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Associations between haemoglobin A_{1c} and mortality rate in the KORA S4 and the Heinz Nixdorf Recall population-based cohort studies

Bernd Kowall[1]† | Wolfgang Rathmann[2,3]† | Oliver Kuß[2,3] | Christian Herder[3,4,5] | Michael Roden[3,4,5] | Andreas Stang[1] | Raimund Erbel[6] | Cornelia Huth[3,7] | Barbara Thorand[3,7] | Christa Meisinger[8,9] | Karl-Heinz Jöckel[6]‡ | Annette Peters[3,7]‡

[1]Center of Clinical Epidemiology, Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University Duisburg-Essen, Essen, Germany

[2]Institute for Biometrics and Epidemiology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University, Düsseldorf, Germany

[3]German Center for Diabetes Research, Düsseldorf, Germany

[4]Institute for Clinical Diabetology, German Diabetes Center, Leibniz Center for Diabetes Research, Heinrich Heine University, Düsseldorf, Germany

[5]Division of Endocrinology and Diabetology, Medical Faculty, Heinrich Heine University, Düsseldorf, Germany

[6]Institute for Medical Informatics, Biometry and Epidemiology, University Clinic Essen, University Duisburg-Essen, Essen, Germany

[7]Institute of Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

[8]Department of Epidemiology, Ludwig-Maximilian-Universität München, UNIKA-T Augsburg, Augsburg, Germany

[9]Independent Research Group Clinical Epidemiology, Helmholtz Zentrum München, German Research Center for Environmental Health, Neuherberg, Germany

Correspondence
Bernd Kowall, Center of Clinical Epidemiology, Institute for Medical Informatics, Biometry and Epidemiology, Medical Faculty, University Duisburg-Essen, Hufelandstraße 55, 45147 Essen, Germany.
Email: bernd.kowall@uk-essen.de

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Abstract

Background: There is limited knowledge about mortality risk in persons with increased haemoglobin A_{1c} (HbA_{1c}) levels below the diabetes threshold. Moreover, little is known about how associations between increased HbA_{1c} and mortality depend on the length of follow-up. Therefore, we studied associations between HbA_{1c} 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 = 1458, baseline visits in 1999 to 2001, baseline age 55 to 74 years, mortality follow-up 16.8 years) and Heinz Nixdorf Recall (HNR) Study (Ruhr area, n = 4613, baseline visits in 2000 to 2003, baseline age 45 to 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 HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and HbA_{1c} 42 to 46 mmol/mol (6.0% to 6.4%) did not have a larger overall mortality

† Shared first authors.

‡ Shared last authors.

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risk than participants with HbA_{1c} < 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 HbA_{1c} 39 to 46 mmol/mol (5.7%-6.4%) was 0.96 (0.85-1.07). Associations between newly detected diabetes (HbA_{1c} ≥ 6.5%) and mortality were weak after 4 and 8 years of follow-up, but were stronger after 12 years of follow-up, whereas associations between previously known diabetes (baseline) and mortality decreased.

Conclusions: HbA_{1c}-defined pre-diabetes is not associated with overall mortality. For newly detected and previously known diabetes, mortality risks vary with length of follow-up.

KEYWORDS

epidemiology, HbA_{1c}, mortality, pre-diabetes, type-2 diabetes

1 | INTRODUCTION

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

Studies on the association between HbA_{1c} and all-cause mortality have often focussed on persons with diabetes, and a J-shaped pattern was observed with slight increases of mortality risk for very low HbA_{1c} values.[4] In the present study, we also took non-diabetic persons into account, and we studied associations between HbA_{1c} and mortality using the novel cut-offs for HbA_{1c}-defined diabetes and pre-diabetes. We mainly addressed two research questions.

First, the mortality risk of persons with intermediate hyperglycaemia has extensively been studied for glucose-based pre-diabetes, but less for increased HbA_{1c} without diabetes. In a recently published meta-analysis on the association between pre-diabetes 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 HbA_{1c} 39 to 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 HbA_{1c} 42 to 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 and high diabetes risk. More recently, in two studies, the mortality risk for HbA_{1c} 42 to 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 HbA_{1c} and mortality, and little is known about the impact of length of follow-up on the associations between HbA_{1c} 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 HbA_{1c} 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 HbA_{1c} mortality associations.

