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ARTICLE

Glycaemic markers and all-cause mortality in older adults with and without diabetes: the Atherosclerosis Risk in Communities (ARIC) study

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Abstract

Aims/hypothesis There is controversy regarding the performance of HbA_{1c} in old age. We evaluated the prognostic value of HbA_{1c} and other glycaemic markers (fructosamine, glycated albumin, fasting glucose) with mortality risk in older adults (66–90 years).

Methods This was a prospective analysis of 5636 participants (31% with diagnosed diabetes, mean age 76, 58% female, 21% black) in the Atherosclerosis Risk in Communities (ARIC) study, baseline 2011–2013. We used Cox regression to examine associations of glycaemic markers (modelled in categories) with mortality risk, stratified by diagnosed diabetes status.

Results During a median of 6 years of follow-up, 983 deaths occurred. Among older adults with diabetes, 30% had low HbA_{1c} (<42 mmol/mol [<6.0%]) and 10% had high HbA_{1c} (≥64 mmol/mol [≥8.0%]); low (HR 1.32 [95% CI 1.04, 1.68]) and high (HR 1.86 [95% CI 1.32, 2.62]) HbA_{1c} were associated with mortality risk vs HbA_{1c} 42–52 mmol/mol (6.0–6.9%) after demographic adjustment. Low fructosamine and glycated albumin were not associated with mortality risk. Both low and high fasting glucose were associated with mortality risk. After further adjustment for lifestyle and clinical risk factors, high HbA_{1c} (HR 1.81 [95% CI 1.28, 2.56]), fructosamine (HR 1.96 [95% CI 1.43–2.69]), glycated albumin (HR 1.81 [95% CI 1.33–2.47]) and fasting glucose (HR 1.81 [95% CI 1.24, 2.66]) were associated with mortality risk. Low HbA_{1c} and fasting glucose were no longer significantly associated with mortality risk. Among participants without diabetes, associations of glycaemic markers with mortality risk were less robust.

Conclusions/interpretation Elevated HbA_{1c}, fructosamine, glycated albumin and fasting glucose were associated with risk of mortality in older adults with diabetes. Low HbA_{1c} and fasting glucose may be markers of poor prognosis but are possibly confounded by health status. Our findings support the clinical use of HbA_{1c} in older adults with diabetes.

Keywords Ageing · Biomarker · Blood · Diabetes · Glucose · HbA_{1c} · Mortality · Prospective

Abbreviations

ALT	Alanine aminotransferase
ARIC	Atherosclerosis Risk in Communities
AST	Aspartate aminotransferase
CKD	Chronic kidney disease
GGT	γ-Glutamyl transferase

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Introduction

HbA_{1c} is central to the diagnosis and management of diabetes. However, our understanding of the association of HbA_{1c} with clinical outcomes is based primarily on studies of middle-aged adults. There has been recent debate regarding the interpretation of age-related increases in HbA_{1c} and whether age-related increases reflect true hyperglycaemia [1–4]. This has implications for the use and interpretation of HbA_{1c} in older age.

Among middle-aged adults, J- or U-shaped curves between HbA_{1c} and risk of mortality have been reported in both adults with and without diabetes in some studies [5–9] but not others

Research in context

What is already known about this subject?

- There is controversy regarding the performance of HbA_{1c} in old age
- Studies of the association of HbA_{1c} with mortality risk have primarily been conducted in middle-aged adults. Some studies have reported J- or U-shaped associations

What is the key question?

- What is the prognostic value of HbA_{1c} and other glycaemic markers (fructosamine, glycated albumin, fasting glucose) with mortality risk in older adults with and without diabetes?

What are the new findings?

- Among older adults with diabetes, high levels of HbA_{1c}, fructosamine, glycated albumin and fasting glucose were all associated with mortality risk
- Low HbA_{1c} and low fasting glucose were associated with an increased risk of mortality in older adults with diabetes, but this association was not statistically significant after adjustment for lifestyle and clinical risk factors
- Among older adults without diabetes, the associations of glycaemic markers with mortality were less consistent

How might this impact on clinical practice in the foreseeable future?

- Our findings support the notion that low HbA_{1c} and fasting glucose are markers of poor prognosis in diabetes but are possibly confounded by current health status. Ultimately, our results support the clinical use of HbA_{1c} among older adults with diabetes

[10, 11]. There is controversy regarding why low HbA_{1c} might be associated with mortality risk [12, 13] and whether there is a J-shaped association in older age [14–19]. This issue is particularly relevant to clinical care for frail older adults with diabetes or those with a presumed limited life expectancy due to concerns of potential overtreatment and risks of hypoglycaemia in the setting of strict glycaemic control [20].

Fructosamine and glycated albumin are serum markers of hyperglycaemia that are highly correlated with HbA_{1c} [21]. Both tests are Food and Drug Administration (FDA)-cleared for clinical use in the USA but are not routinely used. Fructosamine and glycated albumin track with HbA_{1c} and are similarly associated with microvascular [22] and macrovascular outcomes in middle-aged adults [23], however there are scant data on fructosamine and glycated albumin in older adults. Because these biomarkers are haemoglobin-independent and, thus, not subject to the same factors that can affect the interpretation of HbA_{1c} [21], they can help us understand whether associations with outcomes are glycaemic or non-glycaemic in nature.

