Eur J Epidemiol (2011) 26:637–645
DOI 10.1007/s10654-011-9609-y

DIABETES MELLITUS

# Categories of glucose tolerance and continuous glycemic measures and mortality

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Received: 6 April 2011 / Accepted: 13 July 2011 / Published online: 23 July 2011


**Abstract** We investigated the association of undiagnosed diabetes, previously known diabetes and prediabetes (WHO 1999 classification) with all-cause and cause-specific mortality in an older German population. Previous study results for mortality in patients with very low levels of HbA1c, fasting plasma glucose (FPG), and 2-h plasma glucose (2hPG) are still inconclusive. Thus we have extended the analyses to continuous measures of glycemia. A total of 1,466 subjects aged 55–74 years from the population-based KORA survey S4 (conducted from 1999 to 2001) were included in our observational mortality study (152 subjects with previously known diabetes, and 1,314 further subjects who underwent oral glucose tolerance tests). Mortality was followed up for a maximum of 10.0 years (median follow-up 8.8 years). A total of 180 (12.3%) of the 1,466 subjects have died during the follow-up period. The age- and sex-adjusted hazard ratios for all-cause mortality were 2.6 (95%CI, 1.7–3.8) for known diabetes, 2.8 (95%CI, 1.7–4.4) for undiagnosed diabetes, and 1.1 (95%CI, 0.8–1.7) for prediabetes [reference: normal glucose tolerance (NGT)]. After multivariable adjustment, undiagnosed diabetes was associated with 3.0-fold increased cancer mortality, 1.1-fold increased cardiovascular mortality, and 4.7-fold increased non-cancer, non-cardiovascular mortality compared with NGT. For HbA1c, FPG, and 2hPG, J-shaped associations with all-cause mortality were observed. Undiagnosed diabetes is associated with increased all-cause, cancer, and non-cancer non-cardiovascular mortality, but not with cardiovascular mortality in this older population. All-cause mortality in undiagnosed diabetes is similar to that in previously known diabetes but much higher than mortality in prediabetes and NGT.

**Keywords** Type 2 diabetes · All-cause mortality · Cancer mortality · Cardiovascular mortality

**Abbreviations**

| | |
|---|---|
| BMI | Body mass index |
| CI | Confidence interval |
| CVD | Cardiovascular disease |
| DECODE | Diabetes epidemiology: collaborative analysis of diagnostic criteria in Europe |
| FPG | Fasting plasma glucose |
| HDL | High-density lipoprotein |
| HOMA-IR | Homeostatic model assessment of insulin resistance |
| HR | Hazard ratio |
| ICD | International classification of diseases |
| IDI | Integrated discrimination improvement |
| IFG | Impaired fasting glucose |
| IGT | Impaired glucose tolerance |
| KORA | Cooperative health research in the region of Augsburg |

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|---|---|
| NGT | Normal glucose tolerance |
| NHANES | National Health and Nutrition Examination Survey |
| NRI | Net reclassification improvement |
| OGTT | Oral glucose tolerance test |
| PY | Person-year |
| 2hPG | 2-h plasma glucose |
| WHO | World Health Organization |

## Introduction

Diabetes is associated with premature death, and this has recently been confirmed in the analysis of data from 97 prospective studies with 820,900 participants [1]. However, mortality in undiagnosed diabetes has been investigated less often than that in diagnosed diabetes, although a high proportion of individuals with type 2 diabetes is not aware of its diabetes status. According to the results of the DECODE study in 13 European cohorts, the proportions of undiagnosed diabetes range from 39 to 70% depending on sex and age [2]. Among the older participants of the German KORA S4 study, the proportion of undiagnosed diabetes also turned out to be high [3]. In some studies, similar all-cause mortality risks were found in subjects with known and previously undiagnosed diabetes [4–6]. However, in an older study with DECODE data, results depended on glucose classification [7], and in another study with NHANES II (US) data, lower risks for all-cause and cardiovascular mortality were seen in undiagnosed diabetes compared with diagnosed diabetes [8].

Larger all-cause mortality in diabetes is not only due to larger cardiovascular mortality but also to larger cancer mortality. Subjects with diabetes have an increased risk of some cancers [9, 10], and moreover, in some, but not all studies subjects with cancer and preexisting diabetes had a larger mortality risk than subjects with cancer but without preexisting diabetes [9, 11]. Undiagnosed diabetes was related to cancer mortality in the DECODE study [12], but not in the population-based NHANES II survey [13].

Finally, previous findings about the relationship between continuous glucose values and mortality are inconclusive. A variety of results have been previously reported, ranging from associations with glycemic thresholds to linear and J-shaped associations [14–24]. Moreover, results differed depending on the measures of glycemia.

