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Associations between HbA1c and mortality over long-term follow-up: Results from the KORA S4 and the Heinz Nixdorf Recall Study

Short running title: HbA1c and mortality

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Abstract

Aims. There is limited knowledge about mortality risk in persons with increased HbA1c levels below the diabetes threshold. Moreover, little is known about how associations between increased HbA1c and mortality depend on the length of follow-up. Therefore, we studied associations between HbA1c and mortality over long-term follow-up in persons with and without known diabetes.

Methods. We used data from two German population-based cohort studies: KORA S4 Study (Southern Germany, n=1,458, baseline visits in 1999−2001, baseline age 55−74 years, mortality follow-up 16.8 years); Heinz Nixdorf Recall (HNR) Study (Ruhr area, n=4,613, baseline visits in 2000−2003, baseline age 45−75 years, mortality follow-up 17.8 years). Adjusted log-linear models were fitted to estimate relative risks (RRs) with 95% confidence intervals (CI).

Results. In both cohorts, participants with HbA1c 39–41 mmol/mol (5.7–5.9%) and HbA1c 42–46 mmol/mol (6.0–6.4%) did not have a larger overall mortality risk than participants with HbA1c < 39 mmol/mol (5.7%): the corresponding adjusted RRs were 1.00 (95% CI: 0.83−1.21) and 1.01 (0.80−1.27) in KORA, and 0.99 (0.82−1.21) and 0.83 (0.65−1.07) in the HNR Study. For the pooled cohorts, the RR for HbA1c 39-46 mmol/mol (5.7─6.4%) was 0.96 (0.85─1.07). Associations between newly detected diabetes (HbA1c ≥ 6.5%) and mortality were weak after 4 and 8 years of follow-up, but were stronger after 12 years of follow-up,

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whereas associations between previously known diabetes (baseline) and mortality decreased.

Conclusions. HbA1c-defined prediabetes is not associated with overall mortality. For newly detected and previously known diabetes, mortality risks vary with length of follow-up.

Key words: epidemiology; HbA1c; mortality; prediabetes; type-2 diabetes

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Introduction

Both the WHO and the American Diabetes Association (ADA) accepted HbA1c ≥ 6.5% to define diabetes [1,2]. Thus, HbA1c is now established as an appropriate diagnostic test for diabetes. However, international organizations have not agreed upon uniform HbA1c-based definitions of prediabetes: the ADA recommends 39–46 mmol/mol (5.7–6.4%), the International Expert Committee 42–46 mmol/mol (6.0–6.4%), whereas WHO currently does not endorse HbA1c as a criterion for defining prediabetes [3].

Studies on the association between HbA1c and all-cause mortality have often focused on persons with diabetes, and a J-shaped pattern was observed with slight increases of mortality risk for very low HbA1c values [4]. In the present study, we also took non-diabetic persons into account, and we studied associations between HbA1c and mortality using the novel cut-offs for HbA1c-defined diabetes and prediabetes. We mainly addressed two research questions:

First, the mortality risk of persons with intermediate hyperglycaemia has extensively been studied for glucose-based prediabetes, but less for increased HbA1c without diabetes. In a

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recently published meta-analysis on the association between prediabetes and all-cause mortality, the authors found that persons with impaired fasting glucose (IFG) (ADA) and IFG (WHO) both had a slightly increased risk of overall mortality (relative risk (RR)=1.13 (95% confidence interval (CI): 1.02–1.25) and RR=1.13 (1.05–1.21), respectively) [5]. However, for HbA1c 39–41 mmol/mol (5.7–5.9%), mortality risk estimated from four pooled studies was not increased (RR=0.97 (0.88–1.07)) [5]. In addition, for HbA1c 42–46 mmol/mol (6.0–6.4%) the meta-analysis included only one study showing an increased mortality risk (RR=1.21 (0.95–1.26)) [6]. However, the latter study referred to a specific population of persons with normal glucose tolerance (NGT) and high diabetes risk. More recently, in two studies the mortality risk for HbA1c 42–46 mmol/mol (6.0–6.4%) was investigated in general populations, yielding inconsistent results [7,8].

Second, the role of length of follow-up has hardly been taken into account in studies on HbA1c and mortality, and little is known about the impact of length of follow-up on the associations between HbA1c and mortality. Usually, studies with various follow-up times are pooled in meta-analyses.