We sought to test whether HbA_{1c} was associated with all-cause mortality risk in older adults aged 66–90 years with and without diabetes, and compared these associations to those for fructosamine, glycated albumin and fasting glucose. Based on the prior literature in middle-aged adults, we hypothesised there would be J-shaped associations between glycaemic markers and mortality risk among older adults with and without diabetes. We also explored determinants of low HbA_{1c}.

Methods

Study design

The ARIC study is a prospective multi-centre community-based cohort, which began in 1987–1989, when participants were aged 45–64 years [24]. Multiple clinic visits have since taken place. At each clinic visit, participants underwent an interview, physical examination and blood tests. All participants provided written informed consent and ARIC protocols were approved at Institutional Review Boards for each study centre.

We conducted a prospective cohort analysis with visit 5 (2011–2013, attended by 65% of the participants still alive) as baseline when participants were 66 to 90 years old. Of the 6538 visit 5 participants, we excluded 439 who were missing any of the glycaemic measurements, 247 with non-fasting blood tests and 181 where information was missing on other model covariates. Additionally, participants who were neither black nor white as well as black participants at the Maryland and Minnesota centres were excluded due to small numbers ($n = 35$). This resulted in an analytic sample of 5636 participants (31% with diagnosed diabetes) (see electronic supplementary material [ESM] Fig. 1 for details).

Diabetes and glycaemic measurements We conducted all analyses stratified by diagnosed diabetes status, which was defined as history of self-reported physician diagnosis or

current medication use for diabetes (self-reported at visit 5). We did not have information on diabetes type. Duration of diagnosed diabetes at visit 5 was estimated based on the date of the annual (or semi-annual) phone calls where diagnosed diabetes was first reported, and was dichotomised at the median (≥10 vs <10 years). Glycaemic markers were measured at visit 5 in all participants (with and without diagnosed diabetes). HbA_{1c} was measured in whole blood using a Tosoh G7 Automated HPLC Analyzer (Tosoh Bioscience, USA), which was standardised to the DCCT assay. Fructosamine and glycated albumin were both measured in serum on the Roche Modular P800 Chemistry Analyzer (Roche Diagnostics, USA). Fructosamine was measured using a colorimetric assay by Roche Diagnostics. Glycated albumin was measured using a complex method by Asahi Kasei Pharma (Japan). Fasting glucose was measured in serum using the hexokinase method. The laboratory intra-assay CV based on blind duplicate samples for HbA_{1c} was 1.3% and for fasting glucose was 5.7%. For fructosamine, CVs were 3.2% at a concentration of 212.6 μmol/l and 2.5% at a concentration of 856.7 μmol/l. For glycated albumin, CVs were 2.3% at a concentration of 1.579 g/dl and 2.8% at a concentration of 0.426 g/dl.

Other measurements Participants self-reported their demographic characteristics (including race), smoking and drinking status. BMI was calculated from measured height and weight. BP was measured three times, and we used the mean of the second and third measurements. eGFR was calculated using the CKD-EPI equation based on cystatin C and creatinine [25]. Total cholesterol and HDL-cholesterol were measured in plasma using colorimetric methods. Haemoglobin was measured using an Automated Haematology Analyser (ABX Horiba Diagnostics MICROS 60-CS, USA). Anaemia was defined as haemoglobin <135 g/l for men and <120 g/l for women; moderate/severe anaemia was defined as haemoglobin for men <120 g/l and <100 g/l for women [26]. Liver enzymes (alanine and aspartate aminotransferase [ALT, AST] and γ-glutamyl transferase [GGT]) were measured in serum. Elevated liver enzymes were defined by sex-specific 95th percentile thresholds [27]. Participants were asked to bring their medication containers to each visit, and these were transcribed and coded. Prevalent CVD included CHD (defined as either definite or probable myocardial infarction), stroke (definite or probable) and heart failure. Frailty status was based on a standard definition used in prior studies, defined by the presence of ≥3 of the following: low energy, low physical activity, low strength, slowed motor performance and unintentional weight loss [28].

Outcome ascertainment All-cause mortality was identified through annual (semi-annual since 2012) follow-up telephone calls to participants or their proxies, state records and linkage to the National Death Index up to 31 December 2018.

Data analysis

We present baseline (visit 5) participant characteristics across HbA_{1c} categories, stratified by diagnosed diabetes status. We categorised HbA_{1c} among participants without diabetes as <31 mmol/mol, 31–<39 mmol/mol, 39–<48 mmol/mol and ≥48 mmol/mol (undiagnosed diabetes) (<5.0%, 5.0–<5.7%, 5.7–<6.5%, ≥6.5%), and among those with diagnosed diabetes as <42 mmol/mol, 42–<53 mmol/mol, 53–<64 mmol/mol, and ≥64 mmol/mol (<6.0%, 6.0–<7.0%, 7.0–<8.0%, ≥8.0%). Diabetes-specific percentile equivalent cut-points to HbA_{1c} were used for fructosamine and glycated albumin [23]. Fasting glucose was modelled using clinically relevant cut-points in those individuals without diabetes as <5.5, 5.5–<7.0, and ≥7.0 mmol/l. In those with diagnosed diabetes we categorised fasting glucose as <5.5, 5.5–<8.3, 8.3–<11.1, and ≥11.1 mmol/l.

