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Clinical characteristics and mortality in novel subgroups of adult-onset diabetes in an Australian population-based cohort of men

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ABSTRACT

Aims: To determine the prevalence of the novel diabetes subgroups in a population-based study, and investigate clinical characteristics and mortality in these subgroups compared to participants without diabetes.
Methods: Men from the Geelong Osteoporosis study (n = 895) were categorised according to diabetes status. Men with diabetes (n = 105) were categorised into the severe auto-immune diabetes (SAID) subgroup based on islet antibody seropositivity. The remaining men were then classified into the other subgroups using k-means clustering. ANOVA and chi-squared tests were used to determine differences in demographics, lifestyle factors and comorbidities between the novel diabetes subgroups and normoglycaemia (n = 790). Cox proportional hazard models were used to compare mortality over a median of 11.8 years (IQR 9.7–11.3). A p-value< 0.05 was considered significant, models were adjusted for age, physical activity, and systolic blood pressure.
Results: Compared to men with normoglycaemia, mean blood pressure and cardiovascular comorbidities were higher in the mild obesity-related diabetes (MOD), mild age-related diabetes (MARD), and severe insulin-resistant diabetes (SIRD) subgroups. The MARD subgroup was associated with higher mortality in unadjusted models (HR 5.5, 95 %CI 3.6–8.4); although this was attenuated after adjustment. In unadjusted models, mortality was not different in the SIRD subgroup, however, after adjustment this subgroup had higher mortality (HR 2.0; 95 %CI 1.0–3.9).
Conclusions: These data may influence choice of antihyperglycaemic medication and management of cardiovascular risk factors in men with type 2 diabetes particularly in the SIRD subgroup which is associated with cardiovascular-related comorbidities, and mortality.

1. Introduction

Diabetes mellitus is a chronic metabolic disease with highly heterogenous phenotypes resulting in many adverse health outcomes [1]. Insulin deficiency and resistance are the major causes of diabetes [2], although the relative contribution of insulin deficiency and resistance can vary between individuals [3]. Differences in these characteristics are important in management decisions and the development of complications [4], leading to treatment and outcomes that are vastly different. Recently, Ahlqvist et al. [5] proposed new subgroups for diabetes with the goal of improving homogeneity of clinical phenotypes to provide more precise management for people with diabetes. Common features and biomarkers of diabetes were used to define the new subgroups, namely age of onset of diabetes, body mass index (BMI), glycated

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haemoglobin (HbA1c), estimates of insulin resistance (HOMA-IR), and beta cell function (HOMA-B) and presence of glutamic acid decarboxylase antibodies (GADA). The subgroups identified have been termed mild age-related diabetes (MARD), mild obesity-related diabetes (MOD), severe insulin resistant diabetes (SIRD), severe insulin deficient diabetes (SIDD), and severe autoimmune diabetes (SAID).

Complications associated with diabetes occur at varying rates in each subgroup [5]. Individuals in the SIRD subgroup have an increased risk of kidney-related complications, such as chronic kidney disease and diabetic kidney disease in the years following diagnosis. Although Ahlqvist et al. [5] did report that SIRD and MOD increased risk of coronary events in unadjusted models, after adjusting for age and sex these subgroups were not significantly different compared to the other subgroups. Another study identified no difference in all-cause mortality, however cardiovascular-related mortality was higher in the MARD subgroup [6].

To date, differences in clinical characteristics, lifestyle, cardiovascular disease, and mortality between the subgroups have not been well described, especially in Australian men. Previous studies either lack specific lifestyle characteristics [6], or were unable to differentiate between those with high insulin resistance and poor beta cell function [7]. This study aims to determine the prevalence of the novel diabetes subgroups in an Australian population-based study of men and to compare characteristics between groups and to people with diabetes.

2. Methods

2.1. Sample population

This study used data generated by the Geelong Osteoporosis Study (GOS). An age-stratified sample of men was randomly recruited from electoral rolls for the Barwon Statistical Division in south-eastern Australia and were not selected on the basis of any disease. In Australia, voting is compulsory for all residents aged 18 years and older, so the electoral roll provides a comprehensive listing of adults in Australia. The inclusion criterion was a listing on the electoral roll as a resident of the Barwon Statistical Division; individuals who had resided in the region for less than 6 months and those unable to provide written informed consent, were excluded. Details of recruitment are reported elsewhere [8]. This study used data from the male cohort during the baseline visit (2001–06, n = 1540; participation 67 %) or the 5-year follow-up (2007–10, n = 978), corresponding to the visit when blood samples were first collected; for clarity this will be termed "study baseline". At these visits glycaemia status was assessed for 1170 men making them eligible for analysis, the majority of the sample was white (98 %). The Human Research Ethics Committee of Barwon Health (00/56) approved the project. All participants provided written, informed consent. The funders were not involved in any part of this study.

Criteria for classification of diabetes included a fasting plasma glucose (FPG) test $\geq$ 7.0 mmol/L, self-report of diabetes, and/or the use of antihyperglycaemic medications. Participants were classified as having normoglycaemia if FPG was $<$ 5.6 mmol/L [9].

