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ARTICLE

Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study

E. L. M. Barr · E. J. Boyko · P. Z. Zimmet · R. Wolfe · A. M. Tonkin · J. E. Shaw

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Abstract
Aims/hypothesis Hyperglycaemia is a risk factor for cardiovascular disease (CVD) and all-cause mortality in individuals without diabetes. We investigated: (1) whether the risk of all-cause and CVD mortality extended continuously throughout the range of fasting plasma glucose (FPG), 2 h plasma glucose (2hPG) and HbA_{1c} values; and (2) the ability of these measures to improve risk prediction for mortality.
Methods Data on 10,026 people aged ≥25 years without diagnosed diabetes were obtained from the population-based Australian Diabetes, Obesity and Lifestyle study. Between 1999 and 2000, FPG, 2hPG and HbA_{1c} were assessed and all-cause (332 deaths) and CVD (88 deaths) mortality were obtained after 7 years.
Results Both 2hPG and HbA_{1c} exhibited linear relationships with all-cause and CVD mortality, whereas FPG showed J-shaped relationships. The adjusted HR (95% CI) for all-cause mortality per SD increase was 1.2 (1.1–1.3) for 2hPG and 1.1 (1.0–1.2) for HbA_{1c}. The HR for FPG <5.1 mmol/l (per SD decrease) was 2.0 (1.3–3.0); for FPG ≥5.1 mmol/l (per SD increase) the HR was 1.1 (1.0–1.2). Corresponding HRs for CVD mortality were 1.2 (1.0–1.4), 1.2 (1.0–1.3), 4.0 (2.1–7.6) and 1.3 (1.1–1.4). The discriminative ability of each measure was similar; no measure substantially improved individual risk identification over traditional risk factors.
Conclusions/interpretation In individuals without diagnosed diabetes, 2hPG and FPG, but not HbA_{1c} were significant predictors of all-cause mortality, whereas all measures were significant predictors of CVD mortality. However, these glucose measures did not substantially improve individual risk identification.

Keywords Cardiovascular disease · Diabetes · Hyperglycaemia · Mortality

Abbreviations

AusDiab	Australian Diabetes, Obesity and Lifestyle
CVD	cardiovascular disease
DECODE	Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe
FPG	fasting plasma glucose
GHb	total glycated haemoglobin
2hPG	2 h plasma glucose
IDI	integrated discrimination improvement
NDI	Australian National Death Index
NRI	net reclassification improvement

E. L. M. Barr (✉) · E. J. Boyko · P. Z. Zimmet · J. E. Shaw
Baker IDI Heart and Diabetes Institute,
250 Kooyong Road,
Caulfield 3162 VIC, Australia
e-mail: Elizabeth.Barr@bakeridi.edu.au

E. L. M. Barr · P. Z. Zimmet · R. Wolfe · A. M. Tonkin · J. E. Shaw
Department of Epidemiology and Preventive Medicine,
Monash University,
Melbourne, VIC, Australia

Introduction

Uncertainty remains regarding the relationship between glycaemia and each of mortality and cardiovascular disease (CVD), especially below the diagnostic threshold for diabetes [1–5]. The continuous relationships between blood glucose and all-cause or CVD mortality have been described as threshold [6, 7], continuous [8, 9] and J-shaped [10, 11]. For

CVD risk, all meta-analyses report a graded continuous relationship for post-load blood glucose [3, 4, 12]. However, for fasting blood glucose, a graded continuous relationship [3], a J-shaped relationship [12] and a threshold relationship [4] have been reported. The Diabetes Epidemiology: Collaborative Analysis Of Diagnostic Criteria in Europe (DECODE) study [12] evaluated all-cause mortality and reported J-shaped relationships for fasting and post-load blood glucose. However, limitations of these meta-analyses include: (1) the component studies used different blood sample types (e.g. whole blood or plasma) and different glucose assays [3, 4, 12]; (2) failure to fully adjust for concomitant CVD risk factors [3, 4]; (3) lack of data on women [3, 12]; and (4) no data on the nature of the continuous relationships for HbA_{1c} [3, 4, 12]. Furthermore, the findings from these meta-analyses may have limited relevance to contemporary populations as baseline data from the component studies were collected up to 20 years ago [3, 4, 12].

Both fasting and post-load blood glucose, and HbA_{1c} reflect different glycaemic metabolic processes [13], potentially leading to different associations with mortality and CVD. In people without diagnosed diabetes, some studies report that fasting blood glucose is associated with all-cause and CVD mortality [4, 8, 14], whereas others report that post-load blood glucose is more strongly related to these outcomes than fasting blood glucose [3, 12, 15]. HbA_{1c} has also been found to be associated with subsequent CVD [7, 16–18]. Only a few studies have compared all three glycaemic indices in the same population [19–22], with all but one [19] indicating that 2 h blood glucose was most strongly associated with all-cause mortality and/or CVD [20–22]. However, these latter studies were undertaken in men only [22], in middle- to older-aged adults [19, 20, 22] or analysed total glycated haemoglobin (GHb) rather than HbA_{1c} [19]. Therefore, they may not be generalisable to the wider population. Furthermore, these studies did not comprehensively assess the nature of the relationships between each glucose measure and the outcomes of interest or the contribution of the different glucose measures to individual risk discrimination for total and CVD mortality risk [19–22].