We used Cox proportional hazards regression models to examine the associations between categories of glycaemic markers and risk of mortality among participants with and without diabetes. We also modelled the glycaemic biomarkers more flexibly using restricted cubic splines. We compared two models: in Model 1, we adjusted for age, sex and race-centre (Forsyth County, North Carolina-white; Forsyth County, North Carolina-black; Washington County, Maryland-white; Minneapolis, Minnesota-white; Jackson, Mississippi-black). In Model 2, we additionally adjusted for current smoking status (yes/no), current drinking status (yes/no), BMI (continuous), systolic BP (continuous), antihypertension medication use, eGFR (continuous, spline with knot at eGFR <60 ml min^{-1} [1.73 $m]^{-2}$), HDL (continuous), total cholesterol (continuous), cholesterol-lowering medication use (yes/no) and haemoglobin (continuous). We verified the proportional hazards assumption for each model. We used seemingly unrelated regression to compare the strength of the HRs for the associations of HbA_{1c}, fructosamine, glycated albumin and fasting glucose with mortality risk [29]. In a sensitivity analysis, we further adjusted for markers of comorbid health status: prevalent CVD, elevated liver enzymes (AST, ALT, GGT) and frailty.

To evaluate cross-sectional determinants of low levels of HbA_{1c} and other glycaemic markers, we used logistic regression models adjusted for age, sex and race-centre. In these models, we selected variables (BMI, eGFR, CVD, liver disease, frailty, anaemia, diabetes duration and medication use) that have been previously linked to low HbA_{1c} in prior literature and that could confound the association between low glycaemic levels and risk of mortality [30].

We examined results stratified by race, given the ongoing controversy regarding the interpretation of racial differences in HbA_{1c} [31]. We also conducted analyses stratified by anaemia, stage 3+ chronic kidney disease (CKD), and frailty status and formally tested for

multiplicative interaction by these variables. A p value <0.05 was considered statistically significant.

Results

The mean age of the 5636 participants was 76 years, 58% were female and 21% were black. Overall, 31% of the study population had diagnosed diabetes. Over a median of 6 years of follow-up, 983 deaths occurred (400 occurring in those with diagnosed diabetes).

Older adults without diabetes

In people without diagnosed diabetes, compared with those with normal HbA_{1c} 31–<39 mmol/mol (5.0–<5.7%), individuals with low HbA_{1c} <31 mmol/mol (<5.0%) were more likely to be male, black, have prevalent CVD and have moderate or severe anaemia (Table 1). Individuals with HbA_{1c} ≥48 mmol/l (≥6.5%, undiagnosed diabetes) were more likely to be female, black, obese, and to have CVD than those with normal HbA_{1c} 31–<39 mmol/mol (5.0–5.7%).

Among older people without diabetes, HbA_{1c} was weakly associated with fructosamine (Pearson's $r = 0.19$), glycated albumin ($r = 0.28$) and fasting glucose ($r = 0.36$) (ESM Table 1). Low HbA_{1c} <30 mmol/mol (<5.0%) was associated with higher mortality risk after adjustment for demographic variables compared with those with HbA_{1c} 31–<39 mmol/mol (5.0–<5.7%) (Model 1; Fig. 1a and Table 2), but not after additional adjustment for lifestyle and clinical risk factors (Model 2). Undiagnosed diabetes (HbA_{1c} ≥48 mmol/mol or ≥6.5%) was not significantly associated with mortality risk. Individuals with fructosamine and glycated albumin in the ≥98th percentile (vs 6th–55th percentile) had elevated mortality risk (Model 1): HR 1.99 (95% CI 1.39, 2.84) for fructosamine and HR 1.88 (95% CI 1.28, 2.75) for glycated albumin. After adjustment for lifestyle and clinical risk factors, the associations remained significant for fructosamine (HR 1.63 [95% CI 1.12, 2.35]) but was attenuated for glycated albumin (HR 1.38 [95% CI 0.93, 2.06]) (Fig. 1b-c and Table 2). Fasting glucose was not significantly associated with risk of mortality in older adults without diabetes (Fig. 1d and Table 3). Associations between all four glycaemic markers and mortality were not appreciably altered when we adjusted for all variables in Model 2 plus markers of comorbid health status: prevalent CVD, elevated AST, ALT or GGT, and frailty.

There were no statistically significant differences for the association of any of the glycaemic biomarkers with mortality risk according to race (Model 1: all p values for interaction >0.17; ESM Fig. 2a-b), anaemia (p-interactions >0.21; ESM Fig. 3a-b), CKD (p-interactions >0.60; ESM Fig. 4a-b), or frailty (p-interactions >0.26; ESM Fig. 5a-b). While not statistically significant, there were, however, some qualitative differences for race and anaemia. High fructosamine was significantly associated with increased risk of mortality in white people but not black people. High HbA_{1c} was associated with increased risk of mortality in individuals without anaemia but not in those with anaemia. In the subset with frailty and no diabetes, no glycaemic markers were significantly associated with mortality risk (ESM Fig. 5a-b).

