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Prevalence, incidence and risk factors of diabetes in Australian adults aged ≥ 45 years: A cohort study using linked routinely-collected data

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ABSTRACT

Aims: To use linked routinely-collected health data to estimate diabetes prevalence and incidence in an Australian cohort of adults aged ≥ 45 years, and examine risk factors associated with incident disease.

Research design and methods: The EXAMining ouTcomeS in chroNic Disease in the 45 and Up Study (EXTEND45) Study is a linked data study that combines baseline questionnaire responses from the population-based 45 and Up Study (2006–2009, $n = 267,153$) with multiple routinely-collected health databases up to December 2014. Among participants with ≥ 1 linked result for any laboratory test, diabetes status was determined from multiple data sources according to standard biochemical criteria, use of glucose-lowering medication or self-report, and the prevalence and incidence rate calculated. Independent risk factors of incident diabetes were examined using multivariable Cox regression.

Results: Among 152,169 45 and Up Study participants with ≥ 1 linked laboratory result in the EXTEND45 database (mean age 63.0 years; 54.9% female), diabetes prevalence was 10.8% (95% confidence interval [CI] 10.6%–10.9%). Incident disease in those without diabetes at baseline ($n = 135,810$; mean age 62.5 years; 56.1% female) was 10.0 per 1,000 person-years (95% CI 9.8–10.2). In all age groups, diabetes incidence was lower in women compared to men, an association that persisted in the fully adjusted analyses. Other independent risk factors of diabetes were older age, being born outside of Australia (with the highest rate of 19.2 per 1,000 person-years observed in people born in South and Central Asia), lower education status, lower annual household income,

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residence in a major city, family history of diabetes, personal history of cardiovascular disease or hypertension, higher body mass index, smoking and long sleeping hours.

Conclusions: Our study represents an efficient approach to assessing diabetes frequency and its risk factors in the community. The infrastructure provided by the EXTEND45 Study will be useful for diabetes surveillance and examining other important clinical and epidemiological questions.

Introduction

Diabetes is a leading cause of morbidity and mortality worldwide. In 2017, diabetes accounted for an estimated 67.9 million (55.4–82.6 million) disability-adjusted life years and 1.37 million (1.34–1.40 million) deaths [1], imposing a considerable economic burden on individuals and society [2,3]. In Australia, the prevalence of diabetes is estimated to have more than doubled since 1981 [5] whilst less is known about its changing incidence [6].

Temporal trends in the epidemiology of diabetes are an important indicator of the health of the community and are likely shaped by a multitude of factors, which themselves change over time. For instance, preventative initiatives by health services should reduce the burden of disease. At the same time, changes in population structure, lifestyle behaviours, migration patterns and survival from diabetes or other health conditions may all have countervailing impacts on diabetes burden. Continual and reliable estimation of diabetes prevalence and incidence is therefore necessary. However, efforts to date have largely involved repeated cross-sectional surveys (e.g. the Australian National Health Survey, performed every 3 years) [7] or longitudinal cohort studies [5,8,9]. The former are limited in their temporal scope, whilst the latter depend on the repeat voluntary attendance of participants, making them vulnerable to healthy volunteer bias that is compounded over time. Moreover, their high cost and logistical complexity may limit their timely conduct and hence contemporary relevance.

Linked administrative data provide an alternative method for examining the epidemiology of diabetes in Australia, including changes in its frequency over time and assessment of independent risk factors to inform predictions of future burden and guide health policy and planning. In this study, we use data from the EXamining ouTcomeS in chroNic Disease in the 45 and Up Study (EXTEND45) Study, a large Australian linked cohort study comprising multiple routinely-collected health datasets, to assess diabetes prevalence and incidence in adults aged ≥ 45 years living New South Wales (NSW, the most populous state), and explore a range of risk factors for incident disease.