2.2. Blood analysis

After an overnight fast, blood samples were taken and analysed for fasting plasma glucose (FPG) (hexokinase-glucose-6-phosphate dehydrogenase method), HbA1c (CEA190Hu, CLOUD-CLONE), GADA (GAD; RSR anti-GAD65 chemiluminescence immunoassay), and C-peptide. HOMA-IR was calculated as $1.5 + FPG\ (mmol/L) \times fasting\ C\text{-}peptide\ (pmol/L)\ /\ 2800$, and HOMA-B was calculated as $0.27 \times C\text{-}peptide\ (pmol/L)\ /\ (FPG\ (mmol/L)\ -\ 3.5)$ [10]. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI creatinine equation [11]. All eGFR values above 90 mL/min were considered as $>$ 90 mL/min as per the Australasian creatine consensus working group [12].

2.3. Subgroup clustering

Clustering was conducted following the process described by Ahlqvist et al. [5]. At study baseline, 124 men were categorised as having diabetes using the criteria outlined above, and 105 had sufficient data to cluster into subgroups. Initially, hierarchical clustering was used to separate the men who were seropositive for GADA (SAID group, n = 3). The remaining 102 men were differentiated using k-means clustering using the variables HbA1c, age of onset of diabetes, BMI, HOMA-IR, and HOMA-B. Age of onset was defined as self-reported age of diagnosis or the age at the date of visit.

2.4. Other data

Weight was measured to the nearest $\pm$ 0.1 kg using electronic scales and height was measured to the nearest $\pm$ 0.1 cm using a Harpenden stadiometer. These measures were used to calculate BMI as $weight\ (kg)\ /\ height\ (m)^2$. Seated blood pressure was measured with an automated sphygmomanometer (Takeda Medical UA-751).

Physical activity, smoking status, alcohol consumption, and use of medications were self-reported. The physical activity levels "very active, active, sedentary, limited, inactive, chair/bedridden, and bedfast" were categorised as "high" if very active or active were selected and "low" for the remaining responses. Participants were categorised as smokers and non-smokers (which included former smokers). Alcohol consumption (grams per day) was determined using the Cancer Council Victoria food frequency questionnaire [13] and categorised as "low" ($<$ 30 g/day) and "high" ($\geq$ 30 g/day) according to National Health and Medical Research Council (NHMRC) recommendation [14]. Cardiovascular-related medications included using any type of antihypertensives (diuretics, beta-blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers), statin use, and aspirin use.

Socio-economic status (SES) was calculated using the socioeconomic indexes for areas based on census data from the Australian Bureau of Statistics. Participants were then categorised into quintiles based on the Index of Relative Socio-Economic Advantage and Disadvantage (IRSAD) [8]. These were compressed into three groups, low for quintiles 1 and 2 (most disadvantaged), medium for the third quintile, and high for quintiles 4 and 5 (most advantaged).

2.5. Comorbidity and mortality data

Information on comorbidities was obtained through a combination of self-reports, measurement, and data linkage, and then categorised into four major themes (cardiovascular, pulmonary, musculoskeletal, and cancer). The cardiovascular-related comorbidities included cardiovascular disease such as myocardial infarction, stroke, or risk factors for the disease, hypertension (systolic blood pressure $\geq$ 140 mmHg, diastolic blood pressure $\geq$ 90 mmHg, or use of antihypertensive medication [15]), and elevated cholesterol (total cholesterol $\geq$ 5.5 mmol/L [16]) or lipid lowering therapy. Pulmonary included asthma, emphysema, and other lung diseases. Osteoarthritis, osteoporosis (femoral neck or lumbar spine BMD t-score $<$ $-$2.5), rheumatoid arthritis, and muscle weakness, or disease were included in the musculoskeletal theme. All data on cancer (any tumour, leukemia, lymphoma, and metastatic solid tumours) were obtained via linkage with the Victorian Cancer Registry. Incident cancers from 1986 onwards were captured using this linkage.

Mortality data were obtained through linkage with the National Death Index, developed and maintained by the Australian Institute of Health and Welfare. The data included dates and primary and secondary causes of death.

2.6. Statistical analysis

The analyses included 105 men classified into the diabetes subgroups

and 790 men identified as having normoglycaemia (FPG < 5.6 mmol/L, no self-report of diabetes or antihyperglycaemic medication use). All variables were tested for normal distribution using histograms. ANOVA and Tukey's tests were used in conjunction to examine differences between groups for variables that were normally distributed, Kruskal-Wallis and Dunn tests were used for variables that were not normally distributed and chi-squared tests were used for categorical variables.

Participants were followed from study baseline to date of death or the end of the study period (14/07/2017); the median follow-up was 11.8 years (IQR 9.7–11.3). Cause of death was compared between the subgroups. Cox proportional hazards models were used to assess mortality risk in the subgroups, adjusting for age, physical activity, and systolic blood pressure as these were significantly associated with mortality. A p-value< 0.05 was considered significant. These models met the assumption of proportional hazards.

Analyses were completed using Stata version 18 (StataCorp. 2023. Stata Statistical Software: Release 18. College Station, TX: StataCorp LLC). Participants with missing data were excluded from analyses, those with partially missing data were excluded from analyses where data were missing. For example, if a participant had all data except for blood pressure, they would only be excluded from analyses involving blood pressure.

3. Results

3.1. Subgroup characteristics

Based on biochemistry (FPG ≥ 7.0 mmol/L), 70 men were classified as having diabetes, 89 self-reported diabetes, and 76 reported antihyperglycaemic medication use. Many of these criteria overlapped,

Table 1
Descriptive characteristics comparing the diabetes subgroups and normoglycaemia in the sample of predominantly White men. Data shown as n (%), mean±SD, or median (IQR).

