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Associations of mortality and cardiovascular disease risks with diabetes and albuminuria in urban Indigenous Australians: the DRUID follow-up study

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What's new?

- The Darwin Region Urban Indigenous Diabetes (DRUID) follow-up study is one of the few studies to assess the prospective associations of diabetes and albuminuria on mortality and cardiovascular disease (CVD) in an urban indigenousindigenous population.
- We showed that nearly a third of CVD events in our study population were attributable to diabetes and 21% were attributable to albuminuria.
- Public health initiatives that aim to prevent and better manage diabetes and renal disease could have a substantial impact on the burden of CVD in Indigenous Australians.

Abstract

Aim To assess the relationships of diabetes and albuminuria with all-cause mortality and cardiovascular disease outcomes in a population without prior cardiovascular disease using data from the Darwin Region Urban Indigenous Diabetes (DRUID) study.

Methods We conducted a prospective cohort study of 706 participants (aged 15–81 years, 68% women) without prior cardiovascular disease who underwent a 75-g oral glucose tolerance test. Deaths and fatal or non-fatal cardiovascular disease were determined over 7 years, and hazard ratios with 95% CIs and population attributable risks were estimated for baseline glycaemia and albuminuria.

Results Compared with normoglycaemia and after adjustment for age, sex, hypertension, dyslipidaemia and smoking, known diabetes was associated with an adjusted hazard ratio of 4.8 (95% CI 1.5–14.7) for all-cause mortality and 5.6 (95% CI 2.1–15.2) for cardiovascular disease. Compared with normoalbuminuria, the respective adjusted risks for macroalbuminuria were 10.9 (95% CI 3.7–32.1) and 3.9 (95% CI 1.4–10.8). After adjustment

for all-cause mortality and cardiovascular disease, the estimated population attributable risks for diabetes were 27% and 32%, and for albuminuria they were 32% and 21%, respectively.

Conclusions In our study population, the burden of mortality and cardiovascular disease was largely driven by diabetes and albuminuria. This finding on the influence of diabetes and albuminuria is consistent with reports in other high-risk indigenous populations and should be better reflected in risk scores and intervention programmes.

Introduction

Cardiovascular disease (CVD) incidence in high-income countries is decreasing [1], but remains a major public health issue for many indigenous populations, including Indigenous Australians who have experienced rapid social and lifestyle change [2]. The primary prevention of CVD largely focuses on the reduction of well-established risk factors such as smoking, hypertension, hyperlipidaemia and diabetes [3]; however, in indigenous people the pattern of CVD risk is often dominated by high prevalence of diabetes and renal disease compared with other risk factors [2]. In Australia, diabetes prevalence is as high as 30% in some Indigenous communities [4], and prevalence of end-stage renal disease is 10–15 times higher among Indigenous than non-Indigenous Australians [5]. There is limited evidence with regard to the longitudinal associations of diabetes [6–10] and albuminuria [9–11] with CVD outcomes specifically for indigenous populations. Findings from large meta-analyses on diabetes [12,13] and renal disease [14] are largely based on European and Asian populations, and do not provide any specific information on indigenous people.

Within Australia, most studies of CVD risks and outcomes have been conducted in remote settings [9,10,15], but the majority of Indigenous Australians live in urban areas [5]. Factors related to CVD, such as prevalence of diabetes and renal disease [4,16] and healthcare access, [17] differ according to remoteness. It is therefore important to improve our understanding of the contribution of these risk factors to mortality and CVD risk among urban Indigenous populations.

The Darwin Region Urban Indigenous Diabetes (DRUID) study is an observational study established to address the lack of information on the burden of diabetes and related conditions in Indigenous Australians living in an urban setting [18]. Baseline findings showed that a third of participants aged ≥35 years, and half of those aged ≥55 years had diabetes. The prevalence of CVD risk factors in this population was very high, even among young adults

without diabetes, with nearly half of those aged < 35 years having at least two CVD risk factors [19]. In the present study, we looked beyond well-established traditional CVD risk factors and examined the contributions of diabetes and albuminuria to the risk of all-cause mortality and development of CVD over a 7-year follow-up period in people without a history of CVD at baseline.

Participants and Methods

Study population

The DRUID study included men and women who identified as Indigenous Australians living in and around Darwin, a city in Northern Australia [18]. Between 2003 and 2005, 1004 volunteers aged ≥15 years participated in baseline examinations, which represented ~14% of the estimated target population. Compared with census data, the study population underrepresented men, but no substantial differences in age, place of residence, Indigenous group or household income were observed [18].

In 2012, information on fatal and non-fatal CVD and all-cause mortality outcomes was obtained. Of the 1004 participants at baseline, there were 968 participants who did not have a prior CVD event (we excluded 29 with a prior CVD event and seven because their CVD status could not be established). Of these 968 participants, we excluded 229 because data on the variables under examination were not complete. Specifically, participants were excluded from the all-cause mortality analysis because they: did not identify as Indigenous Australians at follow-up (*n*=3); were reported as deceased but could not be identified on the National Death Index in Australia (*n*=5); were pregnant at baseline (*n*=6); had not fasted (*n*=75); had missing data for diabetes classification (*n*=54) or missing urine albumin to creatinine ratio data (*n*=26); had missing total cholesterol data (*n*=3); had missing systolic blood pressure data (*n*=1); had missing information on smoking status (*n*=56); or did not give consent to follow-up on the National Death Index (*n*=33; Table S1). For the fatal or non-fatal CVD analysis we excluded an additional 47 participants: those with no consent for data linkage and medical records review (*n*=13), and those who did not have medical record information and either did not consent to hospital data linkage (*n*=11), or could not be found on the hospital databases (*n*=23).