Developing a better understanding of the magnitude and nature of these relationships, as well as evaluating the extent to which glucose contributes to individual risk stratification would elucidate the potential benefit of glucose control among persons without diabetes and indicate which, if any, measure of glycaemia is the most appropriate for prediction of mortality in the general population. Accordingly, this study used 7 year follow-up data from a cohort of 10,026 people aged ≥25 years without previously diagnosed diabetes, who participated in the Australian Diabetes, Obesity and Lifestyle (AusDiab) Study to examine: (1) the nature and strength of the relationships between each of fasting plasma glucose (FPG), 2 h post-load plasma glucose (2hPG) and HbA_{1c}, and CVD and all-cause mortality; and (2) whether any of the glucose measures improved prediction of CVD and all-cause mortality beyond that achieved by traditional risk factors.

Methods

Study design and population AusDiab is a national Australian prospective population-based cohort study. Baseline measurements were collected from 1999 to 2000 on 11,247 non-institutionalised men and women aged ≥25 years. Detailed methods have been previously described [23]. Briefly, individuals were recruited from 42 randomly selected census districts, six in each state and in the Northern Territory. From the 17,129 eligible households, 20,347 individuals completed a household interview and 11,247 (55.3%) had a biomedical examination, giving an overall response rate of 37%. Participants were excluded if at baseline they had previously known diabetes (n=475; based on self-reported physician-diagnosed diabetes with use of hypoglycaemic medication or FPG ≥7.0 mmol/l or 2hPG ≥11.1 mmol/l), had not fasted for ≥9 h (n=18), were pregnant (n=60) or had missing values for FPG (n=1), 2hPG (n=125), HbA_{1c} (n=61) or other covariates included in the analyses (n=475). Six participants who died could not be matched to the Australian National Death Index (NDI) and were also excluded. Thus, these analyses were undertaken in 10,026 participants. All participants gave informed consent, and ethics approval was provided by the Ethics Committees of the International Diabetes Institute, Monash University and the Australian Institute of Health and Welfare.

Measurements Data on age, sex, use of anti-hypertensive and lipid-lowering medications, history of CVD (angina, myocardial infarction or stroke) and smoking (never, ex- or current smoker) were collected by interview. Measurements included blood pressure [24], anthropometrics [25] and a 75 g OGTT. Values for FPG, 2hPG, fasting serum total cholesterol, triacylglycerol and HDL-cholesterol were measured using an analyser (AU600; Olympus Optical, Tokyo, Japan). GHb was measured from frozen samples of whole blood collected in EDTA tubes and stored at −70°C for 2–36 months, using high performance liquid chromatography (Bio-Rad Variant Hemoglobin Testing System; Bio-Rad, Hercules, CA, USA) with standardised conversion to HbA_{1c} (normal range 4.2–6.3%). Previous studies have confirmed the stability of HbA_{1c} in samples stored for 56 weeks [26]. A validation study conducted on AusDiab samples (n=17) compared HbA_{1c} values on samples stored for 5 months with the results from the same samples after storage for 26 months. The mean (maximum) difference was 0.03 (0.2) percentage points.

Follow-up and outcomes Follow-up for all-cause mortality was to the date of death or 1 June 2006, whichever occurred first. As there is a delay between obtaining vital status data and cause of death information from the NDI, the period of follow-up for CVD and non-CVD mortality was up to the date of death or 5 December 2005. Deaths due to non-CVD causes are a competing risk for CVD mortality and therefore, the associations between the glucose indices and non-CVD mortality were also explored. Mortality status, as well as underlying and contributory causes of death were determined by linking the AusDiab cohort to the NDI using methods previously described [2]. The accuracy of the NDI for ascertainment of vital status and CVD deaths has been established [27]. People who were not matched to the NDI were assumed to be alive. Deaths were attributed to CVD if the underlying cause of death was coded I10-I25, I46.1, I48, I50-I99 or R96 according to the 2006 International Classification of Diseases 10th revision (ICD-10; http://www.who.int/classifications/icd/en/). In cases where the underlying cause of death was uncomplicated diabetes (E109, E119 or E149) or unspecified hyperlipidaemia (E785), CVD was considered to be the cause of death (n=2) if any of the CVD codes (I10-I25, I46.1, I48, I50-I99 or R96) were recorded in the first position on the death certificate.

Statistical analysis FPG, 2hPG and HbA_{1c} were analysed as categorical and continuous variables.

First, FPG, 2hPG and HbA_{1c} were classified into quintiles. The upper quintiles of FPG and 2hPG were further divided to reflect the American Diabetes Association [28] or WHO [29, 30] criteria for impaired fasting glucose, impaired glucose tolerance and diabetes. Unadjusted mortality rates (95% CI) per 1,000 person-years were calculated for each category of FPG, 2hPG and HbA_{1c}. To test differences in means and proportions for baseline characteristics between the categories of FPG, 2hPG and HbA_{1c}, one-way analysis of variance and χ^2 test analyses were used, respectively. Continuous covariates with skewed distributions were logarithmically transformed prior to analysis.

Second, the nature of the continuous relationships between each glucose measure and all-cause, CVD and non-CVD mortality was evaluated by comparing age- and sex-adjusted Cox proportional hazard models fitted with a linear term only to models with linear plus quadratic terms, linear plus quadratic plus cubic terms and linear plus log-transformed terms. These nested models were compared using log-likelihood ratio tests. In addition, piecewise linear splines, which do not assume a particular functional form between the exposure and outcome [31], were also used to explore non-linear relationships between each glucose measure and all-cause, CVD and non-CVD mortality. For each measure, the simplest model with the lowest Akaike's Information Criterion (AIC) [32] was deemed to be the best and was used in subsequent analyses.