	Normoglycaemia (N = 790)	MOD (N = 25)	MARD (N = 30)	SIRD (N = 31)	SIDD (N = 16)	SAID (N = 3)	p value
Age (yr)	57.0 (41.2–74.6)	72.7 (68.5–75.3)	83.0 (79.0–86.4)	64.2 (59.9–70.3)	55.4 (50.8–62.9)	36.7 (30.0–50.8)	< 0.001
Age of onset (yr)	NA	68.0 (65.0–71.0)	81.0 (76.0–83.0)	59.0 (55.0–60.0)	47.5 (45.0–50.0)	31.0 (14.0–36.0)	< 0.001
Weight (kg)	81.2 ± 13.9	88.7 ± 15.3	79.0 ± 12.0	86.9 ± 14.5	86.8 ± 11.6	83.4 ± 8.1	0.011
Height (cm)	174.7 ± 7.4	171.5 ± 7.6	170.8 ± 7.8	172.0 ± 6.1	174.3 ± 4.4	179.3 ± 2.6	0.004
BMI (kg/m^2)	26.6 ± 4.0	30.2 ± 5.2	27.1 ± 3.8	29.4 ± 4.7	28.6 ± 3.7	25.9 ± 1.9	< 0.001
Systolic BP (mmHg)	135.4 ± 17.0	149.5 ± 20.4	147.7 ± 16.8	145.7 ± 18.8	129.6 ± 11.4	132.8 ± 21.1	< 0.001
Diastolic BP (mmHg)	84.9 ± 11.2	92.3 ± 17.0	82.8 ± 15.0	87.3 ± 13.3	81.8 ± 11.4	85.8 ± 7.6	0.022
Physical inactivity	180 (22.8 %)	10 (40.0 %)	15 (50.0 %)	9 (29.0 %)	2 (12.5 %)	0	0.003
Smoking	108 (13.7 %)	1 (3.3 %)	0	5 (16.1 %)	4 (25.0 %)	0	0.101
High alcohol consumption	169 (21.8 %)	2 (8.3 %)	5 (17.2 %)	5 (16.7 %)	2 (12.5 %)	0	0.489
Fasting plasma glucose (mmol/L)	5.0 (4.7–5.2)	7.5 (6.3–8.6)	7.3 (5.9–8.7)	7.6 (6.5–8.6)	8.1 (6.4–9.8)	5.4 (4.2–10.8)	< 0.001
HbA1c (ug/mL)	56.7 (46.1–117.2)	51.9 (39.6–73.6)	63.9 (485–113.6)	116.6 (50.4–129.8)	120.9 (62.4–635.4)	40.0 (21.0–47.0)	< 0.001
HOMA-IR	1.86 ± 0.17	2.20 ± 0.43	2.26 ± 0.64	2.28 ± 0.40	2.17 ± 0.38	1.62	< 0.001
HOMA-B	42.7 ± 43.0	21.8 ± 15.4	26.3 ± 28.8	25.0 ± 33.1	17.3 ± 12.9	9.1	0.001
eGFR< 60	65 (8.3 %)	6 (24.0 %)	10 (33.3 %)	4 (12.9 %)	3 (18.8 %)	0	< 0.001
eGFR (mL/min)	> 90.0 (78.6 - > 90.0)	78.8 (67.2 - > 90.0)	67.6 (53.3–81.8)	82.3 (66.2 - > 90.0)	81.8 (64.4 - > 90.0)	> 90.0 (78.3 - > 90.0)	< 0.001
Insulin preparations	-	0	0	1 (3.2 %)	3 (18.8 %)	2 (66.7 %)	< 0.001
Oral antihyperglycaemic agents[a]	-	10 (40.0 %)	14 (46.7 %)	19 (61.3 %)	13 (81.3 %)	0	< 0.001
Biguanides	-	9 (36.0 %)	8 (26.7 %)	13 (41.9 %)	11 (68.8 %)	0	0.041
Sulfonylureas	-	5 (20.0 %)	8 (26.7 %)	13 (41.9 %)	6 (37.5 %)	0	0.252
Other	-	0	0	0	1 (6.3 %)	0	0.241
Aspirin	129 (16.3)	7 (28.0)	15 (50.0)	8 (25.8)	4 (25.0)	0	< 0.001
Antihypertensives[b]	208 (26.3)	18 (72.0)	23 (76.7)	21 (67.7)	13 (81.3)	0	< 0.001
Statins	106 (13.4)	12 (48.0)	8 (26.7)	10 (32.3)	9 (56.3)	0	< 0.001
Cardiovascular comorbidities[a]	497 (62.9 %)	24 (96.0 %)	28 (93.3 %)	28 (90.3 %)	16 (100 %)	2 (66.7 %)	< 0.001
Pulmonary comorbidities[a]	134 (17.0 %)	4 (16.0 %)	5 (16.7 %)	7 (22.6 %)	3 (18.8 %)	0	0.930
Musculoskeletal comorbidities[a]	168 (21.3 %)	6 (24.0 %)	12 (40.0 %)	8 (25.8 %)	1 (6.3 %)	1 (33.3 %)	0.118
Cancer	73 (9.2 %)	3 (12.0 %)	3 (10.0 %)	2 (6.5 %)	1 (6.3 %)	0	0.962
SES[c]							
1	260 (38.4 %)	10 (47.6 %)	15 (53.6 %)	12 (44.4 %)	7 (50.0 %)	1 (33.3 %)	0.436
2	139 (20.5 %)	7 (33.3 %)	3 (10.7 %)	3 (11.1 %)	2 (14.3 %)	1 (33.3 %)	
3	278 (41.1 %)	4 (19.1 %)	10 (35.7 %)	12 (44.4 %)	5 (35.7 %)	1 (33.3 %)	

