Mean HbA_{1c}, HbA_{1c} variability, and mortality in people with diabetes aged 70 years and older: a retrospective cohort study

Angus Forbes, Trevor Murrells, Henrietta Mulnier, Alan J Sinclair

Lancet Diabetes Endocrinol 2018; 6: 476–86

Published Online April 16, 2018 http://dx.doi.org/10.1016/S2213-8587(18)30048-2

See Comment page 433

Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, King's College London, London, UK (Prof A Forbes PhD, T Murrells MSc, H Mulnier PhD); **Foundation for Diabetes Research in Older People, Diabetes Frail, Luton, UK** (Prof A J Sinclair FRCP); **and Department of Pharmacy, University of Aston, Birmingham, UK** (Prof A J Sinclair)

Correspondence to: Prof Angus Forbes, Florence Nightingale Faculty of Nursing, Midwifery & Palliative Care, King's College London, London SE1 8WA, UK
angus.forbes@kcl.ac.uk

Summary

Background Glycaemic targets for older people have been revised in recent years because of concern that more stringent targets are associated with increased mortality. We aimed to investigate the association between glycaemic control (mean HbA_{1c}) and variability (variability of HbA_{1c} over time) and mortality in older people with diabetes.

Methods We did a 5-year retrospective cohort study using The Health Improvement Network database, which includes data from 587 UK primary care practices. We included patients of either sex who were aged 70 years and older with type 1 or type 2 diabetes. The primary outcome was time to all-cause mortality. Our primary exposure variables were mean HbA_{1c} and variability of HbA_{1c} over time. The observation included a 4-year run-in period (from 2003) as a baseline, with a 5-year follow-up (from 2007 to 2012). We assessed mean HbA_{1c} in three models: a baseline mean HbA_{1c} for 2003–06 (model 1), the mean across the whole follow-up period (model 2), and a time-varying yearly updated mean (model 3). A variability score (from 0 [low] to 100 [high]) was calculated on the basis of number of changes in HbA_{1c} of 0·5% (5·5 mmol/mol) or more from 2003 to 2012 or to the point of mortality, based on changes in the annual mean as per each model with a minimum of six readings.

Findings The cohort consisted of 54 803 people, of whom 17 680 (8614 [30·7%] of 28 017 women and 9066 [33·8%] of 26 786 men) died during the observation period. The overall mortality rate was 77 per 1000 person-years (73 per 1000 person-years for women and 80 per 1000 person-years for men). The data showed a J-shaped distribution for mortality risk in both sexes, with significant increases with HbA_{1c} values greater than 8% (64 mmol/mol) and less than 6% (42 mmol/mol), although excess mortality risk was non-significant in model 1 for men at HbA_{1c} values of 8% (64 mmol/mol) to less than 8·5% (<69 mmol/mol) and in models 1 and 3 for both sexes assessed individually at HbA_{1c} values less than 6% (42 mmol/mol). Mortality increased substantially with increasing HbA_{1c} variability in all models (overall and for both sexes). For the model 2 HbA_{1c} measure, the adjusted hazard ratios comparing patients with a glycaemic variability score of more than 80 to 100 with those with a score of 0 to 20 were 2·47 (95% CI 2·08–2·93) for women and 2·21 (1·87–2·61) for men. Fitting the mean HbA_{1c} models with the glycaemic variability score altered the risk distribution; this observation was most marked in the model 2 analysis, in which a significant increased risk was only apparent with HbA_{1c} values greater than 9·5% (80 mmol/mol) in women and 9% (75 mmol/mol) in men.

Interpretation Both low and high levels of glycaemic control were associated with an increased mortality risk, and the level of variability also seems to be an important factor, suggesting that a stable glycaemic level in the middle range is associated with lower risk. Glycaemic variability, as assessed by variability over time in HbA_{1c}, might be an important factor in understanding mortality risk in older people with diabetes.

Funding King's College London and Diabetes Frail.

Copyright © 2018 Elsevier Ltd. All rights reserved.

Introduction

A key challenge for clinicians to enhance diabetes care in older people (ie, ≥70 years) is the uncertainty about glycaemic thresholds in terms of benefits and risks.[1] Data from observational studies[2–4] have shown J-shaped distributions for mortality and glycaemic control, with not only high HbA_{1c}, but also low HbA_{1c} (≤7% [≤53 mmol/mol]) associated with mortality risk. These data, together with the varied outcomes of recent trials assessing intensive glucose lowering in patients with type 2 diabetes,[5–8] have led to an emphasis on individualised and less stringent glycaemic targets for older people in current guidlines.[9,10] However, although the move towards a more individualised approach is a positive development, a better understanding of the risks conferred by glycaemic exposure is needed to direct clinical decisions and prevent either excess or inadequate use of antihyperglycaemic drug treatments in this population.

In addition to level of glycaemia, in recent years researchers have identified glycaemic variability as a potential risk factor for adverse outcomes in people with diabetes. For example, in a meta-analysis[11] reported in 2015, variability of HbA_{1c} was associated with both microvascular and macrovascular complications and mortality. However, to our knowledge, the link between glycaemic variability and mortality has not previously been specifically investigated in older people with diabetes.

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

Research in context

Evidence before this study

We searched PubMed and Scopus from Jan 1, 1990, to Sept 31, 2017, for relevant studies published in English only using the search terms "older people", "elderly", "elders", "seniors", "all-cause mortality", "mortality hazard", "mortality", "glycaemic control", "glycaemic variability", "glycaemia", "glycemia", and "HbA_{1c}". We also identified current international guidelines for the treatment of older people with diabetes. Overall, data for optimal glycaemic targets for older people are scarce, particularly from prospective studies. In terms of the association between glycaemic control and mortality in older populations, previous findings have suggested a so-called J-shaped relation, although the point at which a significant mortality risk is observed at the lower end of the glycaemic range has varied between studies. In terms of glycaemic variability, previous studies have shown that long-term variations in glycaemic control are associated with increased mortality risk. However, these analyses have neither been further evaluated nor have they been considered in older people for the magnitude or direction of variability. Additionally, previous analyses have not considered the effect of low HbA_{1c} values, which are associated with increased mortality risk independent of diabetes intervention.

Added value of this study

This study provides new insights into the relation between glycaemic control and mortality in older people with diabetes, and is the first, to our knowledge, to consider the relation between clinically significant variations in glycaemic control and mortality in older people with diabetes. We used a novel score to define glycaemic variability, which considers exposure to clinically significant changes in glycaemic control. This approach enabled us to assess the direction of change as well as overall variability. Integration of glycaemic control and glycaemic variability into our models enabled us to consider the importance of glycaemic variability as a potential factor, independent of glycaemic control per se, in understanding the mortality risk in this population.

Implications of all the available evidence

Our data suggest that clinicians might need to rethink how they consider glycaemic targets in older people with diabetes in several different ways. Importantly, glycaemic variability seems to be associated with mortality risk in older people with diabetes. Such variability might be independent of diabetes therapies and might be related to other factors related to ageing. Notably, stability (ie, absence of variability) seems to be associated with reduced mortality risk in medium to higher ranges of glycaemic control. Finally, there might be some important differences between men and women in relation to glycaemic control and mortality risk that are not considered in current guidelines. Although observational data have important limitations, we would advocate that we reconsider glycaemic control not simply as a target to direct therapeutic management, but as an important piece of information in relation to assessing individual risk. Future studies should investigate the role of important measures of ageing, such as frailty, physical activity, and nutrition, in relation to glycaemic control and variability in older people with diabetes. Research is also needed both to investigate the potential of using HbA_{1c} (particularly low or declining values) in assessing risk in older people and to inform optimal approaches to achieving a safe and stable glycaemic level.

Using primary care data from the UK, we aimed to investigate the association between both mean HbA_{1c} and glycaemic variability, as measured by variability in HbA_{1c} over time, and mortality in people with diabetes aged 70 years and older.