Participants provided informed consent and the ethics committees of the Northern Territory Department of Health and Menzies School of Health Research (including the Aboriginal sub committee), the South Australian Health Department, the South Australian Aboriginal Health Council and the Australian Institute of Health and Welfare approved the study. The DRUID study Indigenous Steering Group provided Indigenous leadership, and comprised Indigenous Australians from the Darwin region.

Measurements

Participants provided a fasting (>8 h) blood sample. Plasma glucose [fasting and after 75-g oral glucose tolerance test (OGTT)], total cholesterol, triglycerides, HDL cholesterol and high-sensitivity C-reactive protein (hsCRP; measured using a Hitachi 917 device; Roche, Basel, Switzerland) were assessed. HbA_{1c} was measured as a percentage of total haemoglobin after separation by ion-exchange chromatography on a Pharmacia Mono-S column (results traceable to the Diabetes Control and Complications Trial method). Creatinine (modified kinetic Jaffé reaction measured using a Hitachi 917 device) and albumin (immunonephelometry using a Beckman Coulter Array 360; Beckman Coulter, Brea, CA, USA) were measured from a random urine sample. Samples were assayed at a central laboratory. Seated blood pressure using an automatic monitor (Welch Allyn Medical Products, Skaneateles Falls, CA, USA) and anthropometrics (weight, height, waist and hip circumferences) were taken. Self-reported smoking, household income and education were recorded.

Glycaemia was classified as: known diabetes mellitus: reported physician diagnosis of diabetes or taking diabetes medication; newly diagnosed diabetes: fasting plasma glucose ≥7.0 mmol/l or 2-h post-load plasma glucose ≥11.1 mmol/l; impaired fasting glucose, if fasting plasma glucose was ≥6.1 mmol/l and <7.0 mmol/l and 2-h plasma glucose was <11.1 mmol/l; impaired glucose tolerance, if fasting plasma glucose was <7.0 mmol/l and 2-h plasma glucose was ≥ 7.8 mmol/l and <11.1 mmol/l; and normoglycaemia if fasting plasma glucose was <6.1 mmol/l and 2-h plasma glucose <7.8 mmol/l [20]. HbA_{1c} was also used to classify glycaemia at baseline as follows: normoglycaemia, HbA_{1c} <39 mmol/mol (<5.7%); intermediate hyperglycaemia, HbA_{1c} ≥39 to <48 mmol/mol (≥5.7% to <6.5%); and diabetes, HbA_{1c} ≥48 mmol/mol (≥6.5%) or previously known diabetes [21]. Microalbuminuria was defined as a urine albumin to creatinine ratio of 3–30 mg/mmol and macroalbuminuria was defined as a urine albumin to creatinine ratio of >30 mg/mmol [22]. Serum creatinine was used to calculate the estimated glomerular filtration rate (eGFR) according to the Chronic Kidney Disease Epidemiology Collaboration formula, and eGFR was categorized as ≥90, 60–90 or <60 ml/min/1.73m^2 [23].

Follow-up and outcomes

For all-cause mortality, the person-time denominator was date of death from any cause minus the date of baseline examination, and for fatal or non-fatal CVD, the person-time denominator was the date of first fatal or non-fatal CVD event minus the date of baseline examination. We censored events at 31 December 2011. Deaths were obtained using data linkage to the National Death Index. Causes of death were coded from death certificates according to International Classification of Diseases (ICD) codes used by the Australian Bureau of Statistics. CVD death was defined as cases in which the underlying cause of death was coded I10-I25, I46.1, I48, I50-I99 or R96 (ICD-10). Non-fatal CVD outcomes were obtained by two methods. Firstly, discharge diagnoses ICD-10 (or equivalent ICD-9) codes for myocardial infarction (I21-I23), stroke (I06-I64) and relevant procedure codes for percutaneous transluminal coronary angioplasty or coronary artery bypass surgery, and admission dates were extracted from centralized databases in the Northern Territory and South Australia using data linkage. Secondly, participants were invited to complete a survey and report on hospitalizations for 'heart attack, stroke or heart surgery (stent or bypass)'. Two physicians [L.M.-B. (endocrinologist) and N.K. (cardiologist)] reviewed medical records to adjudicate self-reported CVD events according to the WHO criteria for myocardial infarction [24] and stroke [25], and operation reports for percutaneous transluminal coronary angioplasty and coronary artery bypass surgery. Data linkage used probabilistic matching of participants using personal identifiers (names, gender, date of birth and addresses).

Statistical analyses

One-way analysis of variance, chi-squared tests and t-tests for independent groups were used as appropriate to compare baseline characteristics (1) between those who consented to follow-up and those who did not consent to follow-up (among those who would otherwise have been included), (2) between those who had died and those who remained alive, and (3) between those who experienced a fatal or non-fatal CVD outcome and those who did not. Cox proportional hazards regression was used to estimate the all-cause mortality and CVD hazard ratio (HR) and 95% CI for baseline CVD risk factors. Age was the time scale. To evaluate the contribution of glycaemia and albuminuria to all-cause mortality and CVD, the relationships were evaluated after adjusting for well-established CVD risk factors commonly identified as targets for the primary prevention of CVD: sex, smoking, hypertension (≥140/90 mmHg or anti-hypertensive medication use), total cholesterol to HDL lipoprotein ratio (logarithmic transformed continuous), as well as logarithmic transformed urine albumin to