Thus, our aim was to examine the association between intermediate hyperglycaemia defined by HbA1c and overall and cardiovascular mortality using data from two population-based German cohort studies (KORA S4 Study, Heinz Nixdorf Recall (HNR) Study). Additionally, we right-censored the data after varying intervals of follow-up to study the influence of length of follow-up on HbA1c mortality associations.

Methods

Study participants

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The KORA S4 Study is a population-based prospective cohort study in the region of Augsburg in Southern Germany. Baseline visits took place in 1999 – 2001, and mortality was followed up to 16.8 years. From 1,653 KORA participants, persons with diabetes other than type 2 diabetes, unclear diabetes diagnosis, or missing covariates were excluded leaving a sample of 1,458 participants (51.9% men, aged 55 to 74 years).

The HNR Study is a population-based prospective cohort study in the Ruhr area in Western Germany. Baseline visits took place in 2000 – 2003, and mortality was followed up to 17.8 years. From 4,814 HNR Study participants, persons with diabetes other than type 2 diabetes, or missing values for covariates were excluded leaving 4,613 participants (49.5% men, aged 45 to 75 years). Study designs are described in more detail elsewhere [9,10].

Both studies were approved by the relevant institutional ethics committees (the Bavarian Chamber of Physicians (KORA), and the Ethics Committee of the Medical Faculty of the University Clinic Essen (Recall)). All participants gave their written informed consent.

Variables

In both studies, for measurement of HbA1c immune turbidimetric assays were used: Tina-quant, Roche Diagnostics, Germany; Hitachi 717 Analyzer in KORA S4, and ADVIA 1650, Bayer Diagnostics, in the Recall Study. In KORA, previously known diabetes was defined as self-reports validated by questioning the responsible physician, or as current use of glucose-lowering agents. In the HNR Study, previously known diabetes was defined if participants gave a self-report of physician´s diagnosis, or if glucose-lowering drugs were taken. The following HbA1c categories were used: previously known diabetes with HbA1c ≥ 53 mmol/mol (7.0%) and HbA1c <53 mmol/mol; no previously known diabetes with HbA1c

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≥48 mmol/mol (6.5%), HbA1c 42–46 mmol/mol (6.0–6.4%), HbA1c 39–41 mmol/mol (5.7–5.9%), and HbA1c <39 mmol/mol (5.7%) (reference).

For further details on assessment of covariates, diabetes and prediabetes see references [9,10].

Statistical analyses

For the binary responses “mortality” and “cardiovascular mortality”, log-linear models with a Poisson working likelihood and robust standard errors were fitted, to estimate relative risks (RRs) with 95% confidence intervals (CI) adjusted for age, sex, BMI, smoking, hypertension, physical activity, educational years, total cholesterol, HDL cholesterol and history of cardiovascular diseases. To additionally account for the time until death we fitted an adjusted accelerated failure time (AFT) model for interval-censored data with a Weibull distribution assumed for the event times. The expected time until death for the prediabetes categories is the expected time until death for people with HbA1c <5.7% multiplied by $e^{ß}$ (ß=regression coefficient). For the pooled data set, we additionally fitted a proportional hazards Cox model.

Using the pooled data, we estimated RRs with 95% CI not only for the total follow-up, but we also right-censored the data, and estimated RRs with 95% CI for the first four, eight, and twelve years of the follow-up period.

In an additional analysis on the association between HbA1c levels and all-cause mortality, we only included study participants without previously known diabetes (N=5604, pooled data set), and we used subcategories for HbA1c < 5.7%. The following categories were used: ≤ 4.6%, 4.7 – 4.8%, 4.9 – 5.1%, 5.2 – 5.4%, 5.5 – 5.7%, 5.8 – 6.0%, 6.1 – 6.4%, and ≥ 6.5%. The cut-offs 4.8%, 5.1%, 5.4%, 5.7% and 6.0% refer to the 10th, 25th, 50th, 75th, and 90th percentiles. The two deciles at the extreme ends were subdivided further.

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As 195 and 201 individuals, respectively, were excluded because of missing values, we also used multiple imputation with fully conditional specification, for the analyses of the association between HbA1c and overall mortality.

Analyses were performed with SAS (version 9.4; SAS Institute, Cary, NC, USA).