Research design and methods

Data sources and study cohort

Descriptions of the EXTEND45 Study and the 45 and Up Study, upon which it is built, have been published [10,11]. Briefly, the 45 and Up Study is a population-based cohort study comprising 267,153 NSW residents aged ≥ 45 years at enrolment, designed to enable research into healthy ageing. Between 2006 and 2009, participants were randomly sampled from Services Australia's (formerly the Department of Human Services, and Australia's national health insurance scheme) enrolment database and invited to complete a baseline questionnaire and provide consent to their data being linked to routinely-collected databases. Individuals living in rural areas and those aged ≥ 80 years were oversampled by a factor of two. With a response rate of 18%, the cohort represents $\sim 11\%$ of the NSW population aged ≥ 45 years.

The EXTEND45 Study links 45 and Up Study participants and their baseline questionnaire data (2006–2009) to routine diagnostic testing records held by participating private laboratory service providers (1999–2015) as well as administrative datasets. These include, but are not limited to: (i) NSW Mortality data (Registry of Births, Deaths and Marriages (RBDM) and Australian Bureau of Statistics (ABS),

2006–2014), (ii) Medicare Benefits Schedule (MBS) (2004–2016), and (iii) Pharmaceutical Benefits Scheme (PBS) (2004–2016). MBS and PBS data were provided by the DHS and linked to 45 and Up Study by the Sax Institute. All other data sources were linked by the Centre for Health Record Linkage (CHeReL) (<http://www.cherel.org>) [13,14].

The present study included all 45 and Up Study participants with at least one record (any test) in the linked datasets from laboratory service providers. This selection criterion was chosen to account for regional differences in the catchment areas of different providers and the fact that not all providers are represented in the EXTEND45 Study database. Thus, the requirement of at least one linked test result meant that participants included in the present study are those who are covered by the service providers contributing data to the EXTEND45 Study. Participants were followed up from their date of 45 and Up Study enrolment and censored when: (i) they met at least one of the criteria for diabetes in their linked data (described below), (ii) they died, or (iii) the study ended (30 June 2014).

Ascertainment of outcomes

Prevalent and incident diabetes was derived using the criteria: (i) self-reported diabetes on the 45 and Up Study questionnaire (i.e. answered "Yes" to "Q24. Has a doctor EVER told you that you have diabetes?"), (ii) recorded dispensing of insulin (Anatomical Therapeutic Chemical (ATC) code: A10A) or oral blood glucose-lowering medication (ATC code: A10B) in the PBS dataset (<https://www.pbs.gov.au>, accessed 04 June 2020), (iii) any HbA1c result $\geq 6.5\%$ (48 mmol/mol), (iv) any fasting plasma glucose test ≥ 126 mg/dL (7.0 mmol/L), and (v) any plasma glucose test ≥ 200 mg/dL (≥ 11.1 mmol/L) conducted as part of an oral glucose tolerance test (OGTT) [15,16]. A sixth criterion, an MBS record for a claim for diabetes education (MBS items 81,100, 81,105, 81,110, 81,115, 81,120 and 81,125), was used to define the earliest date that a participant had diabetes but was disregarded if none of the other criteria were met.

Participants were deemed to have prevalent diabetes if they met one of the criteria above up to 6 years before their 45 and Up Study enrolment date (based on the availability of linked data). If they did not have diabetes at enrolment but met at least one of the above criteria thereafter, incident disease was recorded.

Covariates

Plausible risk factors of incident diabetes were selected based on the current literature and those included in the Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) [17,18]. All risk factors were derived from the 45 and Up Study baseline questionnaire, except for clinical history variables, which were also ascertained using PBS data [10][10]. Demographic and socioeconomic risk factors included age, gender, relationship status, country of birth, annual household pre-tax income (in Australian dollars), education level and remoteness of residence. Family (parents and siblings) history of diabetes and personal history of, or treatment for, cardiovascular disease (CVD) or hypertension were also assessed. Modifiable lifestyle factors included body mass index (BMI), alcohol consumption, smoking status, physical activity and sleeping time.