creatinine ratio for glycaemic status, and glycaemic status for categories of albuminuria. A final model that grouped participants into four groups according to glycaemia (based on the OGTT method [20]) and albuminuria was also assessed, whereby the adjusted mortality and CVD risks of participants with (1) abnormal glycaemia and no albuminuria, (2) normoglycaemia and albuminuria, and (3) both abnormal glycaemia and albuminuria, who were compared to a group with no glycaemia and no albuminuria. Multivariate models were adjusted for all covariates simultaneously; however, to examine the potential impact of model overfitting on our results, sensitivity analyses were also undertaken to assess the individual effects of each covariate on the age- and sex-adjusted all-cause mortality and CVD risks associated with glycaemia or albuminuria, respectively, and results are presented in Tables S2 and S3. Proportional hazards assumptions were satisfied as assessed with graphs of log–log plots of the relative hazards by time and by scaled Schoenfeld residuals. The prevalence of risk factors in this cohort, and age- (time scale) and sex-adjusted HR (model 1), as well as multivariate-adjusted HR (model 2) were used to estimate the population attributable risk (PARs) of known diabetes and albuminuria for all-cause mortality and fatal or non-fatal CVD using the following formula, which accounts for the multi-level nominal variable for the five mutually exclusive categories of glucose intolerance [26]:

$$PAR_i = \frac{P_i(HR_i - 1)}{1 + \sum_{j=1}^{x} P_i(HR_i - 1)}$$

where P_i is the proportion of individuals in the *ith* of *x* groups (*x*= 5 groups for glycaemic status: 1=normoglycaemia, 2=impaired fasting glucose, 3=impaired glucose tolerance, 4=newly diagnosed diabetes and 5= known diabetes; and *x* = 2 for albuminuria: 1=no albuminuria and 2=microalbuminuria or macroalbuminuria) and HR_i is the adjusted mortality or CVD HR in each of these groups compared with that of those with normoglycaemia or no albuminuria, respectively. Analyses were performed with STATA statistical software (version 14.2; StataCorp, College Station, TX, USA).

Results

All-cause mortality and cardiovascular disease incidence rates

The median follow-up of 706 participants was 7.6 years. There were 30 deaths [5.7 per 1000 person-years (5.0 per 1000 for women and 7.2 per 1000 for men)]. The underlying causes of death were CVD (20%), cancer (13%), diabetes (13%), external causes (23%), other causes (20%) and undetermined (13%). Fatal and non-fatal CVD follow-up was available for 659

participants without a history of CVD at baseline, with 33 CVD events [6.7 per 1000 person-years (6.0 per 1000 person-years for women and 8.4 per 1000 person years for men)]. Compared with participants who were included in the mortality follow-up analysis (*n*=706), those not consenting (but who would otherwise have been included; *n*=33) had a younger mean age and lower risk profile, reflecting this age differential. In comparison with those included in the analysis, those excluded as a result of incomplete baseline data (primarily from not having a fasting blood test or OGTT) had a slightly lower mean age, similar smoking status, slightly lower mean blood pressure, BMI and waist circumference, but similar urine albumin to creatinine ratio (Table S1). Table 1 shows that participants who died or had a CVD event during the follow-up were older, more likely to be men and had a worse risk profile than those who remained alive.

Risk for all-cause mortality

In unadjusted analyses, baseline risk factors for all-cause mortality included: impaired fasting glucose; impaired glucose tolerance; known diabetes; HbA_{1c} ≥48 mmol/mol or known diabetes; albuminuria; low eGFR; and hypertension. Of the 30 deaths, 14 participants had either newly diagnosed diabetes or known diabetes, and 14 participants had either micro- or macroalbuminuria at baseline. After adjusting for age and sex, strong associations remained for known diabetes, HbA_{1c} ≥48 mmol/mol or known diabetes, macroalbuminuria and low eGFR (Table 2). The mortality rates for known diabetes and macroalbuminuria were 20.6 and 44.8 per 1000 person-years, respectively (Table 3). After further adjustment for hypertension, total cholesterol:HDL and smoking, baseline known diabetes was associated with a nearly fivefold risk, and macroalbuminuria with an elevenfold risk of all-cause mortality (Table 3). When glycaemia was based on HbA_{1c}, the adjusted all-cause mortality HR for known diabetes or an HbA_{1c} ≥48 mmol/mol (≥6.5%) was 2.9 (95% CI 1.1–7.5) compared with an HbA_{1c} <39 mmol/mol (<5.7%). When glycaemic status (based on the OGTT) and albuminuria were modelled together in multivariate models, HR estimates remained stronger for albuminuria than for known diabetes, although the 95% CIs overlapped (Table 3). Furthermore, we showed that the risk for all-cause mortality was very high when hyperglycaemia and albuminuria coexisted (Table 4). The age- (time-scale) and sex-adjusted PAR for all-cause mortality was 27% for known diabetes relative to normolycaemia, and 32% for albuminuria relative to no albuminuria. These PARs remained unchanged after multivariate analysis.

Fatal or non-fatal cardiovascular disease

In unadjusted analyses, baseline impaired fasting glucose, impaired glucose tolerance, HbA_{1c} 39–47 mmol/mol, known diabetes, HbA_{1c} ≥48 mmol/mol or known diabetes, albuminuria, low eGFR, hypertension, high total cholesterol, high hsCRP, dyslipidaemia, high triglycerides, large waist circumference, no post-school qualifications and a lower household income were associated with an increased risk of CVD (Table 2). Of the 33 CVD events, 19 participants had either newly diagnosed or known diabetes at baseline, and 15 participants had micro- or macro-albuminuria at baseline. After adjusting for age and sex, known diabetes, HbA_{1c} ≥48 mmol/mol or known diabetes, micro- and macro-albuminuria, hsCRP ≥3.5 mg/l, dyslipidaemia (HDL <1.0 mmol/l and triglycerides ≥2.0 mmol/l) and having lower or not stated householder income remained associated with CVD (Table 2); however, after inclusion of baseline glycaemia in these age- and sex-adjusted models, associations of hsCRP and dyslipidaemia with CVD were attenuated (data not shown). Interestingly, the associations of low income (HR 6.7, 95% CI 1.4– 30.8) or not stated/missing income (HR 5.3, 95% CI 1.1–25.1) with CVD remained strong after adjusting for baseline glycaemia or albuminuria and the other common risk factors included in our multivariate analysis, although considerable uncertainty was demonstrated by the wide CIs.