Covariates achieving $p<0.25$ in univariate analysis or those considered to be important confounders were entered into the multivariate model. Final models were adjusted for reported history of CVD, smoking, diastolic blood pressure (which showed a stronger association with all-cause and CVD mortality than did systolic blood pressure), waist-to-hip ratio, use of lipid-lowering medication, total cholesterol and triacylglycerol (which showed stronger associations with the outcomes than HDL). In order to compare the strength of the associations between the glucose measures and mortality outcomes, HRs and 95% CIs for each of the glucose measures were expressed per 1 SD. Correlations between blood glucose measures, and between blood glucose measures and other covariates were assessed with Pearson's or Spearman's correlation coefficients. There was no evidence of multicollinearity between covariates for any of the fitted models (variance inflation factor <4 for all independent variables) [33].

Interactions between each glucose measure and sex, age and history of CVD were tested using log–likelihood ratio tests of models containing the variables as single terms nested within models including the first-order interactions. Stratified analyses according to sex were conducted for all-cause mortality but not for cause-specific mortality, because there were fewer deaths.

Proportional hazards assumptions were satisfied for the three principal measures as assessed with graphs of log–log plots of the relative hazards by time for discrete variables and by scaled Schoenfeld residuals.

Log–likelihood ratio statistics tested whether the addition of FPG, 2hPG or HbA_{1c} to a model with only age, sex and other covariates improved model performance, and whether the predictive effect of each multivariate-adjusted model including FPG, 2hPG and HbA_{1c} alone was influenced by adding 2hPG or HbA_{1c}, FPG or HbA_{1c}, and FPG or 2hPG, respectively.

The ability of FPG, 2hPG or HbA_{1c} to identify individual 5 year all-cause and CVD mortality risk was evaluated using the c-statistic, the net reclassification improvement (NRI) and integrated discrimination improvement (IDI) [34]. The c-statistic is obtained by considering all possible pairings of participants with and without the outcome and is equal to the proportion of those pairs in which the participant with the outcome has a higher glucose value than the person surviving. It ranges from 0.5 (poor discrimination) to 1.0 (perfect discrimination). A 0.01 increment corresponds to an additional 1% of pairs where the member of the pair experiencing the outcome has the higher glucose value. The NRI and IDI measures assume that any increases in predicted probabilities for an event due to an improved model for risk are only beneficial among those who experienced an event, whereas any decreases in

Table 1 Baseline characteristics according to categories of FPG, 2hPG and HbA_{1c} in individuals without previously diagnosed diabetes—the AusDiab study