Level of education was classified as no qualification, school certificate, higher school certificate, trade qualification, diploma and university degree to reflect the full range of educational backgrounds in

Australia [19]. Remoteness of residence was derived by mapping the participant's residential postcode to the ABS' Accessibility/Remoteness Index of Australia (ARIA+). ARIA+ is an index of the accessibility of

locations to service centres (<http://www.abs.gov.au/geography>, accessed 04 June 2020) and is classified as major city, inner regional Australia, outer regional Australia, remote and very remote. Due to

Table 1

Baseline characteristics, overall and among those at risk of developing diabetes after enrolment into the 45 and Up Study. Denominators are the number of individuals in the corresponding cohort, except where indicated.

Characteristic	Overall (n = 152,169) ^a	Individuals at risk (n = 135,810) ^a
Demographic		
Age at recruitment (years), mean (SD)	63.0 (11.2)	62.5 (11.2)
Female, n (%)	83,560 (54.9%)	76,236 (56.1%)
Country of birth, n (%)		
Australia	111,475 (73.3%)	100,113 (73.7%)
New Zealand & Pacific Islands	3,542 (2.3%)	3,224 (2.4%)
Europe	24,499 (16.1%)	21,598 (15.9%)
Americas	1,956 (1.3%)	1,771 (1.3%)
Africa & the Middle East	3,045 (2.0%)	2,599 (1.9%)
Southeast Asia	5,041 (3.3%)	4,373 (3.2%)
South & Central Asia	1,291 (0.8%)	1,003 (0.7%)
Missing	1,320 (0.9%)	1,129 (0.8%)
Relationship status, n (%)	n = 151,266	n = 135,022
Not in a relationship	36,928 (24.4%)	32,212 (23.9%)
In a relationship	114,338 (75.6%)	102,810 (76.1%)
Socioeconomic		
Highest qualification, n (%)	n = 149,715	n = 133,733
No qualification	16,723 (11.2%)	13,845 (10.3%)
School certificate	32,840 (21.9%)	28,983 (21.7%)
High school certificate	14,599 (9.8%)	13,030 (9.7%)
Trade qualification	15,897 (10.6%)	13,886 (10.4%)
Certificate/diploma	32,072 (21.4%)	29,168 (21.8%)
University degree	37,584 (25.1%)	34,861 (26.1%)
Annual household income (AU\$), n (%)	n = 144,260	n = 129,061
<\$5,000	2,303 (1.6%)	1,914 (1.5%)
\$5,000–\$9,999	5,836 (4.0%)	4,698 (3.6%)
\$10,000–\$19,999	19,848 (13.8%)	16,418 (12.7%)
\$20,000–\$29,999	13,637 (9.5%)	11,835 (9.2%)
\$30,000–\$39,999	11,401 (7.9%)	10,234 (7.9%)
\$40,000–\$49,999	10,641 (7.4%)	9,668 (7.5%)
\$50,000–\$69,999	15,819 (11.0%)	14,615 (11.3%)
\$70,000+	38,908 (27.0%)	36,735 (28.5%)
Undisclosed	25,867 (17.9%)	22,944 (17.8%)
ARIA + Remoteness, n (%)	n = 149,785	n = 133,660
Major city	97,384 (65.0%)	86,926 (65.0%)
Inner regional	41,241 (27.5%)	36,908 (27.6%)
Outer regional	10,060 (6.7%)	8,858 (6.6%)
Remote/very remote	1,100 (0.7%)	968 (0.7%)
Family and clinical history		
Family history of diabetes mellitus, n (%)	35,110 (23.1%)	27,863 (20.5%)
History of, or treatment for, CVD, n (%) ^b	29,282 (19.2%)	23,720 (17.5%)
History of, or treatment for, hypertension, n (%) ^b	71,934 (47.3%)	58,886 (43.4%)
Modifiable lifestyle factors		
BMI Category (kg/m ²), n(%)	n = 141,480	n = 126,418
<18.5	1,868 (1.3%)	1,769 (1.4%)
18.5–24.9	52,058 (36.8%)	48,925 (38.7%)
25.0–29.9	55,308 (39.1%)	49,744 (39.3%)
30.0–34.9	22,425 (15.9%)	18,732 (14.8%)
35.0–39.9	6,506 (4.6%)	4,914 (3.9%)
40.0+	3,315 (2.3%)	2,334 (1.8%)
Alcoholic drinks per week, n (%)	n = 148,838	n = 133,086
0	49,616 (33.3%)	42,063 (31.6%)
1–6	44,234 (29.7%)	40,164 (30.2%)
7–13	28,312 (19.0%)	26,353 (19.8%)
14–20	16,204 (10.9%)	14,963 (11.2%)
21+	10,472 (7.0%)	9,543 (7.2%)
Smoking status, n (%)	n = 151,737	n = 135,442
Non-smoker (never smoked)	86,605 (57.1%)	78,461 (57.9%)
Current smoker	9,779 (6.4%)	8,697 (6.4%)
Previous smoker	55,353 (36.5%)	48,284 (35.6%)
Average no. of MET-adjusted physical activity sessions per day, mean (SD)	1.61 (1.43)	1.64 (1.44)
Sleep time (hours), n (%)	n = 147,815	n = 132,150
7–9	112,622 (76.2%)	101,922 (77.1%)
<7	23,939 (16.2%)	21,014 (15.9%)
10+	11,254 (7.6%)	9,214 (7.0%)
Number of missing covariates, mean (SD)	0.1 (0.5)	0.2 (0.5)