2 | METHODS

2.1 | Study participants

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 to 2001, and mortality was followed up to 16.8 years. From 1653 KORA participants, persons with diabetes other than type 2 diabetes, unclear diabetes diagnosis or missing covariates were excluded leaving a sample of 1458 participants (51.9% men, aged 55-74 years).

The HNR Study is a population-based prospective cohort study in the Ruhr area in Western Germany. Baseline visits took place in 2000 to 2003, and mortality was followed up to 17.8 years. From 4814 HNR Study participants, persons with diabetes other than type 2 diabetes, or missing values for covariates were excluded leaving 4613 participants (49.5% men, aged 45-75 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.

2.2 | Variables

In both studies, for measurement of HbA_{1c}, immune turbidimetric assays were used: Tina-quant, Roche Diagnostics, Germany; Hitachi 717 Analyser 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 HbA_{1c} categories were used: previously known diabetes with HbA_{1c} ≥ 53 mmol/mol (7.0%) and HbA_{1c} <53 mmol/mol; no previously known diabetes with HbA_{1c} ≥ 48 mmol/mol (6.5%), HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%), HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and HbA_{1c} <39 mmol/mol (5.7%) (reference).

For further details on assessment of covariates, diabetes and prediabetes, see References 9 and 10.

2.3 | 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 RRs with 95% CIs adjusted for age, sex, body mass index, smoking, hypertension, physical activity, educational years, total cholesterol, high-density lipoprotein 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 pre-diabetes categories is the expected time until death for people with HbA_{1c} <5.7% multiplied by e^{β} (β = regression coefficient). For the pooled dataset, 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 4, 8 and 12 years of the follow-up period.

In an additional analysis on the association between HbA_{1c} levels and all-cause mortality, we only included study participants without previously known diabetes (N = 5604, pooled data set), and we used subcategories for HbA_{1c} < 5.7%. The following categories were used: ≤4.6%, 4.7% to 4.8%, 4.9% to 5.1%, 5.2% to 5.4%, 5.5% to 5.7%, 5.8% to 6.0%, 6.1% to 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.

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 HbA_{1c} and overall mortality.

Analyses were performed with SAS (version 9.4; SAS Institute, Cary, North Carolina).

3 | RESULTS

Overall, KORA participants were about 5 years older than HNR Study participants and had higher values of HbA_{1c} at baseline (Table 1). Of 1458 participants of the KORA S4 Study, 566 (38.8%) had HbA_{1c} values in the range of 39 to 46 mmol/mol (5.7%-6.4%) at baseline.

TABLE 1 Baseline characteristics of the study groups: the HNR and the KORA S4 Studies

		HNR Study	KORA
N		4613	1458
Age (y)		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
HbA_{1c} (mmol/mol)		37 ± 9	40 ± 9
HbA_{1c} (%)		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 (y)		15.0 ± 3.4	14.1 ± 3.6

Note: Values are expressed as mean ± SD, median (first quartile, third quartile) or proportion (%).

Abbreviations: BMI, body mass index; HDL, high-density lipoprotein; HNR, Heinz-Nixdorf Recall; $HbA_{1c,}$ haemoglobin A_{1c}; ISCED, International Standard Classification for Education.

Among 4613 participants of the HNR Study, 907 (19.7%) had HbA_{1c} values in this range. Newly detected or previously known diabetes was found in 162 (11.1%) KORA participants and 522 (11.3%) HNR Study population.

KORA participants displayed a higher mortality rate than the HNR Study population (20.7 vs 11.2 per 1000 person-years). However, the mortality rate of the latter increased to 18.9 per 1000 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 HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%) did not have a larger overall mortality risk than participants with HbA_{1c} <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 (Table 2). There were only small differences in progression to death in persons with HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%) compared with HA1c <39 mmol/mol (5.7%; AFT models; Table 2). In participants with newly detected, HbA_{1c}-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 HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and 1.09 (0.71-1.65) for HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%) in KORA, and the corresponding RRs were

TABLE 2 Mortality rates and adjusted relative risks for overall mortality by HbA_{1c} at baseline: the KORA S4 and the Heinz Nixdorf Recall Study

Previously known diabetes[a]	HbA_{1c} [mmol/mol (%)]	N	Deaths n (%)	Mortality rate per 1000 person years (95% CI)	RR (95% CI)[b,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)	…	…

Abbreviations: AFT, accelerated failure time; CI, confidence interval; $HbA_{1c,}$ haemoglobin A_{1c}; RR, relative risk.