Methods

Study design and participants

We did a 5-year retrospective cohort study to examine the relation between glycaemic control and all-cause mortality in patients with diabetes, considering both mean HbA_{1c} and its variability over time. In an attempt to address heterogeneity and complexity within the older population, we took into account diabetes duration, sex, treatment modalities (oral antidiabetes drugs and insulin), other metabolic targets (such as blood pressure and lipids), comorbidities polypharmacy, and socio-demographic factors.

Our analysis used The Health Improvement Network (THIN) dataset, which includes data from 587 UK primary care practices and is constructed using standardised READ codes (version 2). THIN has been validated against normative data for mortality and morbidities.[12] We identified all patients aged 70 years or older on Jan 1, 2007, with a recorded diagnosis of diabetes from at least 6 months before this date using a previously developed algorithm.[13] The sample included patients with both type 1 and type 2 diabetes because the coding of diabetes type in primary care is unreliable; it can be assumed that at least 90% of participants had type 2 diabetes.[14]

Outcomes and exposures

The primary outcome was time to all-cause mortality. Our primary exposure variables were mean HbA_{1c} and HbA_{1c} variability. To assess mean HbA_{1c}, we considered the following exposure models: the mean of the annual mean HbA_{1c} for 2003, 2004, 2005, and 2006 (model 1); mean of the annual mean HbA_{1c} from 2003 to the year before the participant died or the last year of follow-up (model 2); and the updated annual mean from 2003 onwards (used in a time-varying model; model 3). Models 1 and 2 were designed to identify long-term effects of glycaemic control, whereas model 3 was designed to identify more short-term effects. Hence, the exposures were different

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

for each model, although the observation period was the same for each model starting on Jan 1, 2007, and ending on Dec 31, 2012, or at point of death. The baseline observation was from Jan 1, 2003, to Dec 31, 2006, and was the period in which the mean for model 1 was determined and data for other factors such as medicines exposures were calculated. If mean HbA_{1c} was missing for a given year in all three models, it was replaced with the mean of the non-missing annual means—eg, if a person was still alive in 2008 and the mean HbA_{1c} was missing for 2004 and 2006, the cumulative mean was the mean of the annual means for 2003, 2005, and 2007.

Mean HbA_{1c} for each individual were grouped by 0·5% (1·5 mmol/mol) HbA_{1c} increments between 6% and 10% (inclusive) into eight categories; two other categories included outlier values between 3% and less than 6% (9 mmol/mol to <42 mmol/mol) and values greater than 10% (86 mmol/mol).

To calculate a glycaemic variability score using HbA_{1c} values, we counted the number of times successive readings differed by 0·5% (5·5 mmol/mol) or more, divided this number by the number of comparisons, and then multiplied it by 100. For example, if a person had a sequence of HbA_{1c} values of 6·7%, 7·0%, 7·8%, 7·4%, 8·0%, and 7·9%, the number of times that a difference of 0·5% or more was noted would be two and the score would be 40 (ie, [100×2]/5). We used increments of 0·5% (5·5 mmol/mol) in HbA_{1c} as an accepted indicator of a clinically significant difference in glucose exposure. For analysis purposes, scores were grouped into five categories: 0–20, 21–40, 41–60, 61–80, and 81–100. For sensitivity analyses, we identified successive measurements for which HbA_{1c} values rose or declined (directionally increasing or decreasing by HbA_{1c} of ≥0·5%), divided this number by the number of comparisons and multiplied by 100 to produce two additional scores. We also considered the SD of the annual mean HbA_{1c} (analysed by quintile) as an additional measure of glycaemic variability and the slope of charted mean HbA_{1c} over time as an alternative measure of directionality.

In our analyses, we adjusted for age, ethnic origin, social deprivation, diabetes duration, BMI, smoking status, hypertension, LDL cholesterol, chronic kidney disease stage, amputation, laser photocoagulation, comorbidities, polypharmacy, and use of antidiabetes drugs in the 3 months before Jan 1, 2007. Quintile of proportion of ward population who define themselves as white (1=most ethnically diverse; 5=least ethnically diverse) and quintile of Townsend score (1=lowest or least deprived; 5=highest or most deprived) were linked to a person's postcode and used as measures of ethnicity and deprivation, respectively. To assess the overall comorbidity load, we used a primary care equivalent of the Charlson Index[15] and a count of 12 comorbidities (coronary heart disease, heart failure, atrial fibrillation, hypertension, peripheral arterial disease, stroke, cancer, dementia, depression, asthma, chronic obstructive pulmonary disease, and hypothyroidism). Polypharmacy was categorised into four groups (0–2, 3–4, 5–6, and ≥7 medicines) on the basis of the number of therapies (defined by the British National Formulary [BNF] categorisation) received continuously for more than 6 months in the baseline period (2003–06). Duration of diabetes was categorised into four groups (<3, 3 to <5, 5 to <10, and ≥10 years, as of Jan 1, 2007). When data for a variable were missing, an unknown category was added.

Use of antidiabetes drugs was included in the model and analysed by category: sulfonylureas, biguanides, thiazolidinediones, acarbose or guar gum, and insulin. Newer agents such as incretin drugs and selective glucose reuptake inhibitors (as well as repaglinide, which is rarely used in the UK), were not included because exposure to these therapies was negligible during the study period. The continuous variables age, BMI, hypertension, and lipids were grouped into ordinal categories. Smoking was grouped into four categories (unknown, never-smoked, ex-smoker, or current smoker). The individual comorbidities were assessed as binary variables in the sensitivity analysis.

Statistical analysis

We used Cox regression to model time to all-cause mortality and to calculate the unadjusted and adjusted hazard ratios (HRs) for the HbA_{1c} group (reference category 7% to <7·5% [53 mmol/mol to <58 mmol/mol]) and glycaemic variability score quintiles (reference category 0–20) in models 1–3. An additional fully adjusted model for the HbA_{1c} groups was projected adjusting for glycaemic variability. The SAS procedure PHREG, with robust sandwich estimates[16] to correct for intra-cluster dependence (models 1 and 2: general practices; model 3: general practices and individuals), was used to fit the non-time-varying (models 1 and 2) and time-varying (model 3) models. There was some evidence of collinearity among the independent variables. A few variables had variance inflation factors greater than 10; these variables were mainly associated with chronic kidney disease. However, we retained chronic kidney disease in the model because of its importance in predicting mortality. Models were fitted by sex to age groups (70–74, 75–79, 80–84, 85 years and older, and 70 years and older).

Sensitivity analyses were done to investigate the effect of replacing the Charlson Index and comorbidity count with individual comorbidities, SD of mean HbA_{1c} as an alternative to the glycaemic variability score, direction of movement in glycaemic change based on the effect of either increases or decreases in the glycaemic variability score of 20 or more, and linear slope estimated from individual person-level regressions of mean annual HbA_{1c} on year were categorised into five ordinal groups, very low HbA_{1c} values (removal of outlying values <5% [<31 mmol/mol]), BMI and low HbA_{1c} (to assess whether a low HbA_{1c} and a low BMI conflated mortality risk), and diabetes duration (independent risk assessment