^a Denominator = number in cohort, unless otherwise indicated.

^b Based on evidence of treatment in the PBS dataset or self-report in the 45 and Up Study baseline questionnaire.

small sample sizes, the remote and very remote categories were combined.

BMI was calculated from self-reported weight and height on the 45 and Up Study baseline questionnaire and categorised according to the World Health Organisation (WHO) BMI classifications. We elected not to include a correction of self-reported BMI as no correction equation has been demonstrated to be consistently superior to self-report when modelling BMI-disease outcome associations [20]. Consistent with previous 45 and Up Study analyses [21], physical activity was measured by the number of self-reported physical activity sessions per day, adjusted using standard metabolic equivalent (MET) values [22] to reflect intensity of physical activity.

Statistical analysis

Diabetes prevalence, cumulative incidence, and incidence rate (measured as cases per 1,000 person-years) were calculated, together with their 95% confidence intervals (CI). Characteristics of the overall cohort as well as individuals at risk of developing diabetes after study enrolment were summarised using standard measures of central tendency and dispersion.

Cox regression models were used to examine risk factors for incident diabetes. Follow-up began at time of enrolment into the 45 and Up Study and ended at the time of any of the diabetes criteria being met, death or study end, whichever occurred earliest. We used a time-on-study time scale (instead of an age scale) so that the effect of age on diabetes incidence could be explicitly assessed. All potential risk factors were included as categorical variables, with the exception of age and physical activity. Each variable was examined in both an age- and sex-adjusted model and a fully-adjusted model (with all covariates included). Missing data were assumed to be Missing-At-Random. These were imputed using chained equations with linear regression for log-transformed continuous variables, and discriminant analysis for categorical variables [23]. Thirty imputed versions of the dataset were generated and used in the analysis, the results for which were then combined using Rubin's rules [24].

All statistical analyses were conducted in SAS Enterprise Guide version 7.1 (SAS Institute Inc., Cary, NC).

Ethical approval

As part of their consent to participate in the 45 and Up Study, participants agreed to have their baseline questionnaire data be linked to other health databases [10]. Ethical approval for the 45 and Up Study was obtained from the University of New South Wales Human Research Ethics Committee (HREC 05035/HREC 10186). The EXTEND45 Study was granted ethical approval by the NSW Population and Health Services Research Ethics Committee (HREC/13/CIPH/69).

Table 2

Age- and sex-stratified incidence of diabetes between 2006 and 2014 in a cohort of Australian adults aged 45 years and above. Rates are presented as number of cases per 1,000 person-years (95% CI).

