mol), because HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} values was limited (e.g., 22 deceased at an HbA_{1c} level of 5.4% [36 mmol/mol]). To test the robustness of results, the reference was hence set at alternate HbA_{1c} levels, including 5.3% (34 mmol/mol) and 5.5% (37 mmol/mol). Because HbA_{1c} 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 HbA_{1c} in the spline model. Interaction with sex was tested in a separate model by including a product term with sex and HbA_{1c}.

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 HbA_{1c} 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 HbA_{1c} level <5.0% (<31 mmol/mol) and those with an HbA_{1c} level of 5.0 to <5.7% (31 to <39 mmol/mol), those with a lower HbA_{1c} 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 HbA_{1c} level of 5.0 to <5.7% (31 to <39 mmol/mol) slightly increased risk estimates among all groups. Among subjects with an HbA_{1c} 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

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

		Prediabetes			
	Normoglycemia HbA_{1c} <5.7% (<39 mmol/mol) n = 4,000	High diabetes risk HbA_{1c} 5.7–5.9% (39–41 mmol/mol) n = 1,056	Very high diabetes risk HbA_{1c} 6.0–6.4% (42–46 mmol/mol) n = 692	Undiagnosed diabetes HbA_{1c} ≥6.5% (≥48 mmol/mol) n = 238	Known diabetes n = 313
HbA_{1c} (%)	5.2 (0.3)	5.8 (0.1)	6.1 (0.1)	7.1 (1.1)	7.7 (1.7)
HbA_{1c} (mmol/mol)	33 (3.3)	40 (1.1)	43 (1.1)	54 (12.0)	61 (18.6)
Age (years)	40.6 (14.4)	49.6 (14.5)	55.6 (13.1)	60.1 (11.3)	61.4 (11.4)
Male sex (%)	46.4	54.4	52.5	58.0	50.5
Educational level (%)					
Low	37.2	46.6	59.1	68.9	69.7
Medium	48.0	37.9	29.8	22.3	21.7
High	14.8	15.5	11.1	8.8	8.6
BMI (kg/m^2)	25.7 (4.2)	27.4 (4.4)	28.7 (4.8)	30.5 (5.7)	29.6 (5.1)
Waist circumference (cm)					
Women	81.2 (11.4)	88.4 (12.9)	93.9 (12.7)	96.9 (12.8)	96.5 (12.3)
Men	94.3 (10.6)	97.8 (11.7)	99.7 (10.7)	105.8 (13.6)	103.8 (11.7)
History of known diseases (%)					
Hypertension	16.1	25.7	35.8	50.0	62.3
Hyperlipidemia	15.8	25.4	37.4	41.6	42.5
Myocardial infarction	1.1	1.5	3.3	8.8	9.0
Stroke	0.4	1.3	2.3	3.4	6.7
Cancer	2.7	3.9	4.5	3.4	6.4
Sport activity (≥2 h/week) (%)	21.8	16.8	14.0	8.0	8.0
Moderate alcohol consumption (%)	63.9	61.6	64.0	59.2	57.8
Smoking (%)					
Never	46.2	41.7	43.9	42.4	52.4
Former	20.4	24.4	20.4	27.7	27.2
Current	33.4	33.9	35.7	29.8	20.5

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).

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. 1*A*). 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. 1*B* 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 2—Mortality rate and risk for all-cause mortality (HR [95% CI]) according to categories of glycemic status

	Normoglycemia HbA_{1c} <5.7% (<39 mmol/mol)	Prediabetes: High diabetes risk HbA_{1c} 5.7–5.9% (39–41 mmol/mol)	Prediabetes: Very high diabetes risk HbA_{1c} 6.0–6.4% (42–46 mmol/mol)	Undiagnosed diabetes HbA_{1c} ≥6.5% (≥48 mmol/mol)	Known diabetes
Deaths, *n* (%)	195 (4.9)	105 (9.9)	89 (12.9)	72 (30.3)	91 (29.1)
Follow-up (PY)	47,456.4	12,191.5	7,888.1	2,445.5	3,317.4
Mortality rate (per 1,000 PY)	4.1	8.6	11.3	29.4	27.4
Model 1	1.00	1.04 (0.82–1.32)	0.95 (0.73–1.22)	1.87 (1.41–2.47)	1.66 (1.29–2.16)
Model 2	1.00	0.98 (0.77–1.25)	0.85 (0.66–1.11)	1.67 (1.26–2.22)	1.49 (1.15–1.94)
Model 3	1.00	1.02 (0.80–1.30)	0.87 (0.67–1.13)	1.63 (1.23–2.17)	1.41 (1.08–1.84)