Blood glucose	*n*	Deaths	CVD deaths	Age, years	Male	History of CVD[a]	Current or ex-smoking	Hypertension[b]	Systolic BP (mmHg)	Diastolic BP (mmHg)	TC (mmol/)	TG (mmol/l)[c]	Lipid-lowering drugs	WHR	BMI, (kg/m^2)
FPG[d]															
<5.1	2,614	66 (2.5)	20 (0.8)	47 (14)	646 (25)	121 (5)	1,064 (41)	423 (16)	121 (16)	66 (11)	5.5 (1.1)	1.0 (0.8)	98 (4)	0.82 (0.08)	25.2 (4.5)
5.1–	1,569	28 (1.8)	5 (0.3)	49 (14)	615 (39)	97 (6)	677 (43)	379 (24)	126 (17)	69 (11)	5.6 (1.0)	1.2 (0.9)	90 (6)	0.85 (0.09)	26.1 (4.4)
5.3–	2,339	80 (3.4)	13 (0.6)	51 (14)	1,137 (49)	165 (7)	1,030 (44)	739 (32)	130 (18)	70 (11)	5.7 (1.0)	1.3 (0.9)	184 (8)	0.87 (0.09)	26.8 (4.7)
5.6–	2,265	80 (3.5)	23 (1.0)	54 (13)	1,323 (58)	189 (8)	1,060 (47)	875 (39)	133 (18)	73 (11)	5.8 (1.1)	1.4 (1.1)	205 (9)	0.89 (0.08)	27.8 (4.7)
6.1–	1,013	63 (6.2)	20 (2.0)	57 (13)	643 (63)	128 (13)	530 (52)	519 (51)	137 (18)	75 (12)	5.9 (1.1)	1.7 (1.2)	144 (14)	0.92 (0.08)	29.1 (5.0)
>7.0	226	15 (6.6)	7 (3.1)	59 (12)	137 (61)	30 (13)	123 (54)	162 (72)	145 (18)	77 (12)	5.9 (1.2)	2.0 (1.6)	36 (16)	0.94 (0.08)	31.6 (5.8)
2hPG[d]															
<4.8	2,178	34 (1.6)	8 (0.4)	47 (12)	1,083 (50)	93 (4)	1,114 (51)	368 (17)	123 (15)	68 (11)	5.5 (1.0)	1.1 (0.8)	89 (4)	0.85 (0.09)	25.3 (4.1)
4.8–	2,089	47 (2.2)	10 (0.5)	48 (13)	924 (44)	127 (6)	905 (43)	475 (23)	125 (17)	69 (12)	5.6 (1.0)	1.1 (0.8)	112 (5)	0.85 (0.09)	26.0 (4.4)
5.6–	1,785	51 (2.9)	14 (0.8)	49 (14)	792 (44)	115 (6)	729 (41)	457 (26)	127 (17)	70 (11)	5.6 (1.0)	1.2 (0.9)	123 (7)	0.86 (0.09)	26.6 (4.5)
6.3–	2,271	77 (3.4)	22 (1.0)	53 (14)	976 (43)	183 (8)	977 (43)	836 (37)	132 (19)	71 (12)	5.8 (1.1)	1.4 (1.1)	206 (9)	0.87 (0.09)	27.8 (4.9)
7.8–	1,372	87 (6.3)	21 (1.5)	59 (14)	573 (42)	154 (11)	608 (44)	738 (54)	138 (19)	73 (12)	5.9 (1.1)	1.6 (1.2)	171 (12)	0.89 (0.09)	28.8 (5.4)
>11.1	331	36 (10.9)	13 (3.9)	62 (13)	153 (46)	58 (18)	151 (46)	223 (67)	144 (20)	75 (13)	5.9 (1.1)	2.0 (1.6)	56 (17)	0.92 (0.09)	29.7 (6.2)
HbA_{1c}[d]															
<4.9	2,096	32 (1.5)	10 (0.5)	44 (12)	746 (36)	77 (4)	894 (43)	358 (17)	123 (16)	68 (11)	5.3 (1.0)	1.0 (0.8)	72 (3)	0.83 (0.09)	25.2 (4.0)
4.9–	2,043	38 (1.9)	8 (0.4)	47 (13)	871 (43)	88 (4)	905 (44)	431 (21)	125 (17)	68 (11)	5.6 (1.0)	1.1 (0.9)	84 (4)	0.85 (0.09)	26.0 (4.5)
5.0–	1,954	56 (2.9)	14 (0.7)	51 (14)	940 (48)	128 (7)	878 (45)	616 (32)	129 (18)	71 (12)	5.7 (1.0)	1.3 (1.0)	138 (7)	0.86 (0.09)	26.7 (4.6)
5.2–	2,155	98 (4.5)	25 (1.2)	55 (14)	1,052 (49)	196 (9)	942 (44)	782 (36)	132 (18)	71 (12)	5.9 (1.1)	1.4 (1.1)	204 (9)	0.88 (0.09)	27.5 (4.8)
>5.4	1,778	108 (6.1)	31 (1.7)	59 (13)	892 (50)	241 (14)	865 (49)	910 (51)	137 (19)	73 (12)	5.9 (1.1)	1.6 (1.2)	259 (15)	0.91 (0.09)	29.2 (5.5)
Total	10,026	332 (3.3)	88 (0.9)	51 (14)	4,501 (45)	730 (7)	4,484 (45)	3,097 (31)	129 (18)	70 (12)	5.7 (1.1)	1.3 (1.0)	757 (8)	0.86 (0.09)	26.9 (4.9)

Data are *n* (%) or mean (SD)

[a] History of CVD defined as previously reported angina, myocardial infarction or stroke

[b] Hypertension defined as systolic blood pressure ≥140 mmHg or diastolic blood pressure ≥90 mmHg or self-reported use of anti-hypertensive medication

[c] Data are median (interquartile range)

[d] FPG (mmol/l), 2hPG (mmol/l) and HbA_{1c} (%) were classified into quintiles. The top two quintiles of FPG and 2hPG were further divided according to the impaired fasting glucose, impaired glucose tolerance and diabetes criteria outlined by the American Diabetes Association [28] or WHO [29, 30]

Significant differences ($p<0.01$) between categories of FPG, 2hPG and HbA_{1c} were observed for all baseline characteristics

TC, total cholesterol; TG, triacylglycerol

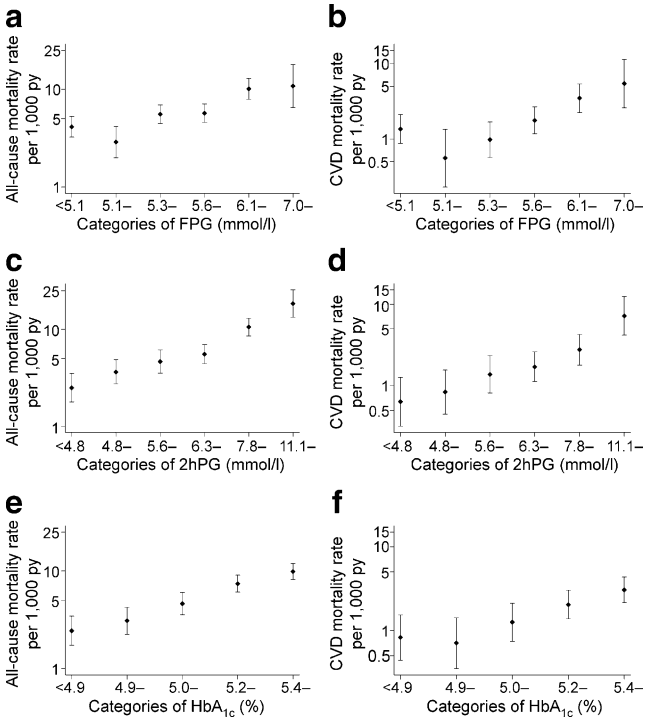

Fig. 1 Unadjusted all-cause and CVD mortality rates per 1,000 person-years (py) (95% CI) for FPG (**a**, **b**), 2hPG (**c**, **d**) and HbA_{1c} (**e**, **f**) in individuals without previously diagnosed diabetes—the AusDiab study (*y*-axis in logarithmic scale)