Age group (years)	Incidence rate per 1,000 person-years (95% confidence interval)		
	Men	Women	All
45–54	8.6 (8.0–9.2)	5.1 (4.8–5.5)	6.4 (6.1–6.7)
55–64	12.9 (12.2–13.5)	8.8 (8.3–9.2)	10.5 (10.1–10.9)
65–74	16.4 (15.5–17.3)	11.0 (10.3–11.7)	13.6 (13.0–14.2)
75–84	14.0 (13.0–15.0)	10.0 (9.2–11.0)	12.1 (11.4–12.8)
85+	10.7 (8.8–13.2)	6.9 (5.5–8.6)	8.5 (7.3–9.9)
All	12.7 (12.3–13.0)	8.0 (7.7–8.3)	10.0 (9.8–10.2)

Results

Overall cohort

Of 267,153 participants recruited to the 45 and Up Study between 2006 and 2009 [10], 152,169 (57.0%) had linked laboratory data in the EXTEND45 Study dataset and were included in the present study (Supplementary Fig. 1). The overall cohort, which included prevalent cases of diabetes, had a mean (SD) age of 63.0 years (11.2), 54.9% were female and the majority (73.3%) were born in Australia (Table 1).

A comparison between the participants included in the present study and those for whom linked laboratory data were not available ($n = 112,917$) revealed that the former comprised a slightly higher proportion of females (54.9% compared to 51.9% in those without linked laboratory data), a lower proportion of Australian-born individuals (73.3% versus 77.2%), almost double the proportion of city-dwellers (65.0% versus 37.0%) and a higher proportion of individuals from higher-income households (27.0% with a household income of $\geq \$70,000$ compared to 21.8%) (Supplementary Table 1).

Prevalence, incidence rate and cumulative incidence of diabetes

In our cohort of 152,169 individuals, the prevalence of diabetes was 10.8% (95% CI 10.6%–10.9%). Of the remaining 135,810 individuals without prevalent diabetes, 8,071 (5.9%) developed the disease during follow-up (7–10 years, 2006–2014), with a rate of 10.0 cases per 1,000 person-years (95% CI 9.8–10.2). Incidence stratified by age group was: for the 45–54 year age group, 6.4 per 1,000 person-years (95% CI 6.1–6.7); for the 55–64 year age group, 10.5 per 1,000 person-years (95% CI 10.1–10.9); for the 65–74 year age group, 13.6 per 1,000 person-years (95% CI 13.1–14.2); for the 75–84 year age group, 12.1 per 1,000 person-years (95% CI 11.4–12.8); and for the 85+ year age group, 8.5 per 1,000 person-years (95% CI 7.3–9.9) (Table 2, Supplementary Fig. 2). The annualised incidence remained largely constant throughout the study period, both overall and for different age groups. Across all age groups, the incidence of diabetes was lower in women compared to men (Table 2). Conversely, a similar U-shaped pattern in diabetes incidence across the age groups was observed in both women and men, with the highest rates in the 65–74 year age group (Table 2).

Risk factors of incident diabetes

In age- and sex-adjusted analyses, being between 55 and 84 years of age, being born outside of Australia (except in the Pacific Islands or the Americas), being single, having no qualifications and having a lower annual household income were all associated with a higher rate of incident diabetes (Supplementary Fig. 3). Family history of diabetes and personal history of CVD or hypertension were also associated with a higher incidence. Having a BMI ≥ 25.0 kg/m², smoking and sleeping too little (<7 h) or too much (≥ 10 h) were associated with a higher incidence of diabetes, while alcohol consumption and physical activity were inversely associated with incident diabetes.

In a fully-adjusted model, risk factors independently associated with a higher rate of incident diabetes included older age (hazard ratio [HR] 1.06, 95% CI 1.05–1.07 for each 5-year increase above 45 years), male gender (HR 0.61, 95% CI 0.58–0.64 in females compared to males), born in Europe (HR 1.16, 95% 1.10–1.23; reference category: Australia), Africa and the Middle East (HR 1.33, 95% 1.16–1.53), Southeast Asia (HR 1.79, 95% 1.59–2.02) or South and Central Asia (HR 2.29, 95% 1.89–2.76), lower educational attainment, annual household income $< \$50,000$ and residing in a major city (HR 0.92, 95% CI 0.87–0.96 for inner regional and HR 0.85, 95% CI 0.77–0.93 for outer regional, compared to major city) (Fig. 1). Having a family history of diabetes (HR 1.65, 95% CI 1.57–1.73), personal history of CVD (HR 1.10, 95% CI 1.04–1.16) and personal history of hypertension (HR 1.75, 95% CI 1.67–1.84) were all associated with a higher rate of incident diabetes.