MOD = Mild obesity-related diabetes, MARD = Mild age-related diabetes, SIRD = Severe insulin-resistant diabetes, SIDD = Severe insulin-deficient diabetes, SAID = Severe autoimmune diabetes, BMI = Body mass index, BP = Blood pressure, HOMA-IR = Homeostatic model assessment for insulin resistance, HOMA-B = Homeostatic model assessment for beta-cell dysfunction, eGFR = estimate of Glomerular filtration rate, SES = Socioeconomic status, NA = Not applicable.
Missing data: HOMA-IR = 8, HOMA-B = 15, HbA1c = 4, eGFR = 5, alcohol consumption = 18, SES = 125, blood pressure measurements = 43.

[a] Cardiovascular included heart attack, stroke, hypertension (systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or use of antihyperglycaemic medications), and elevated cholesterol (total cholesterol ≥ 5.5 mmol/L). Pulmonary included asthma, emphysema, and other lung diseases. Osteoporosis (femoral neck or lumbar spine BMD t-score < −2.5), osteoarthritis, rheumatoid arthritis, and muscle weakness or disease made up the musculoskeletal theme. All data on cancer (any tumour, leukemia, lymphoma, and metastatic solid tumours) were obtained from linkage with the Victorian Cancer Registry (VCR).

[b] Antihypertensives included use of any diuretics, betablockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and angiotensin II receptor blockers.

[c] Socio-economic status (SES) was calculated using the Australian Bureau of Statistics (ABS) Index of Relative Socio-Economic Advantage and Disadvantage. These were compressed into three categories, low for quintiles 1 and 2, medium for the third quintile, and high for quintiles 4 and 5.

resulting in a total of 124 men who were classified with diabetes at study baseline. Among the 105 men with sufficient data for categorisation into subgroups, 3 (2.9 %) were classified as SAID. The MARD subgroup included 30 (28.6 %) men, MOD included 25 (23.8 %), SIRD included 31 (29.5 %), and SIDD included 16 (15.2 %) men. MARD had the highest age of onset of diabetes (81.0 yr, IQR 76.0–83.0), and MOD had the highest BMI (30.2 kg/m^2, SD ± 5.2). SIRD had the highest HOMA-IR (2.28, SD ± 0.4), and SIDD had the lowest HOMA-B (17.3, SD ± 12.9) along with the SAID subgroup (9.1). HOMA-IR was lower, and HOMA-B was higher in normoglycaemia compared to the subgroups (Table 1).

3.2. Non-participation statistics

The 19 men with diabetes who had insufficient biochemical data for allocation to subgroups were younger (median 66.3 (IQR 47.1–71.1) vs 72.0 (62.2–80.8) yr) compared to those who did participate; however, no significant differences were detected in mean weight, height, or BMI. Similarly, there were no differences detected between the participants and non-participants for smoking, alcohol consumption, or physical activity. These men were missing biochemical data so no comparison could be made for HOMA-IR, HOMA-B, HbA1c, and eGFR.

3.3. Sample population statistics

Through post-hoc testing it was identified that the MOD (30.2 ± 5.2 kg/m^2) and SIRD (29.4 ± 4.7 kg/m^2) subgroups had significantly higher BMI compared to normoglycaemia (26.6 ± 4.0 kg/m^2) (Table 1). Systolic blood pressure was highest in the MOD subgroup (149.5 mmHg, SD ± 20.4), the MARD (147.7 mmHg, SD ± 16.8), and SIRD subgroups (145.7 mmHg, SD ± 18.8) also had means higher than normoglycaemia (135.4 mmHg, SD ± 17.0). The MOD subgroup (92.3 mmHg, SD ± 17.0) also had the highest mean values in diastolic blood pressure, with other subgroups having mean values similar to normoglycaemia (84.9 mmHg, SD ± 11.2). The subgroups were less physically active compared to normoglycaemia, however there were no differences in the prevalence of current smokers or high alcohol consumption compared to normoglycaemia. No differences were detected in socioeconomic status between the diabetes subgroups and normoglycaemia.

Poor renal function was more prevalent in the diabetes subgroups; 8.3 % of men with normoglycaemia had eGFR below 60 mL/min, the SIDD subgroup had 18.8 %, SIRD had 12.9 %, MOD had 24.0 %, and MARD had 33.3 %. This pattern remained as median eGFR values were consistently lower in the subgroups compared to normoglycaemia, and was also different between the subgroups, the MARD subgroup had the lowest eGFR.

Use of antihyperglycaemic agents were the highest in the SIDD subgroup (13, 81.3 %), followed by the SIRD subgroup (19, 61.3 %). Less than 50 % of the MOD and MARD subgroups reported use of these medications. No one in the MOD and MARD subgroups reported use of insulin preparations. Only one and three men reported use in the SIRD and SIDD subgroups, respectively. Antihypertensive medication use was higher in all subgroups other than the SAID subgroup, statin use was higher in the MOD, SIDD, and SIRD subgroups, and aspirin use was only higher in the MARD subgroup compared to normoglycaemia. Although, cardiovascular medication use did not differ significantly between the subgroups.