predicted probabilities due to the improved model are only beneficial for risk prediction among those who did not experience an event. The NRI was used to evaluate the extent to which different models reclassified individuals across three a priori categories (0–<10%, 10–<20% and ≥20%) of 5 year predicted CVD death risk, as used previously in CVD risk prediction scores [35, 36]. The IDI examines the change in estimated predicted probabilities as a continuous measure and was used to evaluate 5 year predicted all-cause and CVD death risks. Bootstrap methods were used to derive 95% CIs for the NRI and IDI estimates, and were based on 1,000 replications. Bootstrap replicates in which parameters of interest could not be estimated or were on the boundary of the parameter space were ignored. Analyses were conducted with Stata Statistical Software version 9.2 (StataCorp, College Station, TX, USA).

Results

Table 1 shows that for participants without diagnosed diabetes at baseline, CVD risk generally increased with increasing FPG, 2hPG and HbA_{1c}.

There were 332 deaths (190 in men) after a median follow-up of 6.2 years, and 88 CVD deaths (56 in men) and 204 non-CVD deaths (119 in men) after a median of 5.7 years. Cause of death was available from the NDI for 292 of the 332 deaths: neoplasms (n=125), atherosclerotic CVD (n=88), respiratory disease (n=22), nervous system diseases (n=8), kidney disease (n=6), poisoning (n=6), other heart diseases (n=6), gastrointestinal disease (n=5), accidents (n=4) and other causes (n=22). Figure 1 shows that crude all-cause and CVD mortality rates increased with increasing FPG, 2hPG and HbA_{1c} levels. After adjusting for age and sex, a linear relationship best described the association between both 2hPG and HbA_{1c} and all-cause and CVD mortality, whereas a J-shaped relationship based on a two-slope spline model with a knot at 5.1 mmol/l (cut-point of second quintile) best described the association between FPG and both all-cause and CVD mortality (Fig. 2). Therefore, all subsequent analyses for 2hPG and HbA_{1c} were based on linear models and FPG analyses were based on the two-slope spline model.

Adjustment for other covariates did not greatly attenuate the all-cause and CVD mortality relationships for the glucose measures. FPG and 2hPG remained significant predictors of all-cause mortality, while HbA_{1c} showed borderline significance (p=0.06). All glucose measures were significant predictors of CVD mortality (Table 2). For non-CVD mortality, 2hPG was a significant predictor (HR per SD increase was 1.1, 95% CI 1.0–1.2), but FPG and HbA_{1c} were not significant predictors after adjusting for age and sex (data not shown). Further adjustment for smoking, waist-to-hip ratio and history of CVD did not attenuate the association between 2hPG and non-CVD mortality.

Age and history of CVD were not significant effect modifiers of the relationships between both FPG and 2hPG and all-cause mortality, but significant interactions were observed between FPG and sex (p=0.03), and 2hPG and sex (p=0.02). Sex-stratified analyses revealed that the relative risk of all-cause mortality per SD (0.7 mmol/l) decrease in FPG <5.1 mmol/l was greater in men. The relative risk of all-

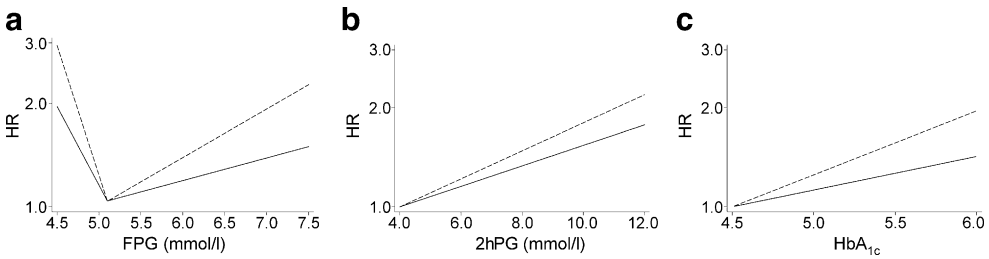

Fig. 2 Relative hazards for all-cause mortality (solid lines) and CVD mortality (dashed lines) according to FPG (**a**), 2hPG (**b**) and HbA_{1c} (**c**) after adjusting for age and sex in individuals without previously diagnosed diabetes—the AusDiab study (*y*-axis in logarithmic scale)

Table 2 Risk of all-cause and CVD mortality according to FPG, 2hPG and HbA_{1c} in individuals without diagnosed diabetes—the AusDiab study

Blood glucose measure (per SD)[ac]	Age- and sex-adjusted		Multivariate-adjusted[b]	
	HR	95% CI	HR	95% CI
All cause mortality				
FPG (two-slope spline)[a]				
<5.1	2.1	1.4–3.3*	2.0	1.3–3.0*
>5.1	1.1	1.0–1.2*	1.1	1.0–1.2*
2hPG[c]	1.2	1.1–1.3*	1.2	1.1–1.3*
HbA_{1c}[c]	1.1	1.0–1.2*	1.1	1.0–1.2
CVD mortality				
FPG (two slope spline)[a]				
<5.1	3.5	1.8–6.7*	4.0	2.1–7.6*
>5.1	1.3	1.1–1.4*	1.3	1.1–1.4*
2hPG[c]	1.2	1.1–1.4*	1.2	1.0–1.4*
HbA_{1c}[c]	1.2	1.1–1.4*	1.2	1.0–1.3*