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/day, women: >0 and ≤10 g/day), BMI (kg/m^2), 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).

consistently slightly lower among people with known diabetes than among those with undiagnosed diabetes. This might be due to diabetes treatment and might also reflect the effect of disease consciousness (11). In our study, additional subgroup analyses revealed similar mortality risks among individuals with undiagnosed diabetes (*n* = 238; HR 1.63 [95% CI 1.23–2.17]) and those with known diabetes treated by antidiabetic medication (*n* = 220; HR 1.65 [95% CI 1.24–2.20]). Because the mean baseline HbA_{1c} value was higher (8.1% [65 mmol/mol] vs. 7.1% [54 mmol/mol]) and the diabetes duration was probably longer in the latter group, this observation might at least partially be due to diabetes treatment. In individuals with known diabetes but without antidiabetic medication, mortality risk was not increased (*n* = 93; HR 0.85 [95% CI 0.50–1.42]). According to their mean baseline HbA_{1c} 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 (HbA_{1c} 5.7–5.9% [39–41 mmol/mol]) or very high diabetes risk (HbA_{1c} 6.0–6.4% [42–46 mmol/mol]), our results are in line with findings from the German Cooperative Health Research in the Region of Augsburg (KORA) Survey. This study showed no association between HbA_{1c} levels of 5.8–6.0% (40–42 mmol/mol) and all-cause mortality (reference: HbA_{1c} 5.4–5.5% [36–37 mmol/mol]) (11). Neither did the Cardiovascular Health Study (HbA_{1c} 5.61–6.20% [38–44 mmol/mol], reference: ≤5.60% [≤38 mmol/mol])

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

	Normoglycemia HbA_{1c} <5.7% (<39 mmol/mol)	Prediabetes: High diabetes risk HbA_{1c} 5.7–5.9% (39–41 mmol/mol)	Prediabetes: Very high diabetes risk HbA_{1c} 6.0–6.4% (42–46 mmol/mol)	Undiagnosed diabetes HbA_{1c} ≥6.5% (≥48 mmol/mol)	Known diabetes
Exclusions of people with <2 years of follow-up (*n* = 52)*	1.00	1.06 (0.82–1.36)	0.84 (0.64–1.11)	1.59 (1.18–2.16)	1.41 (1.06–1.86)
History of myocardial infarction, stroke, or cancer (*n* = 393)†	1.00	1.07 (0.82–1.40)	0.89 (0.66–1.20)	1.78 (1.29–2.47)	1.37 (0.99–1.89)
Baseline conditions known to affect HbA_{1c} (*n* = 444)*‡	1.00	1.04 (0.80–1.36)	0.89 (0.66–1.20)	1.73 (1.26–2.37)	1.58 (1.18–2.13)
	HbA_{1c} <5.0% (<31 mmol/mol)	HbA_{1c} 5.0 to <5.7% (31 to <39 mmol/mol)			
Reference set at HbA_{1c} 5.0 to <5.7% (31 to <39 mmol/mol)*	1.70 (1.16–2.50)	1.00	1.09 (0.85–1.39)	0.92 (0.71–1.20)	1.72 (1.29–2.30)	1.49 (1.14–1.96)

Number (%) of deceased for HbA_{1c} <5.0% (<31 mmol/mol): 32 (3.7%); for HbA_{1c} 5.0 to <5.7% (31 to <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 HbA_{1c} were pregnancy, anemia, chronic kidney disease, hepatitis, or chronic liver disease.