3.4. Cardiovascular-related comorbidity and mortality

Cardiovascular-related comorbidities were more common in all but the SAID subgroup (Table 1). Among those with normoglycaemia, 63 % reported these comorbidities compared to 93 % in the MARD subgroup, 96 % in the MOD subgroup, 90 % in the SIRD subgroup, and 100 % in the SIDD subgroup (Table 1). There was no significant difference detected in the prevalence of other comorbidities between the subgroups.

The total follow-up time was 9663.6 years with a median follow-up of 11.8 years (IQR 9.7–13.3). A total of 245 men died over this period. The diabetes subgroups had higher rates of mortality compared to those with normoglycaemia (25 %). Mortality was greatest in the MARD subgroup (80 %), then the MOD subgroup (40 %), then the SIDD (38 %), and SIRD (32 %) subgroups (Table 2). Of the 231 reported causes of mortality, cardiovascular-related mortality was the most common (n = 95, 41 %), with cancer being the next most common (n = 64, 28 %). The normoglycaemia group had cardiovascular mortality listed for 75 men (41 % of all deaths), this was 10 (44 %) for the MARD subgroup, 6 (67 %) for the SIRD subgroup, and 3 (50 %) for the SIDD subgroup. Cancer was the most common cause in the MOD subgroup being listed 6 (60 %) times (Table 2).

Mortality risk was 5.5 (95 % CI 3.6–8.4) times greater in the MARD subgroup compared to normoglycaemia in an unadjusted model (Table 3). After adjusting for age, systolic blood pressure, and physical activity this was no longer significant (HR 1.3; 95 % CI 0.8–2.0; p = 0.336). However, using the adjusted model the SIRD subgroup had double the risk of mortality (HR 2.0; 95 % CI 1.0–3.9; p = 0.038) (Table 3). HbA1c was not significantly associated with mortality in these models.

4. Discussion

Using methods outlined by Ahlqvist et al. [5], in the GOS cohort five distinct diabetes subgroups were defined with characteristics comparable to the Ahlqvist subgroups. One should note other research groups have been successful in this endeavour [17,18], suggesting that these data-driven clusters are robust and reproducible.

The GOS diabetes subgroups were characterised by greater weight, shorter stature, and higher BMI compared to the group with normoglycaemia. These differences were greatest in the MOD subgroup, together with the SIRD and SIDD subgroups. Obesity is a major risk factor in the progression of cardiovascular disease and cancer [19]; the risk of cardiovascular disease almost doubles with obesity [20]. Diabetes also increases the risk of cardiovascular complications, so the MOD, SIRD, and SIDD subgroups have the potential to be at high risk of these complications [20]. Other studies have also reported similar connections between obesity, cardiovascular disease, and diabetes [21]. The MOD, MARD, and SIRD subgroups also had higher mean systolic blood pressure compared to those with normoglycaemia. Hypertension and diabetes share many mechanisms which cause these pathologies [21], resulting in these conditions being highly linked and often developing together [22]. Together with obesity, these conditions pose an increased risk of cardiovascular disease and other cardiovascular complications [21]. Despite the differences in BMI and hypertension reported in this study, other studies have reported no difference in coronary events between subgroups after adjustment [5]. This study identified that cardiovascular comorbidities were more prevalent overall in the diabetes subgroups compared to normoglycaemia, however, there were no differences detected between the subgroups.

The association between obesity and cancer [19] may explain why the MOD subgroup had higher cancer-related mortalities than the other subgroups. This subgroup also reported greater prevalence of cancers; however, the cancer-related mortality rate and incident cancers were not significantly greater than those with normoglycaemia. Weight loss in diabetes management could reduce this burden, and studies have suggested this to be the case [19]. Further studies are required to elucidate the relationship between this subgroup and cancer along with how weight loss may alter complications.

Those with diabetes had a lower eGFR compared to normoglycaemia, and greater prevalence of reduced renal function (eGFR < 60 mL/min). This relationship may be a consequence of the age-related decline in kidney function [23], as the MOD and MARD subgroups were considerably older than the normoglycaemia group (median age 72.7 and 83.0 years respectively vs 57.0 years). Poor eGFR place these

Table 2
Cause of mortality comparing the diabetes subgroups and normoglycaemia. Data shown as n (%).