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

	Women (n=28 017)	Men (n=26 786)
Age on Jan 1, 2007, at baseline (years)		
70–74	8748 (31·2%)	10 567 (39·4%)
75–79	8143 (29·1%)	8295 (31·0%)
80–84	6151 (22·0%)	5159 (19·3%)
≥85	4975 (17·8%)	2765 (10·3%)
Mean age (SD)	79·00 (6·09)	77·49 (5·41)
Ethnic origin		
1 (most diverse)	6651 (23·7%)	6128 (22·9%)
2	5510 (19·7%)	5355 (20·0%)
3	4642 (16·6%)	4510 (16·8%)
4	3912 (14·0%)	3840 (14·3%)
5 (least diverse)	3798 (13·6%)	3721 (13·9%)
6 (unknown)	3504 (12·5%)	3232 (12·1%)
Social deprivation (Townsend score)		
1 (least deprived)	5361 (19·1%)	6601 (24·6%)
2	5628 (20·1%)	6010 (22·4%)
3	5800 (20·7%)	5408 (20·2%)
4	5850 (20·9%)	4681 (17·5%)
5 (most deprived)	4274 (15·3%)	3171 (11·8%)
6 (unknown)	1104 (3·9%)	915 (3·4%)
Duration of diabetes (years)		
0 to <3	6575 (23·5%)	5775 (21·6%)
3 to <5	4981 (17·8%)	4422 (16·5%)
5 to <10	7844 (28·0%)	7546 (28·2%)
≥10	8617 (30·8%)	9043 (33·8%)
Mean duration (SD)	8·48 (7·84)	9·09 (8·23)
BMI		
<18	6200 (22·1%)	5839 (21·8%)
18 to <20	354 (1·3%)	91 (0·3%)
20 to <25	791 (2·8%)	374 (1·4%)
25 to <30	9590 (34·2%)	12 148 (45·4%)
30 to <35	6346 (22·7%)	6013 (22·4%)
≥35	3866 (13·8%)	1895 (7·1%)
Unknown	870 (3·1%)	426 (1·6%)
Smoking status		
Unknown	207 (0·7%)	153 (0·6%)
Never-smoked	15 223 (54·3%)	6980 (26·1%)
Ex-smoker	10 498 (37·5%)	17 334 (64·7%)
Current smoker	2089 (7·5%)	2319 (8·7%)
Cumulative mean SBP (mm Hg) in 2003–06		
<110	130 (0·5%)	214 (0·8%)
110–119	660 (2·4%)	942 (3·5%)
120–129	2687 (9·6%)	3609 (13·5%)
130–139	7224 (25·8%)	7879 (29·4%)
140–149	9046 (32·3%)	8397 (31·3%)
150–159	5127 (18·3%)	4015 (15·0%)
160–169	1990 (7·1%)	1161 (4·3%)
≥170	944 (3·4%)	410 (1·5%)
Unknown	209 (0·7%)	159 (0·6%)

(Table 1 continues in next column)

(Continued from previous column)

	Women (n=28 017)	Men (n=26 786)
Cumulative mean LDL cholesterol in 2003–06		
<80 mg/dL	19 274 (68·8%)	18 808 (70·2%)
≥80 mg/dL	553 (2·0%)	161 (0·6%)
Unknown	8190 (29·2%)	7817 (29·2%)
Chronic kidney disease stage		
1	768 (2·7%)	1117 (4·2%)
2	6372 (22·7%)	8101 (30·2%)
3	10 070 (35·9%)	7549 (28·2%)
4	936 (3·3%)	649 (2·4%)
5	91 (0·3%)	109 (0·4%)
No chronic kidney disease	9780 (34·9%)	9261 (34·6%)
Amputation	226 (0·8%)	437 (1·6%)
Laser photocoagulation	212 (0·8%)	244 (0·9%)
Antibiotic use	5975 (21·3%)	4568 (17·1%)
Charlson Index		
0	9235 (33·0%)	8534 (31·9%)
1	5609 (20·0%)	5719 (21·4%)
2	6436 (23·0%)	5628 (21·0%)
3	3637 (13·0%)	3398 (12·7%)
≥4	3100 (11·1%)	3507 (13·1%)
Number of comorbidities		
0	1945 (6·9%)	2523 (9·4%)
1	8087 (28·9%)	8144 (30·4%)
2	8011 (28·6%)	7584 (28·3%)
3	5320 (19·0%)	4712 (17·6%)
≥4	4654 (16·6%)	3823 (14·3%)
Myocardial infarction	2461 (8·8%)	4350 (16·2%)
Heart failure	2742 (9·8%)	2834 (10·6%)
Atrial fibrillation	3305 (11·8%)	3389 (12·7%)
Hypertension	20 884 (74·5%)	17 935 (67·0%)
Pulmonary artery disease	2272 (8·1%)	3226 (12·0%)
Stroke	3821 (13·6%)	4104 (15·3%)
Cancer	2924 (10·4%)	2992 (11·2%)
Dementia	1149 (4·1%)	664 (2·5%)
Depression	5553 (19·8%)	2924 (10·9%)
Asthma	2659 (9·5%)	1716 (6·4%)
Chronic obstructive pulmonary disease	3802 (13·6%)	3900 (14·6%)
Hypothyroidism	4705 (16·8%)	1376 (5·1%)
Polypharmacy		
0–2	5047 (18·0%)	5126 (19·1%)
3–4	8965 (32·0%)	8636 (32·2%)
5–6	9539 (34·0%)	9129 (34·1%)
≥7	4466 (15·9%)	3895 (14·5%)
Biguanide	10 868 (38·8%)	10 770 (40·2%)
Sulfonylureas	8174 (29·2%)	8484 (31·7%)
Thiazolidinedione	2257 (8·1%)	2470 (9·2%)
Acarbose or guar gum	139 (0·5%)	169 (0·6%)
Insulin	3444 (12·3%)	3371 (12·6%)

Data are n (%) or mean (SD). SBP=systolic blood pressure.

Table 1: **Participant characteristics**

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

	Model 1*		Model 2†	
	Women	Men	Women	Men
HbA_{1c} (% [mmol/mol])				
3·0 to <6·0 (9 to <42)	2572 (9·9%)	2401 (9·6%)	2412 (9·2%)	2081 (8·2%)
6·0 to <6·5 (42 to <48)	4144 (15·9%)	3807 (15·2%)	4195 (16·0%)	3687 (14·6%)
6·5 to <7·0 (48 to <53)	5663 (21·8%)	5490 (21·9%)	5971 (22·7%)	5870 (23·2%)
7·0 to <7·5 (53 to <58)	5045 (19·4%)	5072 (20·2%)	5310 (20·2%)	5426 (21·4%)
7·5 to <8·0 (58 to <64)	3288 (12·7%)	3407 (13·6%)	3399 (12·9%)	3578 (14·1%)
8·0 to <8·5 (64 to <69)	2038 (7·8%)	2017 (8·1%)	2089 (7·9%)	2101 (8·3%)
8·5 to <9·0 (69 to <75)	1242 (4·8%)	1223 (4·9%)	1210 (4·6%)	1176 (4·6%)
9·0 to <9·5 (75 to <80)	838 (3·2%)	700 (2·8%)	776 (3·0%)	635 (2·5%)
9·5 to <10·0 (80 to <86)	479 (1·8%)	416 (1·7%)	452 (1·7%)	340 (1·3%)
≥10·0 (≥86)	675 (2·6%)	517 (2·1%)	480 (1·8%)	429 (1·7%)
Mean HbA_{1c} (%; SD)	7·23 (1·14)	7·22 (1·09)	7·20 (1·06)	7·22 (1·02)
Mean HbA_{1c} (mmol/mol; SD)	55·53 (12·43)	55·40 (11·90)	55·23 (11·57)	55·40 (11·15)
All	25 984 (100%)	25 050 (100%)	26 294 (100%)	25 323 (100%)
Glycaemic variability score				
0–20	2504 (22·2%)	2449 (20·8%)	2595 (17·6%)	2471 (16·2%)
21–40	2930 (26·0%)	3038 (25·8%)	4227 (28·7%)	4474 (29·3%)
41–60	3111 (27·6%)	3393 (28·9%)	4693 (31·9%)	4972 (32·6%)
61–80	1968 (17·5%)	2105 (17·9%)	2589 (17·6%)	2720 (17·8%)
81–100	748 (6·6%)	774 (6·6%)	611 (4·2%)	616 (4·0%)
Mean (SD)	43·46 (24·53)	44·07 (24·23)	44·07 (24·23)	43·42 (21·44)
All	11 261 (100%)	11 759 (100%)	14 715 (100%)	15 253 (100%)

Data are n (%) or mean (SD). *Baseline mean HbA_{1c} for 2003–06. †The mean across the whole follow-up period (ie, from 2003 to the year before the participant died or the last year of follow-up).