[a] Data for FPG <5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) decrease in FPG below 5.1 mmol/l; data for FPG ≥5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) increase in FPG above 5.1 mmol/l. SD based on whole population distribution

[b] Adjusted for age, sex, history of CVD (angina, myocardial infarction or stroke), smoking (current or ex-smoker), diastolic blood pressure (mmHg), waist-to-hip ratio, lipid-lowering medication use, total cholesterol (mmol/l) and triacylglycerol (mmol/l)

[c] Data for 2hPG and HbA_{1c} are HRs (95% CI) per 1 SD increase of the whole population distribution for 2hPG (2.2 mmol/l) and HbA_{1c} (0.4%), respectively

*$p<0.05$

cause mortality per SD (2.2 mmol/l) increase of 2hPG was greater in women (Table 3). For all-cause mortality, there were no significant interactions between HbA_{1c} and sex, age or history of CVD (data not shown). The relationships of FPG, 2hPG and HbA_{1c} with CVD mortality and of 2hPG with non-CVD mortality did not vary according to sex, age or history of CVD (data not shown).

Table 4 shows the results of simultaneous modelling of the glucose measures. The associations between HbA_{1c} and both all-cause and CVD mortality became non-significant with adjustment for FPG and 2hPG. Prediction of all-cause or CVD mortality by models with FPG alone or 2hPG alone was not significantly improved by adding HbA_{1c}. FPG <5.1 mmol/l remained significantly associated with all-cause and CVD mortality, but the association between FPG ≥5.1 mmo/l and these outcomes was attenuated, particularly after adjusting for 2hPG. The latter was a significant predictor of all-cause mortality independent of

Table 3 Risk of all-cause mortality according to FPG and 2hPG in men and women without previously diagnosed diabetes—the AusDiab study

Blood glucose measure (per SD)[ac]	Age-adjusted		Multivariate-adjusted[b]	
	HR	95% CI	HR	95% CI
Women				
FPG (two-slope spline)[a]				
<5.1	1.5	0.8–2.8	1.5	0.8–2.7
>5.1	1.2	1.0–1.3*	1.1	1.0–1.3
2hPG[c]	1.3	1.2–1.5*	1.3	1.1–1.4*
Men				
FPG (two-slope spline)[a]				
<5.1	4.5	2.4–8.5*	4.4	2.2–8.5*
>5.1	1.1	1.0–1.2	1.1	1.0–1.2
2hPG[c]	1.1	1.0–1.2	1.1	1.0–1.2

[a] Data for FPG <5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) decrease in FPG below 5.1 mmol/l; data for FPG ≥5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) increase in FPG above 5.1 mmol/l. SD based on whole population distribution

[b] Adjusted for age, history of CVD (angina, myocardial infarction or stroke), smoking (current and ex-smoker), diastolic blood pressure (mmHg), waist-to-hip ratio, lipid-lowering medication use, total cholesterol (mmol/l) and triacylglycerol (mmol/l)

[c] Data for 2hPG are HR (95% CI) per 1 SD (2.2 mmol/l) increase of the whole population distribution for 2hPG

*$p<0.05$

Table 4 Risk of all-cause and CVD mortality adjusted for FPG, 2hPG or HbA_{1c} in individuals without previously diagnosed diabetes—the AusDiab study

Blood glucose (per SD)[a]	Model 1		Model 2—adding 2hPG				Model 3—adding FPG				Model 4—adding HbA_{1c}			
	HR (95% CI)	c-statistic	HR (95% CI)	c-statistic	LR test[a]		HR (95% CI)	c-statistic	LR test[a]		HR (95% CI)	c-statistic	LR test[a]	
					χ^2	*p* value			χ^2	*p* value			χ^2	*p* value
All-cause mortality														
FPG[b]														
<5.1	2.0 (1.3–3.0)*	0.863	2.0 (1.4–3.1)*	0.866	11.5	<0.001	–	–	–	–	2.0 (1.3–3.0)*	0.864	0.7	0.40
≥5.1	1.1 (1.0–1.2) *		1.0 (0.9–1.1)				–	–	–	–	1.1 (0.9–1.2)			
2hPG[c]	1.2 (1.1–1.3) *	0.865	–	–	–	–	1.2 (1.1–1.3)*	0.866	9.0	0.01	1.2 (1.1–1.3)*	0.865	0.11	0.74
HbA_{1c}[c]	1.1 (1.0–1.2)	0.862	1.0 (0.9–1.1)	0.865	9.9	0.002	1.1 (0.9–1.2)	0.864	8.0	0.02	–	–	–	–
CVD mortality														
FPG[b]														
<5.1	4.0 (2.1–7.6)*	0.935	4.1 (2.2–7.8)*	0.936	1.3	0.26	–	–	–	–	4.1 (2.1–7.7)*	0.935	0.03	0.86
≥5.1	1.3 (1.1–1.4)*		1.2 (1.0–1.4)				–	–	–	–	1.3 (1.0–1.6)*			
2hPG[c]	1.2 (1.0–1.4)*	0.933	–	–	–	–	1.1 (0.9–1.4)	0.936	12.1	0.002	1.2 (1.0–1.4)	0.933	0.5	0.49
HbA_{1c}[c]	1.2 (1.0–1.3)*	0.933	1.1 (0.9–1.3)	0.933	2.3	0.13	1.0 (0.8–1.2)	0.935	12.6	0.002	–	–	–	–