	Normoglycaemia (N = 790)	MOD (N = 25)	MARD (N = 30)	SIRD (N = 31)	SIDD (N = 16)	SAID (N = 3)	Total
Mortality	195 (24.7 %)	10 (40.0 %)	24 (80.0 %)	10 (32.3 %)	6 (37.5 %)	0	245
Cause of mortality[a]	183 (23.2 %)	10 (40.0 %)	23 (76.7 %)	9 (29.0 %)	6 (37.5 %)	0	231
Cardiovascular system	75 (41.0 %)	1 (10.0 %)	10 (43.5 %)	6 (66.7 %)	3 (50.0 %)	0	95 (41.1 %)
Digestive	8 (4.4 %)	0	0	0	0	0	8 (3.5 %)
Metabolic Disorder	4 (2.2 %)	0	2 (8.7 %)	1 (11.1 %)	1 (16.7 %)	0	7 (3.0 %)
Environmental	8 (4.4 %)	0	1 (4.4 %)	0	0	0	10 (4.3 %)
Infectious Disease	1 (0.5 %)	1 (10.0 %)	0	0	0	0	2 (0.9 %)
Mental disorder	8 (4.4 %)	0	1 (4.4 %)	0	0	0	9 (3.8 %)
Musculoskeletal	1 (0.5 %)	0	0	0	0	0	1 (0.4 %)
Cancer	48 (26.2 %)	6 (60.0 %)	7 (30.4 %)	2 (22.2 %)	2 (33.3 %)	0	64 (27.7 %)
Nervous system	10 (5.5 %)	0	1 (4.4 %)	0	0	0	11 (4.8 %)
Respiratory system	16 (8.6 %)	1 (10.0 %)	1 (4.4 %)	0	0	0	19 (8.2 %)
Urinary system	4 (2.2 %)	1 (10.0 %)	0	0	0	0	5 (2.2 %)

MOD = Mild obesity-related diabetes, MARD = Mild age-related diabetes, SIRD = Severe insulin resistant diabetes, SIDD = Severe insulin deficient diabetes, SAID = Severe autoimmune diabetes, NA = Not applicable.
[a] Cause of death was not available for 12 in Normoglycaemia, 1 in MARD, and 1 in SIRD.

Table 3
Risk for all-cause mortality comparing the diabetes subgroups and normoglycaemia.

	HR $_{Unadjusted}$ (95 %CI)	p value	HR $_{Adjusted}$ (95 %CI)	p value
Normoglycaemia	referent	-	referent	-
MOD	1.78 (0.94–3.4)	0.075	1.03 (0.54–1.96)	0.932
MARD	5.49 (3.56–8.41)	< 0.001	1.26 (0.79–2.00)	0.336
SIRD	1.34 (0.71–2.53)	0.368	2.00 (1.04–3.85)	0.038
SIDD	1.54 (0.68–3.47)	0.296	2.16 (0.95–4.92)	0.066

MOD = Mild obesity-related diabetes, MARD = Mild age-related diabetes, SIRD = Severe insulin resistant diabetes, SIDD = Severe insulin deficient diabetes, SAID = Severe autoimmune diabetes, NA = Not applicable.
Mortality risk was adjusted for age, physical activity, and systolic blood pressure.

subgroups at higher risk of acute kidney injury and may contribute to elevated mortality risk should they develop chronic kidney disease [23]. The normoglycaemia group, and the SIRD and SIDD subgroups had similar median ages, but despite this, the SIRD and SIDD subgroups had a higher prevalence of reduced renal function. The median eGFR was also similar for the SIRD, SIDD, and MOD subgroups. This suggests that kidney function may deteriorate earlier within the SIRD and SIDD subgroups, consistent with observations that chronic kidney disease is more common in the SIRD subgroup [5].

Mortality risk was greater for the MARD subgroup; however, this relationship was primarily driven by age. The relationship was attenuated after adjusting for age and remained non-significant in the final model which was adjusted for the significant confounders age, systolic blood pressure, and physical activity. Mortality risk appeared to be greater in the MOD, SIRD, and SIDD subgroups, but these differences were not significant. However, after adjustment, the SIRD subgroup had a higher risk of mortality. Insulin resistance, cardiovascular disease and mortality are strongly associated [24], this association is present in those without diabetes, greater risk of cardiovascular and all-cause mortality has been attributed to those with high insulin resistance [25]. Furthermore, another study reported that those in the SIRD subgroup had the greatest Framingham score for coronary heart disease [26], used for assessing cardiovascular risk over 10 years. Advancements in diabetes management will be pertinent in this subgroup through the adoption of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide 1 receptor agonists [27]. The cardioprotective qualities of these anti-hyperglycaemic agents will be invaluable as first line therapies in the SIRD subgroup which exhibited high blood pressure and high prevalence of cardiovascular comorbidities in this study. While cardiovascular-related comorbidities were higher in the subgroups, there were no differences in cardiovascular events as the primary cause of death.

The interaction of insulin resistance and beta-cell function is paramount in the pathogenesis of diabetes. Insulin resistance is characterised by reduced glucose uptake by tissues due to reduced insulin sensitivity [28]. Insulin resistance is also associated with hypertension, obesity, and dyslipidaemia, often described as the metabolic syndrome, increasing the risk of vascular complications [29]. Similarly, the subgroups associated with insulin resistance, the MOD subgroup presenting with obesity and hypertension, and the MARD and SIRD subgroups associated with hypertension. Insulin deficiencies are primarily the result of dysfunctions in the pancreatic beta cells, resulting in hindered or a lack of insulin production [30]. Microvascular complications such as retinopathy and neuropathy are more prevalent in type 1 diabetes [31]. Although these were not assessed in this study, Ahlqvist et al. [5] reported the SIDD subgroup had the highest risk for retinopathy. Furthermore, another study reported risk of neuropathy to be higher in this subgroup compared to the other subgroups [32]. The differences in how insulin resistance and deficiency interact with other cellular mechanisms may provide insights into how the condition progresses in each of the subgroups, particularly, within the subgroups with the highest insulin resistance (SIRD) and lowest beta-cell function (SAID and SIDD), where this contrast is the largest.