Table 2: **HbA_{1c} level and glycaemic variability score for model 1 and model 2, by sex**

in those diagnosed younger than 65 years and those diagnosed when aged 65 years or older).

All variables in models 1–3, using the Charlson Index and number of comorbidities as adjusters, were tested individually for non-proportionality. This assessment resulted in 630 tests for models fitting HbA_{1c} level, and 660 tests for models fitting glycaemic variability score.

See Online for appendix

We analysed all data using SAS (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

The study cohort consisted of 54 803 people, with a similar number of men and women (table 1). The mean age was 79·00 years (SD 6·09) for women and 77·49 years (5·41) for men. 8614 (30·7%) of 28 017 women and 9066 (33·8%) of 26 786 men died during the observation period from Jan 1, 2007, to Dec 31, 2012, and the overall mortality rate was 77 per 1000 person-years (73 per 1000 person-years for women and 80 per 1000 person-years for men). Mean duration of diabetes was 8·48 years (SD 7·84) for women and 9·09 years (8·23) for men.

Baseline (Jan 1, 2003, to Dec 31, 2006) mean HbA_{1c} was 7·23% (SD 1·14; 55·53 mmol/mol [SD 12·43]) for women and 7·22% (1·09; 55·40 mmol/mol [11·90]) for men (table 2). The distribution of HbA_{1c} was similar for both sexes and models; for model 1, 5272 (20·3%) of 25 984 women and 4873 (19·5%) of 25 050 men had an HbA_{1c} of 8% (64 mmol/mol) or higher and for model 2 5007 (19·0%) of 26 294 women and 4681 (18·5%) of 25 323 men. Fewer people had a total exposure mean HbA_{1c} less than 6% (42 mmol/mol) compared with those who had a baseline mean HbA_{1c}. The proportion of individuals (women and men combined) with a mean HbA_{1C} lower than 6% (42 mmol/mol) was higher for the baseline 2003–06 (model 1) than for the total exposure (model 2; 4973 [9·7%] of 51 304 *vs* 4493 [8·7%] of 51 617). The glycaemic variability score for the period 2003–06 was 43·46 (SD 24·53) for women and 44·07 (24·23) for men. The proportion of people with a score greater than 80 was 6·6% for the baseline period and 4·1% for total exposure. A small proportion of individuals did not have a recorded or usable (typically measured in units that could not be transformed) HbA_{1c} value for 2003–06 (3769 [6·9%] of54 803) and total exposure (3186 [5·8%] of 54 803).

Table 3 shows the survival data for HbA_{1c} categories and glycaemic variability. The HbA_{1c} categories indicate that survival reduces incrementally with HbA_{1c} values more than 8% (64 mmol/mol) for both sexes, with a reduction also occurring with values less than 6% (42 mmol/mol). Survival is inversely associated with glycaemic variability score for women and men and is strongest for total exposure.

The adjusted HRs for all-cause mortality (time to death) from the three Cox regression models are shown in figure 1 by HbA_{1c} category and in the appendix by age group. The data show a J-shaped distribution for both sexes, in which mortality risk increases significantly with HbA_{1c} values more than 8% (64 mmol/mol) and less than 6% (42 mmol/mol), although mortality risk was non-significant in model 1 for men with HbA_{1c} values in the range 8% to less than 8·5% (64 mmol/mol to <69 mmol/mol) and in models 1 and 3 for both sexes at HbA_{1c} values less than 6% (42 mmol/mol). The adjusted HRs for HbA_{1c} less than 6% (42 mmol/mol) were 6% (model 1) and 15% (model 2) higher than the reference range for women and 4% lower (model 1) and 22% (model 2) higher than the reference range for men. Conversely, in model 3 (short-term effects), the adjusted HRs were 19% lower for women and 25% lower for men when HbA_{1c} was less than 6% (42 mmol/mol). This reduction in risk seemed to be related to the addition of polypharmacy (excluding diabetes therapies) to the time-varying model (HR 0·94–1·08 for women and 0·88–1·02 for men).

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

	Model 1*							Model 2†						
	n	1-year survival	3-year survival	5-year survival	Deaths	Person-years	Crude incidence (per 1000 person- years)	n	1-year survival	3-year survival	5-year survival	Deaths	Person-years	Crude incidence (per 1000 person-years)
People with duration of diabetes of 6 months or more														
Women (% HbA_{1c} [mmol/mol])														
3·0 to <6·0 (9 to <42)	2572	0·92	0·77	0·66	858	10 480	82	2412	0·91	0·75	0·62	890	9403	95
6·0 to <6·5 (42 to <48)	4144	0·94	0·82	0·71	1242	17 771	70	4195	0·94	0·81	0·70	1280	17 822	72
6·5 to <7·0 (48 to <53)	5663	0·94	0·82	0·73	1626	24 717	66	5971	0·94	0·83	0·73	1675	26 333	64
7·0 to <7·5 (53 to <58)	5045	0·94	0·83	0·73	1426	21 951	65	5310	0·94	0·84	0·74	1450	23 470	62
7·5 to <8·0 (58 to <64)	3288	0·94	0·83	0·71	951	14 153	67	3399	0·94	0·82	0·71	1005	14 706	68
8·0 to <8·5 (64 to <69)	2038	0·92	0·77	0·65	730	8297	88	2089	0·92	0·79	0·66	715	8637	83
8·5 to <9·0 (69 to <75)	1242	0·93	0·79	0·67	419	5155	81	1210	0·93	0·78	0·66	401	4867	82
9·0 to <9·5 (75 to <80)	838	0·91	0·75	0·64	294	3263	90	776	0·91	0·74	0·61	308	2949	104
9·5 to <10·0 (80 to <86)	479	0·90	0·74	0·58	203	1801	113	452	0·90	0·73	0·62	174	1722	101
≥10·0 (≥86)	675	0·89	0·70	0·56	287	2469	116	480	0·86	0·66	0·50	226	1599	141
Total	25 984	0·93	0·81	0·70	8036	110 056	73	26 294	0·93	0·81	0·70	8124	111 508	73
Men (% HbA_{1c} [mmol/mol])														
3·0 to <6·0 (9 to <42)	2401	0·92	0·79	0·68	809	10 316	78	2081	0·91	0·75	0·62	806	8388	96
6·0 to <6·5 (42 to <48)	3807	0·93	0·80	0·69	1269	16 560	77	3687	0·93	0·80	0·68	1273	15 906	80
6·5 to <7·0 (48 to <53)	5490	0·93	0·81	0·69	1783	23 752	75	5870	0·94	0·81	0·69	1888	25 548	74
7·0 to <7·5 (53 to <58)	5072	0·93	0·81	0·69	1635	21 887	75	5426	0·94	0·82	0·71	1641	23 945	69
7·5 to <8·0 (58 to <64)	3407	0·93	0·79	0·68	1138	14 420	79	3578	0·93	0·80	0·68	1160	15 331	76
8·0 to <8·5 (64 to <69)	2017	0·92	0·77	0·65	717	8348	86	2101	0·91	0·76	0·64	773	8662	89
8·5 to <9·0 (69 to <75)	1223	0·91	0·75	0·60	494	4904	101	1176	0·91	0·75	0·63	451	4787	94
9·0 to <9·5 (75 to <80)	700	0·93	0·77	0·62	268	2889	93	635	0·93	0·75	0·58	268	2504	107
9·5 to <10·0 (80 to <86)	416	0·90	0·70	0·57	184	1552	119	340	0·89	0·71	0·54	157	1241	126
≥10·0 (≥86)	517	0·87	0·67	0·51	240	1776	135	429	0·84	0·64	0·48	201	1400	144
Total	25 050	0·93	0·79	0·67	8537	106 405	80	25 323	0·93	0·79	0·67	8618	107 712	80
People with duration of diabetes of 5 years or more														
Women (glycaemic variability score)														
0–20	2504	0·95	0·85	0·74	675	11 064	61	2595	0·95	0·85	0·75	661	11 480	58
21–40	2930	0·95	0·83	0·73	819	12 794	64	4227	0·96	0·86	0·74	1138	19 219	59
41–60	3111	0·94	0·82	0·71	953	13 391	71	4693	0·95	0·84	0·72	1425	20 933	68
61–80	1968	0·91	0·77	0·64	701	7921	88	2589	0·93	0·76	0·60	1045	10 269	102
81–100	748	0·89	0·73	0·59	303	2858	106	611	0·86	0·66	0·46	299	2003	149
Total	11 261	0·94	0·81	0·70	3451	48 029	72	14 715	0·95	0·82	0·70	4568	63 905	71
Men (glycaemic variability score)														
0–20	2449	0·94	0·82	0·71	747	10 814	69	2471	0·94	0·82	0·71	750	10 860	69
21–40	3038	0·94	0·81	0·69	990	13 089	76	4474	0·96	0·83	0·71	1392	20 118	69
41–60	3393	0·94	0·79	0·66	1217	14 345	85	4972	0·95	0·82	0·70	1597	22 068	72
61–80	2105	0·91	0·76	0·64	772	8512	91	2720	0·92	0·75	0·60	1152	11 045	104
81–100	774	0·89	0·71	0·58	336	3011	112	616	0·85	0·62	0·43	332	1990	167
Total	11 759	0·93	0·79	0·67	4062	49 770	82	15 253	0·94	0·81	0·68	5223	66 081	79