The CVD event incidence rates for known diabetes and macroalbuminuria were 30.0 and 38.1 per 1000 person-years, respectively (Table 3). In multivariate analyses, those with known diabetes at baseline had a fivefold risk of CVD compared to those with normoglycaemia, and this strong association remained after adjusting for albuminuria (Table 3). When glycaemia was based on HbA_{1c} the adjusted CVD HR for known diabetes or HbA_{1c} ≥48 mmol/mol (≥6.5%) was 2.7 (95% CI 1.1–6.4) compared with an HbA_{1c} <39 mmol/mol (<5.7%). The association between macroalbuminuria with CVD outcomes compared with normoalbuminuria was attenuated in multivariate analyses (Table 3). Furthermore, compared to those without either glycaemia or albuminuria, those with only one of albuminuria or glycaemia had a five- to sixfold increase in the risk of CVD, and those participants with both albuminuria and glycaemia had an eightfold risk of CVD (Table 4).

Sensitivity analyses showed that adjusting for individual baseline CVD risk factors had little effect on the strength of the age- and sex-adjusted all-cause mortality and CVD associations for diabetes and albuminuria (Tables S2 and S3). The age- (time scale) and sex-adjusted and multivariate-adjusted PARs for fatal or non-fatal CVD were 34% and 32%, respectively, for

known diabetes relative to normoglycaemia, and 27% and 21%, respectively, for albuminuria relative to no albuminuria.

Discussion

The DRUID follow-up study shows that the burden of all-cause mortality and CVD in this high-risk urban population of Indigenous Australians is largely driven by diabetes and albuminuria. Diabetes conferred a mortality and CVD risk that was four to five times greater than in those with normoglycaemia, and although the CIs were wide for albuminuria with respect to CVD risk, participants with albuminuria had an 11 times greater risk of all-cause mortality compared with those without albuminuria. These strong associations observed for diabetes and albuminuria were independent of smoking, hypertension and total cholesterol to HDL cholesterol ratio. Furthermore, participants with both diabetes and albuminuria at baseline had very high risks of both all-cause mortality and CVD compared to participants without either condition. The burden of CVD in this urban population of Indigenous Australians was not only driven by a high prevalence of diabetes and CVD risk factors [19], but also by the very strong associations of diabetes with CVD. This is reflected in our PAR estimates, which showed that nearly a third of CVD events were attributable to diabetes in this population. It is possible, however, that the PAR estimates for diabetes in this population overestimate the PAR of diabetes in the target urban Indigenous population. Recent survey data from the Australian Bureau of Statistics indicate that the prevalence of diabetes in urban Indigenous Australians is ~8% [16], which is lower than our reported 13%. Such a lowering of prevalence would inevitably lower the PAR; however, diabetes prevalence from the Australian Bureau of Statistics would have misclassified diabetes cases with isolated 2-h glucose elevations, as the Australian Bureau of Statistics examination did not measure 2-h plasma glucose.

The mortality and CVD risk associations for diabetes observed in this urban population of Indigenous Australians were much higher than those reported for diabetes in other populations of predominantly European ancestry [12,27] and for North American Indigenous populations [6]; however, these strong associations of diabetes with all-cause mortality and CVD were similar to those reported in high-risk Asian populations [13] and a New Zealand Maori population [8]. The four- to fivefold risks for diabetes with mortality and CVD were independent of hypertension, smoking and total cholesterol to HDL cholesterol ratio, and higher than those reported in other Australian Indigenous cohorts from urban [7] and remote

settings [9]. Relative risk estimates for diabetes may have been weakened in other studies of Indigenous Australians that did not define normoglycaemia with an OGTT as we have been able to do, and as such, the reference group may have included those with intermediate hyperglycaemia on post-load plasma glucose [7,9]. Indeed, when we classified baseline glycaemia with HbA_{1c}, the estimated HR for all-cause mortality and CVD attributed to diabetes was lower than that observed for diabetes based on the OGTT. We found that among those who died and were classified as having normoglycaemia on HbA_{1c} (<39 mmol/mol or <5.7%), 40% of these participants had a 2-h plasma glucose level ≥7.8 mmol/l. This may have diminished the relative difference in mortality risk between HbA_{1c} groups in comparison to the OGTT-based glycaemic groups. Furthermore, previous work has shown that half of the cases of newly diagnosed diabetes at baseline would not have been detected without the OGTT [19].

The higher relative risks for all-cause mortality and CVD observed for individuals with diabetes in the present cohort may provide some evidence that diabetes is more aggressive and/or insufficiently managed in Indigenous Australians. This supports the findings from other studies. Recently, another Australian study showed that, among patients with type 2 diabetes, Indigenous Australians had a much worse risk factor profile compared with non-Indigenous people [28]. Additionally, Canadian studies have shown similar medical care gaps for First Nation people compared with their non-indigenous counterparts [29]. Alternatively, because the relative risk of diabetes tends to decrease with increasing age [30], our higher relative risks may reflect the younger cohort in the present study.

In the present urban study, we found strong associations between both micro- and macro-albuminuria with all-cause mortality. Albuminuria also increased the risk of CVD outcomes, although risks were attenuated when we adjusted for other CVD risk factors, particularly when multivariate models included more continuously measured covariates (Model 6, Table S3). Other data from a remote Indigenous Australian community have had similar findings, and showed that, compared with normoalbuminuria, micro- and macro-albuminuria increased the risk of coronary heart disease by two to three times, and that these relationships were independent of age, sex and traditional risk factors [15]. Interestingly, the strong associations observed between albuminuria and mortality remained after including glycaemic status in the multivariate models. This concurs with a study in Pima Indians in the USA, which showed

that the all-cause mortality rates increased with kidney disease, irrespective of diabetes status [31].