This study has both strengths and weaknesses. A major strength is that this was a population-based cohort involving participants who were randomly selected from the electoral roll, and hence is likely to be representative of the underlying population. Diabetes classification was robust given it was identified by several methods (FPG $\geq$ 7.0 mmol/L, self-report and/or use of antihyperglycaemic medications); however, use of self-reported diabetes and medication use means some participants were diagnosed prior to attending, thus data collected may be different from the time of diagnosis. Data relating to mortality, hypertension, cholesterol levels, and cancers were obtained objectively. The number of participants in the SAID subgroup was too small to perform detailed sub-group analyses. Participants with incomplete data were only excluded from analyses where data were missing. As the majority participants were White men, we acknowledge that the results may not be generalisable to women or other populations of men. At the time of writing, these data were available only for the male cohort. Comparable data are currently being collected in the female cohort.

The novel diabetes subgroups described using an Australian community-based cohort differed in clinical characteristics (age, BMI), physical inactivity, and cardiovascular-related comorbidities as well as mortality. The SIRD subgroup may warrant greater attention as this subgroup had significantly higher blood pressure, cardiovascular related comorbidities, and mortality.

Author Contributions

All authors were involved in the conduct of the study and revising content and approved the final version of the manuscript. J.W.H., M.K., J.A.P., and K.L.H-K. were involved in the conception and design of the study. J.W.H. wrote the first draft of the manuscript.

Conflict of Interest

The authors have conflicts of interest to declare.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pcd.2025.06.007.

Data Availability

Some or all datasets generated during and/or analysed during the current study are not publicly available but are available from the corresponding author on reasonable request.