*Baseline mean HbA_{1c} for 2003–06. †The mean across the whole follow-up period (ie, from 2003 to the year before the participant died or the last year of follow-up).

Table 3: **All-cause mortality by HbA_{1c} level and glycaemic variability score for model 1 and model 2**

The addition of the glycaemic variability score into the model for people with diabetes duration of 5 years or more (model 2) reduced the strength of the effect of higher glycaemic thresholds, extending the point at which significantly elevated risk is observed to an HbA_{1c} of about 9·5% (80 mmol/mol) in women and 9% (75 mmol/mol) in men. The risk at the lower threshold (HbA_{1c} 6% [42 mmol/mol]) showed a sharper elevation than the model without glycaemic variability for both sexes in model 2 (figure 2), with adjusted HRs of 25% higher for women and 30% higher for men than the respective values for the reference range (appendix). In men, a significant excess risk was apparent for HbA_{1c} values less than 7% (53 mmol/mol) in model 2. These risk differences were smaller in model 1 with adjusted HRs of 9% for women and 11% for men.

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

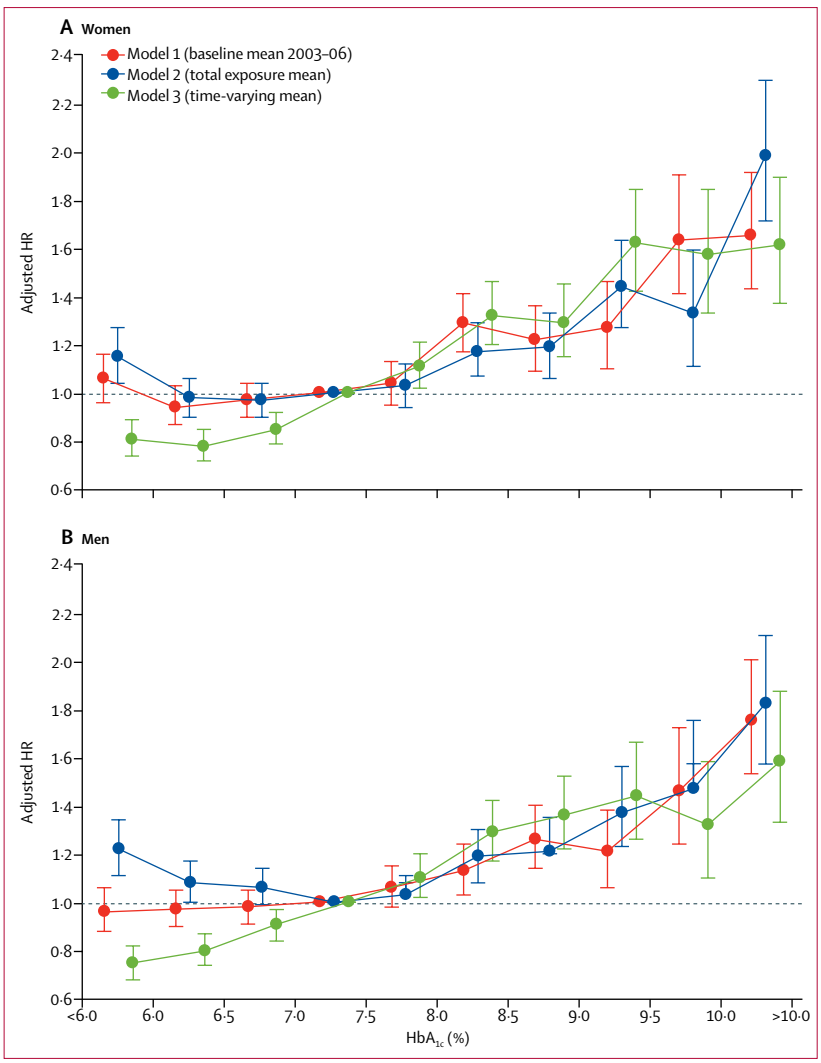

Figure 1: **Adjusted HRs by HbA_{1c} level for all-cause mortality in women (A) and men (B)**
Error bars are 95% CIs. HR=hazard ratio.

Mortality increased substantially with increasing glycaemic variability in both sexes, although this effect was stronger in model 2 than in model 1 (figure 3; appendix). The adjusted HRs comparing the group with a glycaemic variability score of more than 80 to 100 with the group with a score of 0 to 20 were 1·51 (95% CI 1·30–1·75) for women and 1·57 (1·35–1·82) for men in model 1, 2·47 (2·08–2·93) for women and 2·21 (1·87–2·61) for men in model 2, and 1·87 (1·59–2·19) for women and 1·54 (1·32–1·80) for men in model 3.

When the positive and negative direction metrics were added to model 2, people with scores outside the stable range (–20 to 20) had increased mortality risk, with a greater increase in risk seen in people with negative changes than in those with positive changes in HbA_{1c} (HRs 2·47 [95% CI 2·25 to 2·71] *vs* 1·82 [1·61 to 2·05] for women and 2·43 [2·22 to 2·66] *vs* 1·57 [1·40 to 1·75] for men; appendix). Findings for linear slope of mean HbA_{1c} were similar to those for the direction metric. Women with a negative slope of 0·2 or more (HR 2·51, 95% CI 2·32–2·72) or a positive slope of 0·2 or more (1·83, 1·65–2·04) observed increased mortality compared with those with slopes (positive or negative) of less than 0·1 (HR 1·00). The corresponding HRs for men were 2·39 (95% CI 2·20–2·60) for those with a negative slope of 0·2 or more and 1·83 (1·66–2·02) for those with a positive slope of 0·2 or more. A cross-tabulation of the variability and direction scores shows that women with a variability score greater than 40 were more likely to have had reductions in their HbA_{1c}; this observation was seen to a lesser extent in men (appendix). The mortality risk for the final measure of variability (SD of mean HbA_{1c}) confirmed the pattern already seen with increased mortality for those individuals observing the highest level of variability (appendix).