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

[b]For results of the pooled data, compare with Table 4 (right column).

[c]Adjusted for age, sex, body mass index, smoking, hypertension, physical activity, educational years, total cholesterol, high-density lipoprotein cholesterol and 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, HbA_{1c} < 39 mmol/mol) multiplied by 0.67.

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 HbA_{1c} 5.7% to 5.9%, 6.0% to 6.4%, ≥6.5%, known diabetes with HbA_{1c} < 7.0%, and for known diabetes with HbA_{1c} ≥ 7.0% (reference HbA_{1c} < 5.7%).

When both datasets were pooled, the following RRs were obtained for people without previously known diabetes: 0.98 (0.86-1.13) for HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%); 0.91 (0.77-1.08) for HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%); 1.23 (1.01-1.51) for Hb1c ≥48 mmol/L (6.5%; Table 4). For HbA_{1c} 39 to 46 mmol/mol (5.7%-6.4%), the RR was 0.96 (0.85-1.07). When HbA_{1c} <39 mmol/mol (5.7%) was split into HbA_{1c} <31 mmol/mol (5.0%) and HbA_{1c} 31 to 38 mmol/mol (5.0%-5.6%) with the latter subcategory as reference, RRs were 0.98 (0.86-1.13) for HbA_{1c} 39 to 41 mmol/mol (5.7%-5.9%) and 0.91 (0.76-1.08) for HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%).

For the pooled dataset, results of a proportional hazards Cox regression agreed with the results of the Poisson and of the AFT model for the association between HbA_{1c} 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 HbA_{1c} 5.7% to 5.9%, 6.0% to 6.4%, ≥6.5%, known diabetes with HbA_{1c} < 7.0%, and for known diabetes with HbA_{1c} ≥ 7.0% respectively (reference HbA_{1c} < 5.7%).

When the data were right-censored after 4, 8 and 12 years of follow-up, two trends were observed (Table 4): first, associations between diabetes newly detected at baseline and mortality were weak after 4 and 8 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 HbA_{1c} 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 HbA_{1c} 4.9%-5.1%] (cf. Figure 1).

Using multiple imputation with fully conditional specification, results for the association between HbA_{1c} and overall mortality changed slightly: For the Recall Cohort, RRs for HbA_{1c} 5.7% to 5.9%, 6.0% to 6.4%, ≥ 6.5%, known diabetes with HbA_{1c} < 7.0%, and for known diabetes with HbA_{1c} ≥ 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 RRs 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).

4 | DISCUSSION

This study found that increased HbA_{1c} values 39 to 41 mmol/mol (5.7%-5.9%) and HbA_{1c} 42 to 46 mmol/mol (6.0%-6.4%) in people without diabetes were barely associated with overall mortality in two

TABLE 3 Rates of cardiovascular mortality and adjusted relative risks for cardiovascular mortality by HbA_{1c} at baseline: the KORA S4 and the Heinz Nixdorf Recall Study

Previously known diabetes[a]	HbA_{1c} (mmol/mol (%))	N	Deaths n (%)	Mortality rate per 1000 person years (95% CI)	RR (95% CI)[b]	Exp(beta) from AFT model (95% CI)[b,c]
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[d]	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)
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)	…	…

Note: For the results of the pooled data, see Section 3.

Abbreviations: AFT, accelerated failure time; CI, confidence interval; $HbA_{1c,}$ haemoglobin A_{1c}; RR, relative risk.

[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, body mass index, smoking, hypertension, physical activity, educational years, total cholesterol, high-density lipoprotein cholesterol.

[c]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

[d]For five individuals, there was no information on cause of death.

population-based cohort studies with long follow-up periods. Moreover, our study gives evidence that associations between HbA_{1c} and mortality vary over long follow-up periods: in persons with diabetes newly detected at baseline, the mortality risk increased over follow-up, whereas it slightly decreased in persons with diabetes previously known at baseline. Furthermore, our study confirms earlier results showing increased all-cause mortality in persons without diabetes with very low HbA_{1c} values.[4] In the pooled data set, there was an indication that cardiovascular mortality was slightly increased in persons with HbA_{1c} 42-46 mmol/mol (6.0%-6.4%); however, this effect estimate was rather imprecise.