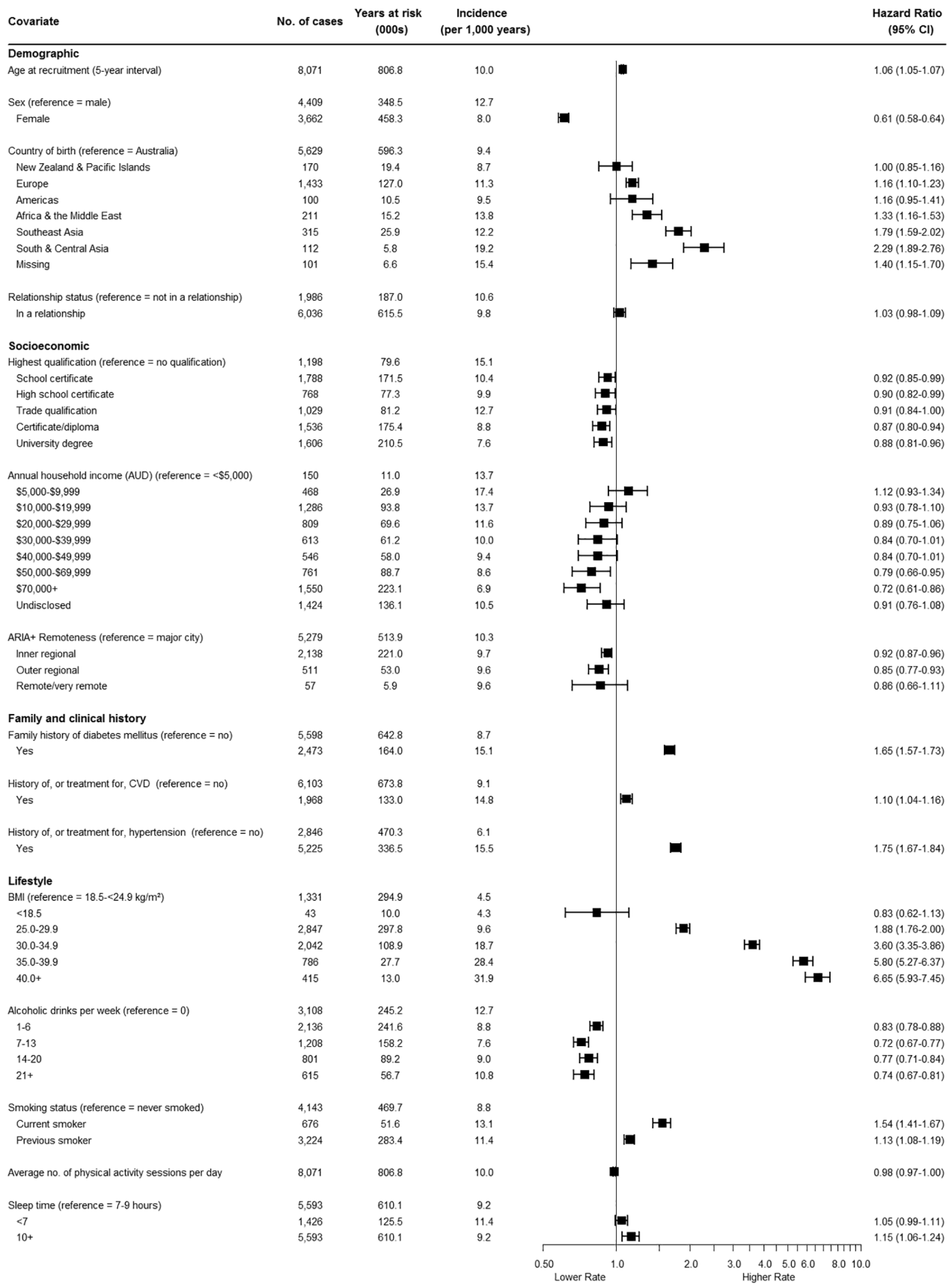


Fig. 1. Results of a fully-adjusted multivariable Cox regression model showing the association between incident diabetes and a range of demographic, socioeconomic, family and clinical history and lifestyle risk factors.