The findings remained similar when the combined comorbidity scores were replaced in models 1–3 by individual comorbidities, with 476 (72·1%) of 660 of the estimated HRs for HbA_{1c} level and glycaemic variability score within a range of 0·03 of each other (appendix). Omission of people with HbA_{1c} values less than 5·5% (56 mmol/mol) attenuated the risk associated with HbA_{1c} less than 6% (42 mmol/mol), reducing adjusted HRs from 1·15 to 1·09 for women and from 1·22 to 1·19 for men in model 2, with risk for all other HbA_{1c} groups unaltered. The association between BMI and HbA_{1c} in model 2 (total exposure) was weak (r=0·10 for women and r=0·08 for men). In model 2, women with a BMI of less than 18 kg/m² were more likely to have HbA_{1c} values less than 6% (42 mmol/mol) than those with a BMI of 20 to less than 25 kg/m² (74 [22·8%] of 325 *vs* 701 [12·0%] of 5827); the findings for men were similar (19 [22·1%] of 86 *vs* 591 [10·7%] of 5529). Age at diagnosis had a small effect on mortality. Men diagnosed with diabetes when younger than 65 years who had a glycaemic variability score of more than 61 had greater risk of mortality than those diagnosed later, whereas the reverse was seen for women (appendix).

We evaluated data completeness for these analyses, the percentage of people with more than one valid HbA_{1c} measurement per annum increased from 55% (30 141 of 54 803) in 2003 to 76% (26 786 of 54 803) in 2005, remaining within 2% of this level for the remainder of the observational period. Non-proportionality ($p<0·05$ and not adjusted for multiple testing) in the models without glycaemic variability score occurred more often in model 1 (40 [19%] of 210 tests) and model 2 (42 [20%] of 210) than in the time-varying model 3 (22 [10%] of 210), for use of antibiotics (22 [73%] of 30), and polypharmacy (27 [90%] of 30). Non-proportionality occurred less often for other variables apart from BMI (eight [27%] of 30) and chronic kidney disease stage (ten [33%] of 30). Use of a more stringent p value to account for multiple testing reduces the number of significant tests from 104 to 25 (ten for use of antibiotics, and nine for polypharmacy) of

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

630. Results were similar when glycaemic variability score was added to the models. The proportional and non-proportional hazard models were not different and risk profiles with increasing HbA_{1c} and variability remained consistent.

Discussion

Our findings show that in an older population, the frequency of clinically significant changes in HbA_{1c} has a monotonically increasing association with mortality risk, with that risk being 60% greater in those with the highest glycaemic variability score compared with those with the lowest score. This estimation is more modest than that reported in a meta-analysis[11] of five studies (18 940 patients with type 2 diabetes) which estimated a relative risk for mortality of 2·89 (95% CI 1·45–5·74) with increased glycaemic variability. However, data from three of these studies reported elevated mortality risks of between 30% and 99%, which were congruent with our data, with one study reporting a three-fold risk elevation and another reporting a very small increase of 4%.

Although previous studies have shown that variability in HbA_{1c} increases risk of diabetes complications and mortality,[11,17,18] these studies were not specific to older people and used estimations of glycaemic variability based on SD of the mean HbA_{1c}. By contrast, our variability score was weighted for clinically significant changes in HbA_{1c} (≥0·5% [≥5·5 mmol/mol]), and we also considered the frequency and direction of variation to provide more granularity in our interpretation. When we considered SD in HbA_{1c} as an alternative assessment of glycaemic variability in our sensitivity analysis, the findings were concordant with those from our primary analysis that used the variability score. In terms of the direction of the observed variability, both increases and decreases heightened the risk of mortality, although the risk seems to be greater in the direction of intensification (ie, reducing HbA_{1c}). Addition of glycaemic variability to our models for glycaemic control altered the risk distribution particularly in women, for which a much wider HbA_{1c} threshold of low mortality risk was observed between about 6·0% (42 mmol/mol) and 9·5% (80 mmol/mol); however, the effect on men was less marked.

Although the pathophysiological mechanisms that might explain these findings remain unknown, they are probably multifactorial. Findings from one study[19] suggested that the effects of glycaemic variability on cardiovascular outcomes and mortality might be explained by fluctuations in glucose control over time but with an aggregate of hyperglycaemia driving tissue damage. Short-term glucose variations have been postulated as a risk factor for vascular complications; although this hypothesis is unproven, an analysis[19] of 7586 participants in the DEVOTE trial of insulin degludec versus insulin glargine considered the effect of variability

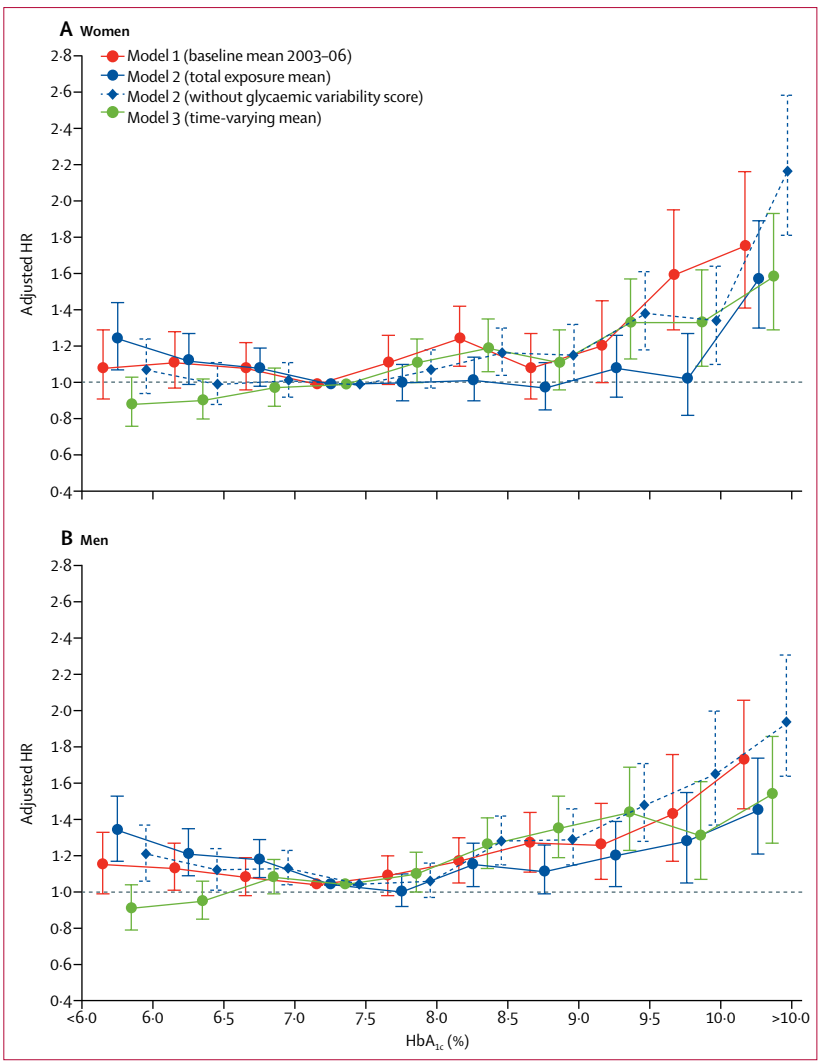

Figure 2: **Adjusted HRs for all-cause mortality, with glycaemic variability score included in the model, by HbA_{1c} level, in women (A) and men (B) with duration of diabetes of 5 years or more**
Error bars are 95% CIs. HR=hazard ratio.

in fasting glucose and identified an increased mortality risk ranging from 33% to 53% between the lowest and highest variability groups in their pooled analysis. However, in the older population, it might also be that the physiological changes that accompany older age, together with altered nutrition and activity, are key drivers of the effect of glycaemic variability on mortality. Further research is needed to explain the mechanisms that drive glycaemic variation or its effects, including in older people with diabetes.