Individuals with low HbA_{1c} <31 mmol/mol (<5.0%) were more likely to have stage 3+ CKD (OR 1.55 [95% CI 1.03, 2.34]), prevalent CVD (OR 1.92 [95% CI 1.25, 2.94]) or moderate/severe anaemia (OR 3.34 [95% CI 1.76, 6.35]) (ESM Table 2), compared with those in the normal HbA_{1c} range 31–<39 mmol/mol (5.0–<5.7%). Individuals with low (vs normal) fructosamine (OR 2.52 [95% CI 1.14, 5.56]) were more likely to have moderate/severe anaemia.

Older adults with diabetes

In people with diagnosed diabetes, compared with those with low HbA_{1c} <42 mmol/mol (<6.0%), individuals with high HbA_{1c} ≥64 mmol/l (≥8.0%) were more likely to be black, obese, have a longer duration of diabetes or to be currently taking diabetes medications (Table 1).

In individuals with diabetes, biomarkers of hyperglycaemia were highly correlated: HbA_{1c} and fructosamine $r = 0.75$; HbA_{1c} and glycated albumin $r = 0.81$; HbA_{1c} and fasting glucose $r = 0.64$ (ESM Table 1). HbA_{1c}, fructosamine and glycated albumin all had similarly shaped associations with mortality risk (Fig. 1e–g). With adjustment for demographic factors, low (HR 1.32 [95%CI 1.04, 1.68]) and high HbA_{1c} (HR 1.86 [95% CI 1.32, 2.62]) were both associated with an increased risk of mortality vs HbA_{1c} 42–52 mmol/mol (6.0–6.9%). Low fructosamine and glycated albumin were not significantly associated with mortality risk. After additional adjustment for lifestyle and clinical risk factors, high levels (≥91st percentile) of HbA_{1c}, fructosamine and glycated albumin were associated with mortality risk, compared with those with markers between the 32nd and 73rd percentile, e.g. HbA_{1c} HR 1.81 (95% CI 1.28, 2.56). Similar to the association observed for HbA_{1c}, fasting glucose followed a J-shaped association in the demographic-adjusted model (Fig. 1h and Table 3); after adjustment for lifestyle and clinical risk factors, elevated glucose carried higher mortality risk, and low fasting glucose was no longer statistically significantly associated with mortality risk (Table 3). When we further adjusted Model 2 for prevalent CVD, elevated liver enzymes and frailty, the associations between HbA_{1c}, fructosamine, glycated albumin and fasting glucose and mortality risk were unchanged.

Associations of the biomarkers of hyperglycaemia and mortality risk were not statistically significantly different according to race (p-interactions >0.08, ESM Fig. 2c-d), anaemia (p-interactions >0.07, ESM Fig. 3c-d), CKD (p-

Table 1 Baseline characteristics by HbA_{1c} categories among individuals with and without diagnosed diabetes at ARIC study visit 5 (2011–2013)