Model 1, adjusted for age, sex, history of CVD (angina, myocardial infarction or stroke), smoking (current and ex-smoker), diastolic blood pressure (mmHg), waist-to-hip ratio, lipid-lowering medication use, total cholesterol (mmol/l) and triacylglycerol (mmol/l)
Model 2, adjusted for model 1 plus 2hPG
Model 3, adjusted for model 1 plus FPG
Model 4, adjusted for model 1 plus HbA_{1c}
[a] Log–likelihood ratio test comparing a model with two glucose measures to a model with a single glucose measure
[b] Data for FPG <5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) decrease in FPG below 5.1 mmol/l; data for FPG ≥5.1 mmol/l are HR (95% CI) per 1 SD (0.7 mmol/l) increase in FPG above 5.1 mmol/l. SD based on whole population distribution
[c] Data for 2hPG and HbA_{1c} are HRs (95% CI) per 1 SD increase of the whole population distribution for 2hPG (2.2 mmol/l) and HbA_{1c} (0.4%), respectively
*$p<0.05$

FPG and HbA_{1c}, but the relationship between 2hPG and CVD mortality was attenuated by FPG. Entering 2hPG into models based on FPG alone or HbA_{1c} alone significantly improved the prediction of all-cause, but not of CVD mortality, whereas entering FPG into models based on 2hPG alone or HbA_{1c} alone significantly improved the prediction of all-cause and CVD mortality.

For individual risk discrimination, there was little difference between the three glucose indices in predicting all-cause and CVD mortality. Table 4 shows that the c-statistics were similar for multivariate-adjusted models containing any of FPG, 2hPG or HbA_{1c} alone. Moreover, the addition of more than one glucose measure into models containing a single glucose measure did not substantially improve the discriminative abilities of FPG, 2hPG or HbA_{1c}, as indicated by small changes in the c-statistic.

The IDI and NRI results were in agreement with the c-statistic findings. For all-cause mortality, the relative IDIs (95% CIs) for adding either FPG, 2hPG or HbA_{1c} to models with age, sex, history of CVD, smoking, diastolic blood pressure, waist-to-hip ratio, lipid-lowering medication use, total cholesterol and triacylglycerol were similar, namely: FPG 2.2% (−0.05 to 11.6%), 2hPG 2.3% (−0.7 to 10.4%) and HbA_{1c} 0.3% (−0.6 to 5.5%). For CVD mortality, the relative IDI (95% CI) for FPG was 13.8% (2.3 to 43.6%), which was greater than that for 2hPG (4.3% [−1.8 to 23.7%]) or HbA_{1c} (3.0% [−1.1 to 16.9%]). However, there were no meaningful differences between the three glucose indices in their ability to classify individuals across three 5 year CVD death risk categories (0 to <10%, 10 to <20% and ≥20%) beyond the classification provided by these traditional risk factors. The NRI (95% CI) was 6.7% (−3.4% to 14.8%) for FPG, 2.3% (−6.6% to 10.3%) for 2hPG, 0.1% (−6.1% to 9.0%) for HbA_{1c} and 5.7% (−19.8% to 15.0%) for all glucose measures added to the same model.

Discussion

The findings from this large contemporary population-based prospective cohort of over 10,000 men and women aged ≥25 years have shown that among individuals without diagnosed diabetes, FPG and 2hPG, but not HbA_{1c} were significantly associated with an increased risk of all-cause mortality, and all three measures were significantly associ-

ated with an increased risk of CVD mortality. The risks of all-cause and CVD mortality progressively increased throughout the range of 2hPG and HbA_{1c}, but a J-shaped relationship was observed for FPG. To the best of our knowledge, this is the largest study using a range of techniques to evaluate, in the same study population, the nature and strength of the relationships between all these glucose measures and both all-cause and CVD mortality.

Our finding of a continuous graded relationship between 2hPG and CVD mortality concurs with some [3, 4, 12] but not all studies [6, 10]. Balkau et al. [10] reported a J-shaped relationship for CVD mortality. Furthermore, others have reported a threshold relationship, where the risk of fatal and/or non-fatal CVD only increased in the upper range of the 2hPG distribution [6]. For all-cause mortality, we also observed a graded continuous relationship for 2hPG. This contrasts with the findings of Balkau et al. [10] and DECODE [12], who both reported J-shaped relationships between 2hPG and all-cause mortality. Differences in study characteristics may explain the discordant findings. The DECODE study, a meta-analysis of individual data from different cohorts, combined different blood sample types and this may have introduced measurement imprecision [12]. Our study included men and women aged ≥25 years and used a 75 g OGTT, whereas other findings were based on men only, [10] or used a 50 g OGTT [6].