Thus, the aim of the present study was to investigate the association between glucose regulation and all-cause, cardiovascular and cancer mortality as well as non-cardiovascular non-cancer mortality in an older population in Germany.

First, the mortality risk of subjects with previously undiagnosed diabetes was compared with the risk of subjects with previously known diabetes, prediabetes or NGT.

Second, the groups of normal glucose regulation and prediabetes were further split to detect categories that are associated with an increased mortality risk. Since different measures of glycemia such as HbA1c, fasting plasma glucose (FPG), and 2-h blood glucose (2hPG) reflect different metabolic processes, all three measures were included in the analyses.

## Methods

### Study population

The population-based KORA (Cooperative Health Research in the Region of Augsburg) S4 Survey was conducted in Southern Germany in the same region and using the same methods as the previous WHO MONICA Augsburg project. The study design, sampling method and data collection have been described in detail elsewhere [2]. The study had been approved by the Ethics Committee of the Bavarian Physician Chamber.

In the population-based KORA survey S4, conducted from 1999 to 2001, 2,656 participants aged 55–74 years were invited for baseline investigations. Overall, 1,653 (62%) subjects participated. Due to 187 dropouts [mainly subjects who were unable to come to the study center in the morning (n = 168)], 1,466 subjects remained for the present analyses. Of these, 152 had known diabetes at baseline, and the remaining 1,314 participants underwent the fasting oral glucose tolerance test (OGTT).

### Ascertainment of diabetes at baseline

Previously known diabetes was defined based on self-reported physician diagnosis, validated by a general practitioner, or use of antidiabetic agents. Newly diagnosed diabetes (≥7.0 mmol/l fasting or ≥11.1 mmol/l 2-h post glucose load), impaired glucose tolerance (IGT), impaired fasting glucose (IFG), and normal glucose tolerance (NGT) were defined according to the 1999 WHO diagnostic criteria based on both fasting and post-challenge glucose values [25]. Prediabetes includes IFG or IGT or both.

Oral glucose tolerance tests (OGTT) were performed in the morning hours (7:00 to 11:00 a.m.). Subjects were instructed to fast for 10 h overnight, to avoid heavy physical activity and not to smoke before or during the OGTT. Exclusion criteria for the OGTT were: (1) use of antidiabetic medication or known diabetes, confirmed by the patient's general practitioner; (2) acute illness (infection, fever, acute gastrointestinal disease); (3) start of the

OGTT later than 11:00 a.m. Fasting venous blood glucose was sampled and 75 g of anhydrous glucose was given (Dextro OGT, Boehringer Mannheim, Germany). The post-load glucose was measured after 2 h.

### Mortality follow-up

Between November 2008 and November 2009, vital status was assessed for all our study subjects of the KORA S4 survey (n = 1,466) by reviewing the municipal population registries inside and outside of the study area. Death certificates with the exact dates of death were obtained from the local health departments and coded for the underlying causes of death by a single trained person, using the 9th revision of the International Classification of Diseases (ICD-9). Cardiovascular diseases were coded according to ICD-9 codes 390–459 including myocardial infarction and stroke, cancer was coded according to ICD-9 codes 140–208. Until November 2009, nine subjects were censored because their vital status could not be assessed: they had either moved to a foreign country or an unknown location, or had requested deletion of their home address data.

### Physical examinations and interviews

Height, weight, waist circumference, systolic and diastolic blood pressure had been measured on the basis of standard protocols as described elsewhere [3]. Medical interviewers had gathered information on medical history, physical activity, alcohol consumption, smoking status, and parental history of diabetes. Subjects with newly diagnosed diabetes in KORA S4 were asked 7 years after initial OGTT results obtained at baseline whether they had shared these results with their general practitioners, whether diabetes diagnosis had been confirmed and if and when they had started antidiabetic treatment.

### Laboratory measurements

Blood was collected without stasis. All blood parameters except for 2hPG were based on fasting blood samples. After blood withdrawal, the blood samples were centrifuged and kept cool (4°C) until analyzing plasma glucose in the central laboratory, which took place within a maximum of 6 h after withdrawal. Plasma glucose, HbA1c, total and HDL-cholesterol, and triglycerides were determined as described elsewhere [3]. Fasting insulin was determined using a microparticle enzyme immunoassay (Abbott Laboratories, Germany).

### *Definition of covariables*

The covariables were categorized as follows: smoking status: current smoker, former smoker, and non-smoker; high alcohol intake: >40 g/day in men, >20 g/day in women; physical activity: participants with less than 1 h of physical activity per week during leisure time in summer or in winter were classified as inactive; actual hypertension: blood pressure of 140/90 mmHg or higher, or use of antihypertensive medication given that the subjects were aware of being hypertensive; low HDL-cholesterol: <40 mg/dl in males, <50 mg/dl in women.