Variable	No diagnosed diabetes ($n = 3866$)				Diagnosed diabetes ($n = 1770$)			
HbA_{1c} category, mmol/mol[a]	<31	31–<39	39–<48	≥48	<42	42–<53	53–<64	≥64
Glycaemic marker percentile	<5th	6th–55th	56th–97th	≥98th	<31st	32nd–73rd	74th–90th	≥91st
n	115	1951	1713	87	527	740	328	*n* = 175
Fructosamine, μmol/l	235 (35)	229 (20)	235 (21)	259 (31)	236 (26)	252 (30)	286 (37)	354 (63)
Glycated albumin, %	13.1 (1.6)	12.9 (1.3)	13.4 (1.4)	15.2 (2.2)	13.4 (1.6)	14.8 (2.1)	17.8 (2.8)	23.7 (5.3)
Fasting blood glucose, mmol/l	5.5 (0.8)	5.6 (0.6)	5.9 (0.7)	7.0 (1.4)	6.0 (0.9)	6.9 (1.4)	8.3 (1.9)	10.4 (3.4)
Age, years	75 (5)	75 (5)	76 (5)	76 (5)	76 (5)	76 (5)	75 (5)	74 (5)
Sex (%)								
Male	57.1	41.3	39.8	43.7	41.4	43.6	48.0	46.4
Female	42.9	58.7	60.2	56.3	58.6	56.4	52.0	53.6
Race (%)								
White	63.9	88.6	77.5	56.3	78.1	72.1	70.4	53.6
Black	36.1	11.4	22.5	43.7	21.9	27.9	29.6	46.4
Current smoker (%)	7.0	5.2	6.2	10.3	6.6	5.4	5.2	4.6
Current alcohol drinker (%)	54.8	57.6	50.1	47.1	44.8	37.2	33.8	34.9
BMI, kg/m^2	27 (6)	27 (5)	28 (6)	30 (6)	29 (5)	31 (6)	31 (6)	33 (6)
BMI categories (%)								
Underweight, <18.5 kg/m^2	2.6	1.4	1.4	0.0	0.2	0.4	0.6	0.0
Ideal, 18.5–<25 kg/m^2	35.7	35.9	24.4	16.1	21.6	12.7	9.1	7.4
Overweight, 25–<30 kg/m^2	40.9	39.5	41.4	43.7	41.4	35.9	37.2	32.0
Obese, ≥30 kg/m^2	20.9	23.2	32.7	40.2	36.8	50.9	53.0	60.6
Systolic BP, mmHg	136 (21)	130 (18)	130 (18)	132 (18)	129 (19)	130 (18)	134 (20)	130 (18)
Antihypertension medication use (%)	67.8	62.4	72.8	81.6	83.1	91.2	93.9	93.7
eGFR <60 ml min^{-1} [1.73 $m]^{-2}$ (%)	36.5	29.9	35.8	32.2	44.0	45.8	46.6	48.6
Total cholesterol, mmol/l	4.8 (1.1)	4.9 (1.1)	4.8 (1.1)	4.8 (1.1)	4.4 (1.0)	4.2 (1.0)	4.3 (1.0)	4.5 (1.2)
HDL-cholesterol, mmol/l	1.4 (0.4)	1.5 (0.4)	1.4 (0.3)	1.3 (0.3)	1.3 (0.3)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
Lipid-lowering medication use (%)	35.7	42.2	57.3	54.0	62.2	74.7	73.2	77.1
Prevalent CVD (%)	30.4	15.9	22.5	29.9	28.8	31.6	33.5	39.4
Elevated ALT[b] (%)	2.6	4.3	5.2	8.0	5.3	5.9	8.8	11.4
Elevated AST[b] (%)	2.6	5.3	5.3	9.2	4.9	5.8	5.8	8.6
Elevated GGT[b] (%)	5.3	4.3	4.7	8.0	5.7	5.9	7.3	9.1
Haemoglobin, g/l	133 (18)	135 (13)	134 (13)	134 (14)	132 (15)	130 (14)	131 (23)	128 (15)
Anaemia[c] (%)								
Mild anaemia	20.0	15.9	19.5	13.8	20.3	29.2	32.6	34.9
Moderate/severe anaemia	13.9	3.3	2.4	6.9	6.1	6.9	7.9	10.3
Frail	41.7	51.6	51.8	47.1	40.0	36.5	35.4	32.6
Diabetes duration (%)								
<10 years	–	–	–	–	71.7	56.5	38.2	21.1
≥10 years	–	–	–	–	28.3	43.5	61.8	78.9
Diabetes medications (%)								
None	–	–	–	–	69.8	36.1	10.7	6.9
Oral only	–	–	–	–	26.6	54.2	61.9	38.3
Insulin only	–	–	–	–	1.9	5.4	11.9	22.9
Insulin and oral	–	–	–	–	1.5	3.9	14.6	30.9

Data are presented as % or mean (SD)

[a] HbA_{1c} categories correspond to <5.0%, 5.0–<5.7%, 5.7–<6.5% and ≥6.5% in individuals without diabetes; and <6.0%, 6.0–<7.0%, 7.0–<8.0% and ≥8.0% in individuals with diabetes

[b] Cut-point of sex-specific 95th percentile

[c] Mild anaemia: haemoglobin in men 120–135 g/l, women 100–120 g/l; moderate/severe anaemia: haemoglobin in men <120 g/l, women 100 g/l

interactions >0.13, ESM Fig. 4c-d), or frailty (*p*-interactions >0.12, ESM Fig. 5c-d). In the subset of participants with diabetes and who were frail, low (<42 mmol/mol, <6.0%) and high (≥8.0%) HbA_{1c} were associated with elevated risk of mortality; fructosamine and glycated albumin were not associated with risk of mortality in this subgroup (Models 1–2, ESM Fig. 5c-d).

In participants with diabetes, those with low HbA_{1c} (<42 mmol/mol, <6.0%) were less likely to be overweight or obese, had a shorter diabetes duration, and were less likely to use diabetes medications than those between 42 and <53 mmol/mol (6.0–<7.0%) (ESM Table 2).

Discussion

Among older adults with diabetes, elevated HbA_{1c}, fructosamine, glycated albumin and fasting glucose were