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Results

Overall, KORA participants were about five years older than HNR Study participants, and had higher values of HbA1c at baseline (Table 1). Of 1,458 participants of the KORA S4 Study, 566 (38.8%) had HbA1c values in the range of 39–46 mmol/mol (5.7–6.4%) at baseline. Among 4,613 participants of the HNR Study, 907 (19.7%) had HbA1c values in this range. Newly detected or previously known diabetes was found in 162 (11.1%) KORA participants, and in 522 (11.3%) of the HNR Study population.

KORA participants displayed a higher mortality rate than the HNR Study population (20.7 versus 11.2 per 1,000 person-years). However, the mortality rate of the latter increased to 18.9 per 1,000 person-years when the analysis was confined to the same age range and length of mortality follow-up of KORA.

In both cohorts, people with HbA1c 39–41 mmol/mol (5.7–5.9%) and HbA1c 42–46 mmol/mol (6.0–6.4%) did not have a larger overall mortality risk than participants with HbA1c <39 mmol/mol (5.7%); the corresponding adjusted relative risks (RRs) were 1.00 (95% CI: 0.83–1.21) and 1.01 (0.80–1.27) in KORA and 0.99 (0.82–1.21) and 0.83 (0.65–1.07) in the HNR Study (Table 2). There were only small differences in progression to death in persons with HbA1c 39–41 mmol/mol (5.7–5.9%) and HbA1c 42–46 mmol/mol (6.0–6.4%) compared to HA1c <39 mmol/mol (5.7%) (AFT models; Table 2). In participants with newly detected,

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HbA1c-defined diabetes, the overall mortality risk was slightly increased (RR=1.15 (0.81–1.64) in KORA and 1.27 (1.00–1.61) in the HNR Study).

For cardiovascular mortality, RRs were 0.96 (0.66–1.38) for HbA1c 39–41 mmol/mol (5.7–5.9%) and 1.09 (0.71–1.65) for HbA1c 42–46 mmol/mol (6.0–6.4%) in KORA, and the corresponding RRs were 1.17 (0.76–1.80) and 1.14 (0.70–1.85) in the HNR Study (Table 3). For the pooled data set, RRs were 1.01 (0.77–1.34), 1.10 (0.80–1.52), 1.32 (0.85–2.04), 1.89 (1.38–2.58), and 2.49 (1.78–3.49) for HbA1c 5.7-5.9%, 6.0-6.4%, ≥ 6.5%, known diabetes with HbA1c < 7.0%, and for known diabetes with HbA1c ≥ 7.0% (reference HbA1c < 5.7%).

When both data sets were pooled, the following RRs were obtained for people without previously known diabetes: 0.98 (0.86–1.13) for HbA1c 39–41 mmol/mol (5.7–5.9%); 0.91 (0.77–1.08) for HbA1c 42–46 mmol/mol (6.0–6.4%); 1.23 (1.01–1.51) for Hb1c ≥48 mmol/l (6.5%) (Table 4). For HbA1c 39-46 mmol/mol (5.7–6.4%), the RR was 0.96 (0.85–1.07). When HbA1c <39 mmol/mol (5.7%) was split into HbA1c <31 mmol/mol (5.0%) and HbA1c 31–38 mmol/mol (5.0-5.6%) with the latter subcategory as reference, RRs were 0.98 (0.86–1.13) for HbA1c 39–41 mmol/mol (5.7-5.9%) and 0.91 (0.76–1.08) for HbA1c 42–46 mmol/mol (6.0–6.4%).

For the pooled data set, results of a proportional hazards Cox regression agreed with the results of the Poisson and of the AFT model for the association between HbA1c and all-cause mortality. The hazard ratios with 95% CI were 0.95 (0.80 – 1.12), 0.91 (0.74 – 1.11), 1.29 (1.00 – 1.68), 1.69 (1.36 – 2.09), and 1.78 (1.40 – 2.27) for HbA1c 5.7-5.9%, 6.0-6.4%, ≥ 6.5%, known diabetes with HbA1c < 7.0%, and for known diabetes with HbA1c ≥ 7.0%, respectively (reference HbA1c < 5.7%).