In the present study, high hsCRP level, a combination of low HDL cholesterol and high triglycerides, and low income also had strong associations with CVD outcomes after adjusting for age and sex, but were attenuated when modelled with glycaemia, demonstrating the known associations between these metabolic factors and diabetes [20]. The presence of both albuminuria and abnormal glycaemia conferred greater risks of all-cause mortality and CVD than either condition in isolation. This supports the findings of another study from a remote setting [9]. Together, these results highlight the considerable independent impact that these risk factors have on total mortality and CVD in Indigenous Australians.

The following limitations need to be considered. First, the generalizability of these findings to the wider urban Indigenous population is limited by the self-selection of participants to the study, the original cohort representing 14% of the estimated target population, which underrepresented men [18], and the follow-up analyses being based on ~70% of the original cohort. Whether these selection biases led to over- or under-estimation of the relative risk estimates and PARS presented here for diabetes and albuminuria is not known. Second, we were not able to assess the influence of intra-individual variation in baseline risk factors, as measurements were only taken on one occasion; however, any measurement imprecision would have been random, leading to attenuation of study findings. Nevertheless, our findings on the associations between diabetes and albuminuria with mortality and CVD are consistent with other observational studies [9,15]. Finally, our multivariate models have a low ratio of events per predictor variable, and this may have led to inadequate adjustment for confounding factors and inaccurate inferences from the relationships observed; however, sensitivity analyses showed that the all-cause mortality and CVD risk estimates for abnormal glycaemia and albuminuria were similar, even with individual adjustment of covariates (Tables S2 and S3).

In this high-risk population of Indigenous Australians, we have provided additional evidence on the significance of both diabetes and albuminuria on the risk of subsequent all-cause mortality and CVD outcomes in an urban population. We showed that relative risk estimates for diabetes based on an OGTT are marked in this population, and given that nearly a third of CVD events were attributable to diabetes and 22% were attributable to albuminuria, public health initiatives aiming to prevent and better manage diabetes and renal disease could have a

substantial impact on the burden of CVD in Indigenous Australians. This finding on the influence of diabetes and albuminuria largely concurs with that reported in other high-risk indigenous populations and suggests that risk equations for this population need to be evaluated to adequately account for the dominant effects of diabetes and macroalbuminuria. The present study further highlights the importance of the management of diabetes and albuminuria in addition to traditional risk factors in the prevention of premature mortality and CVD in this high-risk population.

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Competing interests

None declared.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Table S1. Baseline characteristics according to data availability and consent status for mortality follow-up among participants without a prior history of CVD at baseline: the DRUID study.

Table S2. Risk of all-cause mortality according to baseline glycaemia status and baseline albuminuria, adjusting for individual co-variates and comparing multivariate models: the DRUID follow-up study

Table S3. Risk of fatal or non-fatal CVD according to baseline abnormal glycaemia and albuminuria, adjusting for individual covariates and comparing different multivariate models: the DRUID follow-up study.

Table 1 Baseline characteristics according to cardiovascular disease and all-cause mortality outcomes: the DRUID study

	All-cause mortality			Fatal and non-fatal CVD events		
	Alive	**Dead**	**Total**	**No CVD**	**Yes CVD**	**Total**
n	676	30	706	626	33	659
Age, years	36 (14)	48 (17)	37 (14)	36 (14)	51 (11)	36 (15)
Women, *n* (%)	463 (68)	18 (60)	481 (68)	430 (69)	20 (61)	450 (68)
Normal glycaemia[a], *n* (%)	473 (70)	9 (30)	482 (68)	440 (70)	7 (21)	447 (68)
Impaired fasting tolerance, *n* (%)	22 (3)	2 (7)	24 (3)	21 (3)	2 (6)	23 (3)
Impaired glucose tolerance, *n* (%)	70 (10)	5 (17)	75 (11)	64 (10)	5 (15)	69 (10)
Newly diagnosed diabetes, *n* (%)	38 (6)	1 (3)	39 (6)	35 (6)	2 (6)	37 (6)
Previously diagnosed diabetes, *n* (%)	73 (11)	13 (43)	86 (12)	66 (11)	17 (52)	83 (13)
Fasting glucose, mmol/l	5.1 (4.8, 5.7)	5.9 (5.1, 8.1)	5.2 (4.8, 5.8)	5.1 (4.8, 5.7)	6.4 (5.4, 10.1)	5.2 (4.8, 5.8)
2-h glucose , mmol/l	6.0 (5.0, 7.4)	5.6 (4.7, 8.0)	6.0 (5.0, 7.4)	5.9 (4.9, 7.4)	8.1 (5.7, 10.9)	6.0 (4.9, 7.4)
HbA_{1c}, mmol/mol	34 (31, 40)	44 (36, 67)	34 (31, 40)	34 (31, 40)	44 (40, 68)	34 (31, 40)
HbA_{1c}, %	5.3 (5.0, 5.8)	6.2 (5.4, 8.3)	5.3 (5.0, 5.8)	5.3 (5.0, 5.7)	6.2 (5.7, 8.4)	5.3 (5.0, 5.8)
No albuminuria[b], *n* (%)	590 (87)	16 (53)	606 (86)	546 (87)	18 (55)	564 (86)
Microalbuminuria, *n* (%)	69 (10)	7 (23)	76 (11)	62 (10)	9 (27)	71 (11)
Macroalbuminuria, *n* (%)	17 (3)	7 (23)	24 (3)	18 (3)	6 (18)	24 (4)
Urine albumin to creatinine ratio, mg/l	0.6 (0.3, 1.2)	1.7 (0.6, 23.5)	0.6 (0.3, 1.3)	0.6 (0.4, 1.2)	2.0 (0.5, 23.3)	0.6 (0.4, 1.3)
CKD-EPI eGFR categories[c]						
≥90 ml/min/1.73m^2	554 (82)	9 (30)	563 (80)	505 (81%)	18 (55%)	523 (79%)
60–90 ml/min/1.73m^2	115 (17)	18 (60)	133 (19)	114 (18%)	13 (39%)	127 (19%)
<60 ml/min/1.73m^2	7 (1)	3 (10)	10 (1)	7 (1%)	2 (6%)	9 (1%)
Non-smoker, *n* (%)	226 (33)	6 (20)	232 (33)	206 (33)	10 (30)	216 (33)
Ex-smoker, *n* (%)	155 (23)	11 (37)	166 (24)	150 (24)	5 (15)	155 (24)
Current smoker, *n* (%)	295 (44)	13 (43)	308 (44)	270 (43)	18 (55)	288 (44)
Systolic blood pressure, mmHg	116.1 (15.1)	125.8 (25.3)	116.5 (15.8)	115.6 (15.1)	133.1 (22.1)	116.5 (16.0)
Diastolic blood pressure, mmHg	73.4 (9.9)	75.5 (9.4)	73.5 (9.9)	73.0 (9.8)	80.3 (11.2)	73.4 (10.0)
Hypertension[d], *n* (%)	115 (17)	12 (40)	127 (18)	104 (17)	17 (52)	121 (18)
Total cholesterol, mmol/l	5.0 (1.1)	4.9 (1.2)	5.0 (1.1)	5.0 (1.0)	5.6 (1.4)	5.0 (1.1)
HDL cholesterol, mmol/l	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)	1.2 (0.3)	1.1 (0.3)	1.2 (0.3)