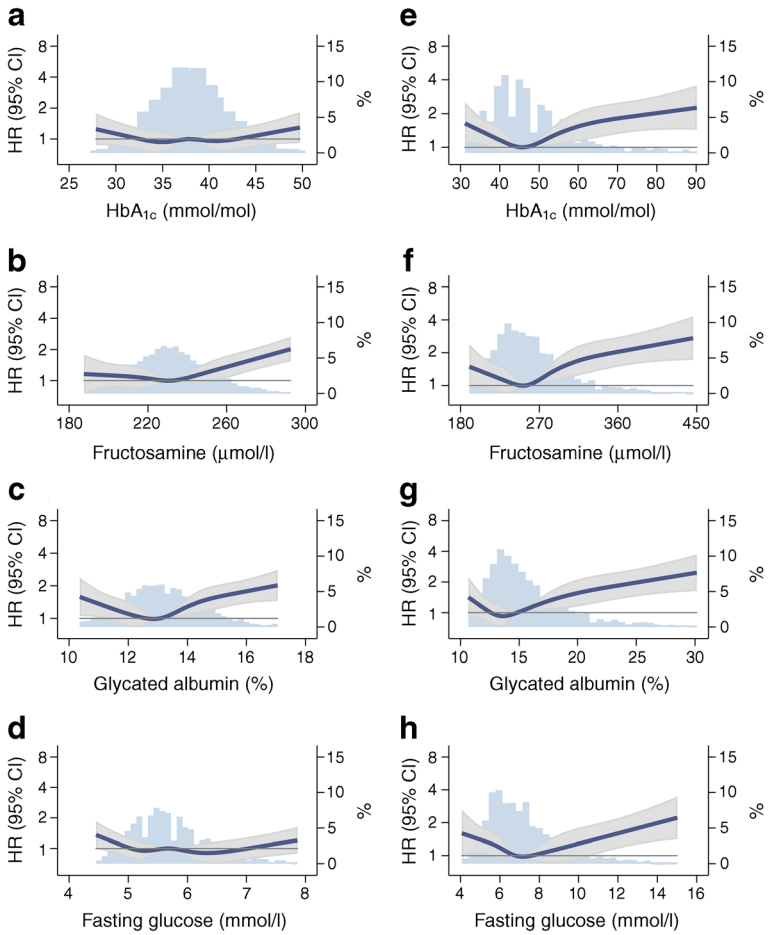

Fig. 1 Associations of glycaemic markers with all-cause mortality, stratified by diabetes diagnosis status (**a**–**d**, no diagnosed diabetes; **e**–**h**, diagnosed diabetes), for the ARIC study 2011–2018, showing HR (95% CI) and proportion of the population (%). Restricted cubic splines adjusted for age, sex and race. Knots at 5th, 35th, 65th, and 95th percentiles, and centred at the median; >99th and <1st percentile removed to minimise influence of extreme values and for ease of display

robustly associated with risk of mortality; low HbA_{1c} and fasting glucose were associated with mortality (J-shaped) but these associations were not statistically significant after further adjusting for confounding factors. In older adults without diabetes, associations between glycaemic markers and mortality risk were less consistent. Elevated fructosamine was associated with an increased risk of mortality. Low HbA_{1c} was associated with elevated risk of mortality after adjusting for demographic characteristics, but this association was no longer significant with further adjustment. Our findings support the clinical use of HbA_{1c} among older adults with diabetes and suggest that the performance of fructosamine, glycated albumin and fasting glucose as markers of risk is similar compared with HbA_{1c}.

The strength of risk factor associations differ across the life course; typically, risk factors measured in mid-life are more strongly associated with cardiovascular outcomes [32, 33] and mortality risk [32–34] than those same risk factors measured in late-life. Understanding the HbA_{1c}-mortality relationship in late-life has implications for diabetes care in older adults. HbA_{1c} is an important risk factor for microvascular outcomes (CKD, end-stage renal disease, retinopathy) [35, 36], CVD [37–39] and all-cause mortality [37, 38, 40, 41] in middle-aged adults. In our study population with diabetes (aged 75+), we found that HbA_{1c} was positively associated with risk of mortality. Consistent with prior observations, the association between HbA_{1c} and mortality risk was less robust than that observed in middle-age (aged 48–67) [23, 38]. Indeed, in individuals without diabetes, we did not observe significant associations of HbA_{1c} with mortality risk after adjustment for confounding factors.

Previous research in older adults has not examined alternative glycaemic markers with risk of mortality; this can help us discern if associations are glycaemic or non-glycaemic in nature. We found that glycated albumin and fructosamine were correlated with HbA_{1c}—especially in individuals with diabetes—and their associations with mortality were generally similar in magnitude and shape as compared with HbA_{1c}. This suggests that the associations that we observed between HbA_{1c} and mortality risk primarily reflect hyperglycaemia-related processes.

Some [5–9, 15] but not all [10, 11, 14] prior studies in individuals without diabetes have reported J-shaped curves between HbA_{1c} and mortality risk. In a prior ARIC analysis, no one specific cause of death (cancer, cardiovascular, respiratory, digestive/liver, genitourinary/kidney) accounted for

Table 2 HRs (95% CIs) for all-cause mortality in older adults by diabetes diagnosis status and HbA_{1c} percentile categories in the ARIC study, 2011–2018