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When the data were right-censored after four, eight and twelve years of follow-up two trends were observed (Table 4): First, associations between diabetes newly detected at baseline and mortality were weak after four and eight years of follow-up (RR=0.73 (0.32-1.67), and 1.11 (0.74-1.67), respectively), but became stronger after 12-year follow-up (RR=1.32 (1.04-1.69)). Second, associations between diabetes known before baseline and mortality slightly decreased over follow-up (Table 4).

After splitting HbA1c into subcategories, we observed a J-shaped pattern with an indication for an increased all-cause mortality for Hb1Ac ≤ 4.6% (adjusted RR=1.25 (95% CI: 0.88 – 1.79), reference HbA1c 4.9 – 5.1%) (cf. figure 1).

Using multiple imputation with fully conditional specification, results for the association between HbA1c and overall mortality changed slightly: For the Recall Cohort, relative risks for HbA1c 5.7-5.9%, 6.0-6.4%, ≥ 6.5%, known diabetes with HbA1c < 7.0%, and for known diabetes with HbA1c ≥ 7.0% were 1.01 (0.84-1.23), 0.86 (0.67- 1.09), 1.29 (1.02-1.63), 1.43 (1.17-1.75), and 1.44 (1.15-1.81), respectively. For the KORA cohort, the corresponding relative risks were 0.98 (0.82-1.18), 0.96 (0.77-1.21), 1.07 (0.76-1.52), 1.47 (1.14-1.88), and 1.74 (1.32-2.31).

Discussion

This study found that increased HbA1c values 39–41 mmol/mol (5.7–5.9%) and HbA1c 42–46 mmol/mol (6.0–6.4%) in people without diabetes were barely associated with overall mortality in two population-based cohort studies with long follow-up periods. Moreover, our study gives evidence that associations between HbA1c and mortality vary over long follow-up periods: in persons with diabetes newly detected at baseline, the mortality risk increased

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over follow-up, whereas it slightly decreased in persons with diabetes previously known at baseline. Furthermore, our study confirms earlier results showing increased all-casuse mortality in persons without diabetes with very low HbA1c values [4]. In the pooled data set, there was an indication that cardiovascular mortality was slightly increased in persons with HbA1c 42–46 mmol/mol (6.0–6.4%), however, this effect estimate was rather imprecise.

So far, results from the few studies on HbA1c in the prediabetes range and overall mortality were inconsistent. In a large cohort study using Health Survey for England data, HbA1c 39–46 mmol/mol was not associated with increased mortality (HR=0.95 (0.84–1.08)) [11]. From the ARIC Study (US), contradicting results were reported when HbA1c 39-46 mmol/mol (5.7–6.4%) was compared to HbA1c < 39 mmol/mol (5.7%): With participants from visits 2 and 4, a strong association was found for the fully adjusted model (HR=1.31 (1.21–1.43)) [8]. However, in a recent analysis with older ARIC participants from visit 5 (age 66–90), barely any association was found between HbA1c in the prediabetic range (39-46 mmol/mol (5.7–6.4%)) and total and cardiovascular mortality, respectively (HR=1.03 (0.85–1.23), and HR=1.00 (0.70–1.43)) [12]. Some studies indicated that the mortality risk increases for HbA1c <31 mmol/mol [13]. However, the choice of the reference category does not explain our results: when we split HbA1c <39 mmol/mol (5.7%) and used HbA1c 31–38 mmol/mol (5.0–5.6%) as reference, this had very little impact on our results.

Our results have strong implications for the identification of high-risk populations for diabetes prevention [2]. Both glucose- and HbA1c-based criteria have been proposed to be equally suitable to select high-risk individuals for diabetes prevention [2]. Moreover, combining glucose-based criteria with HbA1c was shown to improve identification of persons with higher risk of CVD [14]. The optimal choice of the screening method depends on the long-term goal

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of a prevention program. With respect to mortality, using HbA1c criteria alone may miss high-risk individuals who should receive preventive interventions. In various other studies, prediabetes defined by fasting glucose demonstrated associations with long-term mortality [5]. These findings contribute to the recommendations regarding definitions of high-risk individuals for diabetes prevention programs [15].