### Statistical analyses

Baseline characteristics were compared between subjects with NGT, prediabetes, previously undiagnosed type 2 diabetes, and previously known type 2 diabetes by using the *F*-test if variables were normally distributed. For log-normal variables, the *F*-tests were performed on a log-scale. Logistic regression models were used to compare binomial proportions. All comparisons were adjusted for age and sex.

The duration of the follow-up was estimated from the date of baseline to the date of death or the date of the last information about the vital status. Crude mortality rates and corresponding 95% confidence intervals (CI) were calculated per 1,000 person-years. Mortality rates were additionally adjusted for age and sex by using the distribution of age and sex in the subjects with NGT as the reference.

### *Categories of glucose regulation and mortality*

For the categories of glucose regulation (NGT as the reference, prediabetes, undiagnosed type 2 diabetes, previously known diabetes), Cox proportional hazards models were fitted to calculate the hazard ratios (HR) for all-cause mortality with adjustment for age and sex in a basic model, and with adjustment for further covariables in an extended model (BMI, HDL cholesterol, blood pressure, parental diabetes, smoking status, alcohol consumption, physical activity, and former myocardial infarction or stroke). Regression analyses were also carried out to calculate the HRs for cardiovascular disease and cancer mortality as well as for non-cardiovascular non-cancer mortality. For cancer mortality, additional Cox regression models were fitted, excluding subjects who had died of cancer during the first 3 years after the baseline investigation.

*Continuous glycemic measures and mortality*

Further Cox regression models with adjustment for the same covariables as mentioned above were fitted, but excluding subjects with previously known diabetes. The HRs for all-cause mortality were calculated for the categories of HbA1c, fasting plasma glucose (FPG) or 2 h blood glucose (2hPG). These categories were defined according to the 10th, 25th, 50th, 75th, and 90th percentiles, and the categories with the lowest mortality rates were used as reference groups. In additional analyses, both subjects with known and undiagnosed diabetes were excluded.

Meeting the proportional hazard assumption was verified by including time-dependent covariables (interaction terms of the independent variable and survival time).

The added value of categories of diabetes for prediction of all-cause mortality was assessed by calculating c statistics and reclassification measures [net reclassification improvement (NRI) and integrated discrimination improvement (IDI)].

The level of statistical significance was 5%. All analyses were performed using the SAS version 9.2 (SAS institute, Cary, NC, USA).

## Results

### Study population characteristics

Baseline characteristics of the study population stratified by categories of glucose regulation are shown in Table 1. As expected, the subjects in the NGT group were younger, were mostly women, and had a better metabolic profile than subjects with prediabetes or diabetes. In the prediabetes group, the anthropometric measures, lipid levels, systolic blood pressure, and glucose levels were less favorable than in the NGT group but more favorable than in subjects with previously undiagnosed or diagnosed diabetes. Subjects with undiagnosed diabetes had a more favorable BMI, waist circumference, HbA1c, and HDL cholesterol and thus a better risk profile than subjects with

**Table 1** Baseline characteristics stratified by categories of glucose regulation: the KORA S4 study

| | NGT | Prediabetes | Undiagnosed diabetes | Previously known diabetes | *P* value |
|---|---|---|---|---|---|
| N | 875 | 348 | 91 | 152 | |
| Age | 63.4 ± 5.6 | 65.0 ± 5.3 | 65.8 ± 5.4 | 65.0 ± 4.8 | <0.001**,# |
| Sex (% male) | 47.5 | 58.6 | 59.3 | 55.3 | 0.002**,### |
| BMI | 27.7 ± 4,1 | 29.5 ± 4,0 | 30.2 ± 3,9 | 31.8 ± 5,0 | <0.001**,# |
| Waist circumference | 93.2 ± 11,2 | 99.2 ± 10,3 | 102.3 ± 10,8 | 104.6 ± 11,8 | <0.001**,# |
| HDL cholesterol (mmol/l) | 1.56 ± 0.42 | 1.44 ± 0.39 | 1.34 ± 0.41 | 1.24 ± 0.32 | <0.001**,# |
| Triglycerides (mmol/l) | 1.21 (0.89,1.66) | 1.42 (1.04,2.03) | 1.62 (1.22,2.15) | 2.35[a] (1.54,3.25) | <0.001**,## |
| Systolic blood pressure (mmHg) | 131.7 ± 19.0 | 140.3 ± 19.1 | 146.8 ± 21.5 | 145.5 ± 21.6 | <0.001**,# |
| Diastolic blood pressure (mmHg) | 78.9 ± 10.1 | 81.9 ± 10.5 | 81.6 ± 10.6 | 83.2 ± 12.1 | <0.001**,# |
| Fasting plasma glucose (mmol/l) | 5.30 ± 0.39 | 5.96 ± 0.53 | 7.40 ± 1.76 | – | <0.001**,# |
| 2 h plasma glucose (mmol/l) | 5.66 ± 1.16 | 8.18 ± 1.68 | 12.89 ± 3.54 | – | <0.001**,# |
| HbA1c (%) | 5.6 ± 0.3 | 5.6 ± 0.4 | 6.2 ± 0.8 | 7.1 ± 1.4 | <0.001**,# |
| HOMA-IR | 2.1 (1.5, 3.0) | 3.3 (2.3, 4.9) | 4.7 (2.8, 7.6) | – | <0.001**,## |
| Active smokers (%) | 14.8 | 10.6 | 23.1 | 11.8 | 0.008**,### |
| Former smokers (%) | 35.6 | 39.7 | 44.0 | 42.1 | 0.76### |
| Physically active (%) | 47.0 | 38.0 | 36.3 | 28.5 | <0.001**,### |
| High consumption of alcohol (%)[b] | 19.9 | 21.9 | 24.2 | 12.6 | 0.08### |
| Former myocardial infarction or stroke (%) | 5.1 | 8.1 | 11.0 | 13.2 | 0.02*,### |
| Parental diabetes (%) | 20.9 | 24.4 | 31.9 | 34.9 | <0.001**,### |