	No diagnosed diabetes[a]				Diagnosed diabetes[a]			
	<5th percentile[b]	6th–55th percentile[b]	56th–97th percentile[b]	≥98th percentile[b]	<31st percentile[b]	32nd–73rd percentile[b]	74th–90th percentile[b]	≥91st percentile[b]
HbA_{1c}								
Range, mmol/mol	14–30	31–38	39–47	48–67	22–41	42–52	53–63	64–128
Range, %	3.4–4.9	5.0–5.6	5.7–6.4	6.5–8.3	4.2–5.9	6.0–6.9	7.0–7.9	8.0–13.9
n	115	1951	1713	87	527	740	328	175
n deaths	25	271	269	18	128	142	85	45
Model 1[c]	1.77 (1.17, 2.68)	1 (Ref)	1.10 (0.93, 1.31)	1.48 (0.91, 2.39)	1.32 (1.04, 1.68)	1 (Ref)	1.47 (1.12, 1.93)	1.86 (1.32, 2.62)
Model 2	1.48 (0.97, 2.25)	1 (Ref)	1.08 (0.91, 1.29)	1.48 (0.91, 2.42)	1.24 (0.97, 1.58)	1 (Ref)	1.48 (1.13, 1.94)	1.81 (1.28, 2.56)
Fructosamine								
Range, μmol/l	131.1–198.2	198.3–233.5	233.6–275.7	275.9–492.6	154.9–235.4	235.5–280.3	280.4–323.1	323.2–700.2
n	158	1971	1622	115	532	761	300	177
n deaths	21	255	271	36	112	146	84	58
Model 1[c]	1.11 (0.71, 1.74)	1 (Ref)	1.13 (0.95, 1.35)	1.99 (1.39, 2.84)	1.20 (0.94, 1.54)	1 (Ref)	1.49 (1.13, 1.95)	2.24 (1.65, 3.05)
Model 2	1.04 (0.66, 1.62)	1 (Ref)	1.08 (0.90, 1.29)	1.63 (1.12, 2.35)	1.25 (0.98, 1.61)	1 (Ref)	1.48 (1.13, 1.95)	1.96 (1.43, 2.69)
Glycated albumin								
Range, %	8.75–10.95	10.96–13.25	13.26–16.02	16.06–20.58	8.94–13.56	13.57–16.94	16.95–20.57	20.58–55.34
n	155	1972	1623	116	535	759	299	177
n deaths	17	241	293	32	103	159	79	59
Model 1[c]	1.11 (0.68, 1.81)	1 (Ref)	1.27 (1.07, 1.51)	1.88 (1.28, 2.75)	0.98 (0.76, 1.26)	1 (Ref)	1.32 (1.01, 1.74)	2.06 (1.53, 2.79)
Model 2	1.15 (0.70, 1.89)	1 (Ref)	1.16 (0.97, 1.38)	1.38 (0.93, 2.06)	1.02 (0.79, 1.32)	1 (Ref)	1.31 (1.00, 1.72)	1.81 (1.33, 2.47)

Model 1: age, sex, race-centre

Model 2: Model 1 + current smoking status, current drinking status, BMI, systolic BP, antihypertension medication use, eGFR (spline knot at eGFR <60 ml min^{-1} [1.73 $m]^{-2}$), HDL, total cholesterol, lipid-lowering medication use, haemoglobin

[a] Diabetes defined as self-reported physician diagnosis or current medication use for diabetes

[b] HbA_{1c} categories correspond to <31 mmol/mol, 31–<39 mmol/mol, 39–<48 mmol/mol and ≥48 mmol/mol (<5.0%, 5.0–<5.7%, 5.7–<6.5% and ≥6.5%) in individuals without diabetes; and <42 mmol/mol, 42–<53 mmol/mol, 53–<64 mmol/mol, and ≥64 mmol/mol (<6.0%, 6.0–<7.0%, 7.0–<8.0% and ≥8.0%) in individuals with diabetes

[c] Using seemingly unrelated regression, test of differences in HR in no diagnosed diabetes for HbA_{1c} vs fructosamine (p value = 0.46), HbA_{1c} vs glycated albumin (p = 0.13), fructosamine vs glycated albumin (p = 0.33); in diagnosed diabetes, HbA_{1c} vs fructosamine (p value = 0.39), HbA_{1c} vs glycated albumin (p = 0.06), fructosamine vs glycated albumin (p = 0.33)

Table 3 HRs (95% confidence intervals) for fasting blood glucose categories according to diabetes diagnosis status

	No diagnosed diabetes[a]			Diagnosed diabetes			
Fasting glucose category, mmol/l	4.0–<5.5	5.5–<7.0	≥7.0	<5.5	5.5–<8.3	8.3–<11.1	≥11.1
Range, mmol/l	4.1–5.4	5.5–6.9	7.0–13.3	2.6–5.4	5.5–8.2	8.3–11.0	11.1–22.9
n	1484	2181	199	269	1098	303	100
n deaths	231	321	30	72	223	73	32
Model 1[b]	1 (Ref.)	0.92 (0.77, 1.09)	0.90 (0.62, 1.32)	1.41 (1.08, 1.85)	1 (Ref.)	1.17 (0.89, 1.52)	1.81 (1.24, 2.62)
Model 2	1 (Ref.)	1.05 (0.88, 1.25)	1.03 (0.70, 1.53)	1.21 (0.92, 1.59)	1 (Ref.)	1.30 (1.00, 1.70)	1.81 (1.24, 2.66)
Model 3	–	–	–	1.17 (0.88, 1.54)	1 (Ref.)	1.24 (0.93, 1.64)	1.58 (1.06, 2.36)

Model 1: age, sex, race-centre

Model 2: Model 1 + current smoking status, current drinking status, BMI, systolic BP, antihypertension medication use, eGFR (spline knot at eGFR <60 ml min^{-1} [1.73 $m]^{-2}$), HDL, total cholesterol, lipid-lowering medication use, haemoglobin

Model 3 (in diagnosed diabetes only): Model 2 + diabetes medication use (oral only, insulin only, insulin and oral, unknown, none [Ref.])