To our knowledge, the influence of length of follow-up on the association between HbA1c and mortality has not been considered in earlier studies. In the present study, the relative risk for overall mortality among persons with diabetes newly detected at baseline was weak in the first years of follow-up and increased with longer follow-up. This is plausible because mortality may not yet increase strongly in the very first years after diabetes onset. In older adults of the ARIC Study, e.g., overall mortality was much larger in long-standing diabetes (≥ 10 years) than in short-term diabetes [12]. In persons with diabetes previously known at baseline our observation that relative risks decreased with longer follow-up may be explained with increasing age during long follow-up periods. In earlier studies, it was shown that hazards ratios for the association between diabetes and mortality decrease with old age [16,17]. Using data from the Swedish National Diabetes Register, e.g., it was shown that the corresponding hazards ratios decreased from 2.18 (2.02–2.34) in persons younger than 55 years to 1.02 (1.01–1.03) in persons older than 75 years [17].

Strengths of our study are the use of data from two independent cohort studies, and the long mortality follow-up of 17 years. Our study has several limitations. First, the number of deaths was rather small. Second, different devices were used to measure HbA1c in the two cohort studies. However, both assays were traceable to the NGSP (National Glucose Standardisation Program) reference system, and, therefore, they were well comparable. Third, results may not be generalizable to the younger age, and may not apply to Non-

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Caucasians. Fourth, despite adjustment for multiple confounders we cannot exclude residual confounding.

To conclude, HbA1c may not be a good predictor of mortality for persons with intermediate hyperglycaemia. Additionally, the length of follow-up periods should receive more attention in future studies.

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Duality of interest: There are no competing interests to declare.

Data availability

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Due to data security reasons (i.e., data contain potentially participant identifying information), the HNR Study does not allow sharing data as a public use file. Data requests can be addressed to recall@uk-essen.de. The data of the KORA Study are subject to national data protection laws and restrictions were imposed by the Ethics Committee of the Bavarian Chamber of Physicians to ensure data privacy of the study participants. Therefore, data cannot be made freely available in a public repository. However, data can be requested through an individual project agreement with KORA via the online portal KORA.passt. Please contact the corresponding author in case of further questions.

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Contribution statement

BK and WR conceived and designed the study. BK analysed the data and BK and WR wrote the manuscript. AS, RE and KHJ contributed to conception and design of the HNR Study. BT, CM and AP contributed to conception and design of KORA. All authors contributed to the interpretation of the results and critically reviewed the manuscript. All authors read and approved the final manuscript.

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Table 1. Baseline characteristics of the study groups: the Heinz-Nixdorf Recall (HNR) and the KORA S4 Study

		HNR Study	KORA
N		4,613	1,458
Age (years)		59.6 ± 7.8	64.1 ± 5.5
Sex (males (%))		49.5	51.9
Years of education (ISCED)		14.0 ± 2.4	10.7 ± 2.4
BMI (kg/m^2)		27.9 ± 4.6	28.7 ± 4.4
HbA1c (mmol/mol)		37 ± 9	40 ± 9
HbA1c [%]		5.5 ± 0.8	5.8 ± 0.8
Systolic blood pressure (mm Hg)		133.1 ± 20.9	136.2 ± 20.3
Diastolic blood pressure (mm Hg)		81.5 ± 10.9	80.3 ± 10.5
Hypertension (%)		56.0	56.7
Total cholesterol (mg/dl)		229.1 ± 39.2	242.7 ± 42.1
HDL cholesterol (mg/dl)		57.9 ± 17.1	57.5 ± 16.3
Smoking (%)	Current	23.3	13.4
	Former	34.5	39.0
	Never	42.2	47.5
History of stroke (%)		2.8	2.9
History of myocardial infarction (%)		4.8	4.5
Follow-up time (years)		15.0 ± 3.4	14.1 ± 3.6

Values are expressed as mean ± standard deviation, median (first quartile, third quartile), or proportion (%), ISCED: International Standard Classification for Education

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Table 2. Mortality rates and adjusted relative risks for overall mortality by HbA1c at baseline: the KORA S4 and the Heinz Nixdorf Recall Study [a]