Mean ± standard deviation, median (first quartile, third quartile), or proportion

* $P < 0.05$; ** $P < 0.01$

# *F*-Test; ## log *F*-Test; ### logistic regression. All analyses adjusted for age and sex

[a] Subjects with known diabetes had not been asked to fast overnight

[b] High alcohol intake: >40 g/day in men, >20 g/day in women

previously known diabetes. However, the proportions of active and former smokers and of subjects with high alcohol consumption were highest in subjects with undiagnosed diabetes. Finally, the level of physical activity was highest in the NGT group and lowest in the group with known diabetes.

Seven years after obtaining OGTT results at the baseline investigation of KORA, 30 of 47 subjects (64%) with newly diagnosed diabetes had reported being retested for diabetes, and 25 of these 30 stated that the diabetes diagnosis had been confirmed by their general practitioners. Furthermore, 20 of these 25 subjects have been receiving antidiabetic treatment during the follow-up period.

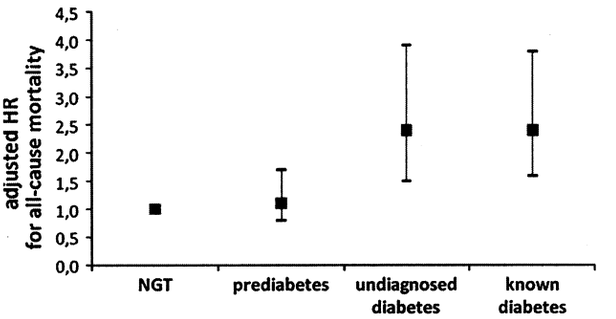


**Fig. 1** Multivariable adjusted hazard ratios (HR, 95%CI) for all-cause mortality by baseline categories of glucose regulation

## Mortality by glucose tolerance categories

During the 10-year follow-up period, 180 (12.3%) of our 1,466 study subjects have died. For the whole study group, the crude rate for all-cause mortality was 14.6 (95%CI, 12.5–16.9) per 1,000 person-years. The age- and sex-adjusted mortality rates were almost equal in the NGT and prediabetes groups and strongly increased in subjects with previously undiagnosed or known diabetes at baseline (Table 2). In the age-sex-adjusted model, the all-cause mortality risk was similar in undiagnosed and diagnosed diabetes. After multivariable adjustment, the HRs for these two groups were nearly identical, indicating that the risk of all-cause mortality was 2.4-fold larger in the subjects with both diagnosed and undiagnosed diabetes at baseline than in subjects with NGT at baseline (Fig. 1).

The different categories of diabetes had a significant additional value for predicting all-cause mortality beyond the common risk factors: When comparing the logistic regression model which included all the variables used for multivariable adjustment with the logistic regression model which additionally included different categories of diabetes status, the c-values increased from 0.720 to 0.749 ($P = 0.01$); furthermore, NRI was 0.149 ($P < 0.01$) and IDI was 0.020 ($P < 0.01$).