hsCRP, mg/l	3.4 (1.3, 7.5)	4.8 (1.9, 11.5)	3.4 (1.3, 7.7)	3.4 (1.2, 7.4)	5.5 (4.2, 11.5)	3.4 (1.3, 7.7)
Dyslipidaemia[e], *n* (%)	102 (15)	6 (20)	108 (15)	91 (15)	10 (30)	101 (15)
Triglycerides, mmol/l	1.4 (1.0, 2.0)	1.7 (1.3, 3.4)	1.4 (1.0, 2.0)	1.4 (1.0, 2.0)	2.1 (1.5, 2.9)	1.4 (1.0, 2.0)
BMI, kg/m^2	28.6 (7.0)	28.8 (8.5)	28.6 (7.1)	28.4 (7.1)	30.2 (6.3)	28.5 (7.0)
Mean waist circumference, cm	94.9 (16.7)	98.6 (16.7)	95.1 (16.7)	94.6 (16.6)	103.2 (14.1)	95.0 (16.6)
Insufficient fruit and vegetable intake[f], *n* (%)	626 (93)	29 (97)	655 (93)	578 (93)	31 (94)	609 (93)
No post-school qualifications, *n* (%)	373 (55)	19 (63)	392 (56)	344 (55)	25 (76)	369 (56)
Weekly household income <AUD$199, *n* (%)	153 (23)	11 (37)	164 (23)	145 (23)	13 (39)	158 (24)
AUD$200–499, *n* (%)	215 (32)	6 (20)	221 (31)	197 (31)	9 (27)	206 (31)
≥AUD$500, *n* (%)	167 (25)	4 (13)	171 (24)	149 (24)	2 (6)	151 (23)
Not stated or missing, *n* (%)	141 (21)	9 (30)	150 (21)	135 (22)	9 (27)	144 (22)

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated GFR; hsCRP, high-sensitivity C-reactive protein.

For continuous variables data are mean (standard deviation) or median (25^{th}, 75^{th} percentiles), and for discrete variables data are numbers (%). [a]Glycaemic status defined according to WHO criteria [20]. [b]Albuminuria: microalbuminuria defined as 3--30 mg/mmol and macroalbuminuria defined as ≥30 mg/mmol [22]. [d]Hypertension defined as mean systolic blood pressure ≥140/90 mmHg or self-reported anti-hypertensive medication use. [e]Dyslipidaemia defined as HDL <1.0 and Triglycerides ≥2.0 mmol/l. [f]Insufficient fruit and vegetable intake defined as self-reported consumption of <2 servings of fruit and <4 servings vegetables.

Table 2 Unadjusted and age adjusted all-cause mortality and cardiovascular disease risks according to baseline risk factors: the DRUID study

	All-cause mortality					Fatal and non-fatal CVD events				
	Deaths *n* (%)	**Unadjusted HR**	**95% CI**	**Age and sex adjusted HR**	**95% CI**	**CVD *n* (%)**	**Unadjusted HR**	**95% CI**	**Age and sex adjusted HR**	**95% CI**
Normal glycaemia[a]	9 (2)	1.0		1.0		7 (2)	1.0		1.0	
Impaired fasting glucose	2 (8)	4.6	1.0–21.3	3.7	0.7–18.2	2 (9)	5.8	1.2–28.1	3.3	0.7–16.3
Impaired glucose tolerance	5 (7)	3.6	1.2–10.7	2.6	0.8–8.6	5 (7)	4.7	1.5–14.8	2.7	0.8–8.7
Newly diagnosed diabetes	1 (3)	1.4	0.2–10.8	1.0	0.1–8.1	2 (5)	3.5	0.7–16.8	1.7	0.3–8.3
Known diabetes	13 (15)	8.5	3.6–20.0	4.8	1.6–14.3	17 (20)	14.5	6.0–35.0	6.4	2.4–16.5
HbA_{1c} <39 mmol/mol (<5.7%)[b]	12 (2)	1.0		1.0		10 (2)	1.0		1.0	
HbA_{1c} 39-47 mmol/mo (5.7–6.5%)l	4 (5)	2.0	0.6–6.1	1.6	0.5–5.2	6 (8)	3.7	1.3–10.0	1.8	0.6–5.2
Known diabetes or HbA_{1c} ≥48 mmol/mol (≥6.5%)	14 (12)	5.4	2.5–11.6	3.0	1.2–7.5	17 (15)	7.8	3.6–17.0	3.3	1.4–7.8
Normal albuminuria[c]	16 (3)	1.0		1.0		18 (3)	1.0		1.0	
Microalbuminuria	7 (9)	3.6	1.5–8.7	2.7	1.1–6.9	9 (13)	4.1	1.8–9.1	2.9	1.3–6.5