References

[1] K. Papatheodorou, M. Banach, E. Bekiari, M. Rizzo, M. Edmonds, Complications of Diabetes 2017, J. Diabetes Res. 2018 (2018) 3086167.
[2] Y. Zheng, S.H. Ley, F.B. Hu, Global aetiology and epidemiology of type 2 diabetes mellitus and its complications, Nature reviews, Endocrinology 14 (2018) 88–98.
[3] P. Basukala, B. Jha, B.K. Yadav, P.K. Shrestha, Determination of insulin resistance and beta-cell function using homeostatic model assessment in type 2 diabetic patients at diagnosis, J. Diabetes Metab. 9 (2018).
[4] U. Galicia-Garcia, A. Benito-Vicente, S. Jebari, A. Larrea-Sebal, H. Siddiqi, K. B. Uribe, H. Ostolaza, C. Martín, Pathophysiology of type 2 diabetes mellitus, Int. J. Mol. Sci. 21 (2020).
[5] E. Ahlqvist, P. Storm, A. Käräjämäki, M. Martinell, M. Dorkhan, A. Carlsson, P. Vikman, R.B. Prasad, D.M. Aly, P. Almgren, Y. Wessman, N. Shaat, P. Spégel, H. Mulder, E. Lindholm, O. Melander, O. Hansson, U. Malmqvist, Å. Lernmark, K. Lahti, T. Forsén, T. Tuomi, A.H. Rosengren, L. Groop, Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables, Lancet Diabetes Endocrinol. 6 (2018) 361–369.
[6] P.F. Li, W.L. Chen, Are the different diabetes subgroups correlated with all-cause, cancer-related, and cardiovascular-related mortality? J. Clin. Endocrinol. Metab. 105 (2020).
[7] M.P. Bancks, H. Chen, A. Balasubramanyam, A.G. Bertoni, M.A. Espeland, S. E. Kahn, S. Pilla, E. Vaughan, L.E. Wagenknecht, Type 2 diabetes subgroups, risk for complications, and differential effects due to an intensive lifestyle intervention, Diabetes care 44 (2021) 1203–1210.
[8] J.A. Pasco, G.C. Nicholson, M.A. Kotowicz, Cohort profile: Geelong Osteoporosis Study, Int J. Epidemiol. 41 (2012) 1565–1575.
[9] S. Genuth, K.G. Alberti, P. Bennett, J. Buse, R. Defronzo, R. Kahn, J. Kitzmiller, W. C. Knowler, H. Lebovitz, A. Lernmark, D. Nathan, J. Palmer, R. Rizza, C. Saudek, J. Shaw, M. Steffes, M. Stern, J. Tuomilehto, P. Zimmet, Follow-up report on the diagnosis of diabetes mellitus, Diabetes Care 26 (2003) 3160–3167.
[10] X. Li, Z.G. Zhou, H.Y. Qi, X.Y. Chen, G. Huang, Replacement of insulin by fasting C-peptide in modified homeostasis model assessment to evaluate insulin resistance and islet beta cell function, Zhong Nan Da Xue Xue Bao Yi Xue Ban. 29 (2004) 419–423.
[11] A.S. Levey, L.A. Stevens, C.H. Schmid, Y.L. Zhang, A.F. Castro 3rd, H.I. Feldman, J. W. Kusek, P. Eggers, F. Van Lente, T. Greene, J. Coresh, A new equation to estimate glomerular filtration rate, Ann. Intern Med. 150 (2009) 604–612.
[12] D.W. Johnson, G.R. Jones, T.H. Mathew, M.J. Ludlow, M.P. Doogue, M.D. Jose, R. G. Langham, P.D. Lawton, S.J. McTaggart, M.J. Peake, Chronic kidney disease and automatic reporting of estimated glomerular filtration rate: new developments and revised recommendations, Med. J. Aust. 197 (2012) 222–223.
[13] G. Giles, P. Ireland, Dietary questionnaire for epidemiological studies (version 2), The Cancer Council Victoria, Melbourne, 1996.
[14] National Health and Medical Research Council, Australian Guidelines to Reduce Health Risks from Drinking Alcohol, in, 2020.
[15] Australian Institute of Health and Welfare, High blood pressure, AIHW, Canberra, 2023.
[16] Australian Institute of Health and Welfare, Abnormal blood lipids (dyslipidaemia), AIHW, Canberra, 2023.
[17] O.P. Zaharia, K. Strassburger, A. Strom, G.J. Bönhof, Y. Karusheva, S. Antoniou, K. Bódis, D.F. Markgraf, V. Burkart, K. Müssig, J.H. Hwang, O. Asplund, L. Groop, E. Ahlqvist, J. Seissler, P. Nawroth, S. Kopf, S.M. Schmid, M. Stumvoll, A.F. H. Pfeiffer, S. Kabisch, S. Tselmin, H.U. Häring, D. Ziegler, O. Kuss, J. Szendroedi, M. Roden, Risk of diabetes-associated diseases in subgroups of patients with recent-onset diabetes: a 5-year follow-up study, Lancet Diabetes Endocrinol. 7 (2019) 684–694.
[18] R.M. Anjana, V. Baskar, A.T.N. Nair, S. Jebarani, M.K. Siddiqui, R. Pradeepa, R. Unnikrishnan, C. Palmer, E. Pearson, V. Mohan, Novel subgroups of type 2 diabetes and their association with microvascular outcomes in an Asian Indian population: a data-driven cluster analysis: the INSPIRED study, BMJ Open Diabetes Res. Care 8 (2020).
[19] K.I. Avgerinos, N. Spyrou, C.S. Mantzoros, M. Dalamaga, Obesity and cancer risk: Emerging biological mechanisms and perspectives, Metabolism 92 (2019) 121–135.
[20] S.N. Bhupathiraju, F.B. Hu, Epidemiology of obesity and diabetes and their cardiovascular complications, Circ. Res 118 (2016) 1723–1735.
[21] G. Lastra, S. Syed, L.R. Kurukulasuriya, C. Manrique, J.R. Sowers, Type 2 diabetes mellitus and hypertension: an update, Endocrinol. Metab. Clin. North Am. 43 (2014) 103–122.
[22] V. Tsimihodimos, C. Gonzalez-Villalpando, J.B. Meigs, E. Ferrannini, Hypertension and diabetes mellitus: coprediction and time trajectories, Hypertension 71 (2018) 422–428.
[23] A. Denic, R.J. Glassock, A.D. Rule, Structural and functional changes with the aging kidney, Adv. Chronic Kidney Dis. 23 (2016) 19–28.
[24] C.E. Kosmas, M.D. Bousvarou, C.E. Kostara, E.J. Papakonstantinou, E. Salamou, E. Guzman, Insulin resistance and cardiovascular disease, J. Int Med Res 51 (2023), 3000605231164548.
[25] X. Zhang, J. Li, S. Zheng, Q. Luo, C. Zhou, C. Wang, Fasting insulin, insulin resistance, and risk of cardiovascular or all-cause mortality in non-diabetic adults: a meta-analysis, Biosci. Rep. 37 (2017).
[26] N. Saatmann, O.P. Zaharia, K. Strassburger, D.H. Pesta, V. Burkart, J. Szendroedi, N. Gerdes, M. Kelm, M. Roden, Physical fitness and cardiovascular risk factors in novel diabetes subgroups, J. Clin. Endocrinol. Metab. 107 (2022) 1127–1139.
[27] A. Liakos, T. Karagiannis, I. Avgerinos, K. Malandris, A. Tsapas, E. Bekiari, Management of type 2 diabetes in the new era, Horm. (Athens) 22 (2023) 677–684.

[28] H.E. Lebovitz, Insulin resistance: definition and consequences, Exp. Clin. Endocrinol. Diabetes 109 2 (2001) S135–S148.
[29] J.L. Silveira Rossi, S.M. Barbalho, R. Reverete de Araujo, M.D. Bechara, K.P. Sloan, L.A. Sloan, Metabolic syndrome and cardiovascular diseases: going beyond traditional risk factors, Diabetes Metab. Res Rev. 38 (2022) e3502.
[30] L.A. DiMeglio, C. Evans-Molina, R.A. Oram, Type 1 diabetes, Lancet (Lond. Engl.) 391 (2018) 2449–2462.
[31] O.P. Zaharia, S. Lanzinger, J. Rosenbauer, W. Karges, K. Müssig, S.M. Meyhöfer, V. Burkart, M. Hummel, D. Raddatz, M. Roden, J. Szendroedi, R.W. Holl, Comorbidities in recent-onset adult type 1 diabetes: a comparison of german cohorts, Front Endocrinol. (Lausanne) 13 (2022) 760778.
[32] O. Fedotkina, O. Sulaieva, T. Ozgumus, L. Cherviakova, N. Khalimon, T. Svietleisha, T. Buldenko, E. Ahlqvist, O. Asplund, L. Groop, P.M. Nilsson, V. Lyssenko, Novel Reclassification of adult diabetes is useful to distinguish stages of β-cell function linked to the risk of vascular complications: the DOLCE study from Northern Ukraine, Front Genet 12 (2021) 637945.