A total of 75 subjects have died of cardiovascular disease and 71 have died of cancer. In age- and sex-adjusted models, cancer mortality was significantly increased in subjects with both undiagnosed and previously known diabetes, whereas cardiovascular mortality was significantly increased only in subjects with known diabetes (Table 3). Multivariable adjustment attenuated these associations, but risk of cancer mortality was still significantly increased in the subjects with undiagnosed diabetes, and risk of cardiovascular mortality was still increased in those with known diabetes. The risk of non-cardiovascular non-cancer mortality was significantly increased in both groups of undiagnosed and previously known diabetes.

**Table 2** Rates of all-cause mortality (crude and age-sex adjusted) and adjusted HRs (95%CI) for all-cause mortality according to categories of glucose regulation (WHO 1999 classification)

| | NGT | Prediabetes | Undiagnosed diabetes | Previously known diabetes |
|---|---|---|---|---|
| N | 875 | 348 | 91 | 152 |
| Deaths (n) | 79 | 39 | 25 | 37 |
| Crude mortality rate per 1,000 PY | 10.51 (8.32–13.10) | 13.31 (9.47–18.19) | 35.42 (22.92–52.29) | 30.74 (21.64–42.37) |
| Age and sex adjusted mortality rate[a] per 1,000 PY | 10.51 (8.32–13.10) | 10.52 (7.67–14.42) | 33.05 (21.88–49.91) | 28.78 (20.62–40.16) |
| HR[b,d] | 1 | 1.1 (0.8–1.7) | 2.8 (1.7–4.4) | 2.6 (1.7–3.8) |
| HR[c,d] | 1 | 1.1 (0.8–1.7) | 2.4 (1.5–3.9) | 2.4 (1.6–3.8) |

*HR* hazard ratio, *CI* confidence interval, *NGT* normal glucose tolerance, *PY* person-year

[a] Adjusted for age and sex by using the age and sex distribution of NGT subjects as reference

[b] Adjusted for age and sex

[c] Adjusted for age, sex, BMI, HDL cholesterol, blood pressure, parental diabetes, smoking, alcohol consumption, physical activity, former myocardial infarction or stroke

[d] Only subjects with complete data for age, sex, BMI, HDL cholesterol, blood pressure, parental diabetes, smoking, alcohol consumption, physical activity, former myocardial infarction or stroke (n = 1,447)

**Table 3** Adjusted HRs (95%CI) for cancer mortality, cardiovascular mortality, and non-cancer, non-cardiovascular mortality according to categories of glucose regulation (WHO 1999 classification)

| | NGT | Prediabetes | Undiagnosed diabetes | Previously known diabetes |
|---|---|---|---|---|
| N | 874 | 347 | 90 | 152 |
| Cancer deaths (n) | 33 | 13 | 13 | 12 |
| HR[a,c] | 1 | 0.9 (0.5–1.8) | 3.7 (1.9–7.1) | 2.2 (1.1–4.3) |
| HR[b,c] | 1 | 0.9 (0.5–1.8) | 3.0 (1.5–6.1) | 1.9 (0.9–4.0) |
| CVD deaths (n) | 33 | 18 | 6 | 18 |
| HR[a,c] | 1 | 1.2 (0.7–2.1) | 1.5 (0.6–3.5) | 2.8 (1.5–5.1) |
| HR[b,c] | 1 | 1.1 (0.6–2.0) | 1.1 (0.4–2.8) | 2.3 (1.2–4.5) |
| Non-cancer non-CVD deaths | 12 | 7 | 5 | 7 |
| HR[a,c] | 1 | 1.4 (0.5–3.6) | 3.7 (1.3–10.9) | 3.1 (1.2–8.5) |
| HR[b,c] | 1 | 1.6 (0.6–4.3) | 4.7 (1.5–14.9) | 4.2 (1.4–12.6) |

*HR* hazard ratio, *CI* confidence interval, *NGT* normal glucose tolerance, *CVD* cardiovascular disease

[a] Adjusted for age and sex

[b] Adjusted for age, sex, BMI, HDL cholesterol, blood pressure, parental diabetes, smoking, alcohol consumption, physical activity, former myocardial infarction or stroke

[c] Only subjects with complete data for age, sex, BMI, HDL cholesterol, blood pressure, parental diabetes, smoking, alcohol consumption, physical activity, former myocardial infarction or stroke (n = 1,444, in three cases of death, the underlying causes of death could not be determined)

To analyze the risk of cancer mortality, Cox regression models were fitted again excluding subjects who had died of cancer in the first 3 years after the baseline investigation (data not shown in the table). For subjects with newly diagnosed diabetes, HRs were attenuated in the age- and sex-adjusted model (HR: 3.2, 95%CI, 1.4–7.2) and in the multivariable-adjusted model (HR: 2.3, 95%CI, 0.96–5.4).