So far, results from the few studies on HbA_{1c} in the pre-diabetes range and overall mortality were inconsistent. In a large cohort study using Health Survey for England data, HbA_{1c} 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 HbA_{1c} 39 to 46 mmol/mol (5.7%-6.4%) was compared with HbA_{1c} < 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 HbA_{1c} in the pre-diabetic 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 HbA_{1c} <31 mmol/mol.[13] However, the choice of the reference category does not explain our results: when we split HbA_{1c} <39 mmol/mol (5.7%) and used HbA_{1c} 31 to 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 HbA_{1c}-based criteria have been proposed to be equally suitable to select high-risk individuals for diabetes prevention.[2] Moreover, combining glucose-based criteria with HbA_{1c} 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 of a prevention programme. With respect to mortality, using HbA_{1c} criteria alone may miss high-risk individuals who should receive preventive interventions. In various other studies, pre-diabetes 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 programmes.[15]

To our knowledge, the influence of length of follow-up on the association between HbA_{1c} and mortality has not been considered in earlier studies. In the present study, the RR 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,

TABLE 4 Adjusted relative risks for overall mortality by HbA_{1c} at baseline and by duration of follow-up: pooled data of the KORA S4 and the Heinz Nixdorf Recall Study

Previously known diabetes[a]	HbA_{1c} [mmol/mol (%)]	Four years follow-up RR (95% CI)	Eight years follow-up RR (95% CI)	Twelve years follow-up RR (95% CI)	Total follow-up RR (95% CI)
		Year 0 to year 4[b,c]	Year 0 to year 8[b,c]	Year 0 to year 12[b,c]	Year 0 to end of follow-up[b,c]
		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)

Abbreviations: AFT, accelerated failure time; CI, confidence interval; HbA_{1c}, haemoglobin A_{1c}; RR, relative risk.

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

[b]Year 0: baseline; year 4: 4 y after baseline and so forth.

[c]Adjusted for age, sex, body mass index, smoking, hypertension, physical activity, educational years, total cholesterol, high-density lipoprotein cholesterol, history of cardiovascular diseases and study centre.

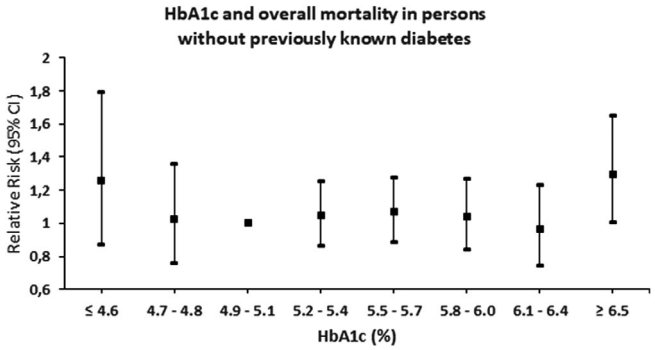

FIGURE 1 HbA_{1c} and overall mortality in persons without previously known diabetes. HbA_{1c}, haemoglobin A_{1c}

for example, 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 RRs 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, for example, 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 HbA_{1c} in the two cohort studies. However, both assays were traceable to the NGSP (National Glucose Standardization 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-Caucasians. Fourth, despite adjustment for multiple confounders we cannot exclude residual confounding.

To conclude, HbA_{1c} 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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CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

AUTHOR CONTRIBUTIONS

B.K. and W.R. conceived and designed the study. B.K. analysed the data. B.K. and W.R. wrote the manuscript. A.S., R.E. and K.H.J. contributed to conception and design of the HNR Study. B.T., C.M. and A.P. 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.

DATA ACCESSIBILITY

Due to data security reasons (ie, 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.

ORCID

Bernd Kowall https://orcid.org/0000-0003-4163-1696
Christian Herder https://orcid.org/0000-0002-2050-093X
Barbara Thorand https://orcid.org/0000-0002-8416-6440

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