[a] Excluding individuals with no diagnosed diabetes with fasting blood glucose <4.0 mmol/l (<70 mg/dl) due to small numbers ($n = 2$)

[b] Using seemingly unrelated regression, test of differences in HR in no diagnosed diabetes for fasting glucose vs HbA_{1c} (p value = 0.12), fasting glucose vs fructosamine (p value = 0.02), fasting glucose vs glycated albumin ($p = 0.002$); in diagnosed diabetes, fasting glucose vs HbA_{1c} ($p = 0.47$), fasting glucose vs fructosamine ($p = 0.21$), fasting glucose vs glycated albumin ($p = 0.06$)

the elevated risk among individuals with low HbA_{1c} who were middle-aged at the time [41]. After accounting for potential confounding factors, we did not find robust associations between low HbA_{1c} and mortality risk in this older population. Liver disease has been postulated as a mechanism by which low HbA_{1c} leads to mortality [42]. In analyses of the National Health and Nutrition Examination Survey (NHANES), adults without diabetes who had very low HbA_{1c} (<20 mmol/mol; <4.0%) had much higher prevalence of elevated liver enzymes, hepatitis C seropositivity [5, 42] and ultrasound-detected steatosis as compared with those with HbA_{1c} between 31 and <37 mmol/mol (5.0–<5.5%) [42]. In middle-aged ARIC participants without diabetes, a J-shaped curve between HbA_{1c} and risk of liver hospitalisations has also been reported [41]. By contrast, in our study among the now older ARIC participants, liver enzymes were not particularly elevated among individuals with low HbA_{1c} (or other glycaemic biomarkers). Anaemia and conditions relating to red-cell turnover are also plausible explanations linking low HbA_{1c} and mortality [43]. We found that moderate or severe anaemia was a strong determinant (threefold higher) of having low HbA_{1c} (vs normal) in older adults without diabetes. Moderate or severe anaemia was also a predictor of having low fructosamine (and glycated albumin, albeit non-statistically significantly), which are not haemoglobin-dependent glycaemic markers. The effect estimates between the individual glycaemic markers and mortality risk were slightly larger among individuals without anaemia than among those with anaemia. We did not find, however, any statistical evidence to suggest that the association between HbA_{1c} and other glycaemic markers differed according to anaemia status (nor did adjustment for haemoglobin affect our results) in older adults with or without diabetes.

In older individuals with diabetes, some experts have raised concerns of potential overtreatment and whether goals for glycaemic control should be less stringent in frail individuals or those with complex health status. Low HbA_{1c} may be a confounded marker of poor prognosis in older adults with diabetes, particularly those who are frail. In our study population, low HbA_{1c}, in older adults with diabetes, was not a robust predictor of mortality risk after adjustment; similar patterns were observed for fructosamine, glycated albumin and fasting glucose. These results suggest that, in older adults, well-controlled diabetes (i.e. HbA_{1c} <53 mmol/mol or <7.0%) is not a robust marker for mortality. Indeed, individuals with diabetes and low HbA_{1c} were more likely to have a shorter duration of diabetes and were less likely to be taking glucose-lowering medications.

There are limitations of this study. First, we had limited power for testing for interaction and estimating moderate effects in subgroups. Second, elevated HbA_{1c} without a diagnosis of diabetes—i.e. undiagnosed diabetes—was uncommon in this study population, limiting our power to detect associations of undiagnosed diabetes with mortality risk. Lastly, while we adjusted for major confounders, residual confounding remains a possibility [30]. Strengths of this study include the standardised assessment and rigorous measurement of covariates in a research setting and active surveillance for mortality. To our knowledge, our study is the first examination of glycated albumin and fructosamine with mortality risk in a community-based population of older adults with and without diabetes.

In conclusion, elevated HbA_{1c}, fructosamine, glycated albumin and fasting glucose were associated with risk of mortality in older adults with diabetes. We also found evidence that low levels of HbA_{1c} and fasting glucose were

associated with mortality risk (J-shaped associations) in those with diabetes, and that low HbA_{1c} was associated with mortality risk in those without diabetes, but these associations were attenuated after accounting for confounding characteristics. Among participants without diabetes, associations of glycaemic markers with risk of mortality were less robust. Our results support the notion that low HbA_{1c} is a confounded marker of poor outcomes, rather than a direct risk factor for mortality. Collectively, our findings support the complementary nature of glycaemic biomarkers and the clinical utility of HbA_{1c} among older adults.

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Data availability The datasets analysed within this study are not publicly available due to the possibility that some information in these data might compromise research participants' privacy or consent. However, data may be available from the corresponding author on request.

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