## Glycemic measures and mortality

All three measures of glycemia (HbA1c, FPG, and 2hPG) showed a J-shaped association with all-cause mortality in the study subjects excluding those with known diabetes (Table 4). Multivariable adjusted HRs for all-cause mortality by categories of HbA1c are shown in Fig. 2.

When the age- and sex-adjusted analyses (Table 4) were replicated, excluding the subjects with previously undiagnosed diabetes [FPG and 2hPG in the diabetes range (≥126 mg/dl and ≥200 mg/dl, respectively)], the subjects with FPG in the upper prediabetes range still had a larger mortality risk than the subjects in the next category. For FPG ≥116 mg/dl and FPG ≥107, <116 mg/dl, hazard

**Table 4** Rates of crude all-cause mortality and adjusted HRs (95%CI) for all-cause mortality according to the different categories of the HbA1c, FPG, and 2-h glucose

| Categories of glycemic measures[a] | Crude mortality rate per 1,000 PY | HR[b] | HR[c] |
|---|---|---|---|
| HbA1c | | | |
| <5.2% | 16.34 (9.52–26.16) | 2.0 (1.04–3.9) | 1.8 (0.9–3.6) |
| 5.2/5.3% | 9.75 (5.33–16.36) | 1.2 (0.6–2.5) | 1.1 (0.5–2.2) |
| 5.4/5.5% | 7.87 (4.67–12.45) | 1 | 1 |
| 5.6/5.7% | 12.46 (8.63–17.41) | 1.4 (0.8–2.4) | 1.3 (0.7–2.4) |
| 5.8–6.0% | 13.85 (9.53–19.45) | 1.7 (0.96–3.0) | 1.6 (0.9–2.8) |
| ≥6.1% | 21.39 (14.10–31.12) | 2.5 (1.4–4.5) | 2.0 (1.1–3.8) |
| FPG | | | |
| <88 mg/dl | 9.25 (4.23–17.56) | 1.9 (0.8–4.6) | 1.8 (0.7–4.6) |
| ≥88, <93 | 5.43 (2.60–9.99) | 1 | 1 |
| ≥93, <99 | 13.81 (9.73–19.04) | 2.5 (1.2–4.9) | 2.4 (1.2–4.9) |
| ≥99, <107 | 12.79 (8.91–17.78) | 2.2 (1.1–4.5) | 2.3 (1.1–4.8) |
| ≥107, <116 | 14.41 (9.41–21.10) | 2.4 (1.1–4.9) | 2.4 (1.2–5.1) |
| ≥116 | 23.22 (15.17–34.02) | 3.6 (1.7–7.5) | 3.1 (1.4–6.6) |
| 2hPG | | | |
| <79 mg/dl | 11.19 (5.78–19.55) | 1.8 (0.8–4.2) | 2.0 (0.9–4.9) |
| ≥79, <94 | 5.64 (2.71–10.38) | 1 | 1 |
| ≥94, <114 | 12.54 (8.64–17.62) | 2.0 (0.99–4.1) | 2.3 (1.1–4.9) |
| ≥114, <140 | 12.20 (8.55–16.89) | 1.9 (0.9–3.8) | 1.9 (0.9–4.0) |
| ≥140, <177 | 11.53 (6.94–18.00) | 1.6 (0.7–3.5) | 1.8 (0.8–4.0) |
| ≥177 | 30.80 (21.20–43.25) | 3.8 (1.9–7.9) | 3.9 (1.8–8.3) |

Inclusion of subjects with NGT, prediabetes, or newly diagnosed diabetes only, exclusion of subjects with known diabetes

*HR* hazard ratio, *CI* confidence interval, *PY* person-year, *FPG* fasting plasma glucose, *2hPG* 2-h plasma glucose

[a] For each of the glycaemic measures, six categories were built according to the 10th, the 25th, the 50th, the 75th, and the 90th percentile

[b] Adjusted for age and sex

[c] Adjusted for age, sex, BMI, HDL cholesterol, blood pressure, parental diabetes, smoking, alcohol consumption, physical activity, former myocardial infarction or stroke

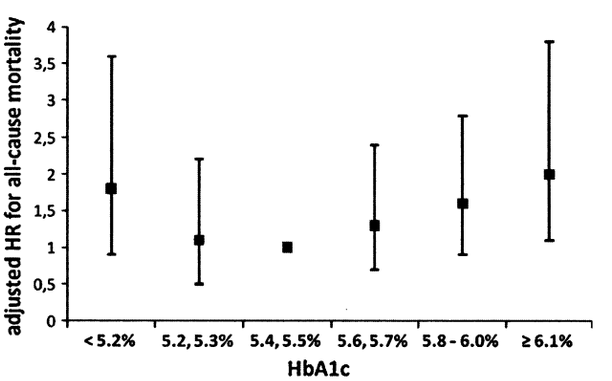


**Fig. 2** Multivariable adjusted hazard ratios (HR, 95%CI) for all-cause mortality by categories of baseline HbA1c

ratios were 3.3 (95%CI: 1.3–8.2) and 2.1 (95%CI: 0.97–4.7), respectively. For 2hPG, an increased mortality was also seen in the upper prediabetes range: For 2hPG ≥177 mg/dl and 2hPG ≥140, <177 mg/dl, hazard ratios were 3.0 (95%CI: 1.3–6.9) and 1.3 (95%CI: 0.6–3.0), respectively.