Previously known diabetes [b]	HbA1c (mmol/mol (%))	N	Deaths n (%)	Mortality rate per 1,000 person years (95% CI)	RR (95% CI) [a, c]	Exp(beta) from AFT model (95% CI) [c, d]
KORA Study						
No	< 39 (5.7)	730	187 (25.6%)	17.8 (15.4 – 20.6)	1	1
No	39–41 (5.7–5.9)	369	99 (26.8%)	18.8 (15.3 – 22.9)	1.00 (0.83 – 1.21)	1.02 (0.89 – 1.16)
No	42–46 (6.0–6.4)	197	56 (28.4%)	20.5 (15.5 – 26.6)	1.01 (0.80 – 1.27)	0.94 (0.79 – 1.10)
No	≥ 48 (≥ 6.5)	43	18 (41.9%)	31.0 (18.4 – 48.9)	1.15 (0.81 – 1.64)	0.91 (0.69 – 1.19)
Yes	< 53 (< 7.0)	65	34 (52.3%)	42.0 (29.1 – 58.7)	1.62 (1.28 – 2.04)	0.67 (0.55 – 0.82)
Yes	≥ 53 (≥ 7.0)	54	31 (57.4%)	48.9 (33.3 – 69.5)	1.93 (1.47 – 2.55)	0.60 (0.48 – 0.74)
All		1458	425 (29.2%)	20.7 (18.8 – 22.8)	-	-
Heinz Nixdorf Recall Study						
No	< 39 (5.7)	3184	453 (14.2%)	9.4 (8.5 – 10.3)	1	1
No	39–41 (5.7–5.9)	554	93 (16.8%)	11.2 (9.1 – 13.8)	0.99 (0.82 – 1.21)	1.04 (0.88 – 1.23)
No	42–46 (6.0–6.4)	353	56 (15.9%)	10.5 (7.9 – 13.6)	0.83 (0.65 – 1.07)	1.22 (0.98 – 1.51)
No	≥ 48 (≥ 6.5)	174	46 (26.4%)	18.3 (13.4 – 24.4)	1.27 (1.00 – 1.61)	0.80 (0.63 – 1.01)
Yes	< 53 (< 7.0)	197	70 (35.5%)	26.7 (20.9 – 33.8)	1.45 (1.18 – 1.77)	0.69 (0.57 – 0.85)
Yes	≥ 53 (≥ 7.0)	151	53 (35.1%)	26.3 (19.7 – 34.4)	1.36 (1.07 – 1.73)	0.75 (0.59 – 0.94)
All		4613	771 (16.7%)	11.2 (10.4 – 12.0)	-	-

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RR: relative risk; CI: confidence interval; AFT: accelerated failure time

[a] For results of the pooled data, cf table 4 (right column)
[b] Previously known diabetes includes self-report of physician's diagnosis or intake of glucose-lowering drugs (ATC code A10)
[c] adjusted for age, sex, BMI, smoking, hypertension, physical activity, educational years, total cholesterol, HDL cholesterol, history of cardiovascular diseases
[d] For example, in the KORA Study, for previously known diabetes with Hb1Ac < 53 mmol/mol, exp(beta)=0.67 means: the expected time until death for this category is the expected time until death for the reference category (no previously known diabetes, HbA1c < 39 mmol/mol) multiplied by 0.67.

Table 3. Rates of cardiovascular mortality and adjusted relative risks for cardiovascular mortality by HbA1c at baseline: the KORA S4 and the Heinz Nixdorf Recall Study [a]

Previously known diabetes [b]	HbA1c (mmol/mol (%))	N	Deaths n (%)	Mortality rate per 1,000 person years (95% CI)	RR (95% CI) [c]	Exp(beta) from AFT model (95% CI) [c, d]
KORA Study						
No	< 39 (5.7)	728	72 (9.9%)	6.9 (5.4 – 8.7)	1	1
No	39–41 (5.7–5.9)	367	36 (9.8%)	6.9 (4.8 – 9.5)	0.96 (0.66 – 1.38)	1.03 (0.84 – 1.27)
No	42–46 (6.0–6.4)	197	23 (11.7%)	8.4 (5.3 – 12.6)	1.09 (0.71 – 1.65)	0.91 (0.71 – 1.16)
No	≥ 48 (≥ 6.5)	42	8 (19.1%)	13.9 (6.0 – 27.4)	1.37 (0.69 – 2.72)	0.82 (0.56 – 1.20)
Yes	< 53 (< 7.0)	65	20 (30.8%)	24.7 (15.1 – 38.2)	2.35 (1.55 – 3.57)	0.56 (0.43 – 0.73)
Yes	≥ 53 (≥ 7.0)	54	18 (33.3%)	28.4 (16.8 – 44.9)	2.89 (1.80 – 4.63)	0.51 (0.38 – 0.68)
All		1453 [e]	177 (12.2%)	8.6 (7.4 – 10.0)	-	-
Heinz Nixdorf Recall Study						
No	< 39 (5.7)	3184	104 (3.3%)	2.2 (1.8 – 2.6)	1	1
No	39–41 (5.7–5.9)	554	25 (4.5%)	3.0 (2.0 – 4.5)	1.17 (0.76 – 1.80)	0.91 (0.63 – 1.33)