From a clinical perspective, our findings suggest that glycaemic variability might be an important indicator and possibly a risk predictor in older people with diabetes. Although these data suggest the need for caution in intensifying glycaemic control too aggressively in older people, health-care professionals must consider that there might be other factors that influence glycaemic variability

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

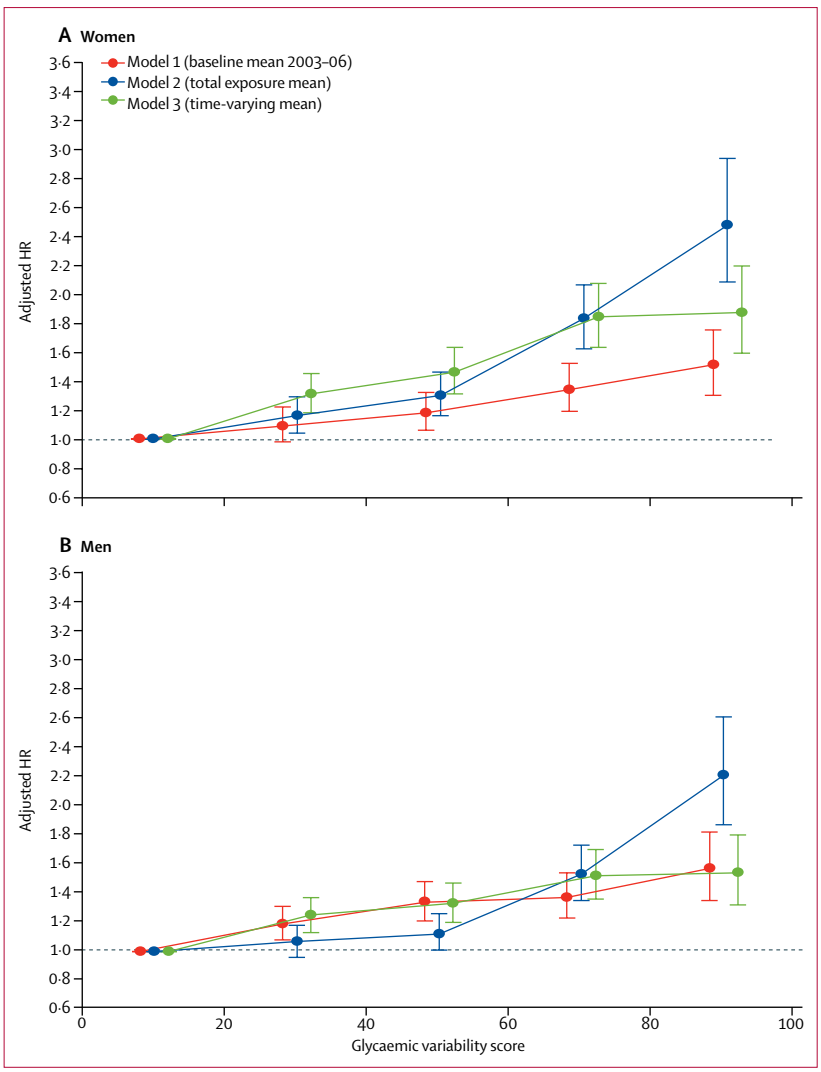

Figure 3: **Adjusted HRs for all-cause mortality, by glycaemic variability score, in women (A) and men (B) with duration of diabetes of 5 years or more**
Error bars are 95% CIs. HR=hazard ratio.

that independently confer mortality risk. In a post-hoc analysis of the ADVANCE study[20] exploring glycaemic variation, mortality risk was increased in relation to higher variability in HbA_{1c} in both the intensively treated and control groups, suggesting that variability was associated with mortality independent of glucose-control intensification. Additionally, long-term follow-up of studies with intensive glycaemic control suggest a sustained survival advantage in the intensively treated groups,[21] although one follow-up study of a large intensification trial did not show any effect on mortality.[21] Furthermore, in our study, we observed glucose lowering therapies conveyed a very modest level of risk and this risk was exclusive to sulfonylureas and insulin; therefore, it is unlikely that overtreatment explains the mortality risk observed with lower levels of HbA_{1c}. Huang and colleagues[3] reported that the patients in the lower glycaemic group (HbA_{1c} <6%) in the Diabetes and Aging Study had significantly less exposure to glucose-lowering drugs than did those with better glycaemic control. Hence, it would seem unlikely that the increased mortality risk observed at the lower threshold of HbA_{1c} can be attributed solely to excess glucose lowering; in the older population, it might be that other factors such as frailty and malnutrition[22] or hypoglycaemia[23] are also important contributory factors.

In terms of glycaemic control and mortality, our data concur with previous studies that have shown a J-shaped distribution for risk.[2–4] However, our study provides more specific estimations in relation to this distribution by using finer HbA_{1c} increments (0·5% [5·5 mmol/mol]), 5-year age bands (extending to those aged >85 years), considering differences between women and men, and adjusting for the effect of low HbA_{1c} values (<5·5% [<37 mmol/mol]) in our sensitivity analysis. In our study, the J-shaped distribution for mortality and mean HbA_{1c} was only significant for HbA_{1c} values less than 6% in both sexes, although there was an incremental increase in risk with HbA_{1c} values greater than 8% (64 mmol/mol) in men and 8·5% (69 mmol/mol) in women. These observations are partially congruent with findings from an observational study of 1279 adults (aged >65 years), which showed significant increases in mortality risk with HbA_{1c} greater than 8% (64 mmol/mol), but no J-shaped distribution was noted.[24] Therefore, the range for glycaemic control with lower risk might be broader than was suggested by earlier analyses[2,3] and the risk in the lower range less substantial than has been previously reported,[2] with the lower risk margins being broader when the effect of glycaemic variability is taken into account.

Our findings suggest that health-care professionals might need to re-evaluate how they interpret low HbA_{1c} values in older people with diabetes. Exceptionally low HbA_{1c} values have previously been linked to mortality. Paprott and colleagues[25] analysed data from 6299 patients with diabetes over 11 years and reported a 70% increased risk of mortality in patients who had an HbA_{1c} of 5% (31 mmol/mol) or less, compared with a reference group with an HbA_{1c} of 5% (31 mmol/mol) to 5·7% (39 mmol/mol). Low HbA_{1c} levels have been associated with increased inflammatory activity and altered liver function,[26] and in an older population these changes might be linked to the physical and metabolic decline observed in frailty.[26] Indeed, in a prospective study, frailty risk in diabetes was shown to also follow a J-shaped distribution with HbA_{1c}, with the risk of frailty increasing with HbA_{1c} values of less than 7·5% (58 mmol/mol).[27] Although we had no direct measure for frailty in our study, we did consider BMI as a proxy measure; although we identified no correlation between low BMI and low HbA_{1c}, we did note a significantly increased mortality risk in those with a BMI of 20 or less. Overall, our data suggest that lower HbA_{1c} values in older people are more likely to be a marker for elevated risk of mortality, rather than a consequence of excess glucose intensification.

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

Our data broadly support the glycaemic targets identified in current guidelines for diabetes in older people,[9,10,28,29] but they also suggest that some of the factors such as comorbidities and disease duration used in these guidelines to indicate the need for less stringent glycaemic control do not adequately reflect the complex interaction between ageing and the exposures that follow a diagnosis of diabetes. Furthermore, although these guidelines promote individual targets, an emphasis on fixed glycaemic targets to guide therapy still exists, rather than on managing or reducing the exposure to glycaemic variability. Our findings suggest that in older people changes in glycaemic control, particularly a lowering in HbA_{1c}, that occur independent of therapeutic intervention should be considered in clinical risk assessment and management. Perhaps guidelines should encourage clinicians to be more attentive to both decreasing and increasing HbA_{1c} levels, with an emphasis on gradual intensification and glycaemic stability.