## Discussion

This study demonstrates for an older population that subjects with undiagnosed diabetes have a similar all-cause mortality risk as subjects with previously known diabetes, and that all-cause mortality in persons with undiagnosed or known diabetes is strongly increased compared with persons with prediabetes and NGT. Undiagnosed diabetes in older patients is also associated with cancer mortality but not with cardiovascular mortality. Furthermore, mortality is also increased in subjects with very low levels of glycemia as indicated by values of HbA1c, FPG, or 2hPG in the lowest decile.

### All-cause mortality in known and undiagnosed diabetes

The KORA S4 study is one of the few studies on all-cause mortality in different glucose tolerance categories focusing on older subjects. In the Edinburgh Artery Study cohort with a study population in the same age range (i.e., 55–74 years), HR for known diabetes (1.75; 95%CI, 1.15–2.67) was only slightly larger than that for newly detected diabetes (1.60; 95%CI, 1.20–2.13) after adjustment for age and sex [6]. In the Asturias and the DECODE studies, both including participants of middle and old ages, similar mortality risks were also found for known and undiagnosed diabetes [4, 5]. By contrast, mortality risks in the AusDiab study were higher for known diabetes than for previously undiagnosed diabetes [26].

Whether subjects with newly diagnosed diabetes should be expected to have a similar mortality risk as subjects with known diabetes—as our study suggests—may depend on several factors. One factor is the profile of metabolic and lifestyle risk factors at baseline. The comparison of risk factors in subjects with previously undiagnosed diabetes and subjects with previously known diabetes was ambiguous. Subjects with previously undiagnosed diabetes showed a better profile in some regards (lower BMI, lower waist circumference, lower glucose levels, more HDL cholesterol), but smoking and high alcohol consumption was less common in persons with known diabetes. However, the hazard ratios of both groups compared with NGT were nearly identical after adjustment for metabolic and lifestyle factors.

A second factor is the duration of diabetes since onset. Subjects with known diabetes had been diagnosed with the disease about 7 years before the baseline investigation, so they were very likely to have diabetes for a much longer time than subjects with newly diagnosed diabetes.

A third factor that may affect all-cause mortality is the different treatment of diabetes in the two groups. In our study, the subjects with newly detected diabetes had received their diagnosis at baseline. However, we have only limited information about their subsequent diabetes treatment: In a subgroup of 47 subjects with newly diagnosed diabetes, about two thirds of them stated that they had seen their general practitioners for potential retesting. Of those with a confirmed diagnosis by the doctor, 80% actually received antidiabetic treatment. This finding is in line with the Spanish Asturias Study, where only 60% of the subjects with previously undiagnosed diabetes actually informed their treating physicians about their new diagnosis [4]. An additional factor related to diabetes treatment refers to potential differences in health consciousness. It might be assumed that subjects with undiagnosed diabetes are less health-conscious and participate less often in medical checkups than those with known diabetes.

### Cancer and cardiovascular mortality in known and undiagnosed diabetes

In the present study, a strong increase in cancer mortality risk was found in subjects with undiagnosed diabetes, which is in line with results of the DECODE study but contrary to those of the NHANES II study [12, 13]. In the KORA study, the association between undiagnosed diabetes and cancer mortality can most likely not be explained by reverse causality (i.e., pancreas cancer causing diabetes) or by subclinical or undiagnosed cancer at baseline, because the association was still significant after excluding the cases of cancer deaths occurring in the first 3 years after baseline investigation. Furthermore, the higher cancer mortality in undiagnosed diabetes cannot be ascribed to risk factors common in subjects with diabetes, because undiagnosed diabetes was still associated with cancer mortality after multivariable adjustment.

Our study results of the analysis of the cardiovascular death risk showed a significant association with known diabetes but not with newly diagnosed diabetes. However, this result might have been due to the low study power due to the small number of subjects who died of cardiovascular diseases (only six of the subjects with newly diagnosed diabetes).

In the NHANES II study, the risk of cardiovascular mortality was smaller in undiagnosed diabetes than in diagnosed diabetes as seen by the HRs of 1.54 (95%CI, 0.85–2.79), and 2.62 (95%CI, 1.81–3.78), respectively [8].