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No	42–46 (6.0–6.4)	353	18 (5.1%)	3.4 (2.0 – 5.3)	1.14 (0.70 – 1.85)	0.94 (0.61 – 1.45)
No	≥ 48 (≥ 6.5)	174	11 (6.3%)	4.4 (2.2 – 7.8)	1.29 (0.72 – 2.30)	0.78 (0.46 – 1.34)
Yes	< 53 (< 7.0)	197	20 (10.2%)	7.6 (4.7 – 11.8)	1.59 (1.00 – 2.51)	0.60 (0.39 – 0.92)
Yes	≥ 53 (≥ 7.0)	151	19 (12.6%)	9.4 (5.7 – 14.7)	2.18 (1.36 – 3.50)	0.47 (0.30 – 0.74)
All		4613	197 (4.3%)	2.9 (2.5 – 3.3)	-	-

RR: relative risk; CI: confidence interval; AFT: accelerated failure time

[a] For the results of the pooled data, cf. results section
[b] Previously known diabetes includes self-report of physician's diagnosis or intake of glucose-lowering drugs (ATC code A10)
[c] adjusted for age, sex, BMI, smoking, hypertension, physical activity, educational years, total cholesterol, HDL cholesterol
[d] For example, in the KORA Study, for previously known diabetes with Hb1Ac < 53 mmol/mol, exp(beta)=0.82 means: the expected time until cardiovascular death for this category is the expected time until death for the reference category (no previously known diabetes, HbA1c < 39 mmol/mol) multiplied by 0.82
[e] For five individuals, there was no information on cause of death

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Table 4: Adjusted relative risks for overall mortality by HbA1c at baseline and by duration of follow-up: pooled data of the KORA S4 and the Heinz Nixdorf Recall Study

Previously known diabetes [a]	**HbA1c (mmol/mol (%))**	**4 years follow-up RR (95% CI)**	**8 years follow-up RR (95% CI)**	**12 years follow-up RR (95% CI)**	**Total follow-up RR (95% CI)**
		Year 0 – year 4 [c]	Year 0 – year 8 [c]	Year 0 – year 12 [c]	Year 0 – end of follow-up
		178 deaths (2.9%)	487 deaths (8.0%)	867 deaths (14.3%)	1196 deaths (19.7%)
No	< 39 (5.7)	1	1	1	1
No	39–41 (5.7–5.9)	0.83 (0.53 – 1.31)	1.11 (0.87 – 1.41)	1.06 (0.89 – 1.26)	0.98 (0.86 – 1.13)
No	42–46 (6.0–6.4)	0.89 (0.53 – 1.50)	0.95 (0.70 – 1.28)	0.97 (0.79 – 1.19)	0.91 (0.77 – 1.08)
No	≥ 48 (≥ 6.5)	0.73 (0.32 – 1.67)	1.11 (0.74 – 1.67)	1.32 (1.04 – 1.69)	1.23 (1.01 – 1.51)
Yes	< 53 (< 7.0)	1.81 (1.13 – 2.89)	1.71 (1.29 – 2.28)	1.58 (1.30 – 1.92)	1.46 (1.25 – 1.71)
Yes	≥ 53 (≥ 7.0)	1.81 (1.05 – 3.12)	1.89 (1.38 – 2.59)	1.73 (1.38 – 2.16)	1.55 (1.29 – 1.86)

[a] Previously known diabetes includes self-report of physician's diagnosis or intake of glucose-lowering drugs (ATC code A10)

[b] adjusted for age, sex, BMI, smoking, hypertension, physical activity, educational years, total cholesterol, HDL cholesterol, history of cardiovascular diseases, study center

[c] year 0: baseline; year 4: 4 years after baseline etc.

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Figure 1: HbA1c and overall mortality in persons without previously known diabetes

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