Macroalbuminuria	7 (29)	13.5	5.6–33.0	9.7	3.7–25.8	6 (25)	8.9	3.5–22.5	5.3	2.0–13.7
eGFR ≥90 ml/min/1.73m^2 [d]	9 (2)	1.0		1.0		18 (3)	1.0		1.0	
eGFR 60-90 ml/min/1.73m^2	18 (14)	8.8	3.9–19.5	6.7	2.4–19.0	13 (10)	3.1	1.5–6.2	1.1	0.5–2.4
eGFR <60 ml/min/1.73m^2	3 (30)	22.2	6.0–82.0	21.1	4.7–94.8	2 (22)	7.1	1.7–30.7	2.7	0.6–12.6
Non-smoker	6 (3)	1.0		1.0		10 (5)	1.0		1.0	
Ex-smoker	11 (7)	2.6	1.0–7.0	2.2	0.8–6.1	5 (3)	0.7	0.2–2.0	0.6	0.2–1.7
Smoker	13 (4)	1.6	0.6–4.3	2.0	0.7–5.3	18 (6)	1.4	0.6–3.0	1.4	0.6–3.2
No hypertension	18 (3)	1.0		1.0		16 (3)	1.0		1.0	
Hypertension[e]	12 (9)	3.1	1.5–6.4	1.2	0.5–2.9	17 (14)	4.9	2.5–9.8	1.9	0.9–4.1
Total cholesterol <5.5 mmol/l	21 (4)					15 (3)	1.0		1.0	
Total cholesterol ≥5.5 mmol/l	9 (4)	0.9	0.4–1.9	0.8	0.4–1.8	18 (9)	2.7	1.4–5.5	1.8	0.9–3.6
HDL ≥1.0 mmol/l	20 (4)	1.0		1.0		22 (5)	1.0		1.0	
HDL <1.0 mmol/l	10 (5)	1.1	0.5–2.4	1.3	0.6–2.8	11 (6)	1.4	0.7–2.8	1.4	0.7–3.0
hsCRP <3.5 mg/l	11 (3)	1.0		1.0		7 (2)	1.0		1.0	
hsCRP ≥3.5 mg/l	19 (5)	1.8	0.8–3.7	1.8	0.8–4.2	26 (8)	3.9	1.7–8.9	2.7	1.1–6.3
No dyslipidaemia	24 (4)	1.0		1.0		23 (4)	1.0		1.0	
HDL cholesterol <1.0 and triglycerides ≥2.0 mmol/l	6 (6)	1.4	0.6–3.3	1.3	0.5–3.3	10 (10)	2.5	1.2–5.2	2.2	1.0–4.8
Triglycerides <2.0 mmol/l	19 (4)	1.0		1.0		16 (3)	1.0		1.0	
Triglycerides ≥ 2.0 mmol/l	11 (6)	1.5	0.7–3.2	1.1	0.5–2.4	17 (10)	2.9	1.5–5.8	1.7	0.9–3.5
Normal BMI ≥18.5 and < 23 kg/m^2	5 (4)	1.0		1.0		4 (4)	1.0		1.0	
BMI <18.5 kg/m^2	3 (10)	2.6	0.6–11.0	4.3	0.9–20.8	1 (4)	1.0	0.1–8.8	2.3	0.2–21.6
BMI 23–27 kg/m^2	5 (3)	0.7	0.2–2.4	0.6	0.2–2.3	3 (2)	0.5	0.1–2.4	0.4	0.1–1.8
BMI ≥27 kg/m^2	16 (4)	0.9	0.3–2.6	0.7	0.2–2.1	25 (7)	1.9	0.7–5.5	1.0	0.3–2.8
Normal waist circumference	5 (3)	1.0		1.0		4 (2)	1.0		1.0	
Obese waist circumference[e]	23 (5)	1.7	0.7–4.5	1.2	0.4–3.5	29 (6)	2.8	1.0–7.9	1.1	0.4–3.2
Sufficient fruit and vegetable intake	1 (2)	1.0		1.0		2 (4)	1.0		1.0	
Insufficient fruit and vegetable intake[g]	29 (4)	2.3	0.3–16.5	3.4	0.5–25.6	31 (5)	1.2	0.3–5.2	1.7	0.4–7.2
Post-school qualifications	11 (4)	1.0		1.0		8 (3)	1.0		1.0	
No qualifications after school	19 (5)	1.4	0.7–2.9	1.1	0.5–2.4	25 (7)	2.5	1.1–5.5	1.9	0.8–4.2
≥AUD$500 household weekly income	4 (2)	1.0		1.0		2 (1)	1.0		1.0	
AUD$1-199 household weekly income	11 (7)	3.1	1.0–9.8	2.7	0.8–8.8	13 (8)	6.6	1.5–29.3	7.3	1.6–33.1
AUD$200–499 household weekly income	6 (3)	1.2	0.3–4.1	0.7	0.2–2.7	9 (4)	3.4	0.7–15.8	3.1	0.7–14.5

Not stated or missing income	9 (6)	2.7	0.8–8.8	2.8	0.8–9.6	9 (6)	4.9	1.1–22.8	7.5	1.6–35.0

CKD-EPI, Chronic Kidney Disease Epidemiology Collaboration; CVD, cardiovascular disease; eGFR, estimated GFR; hsCRP, high-sensitivity C-reactive protein;

[a]Glycaemic status defined according to WHO criteria [20]. [b]Glycaemic status defined according to American Diabetes Association HbA_{1c} criteria [21]. [c]Albuminuria:microalbuminuria defined 3–30 mg/mmol and macroalbuminuria defined as ≥30 mg/mmol [22]. [d]eGFR: estimated glomerular filtration rate categories based on Chronic Kidney Disease Epidemiology Collaboration [23]. [e]Hypertension defined as mean systolic blood pressure ≥140/90 mmHg or self-reported anti-hypertensive medication use. [f]Abdominal obesity defined as waist circumference ≥90cm for men and ≥80 cm for women. [g]Insufficient fruit and vegetable intake defined as self-reported consumption of < 2 servings of fruit and < 4 servings vegetables.