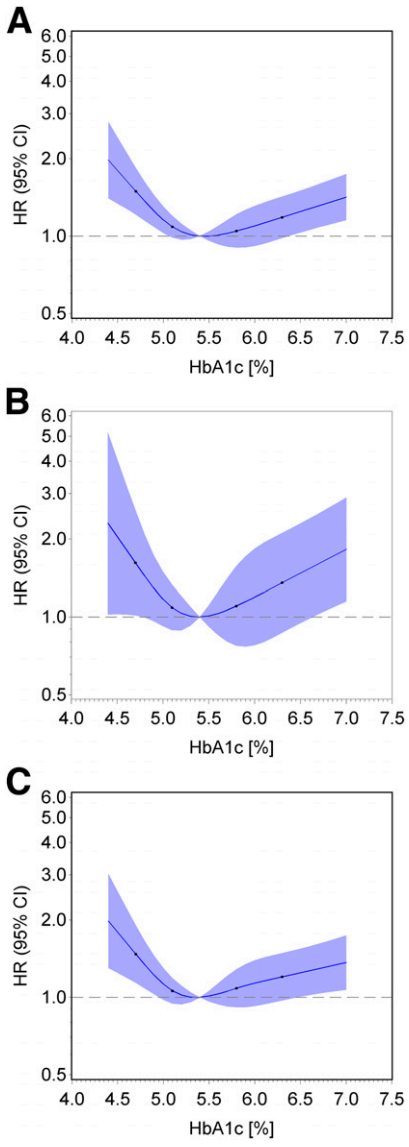

Figure 1—Risk for all-cause mortality (HR [95% CI]) according to restricted cubic spline regression among participants without known diabetes. Knots were set at the 5th, 25th, 75th, and 95th percentile. Reference was set at the median HbA_{1c} level. Plot is truncated at the 1st and 99th percentile. 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 (HbA_{1c} 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.

The Atherosclerosis Risk in Communities (ARIC) study, in contrast, used the same cutoff criteria to define prediabetes (HbA_{1c} 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 National Health and Nutrition Examination Survey (NHANES) III and the European Prospective Investigation into Cancer and Nutrition (EPIC)-Norfolk study in relation to HbA_{1c} levels of 5.5–5.9% (37–41 mmol/mol) and 6.0–6.4% (42–47 mmol/mol) compared with HbA_{1c} levels of 5.0–5.4% (31–36 mmol/mol) as a reference (9,16). HbA_{1c} 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 HbA_{1c} levels of <5.0% (<31 mmol/mol) (10).

Inconclusive results regarding the relationship between prediabetic HbA_{1c} 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 (HbA_{1c} 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. HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels. For example, the risk in NHANES III was significantly increased at HbA_{1c} 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 HbA_{1c} levels <5.0% (<31 mmol/mol) compared with HbA_{1c} 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 HbA_{1c} levels <4.0% (<20 mmol/mol) compared with HbA_{1c} 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 HbA_{1c} levels <5.0% (<31 mmol/mol) compared with HbA_{1c} 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 HbA_{1c} range; risk was similar for HbA_{1c} values <5.5% (<37 mmol/mol) and significantly increased afterward (9). Some other studies also tested for nonlinearity of the association between HbA_{1c} levels and all-cause mortality but confirmed linear relationships (17–19).

Therefore, whether low HbA_{1c} levels are a predictor of increased mortality risk remains controversial. Low HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} levels and detailed assessment of morbid conditions would be important to

further investigate mechanisms underlying the increased mortality risk in the lower HbA_{1c} range (16).

There is evidence that older age is associated with higher HbA_{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_{1c} levels and mortality among elderly individuals showed diverging results (11–13,37). Our results indicate that the mortality risk associated with increased HbA_{1c} levels might be more pronounced among younger than older persons without known diabetes, although the test for interaction between HbA_{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_{1c} cutoffs following ADA diagnostic criteria for diabetes and prediabetes. However, HbA_{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 most of these factors. In addition, we only measured HbA_{1c} once at baseline and due to random variability in HbA_{1c} levels, misclassification of participants might have occurred. However, the within-subject variation has been shown to be minimal (38), and HbA_{1c} measurement in the current study could be done with high precision using an established high-performance liquid chromatography analytic system. Further, we do not have information on changes in lifestyle, glycemic status, or drug treatment during follow-up. Thus, the influence of HbA_{1c} on mortality might have been under- or overestimated. Moreover, the diagnosis of known diabetes largely relied on self-report, and we did not have the information to exclude women with gestational diabetes. However, we were able to consider information on antidiabetic agent use based on a detailed medication review. Still, misclassification for known diabetes may have occurred. Another limitation is that we were not able to report cause-specific mortality risks. This would have been valuable for the evaluation of potential differences in the proportion of cause-specific deaths across HbA_{1c} categories.

In summary, known diabetes and HbA_{1c}-defined undiagnosed diabetes were both associated with an increased risk for all-cause mortality after 11.6 years of follow-up in this nationwide German cohort. However, adults with prediabetes, as defined by HbA_{1c}, did not differ in their mortality risk from those with normoglycemia. A U-shaped association was found between continuous HbA_{1c} measures and all-cause mortality, suggesting that not only high but also low HbA_{1c} levels might be associated with an increased risk of death.

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