Similar findings were reported for the Edinburgh Artery Study cohort: HR for new diabetes was 1.39 (95%CI, 0.88–2.20), and HR for known diabetes was 2.04 (95%CI, 1.16–3.59) [6]. Finally, in the DECODE Study, the risk of cardiovascular mortality was larger in known diabetes [HR = 1.96 (95%CI, 1.62–2.37)] than in previously undiagnosed diabetes (HR = 1.48 (95%CI, 1.15–1.91) for diagnosis by fasting glucose criteria, and HR = 1.55 [(95%CI, 1.20–2.01) for diagnosis by 2 h-glucose criteria] [5]. Judging by the limited data available to date, the mortality risk seems to be smaller in undiagnosed than in diagnosed diabetes, but compared with the results of the present study, association of undiagnosed diabetes with cardiovascular mortality is somewhat stronger in other cohort studies.

For non-cancer non-cardiovascular mortality, in the present study significant associations with undiagnosed and previously known diabetes were found in spite of a low study power due to small subject numbers.

### Relationship between continuous glucose measures and mortality

For FPG and 2hPG, the categories with the lowest mortality were located far below the thresholds between NGT and prediabetes as given by the WHO classification [25]. Different mortality rates within a category of glucose tolerance (WHO) were not only found for NGT, but also for prediabetes: When known and newly diagnosed diabetes were excluded from analyses, mortality was higher in the upper than in the lower range of prediabetic FPG and 2hPG, respectively.

A review of reports on the relationship of FPG or 2hPG to all-cause mortality showed that mortality risks are increased in the diabetic and prediabetic ranges [27]. However, studies on continuous associations between glycemia and all-cause mortality led to rather inconclusive results for low levels of glycemia [14–24, 28, 29]. For HbA1c, linear [15, 17, 21, 22] and J-shaped [14, 23, 24] associations with total mortality were reported. This was also the case for FPG with observations of linear [14, 17] and J-shaped [15, 16, 19, 20] relationships. In the Whitehall study [18], a 2hPG threshold was reported to describe the association with mortality, whereas other studies found linear [15, 17] or J-shaped [20] associations. These discordant findings may be explained partly by different age ranges of the study populations and different definitions of low level categories of glycemia between these studies.

The underlying causes for the association between low glucose values and increased all-cause mortality are unclear. Confounding by preexisting chronic disease, occult cancer associated with hypoglycemia, low cardiorespiratory fitness, heavy alcohol intake and liver diseases associated with liver dysfunction and hypoglycemia, and low glucose values associated with low body mass index have all been suggested [19]. In the present study, the J-shaped association remained true after adjusting for BMI and alcohol intake. However, we cannot preclude that an undiagnosed chronic disease (e.g., occult cancer) may have been present.

### Study limitations and strengths

Several limitations apply to this study. Since the numbers of cancer and cardivascular deaths was rather small, we only assessed the association between larger categories of glucose regulation (NGT, prediabetes, diabetes following the WHO classification) and cause-specific mortality (cancer, CVD), but we did not assess the relationship between measures of glycemia and cause-specific mortality. Moreover, OGTT was assessed only once at baseline. Furthermore, we have assessed the medical care of subjects with newly diagnosed diabetes only for a few participants and only 7 years after initial diabetes diagnosis, which potentially might have caused false subject reportings in regard to antidiabetic treatment.

This study has several strengths. It is population-based and the mortality follow-up period is rather long. We have included three different measures of glycemia in our study (reflecting different metabolic processes), and the main cardiovascular and lifestyle risk factors are used for multivariable adjustment of the regression models.

## Conclusion

In an older population (aged 55–74 years) in Germany, all-cause mortality in undiagnosed diabetes is as high as in previously diagnosed diabetes. In undiagnosed diabetes, cancer mortality but not cardiovascular mortality is increased. All-cause mortality is also increased in subjects with very low levels of fasting glucose, 2 h glucose, and HbA1c.

**Acknowledgments** The Diabetes Cohort Study was funded by a German Research Foundation project grant to the first author (DFG; RA 459/2-1). The German Diabetes Center is funded by the German Federal Ministry of Health and the Ministry of Innovation, Science, Research and Technology of the federal state of North Rhine Westfalia. The KORA research platform and the KORA Augsburg studies are financed by the Helmholtz Zentrum München, German Research Center for Environmental Health, which is funded by the German Federal Ministry of Education, Science, Research and Technology and by the State of Bavaria. We thank the field staff in Augsburg who was involved in conducting the studies. Cornelia Huth was supported by a grant from the German Federal Ministry of Education and Research (BMBF) to the German Center for Diabetes Research (DZD e.V.).

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