We recognise some important limitations of our study. As with all studies using large datasets of routinely collected data, some variation in the accuracy of data exists, although the data used were in accordance with other UK national datasets.[12] We were also limited by not having any specific data for important indicators such as frailty. This limitation might be remedied in future UK studies, as the new contract for general practice includes frailty screening for people older than 65 years. Additionally, we did not characterise diabetes type, because this characterisation is challenging in primary care data. It is also important to emphasise that we did not have access to blood glucose measurements that would reflect glucose variability, because these measurements are not recorded in primary care. Therefore, we could not explore the relation between glycaemic variability and variations in diurnal blood glucose patterns, which might be important in the context of the study population. Furthermore, the HbA_{1c} data were not collected in a controlled time-specified way; a more regulated framework of data collection would have reduced potential measurement bias.

In conclusion, our findings suggest that glycaemic variability might be an important factor in understanding mortality risk in older people with diabetes, affirming the need to develop better strategies for glucose management in this population. Although development of a strategy to more reliably achieve stable glycaemic control in older people might be important, further examination of the relationship between glycaemic variability and clinical outcomes is required to inform appropriate treatment targets and models for glycaemic control in this population. Further understanding of this relationship might enable determination of dynamic, risk-modelled, and individualised targets for older people rather than fixed thresholds, which might also reflect differences between women and men. Our study also suggests that health-care professionals need to reconsider how they evaluate the J-shaped curve observed in the relation between HbA_{1c} thresholds and mortality, suggesting that mortality at the lower end of this distribution might be related to age-related factors rather than excess glycaemic intensification.

Contributors

AF led the study design and analytical interpretation of the study findings, and contributed to data assessment and statistical interpretation. TM was the study statistician and led the data management and statistical analysis. TM also coordinated the necessary approvals and licensing of the dataset. HM contributed to the analytical interpretation of the data. AJS provided oversight of the study design, context, and analytical interpretation of the data.

Declaration of interests

AF has previously received honoraria or unrestricted educational grants unrelated to this study from Ascensia Diabetes Care, Abbott, Roche, and Eli Lilly. AJS has previously received honoraria or unrestricted educational grants unrelated to this study from MSD, Pfizer, Takeda, Sanofi, and Eli Lilly. TM and HM declare no competing interests.

Acknowledgments

This study was funded by King's College London (London, UK) and Diabetes Frail. We acknowledge The Health Improvement Network (THIN), who compile and distribute the THIN dataset.

References

1 Huang ES, Davis AM. Glycemic control in older adults with diabetes mellitus. *JAMA* 2015; **314:** 1509–10.

2 Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA_{1c} in people with type 2 diabetes: a retrospective cohort study. *Lancet* 2010; **375:** 481–89.

3 Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the Diabetes and Aging Study. *Diabetes Care* 2011; **34:** 1329–34.

4 Grembowski D, Ralston JD, Anderson ML. Hemoglobin A_{1c}, comorbid conditions and all-cause mortality in older patients with DM: a retrospective 9-year cohort study. *Diabetes Res Clin Pract* 2014; **106:** 373–82.

5 Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; **358:** 2560–72.

6 Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; **358:** 2545–59.

7 Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; **360:** 129–39.

8 Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientific statement of the American College of Cardiology Foundation and the American Heart Association. *J Am Coll Cardiol* 2009; **53:** 298–304.

9 Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012; **35:** 2650–64.

10 Sinclair A, Morley JE, Rodriguez-Mañas L, et al. Diabetes mellitus in older people: position statement on behalf of the International Association of Gerontology and Geriatrics (IAGG), the European Diabetes Working Party for Older People (EDWPOP), and the International Task Force of Experts in Diabetes. *J Am Med Dir Assoc* 2012; **13:** 497–502.

11 Gorst C, Kwok C, Aslam S, et al. Long-term glycemic variability and risk of adverse outcomes: a systematic review and meta-analysis. *Diabetes Care* 2015; **38:** 2354–69.

12 Blak BT, Thompson M, Dattani H, Bourke A. Generalisability of The Health Improvement Network (THIN) database: demographics, chronic disease prevalence and mortality rates. *Inform Prim Care* 2011; **19:** 251–55.

13 Murrells T, Ball J, Maben J, Ashworth M, Griffiths P. Nursing consultations and control of diabetes in general practice: a retrospective observational study. *Br J Gen Pract* 2015; **65:** 639–42.

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.

14 Public Health England. Diabetes prevalence model. 2016. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/612306/Diabetesprevalencemodelbriefing.pdf (accessed March 4, 2018).

15 Khan N, Perera R, Harper S, Rose W. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC Fam Pract* 2010; **11:** 1.

16 Lin DY, Wei LJ. The robust inference for the proportional hazards model. *J Am Stat Assoc* 1989; **84:** 1074–78.

17 Kilpatrick ES, Rigby AS, Atkin SL. A_{1c} variability and the risk of microvascular complications in type 1 diabetes: data from the Diabetes Control and Complications Trial. *Diabetes Care* 2008; **31:** 2198–202.

18 Kilpatrick ES. Haemoglobin A_{1c} in the diagnosis and monitoring of diabetes mellitus. *J Clin Pathol* 2008; **61:** 977–82.

19 Zinman B, Marso SP, Poulter NR, et al. Day-to-day fasting glycaemic variability in DEVOTE: associations with severe hypoglycaemia and cardiovascular outcomes (DEVOTE 2). *Diabetologia* 2018; **61:** 48–57.

20 Hirakawa Y, Arima H, Zoungas S, et al. Impact of visit-to-visit glycemic variability on the risks of macrovascular and microvascular events and all-cause mortality in type 2 diabetes: the ADVANCE trial. *Diabetes Care* 2014; **37:** 2359–65.

21 Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. *N Engl J Med* 2008; **359:** 1577–89.

22 Castro-Rodríguez M, Carnicero JA, Garcia-Garcia FJ, et al. Frailty as a major factor in the increased risk of death and disability in older people with diabetes. *Am Med Dir Assoc* 2016; **17:** 949–55.

23 Tong CV, Noor NM, Mohamad M, Nesaratnam S, Hussein Z. Glycemic variability among older adults with type 2 diabetes. *J Diabetes Metab* 2016; **7:** 652.

24 Palta P, Huang E, Kalyani R, Golden SH, Yeh H-C. Hemoglobin A_{1c} and mortality in older adults with and without diabetes: results from the National Health and Nutrition Examination Surveys (1988–2011). *Diabetes Care* 2017; **40:** 453–60.

25 Paprott R, Schaffrath A, Markus R, Heidemann C. Association between hemoglobin A_{1c} and all-cause mortality: results of the mortality follow-up of the German National Health Interview and Examination Survey 1998. *Diabetes Care* 2015; **38:** 249–56.

26 Carson AP, Fox CS, McGuire DK, et al. Low hemoglobin A1c and risk of all-cause mortality among US adults without diabetes. *Circ Cardiovasc Qual Outcomes* 2010; **3:** 661–67.

27 Zaslavsky O, Walker RL, Crane PK, Gray SL, Larson EB. Glucose levels and risk of frailty. *J Gerontol A Biol Sci Med Sci* 2016; **71:** 1223–29.

28 Dunning T, Sinclair A, Colagiuri S. IDF guideline for managing type 2 diabetes in older people. *Diabetes Res Clin Pract* 2014; **103:** 538–40.

29 California Healthcare Foundation/American Geriatrics Society Panel on Improving Care for Elders with Diabetes. Guidelines for improving the care of the older person with diabetes mellitus. *J Am Geriatr Soc* 2003; **51** (suppl 5)**:** 265–80.

Downloaded for Anonymous User (n/a) at Australian National University from ClinicalKey.com.au by Elsevier on March 13, 2023. For personal use only. No other uses without permission. Copyright ©2023. Elsevier Inc. All rights reserved.