Table 3 Adjusted risk of all-cause mortality and cardiovascular disease according to baseline glucose tolerance and albuminuria: the DRUID study

			All-cause mortality						Fatal or non-fatal CVD			
			Model 1		Model 2				Model 1		Model 2	
	Deaths *n* (%)	Mortality rates (per 1000 person-years)	HR	95% CI	HR	95% CI	CVD *n* (%)	CVD incidence rates (per 1,000 person-years)	HR	95% CI	HR	95% CI
Normal glycaemia[a]	9 (2)	2.5 (1.3–4.8)	1.0		1.0		7 (2)	2.1 (1.0–4.4)	1.0		1.0	
Impaired fasting glucose*	2 (8)	11.4 (2.8–45.5)	3.5	0.7–17.3	2.7	0.5–13.8	2 (9)	12.0 (3.0–48.1)	3.0	0.6–15.0	2.5	0.5–12.4
Impaired glucose tolerance*	5 (7)	8.9 (3.7–21.3)	2.4	0.7–8.1	2.2	0.6–7.8	5 (7)	9.7 (4.0–23.3)	2.5	0.8–8.2	2.5	0.8–8.2
Newly diagnosed diabetes*	1 (3)	3.4 (0.5–24.1)	0.8	0.1–7.2	0.8	0.1–6.6	2 (5)	7.3 (1.8–29.2)	1.1	0.2–5.6	1.0	0.2–5.0
Known diabetes mellitus*	13 (15)	20.6 (12.0–35.5)	4.8	1.5–14.7	3.3	1.1–10.0	17 (21)	30.0 (18.7–48.3)	5.6	2.1–15.2	4.6	1.7–12.5
Normal albuminuria[b]	16 (3)	3.5 (2.1–5.7)	1.0		1.0		18 (3)	4.3 (2.7–6.8)	1.0		1.0	
Microalbuminuria**	7 (9)	12.4 (5.9–26.1)	2.9	1.1–7.7	2.8	1.1–7.4	9 (13)	17.5 (9.1–33.7)	2.5	1.1–5.7	2.4	1.0–5.4
Macroalbuminuria**	7 (29)	44.8 (21.4–94.0)	10.9	3.7–32.1	9.2	3.0–27.8	6 (25)	38.1 (17.1–84.8)	3.9	1.4–10.8	3.1	1.1–8.7

CVD, cardiovascular disease; HR, hazard ratio.

[a]Glycaemic status defined according to WHO criteria [20]. [b]Albuminuria: microalbuminuria defined 3–30 mg/mmol and macroalbuminuria defined as ≥30 mg/mmol [22].

Model 1: adjusted for age (time-scale), sex, hypertension (≥140/90 mmHg or anti-hypertensive medication use), total cholesterol:HDL (continuous) and smoking.

Model 2: adjusted for all variables in Model 1 plus urine albumin creatinine ratio* or glycaemic status**

Table 4 Risk of all-cause mortality and cardiovascular disease according to baseline abnormal glycaemia and albuminuria combined: the DRUID study

	All-cause mortality						Fatal or non-fatal CVD					
			Model 1		Model 2				Model 1		Model 2	
	Deaths *n* (%)	Mortality rates (per 1,000 person years)	HR	95% CI	HR	95% CI	CVD *n* (%)	CVD incidence rates (per 1,000 person years)	HR	95% CI	HR	95% CI
Normal glycaemia and no albuminuria	7 (2)	2.1 (1.0–4.5)	1.0		1.0		3 (1)	1.0 (0.3–3.1)	1.0		1.0	
Abnormal glycaemia[a] and no albuminuria	9 (5)	7.0 (3.6–13.4)	2.2	0.7–6.9	2.0	0.6–6.7	15 (9)	12.7 (7.6–21.0)	6.1	1.7–21.8	5.2	1.4–19.0
Normal glycaemia and micro- or macro-albuminuria[b]	2 (4)	5.9 (1.5–23.5)	2.8	0.6–13.9	2.9	0.6–14.5	4 (9)	12.1 (4.5–32.2)	8.7	1.9–39.7	6.3	1.3–29.9
Both abnormal glycaemia[a] and micro- and macro-albuminuria[b]	12 (22)	31.7 (18.0–55.9)	9.1	3.0–27.8	9.8	3.0–32.4	11 (22)	32.4 (18.0–58.5)	14.1	3.8–51.8	8.4	2.1–34.4

Glycaemic status defined according to WHO criteria [20]; Albuminuria: microalbuminuria defined 3-30 mg/mmol and macroalbuminuria defined as ≥30 mg/mmol [22]

[a]Abnormal glycaemia defined as having either impaired fasting glucose, impaired glucose tolerance or diabetes.

[b]Albuminuria: microalbuminuria defined 3-30 mg/mmol and macroalbuminura defined as ≥30 mg/mmol.

Model 1 adjusted for age (time-scale) and sex.

Model 2 adjusted for age (time-scale), sex, systolic blood pressure (continuous), total cholesterol (continuous), HDL (continuous), anti-hypertensive medication and smoking