The nature of the relationship between HbA_{1c} and both all-cause mortality and CVD in people without diagnosed diabetes has been reported in other observational studies [7, 16–18, 37, 38]. Several studies reported a consistent graded relationship between HbA_{1c} and both all-cause mortality [16, 18, 37, 38] and fatal and/or non-fatal CVD [16, 18]. In contrast, Selvin et al. [7] found that the risk of coronary heart disease only increased above an HbA_{1c} of 4.6%. None of these studies adjusted for other glucose measures. Our study extends these observations by demonstrating that a graded continuous relationship between HbA_{1c} and both all-cause and CVD mortality diminished after adjusting for FPG or 2hPG. This can be explained by the fact that HbA_{1c} reflects blood glucose concentration over the previous 2 to 3 months [13].

Low FPG, particularly in men, was associated with an increased risk of all-cause and CVD mortality. This supports several other studies [10–12, 39, 40], although different nadirs ranging from 3.3 to 5.2 mmol/l have been reported [40]. These differences may reflect varying study characteristics and methods. The physiological mechanism underlying this association is unclear. Although low fasting blood glucose may indicate poor general health [40], we found that even after excluding individuals who died in the first year (i.e. those people possibly terminally ill at baseline), individuals with a low FPG were still at risk of death from all causes or CVD.

This study also revealed that 2hPG, rather than FPG or HbA_{1c}, was significantly associated with non-CVD mortality, a finding consistent with other studies that have found abnormal glucose metabolism to be related to cancer mortality [41–43]. In our study it was not possible to specifically investigate the relationship between plasma glucose and cancer mortality, as the relatively short period of follow-up reduced the power to undertake this analysis. However, 61.3% of non-CVD deaths were attributable to malignant neoplasm. The mechanisms underlying the association between abnormal glucose metabolism and cancer are not fully understood. However, it is thought that abnormal glucose metabolism may increase tumour growth and cell proliferation through hyperinsulinaemia and systemic inflammatory responses [44, 45]. It is thought that 2hPG, rather than FPG, is more strongly linked to hyperinsulinaemia [13] and may therefore help to explain our findings of an association between 2hPG and non-CVD mortality.

Few studies have compared the predictive capabilities of all three measures in the same study population [19–22]. In the Rancho Bernardo Study [19], GHb was found to be a better predictor of CVD and ischaemic heart disease mortality than FPG or 2hPG in women only. In contrast, other studies found that post-load blood glucose was a better predictor of mortality and/or CVD outcomes than FPG or HbA_{1c} [20–22]. In our study, HbA_{1c} did not predict all-cause and CVD mortality independent of FPG or 2hPG. When FPG and 2hPG were included in the same model, FPG <5.1 mmol/l remained significantly associated with all-cause and CVD mortality, but the associations diminished for FPG ≥5.1 mmol/l, and although 2hPG remained significantly associated with all-cause mortality, this was attenuated for CVD mortality.

Our study has extended these findings by also evaluating the discriminative ability of FPG, 2hPG and HbA_{1c} to identify individuals at higher risk of all-cause and CVD mortality. Although 2hPG had slightly superior discriminative ability for all-cause mortality than FPG and HbA_{1c}, and FPG had slightly superior discriminative ability for CVD mortality than 2hPG and HbA_{1c}, the actual differences in the c-statistics of these models were of a small magnitude (<0.003). In addition, all measures displayed similar IDI estimates for all-cause mortality, and although the IDI estimate for CVD mortality was greater for FPG than for 2hPG and HbA_{1c}, all measures displayed similar non-significant improvements in the NRI estimations. This therefore suggests that an OGTT adds only a small and possibly clinically unimportant amount of information on individual mortality risk discrimination over and above FPG and HbA_{1c}.

Despite our findings of significant independent associations between both FPG and 2hPG and all-cause mortality,

and between the three glucose variables FPG, 2hPG and HbA_{1c} and CVD mortality, the ability of blood glucose to classify individual risk was only modest when traditional risk factors such as prior CVD, smoking, blood pressure, hyperlipidaemia, lipid-lowering medication and abdominal adiposity were considered. This finding has been reported by others [21, 46]. The phenomenon of a significant independent risk factor not substantially improving individual risk classification is not uncommon, as such discrimination often requires very strong measures of association [47]. Nevertheless, our findings do indicate that glucose measures are important in characterising population risk of mortality even among individuals without diagnosed diabetes, and suggest that intermediate hyperglycaemia may play a role in the development of CVD.

The findings of this study should be interpreted in the context of its limitations. The response rate of 37% of those eligible for testing may indicate that the study cohort was not fully representative of the Australian adult population. However, differences between responders and non-responders are unlikely to impact on the associations between blood glucose and mortality. A single 75 g OGTT was used to measure FPG and 2hPG. These measures are subject to within-person variability [48], and this may have introduced some imprecision and regression dilution bias, leading to underestimation of the relative risk of mortality. It is also possible that storage of samples had an effect on HbA_{1c} values, but we could find no evidence for such an effect. Furthermore, the relatively short follow-up period may have reduced the power to detect a significant association between HbA_{1c} and all-cause mortality, which showed borderline significance. The findings from observational studies such as ours, while identifying population-based associations, need to be supported by physiological experiments and clinical trials to help unravel the effects different indices of glycaemia have on CVD and mortality.

In summary, we compared three glycaemic indices with respect to all-cause and CVD mortality in people without diagnosed diabetes. The results indicate that 2hPG and FPG, rather than HbA_{1c}, were important independent predictors of all-cause and CVD mortality. Although these glucose measures did not substantially improve individual risk identification, the findings nevertheless highlight the potentially important role of glycaemia in the development of CVD and all-cause mortality in the general population.

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