All modifiable lifestyle factors except physical activity were independently associated with incident diabetes, after adjusting for all other variables (Fig. 1). BMI had a positive linear association, with the HR ranging from 1.88 (95% CI 1.76–2.00) for the BMI category 25.0 to <30.0 kg/m² to 6.65 (95% CI 5.93–7.45) for the BMI category ≥40.0 kg/m², compared to the referent BMI of 18.5 to <25.0 kg/m². Alcohol consumption was associated with a lower incidence of diabetes. Relationship status and physical activity were not independently associated with incident diabetes.

Diabetes ascertainment via routinely-collected data: contribution of different data sources

Of the 16,359 individuals with prevalent diabetes, the majority (82.0%) were identified through more than one data source up to 6 years prior to, or at, study enrolment. Around 10% (9.34%) of cases were identified through self-report alone, whilst 717 (4.4%) prevalent cases were identified through pathology data alone and a further 704 (4.3%) cases through PBS data alone. In 44.8% of prevalent cases, the first indication of diabetes in the linked dataset was through laboratory data. A breakdown of the specific criteria through which prevalent diabetes was first identified is provided in [Supplementary Table 3](#). Of those first identified through laboratory data, 63.6% had an elevated HbA1c, 16.4% had an elevated fasting plasma glucose result and 20.1% had an elevated OGTT result.

The ascertainment of incident diabetes after *45 and Up Study* enrolment was heavily reliant on the use of the different data sources, with incident disease identified through pathology data alone in 35.8% ($n = 2,887$) of incident cases, PBS data alone in 34.8% ($n = 2,807$) of cases and some combination of pathology, MBS and PBS data in 29.5% ($n = 2,377$) of cases. Over half of incident cases (57.3%) were first identified from pathology data ([Supplementary Table 3](#)); of these 23.8% had an elevated HbA1c, 40.6% had an elevated fasting plasma glucose result and 35.7% had an elevated OGTT result.

Discussion

This study is, to our knowledge, the largest Australian population-based cohort study that examines diabetes prevalence, incidence and associated risk factors. Using data from the linked EXTEND45 Study, we estimated that, between 2006 and 2009, the prevalence of diabetes in NSW residents aged ≥45 years was 10.8% (95% CI 10.6%–10.9%) and the cumulative incidence over 7–10 years of follow-up was 5.9%. Diverse risk factors, including demographic, socioeconomic, family and clinical history and modifiable lifestyle behaviours, were independently associated with incident diabetes in a large multivariable analysis.

Our prevalence estimate of 10.8% is higher than previous Australia-specific estimates, which may in part reflect true increases in diabetes prevalence over time. For instance, our estimate is higher compared to the 8.8% estimated from a similar age cohort in the NSW-based Blue Mountains Eye Study (BMES) completed 20 years ago [25]. Our estimate is also higher than the 7.4% reported among 11,247 adults (≥25 years) surveyed in the first iteration of the Australian Diabetes, Obesity and Metabolism (AusDiab) Study, despite similar criteria used for defining diabetes. This is likely explained by a combination of: the wider age range of the AusDiab Study, its earlier era (1999–2000) and the additional criterion of HbA1c ≥ 6.5% in our study. In relation to more recent studies, the lower prevalence of 9.2% reported for individuals aged ≥45 years in the ABS 2007–08 National Health Survey (NHS, accessed via data query on ABS website on 20 June 2019) may be explained by the survey's reliance on self-report of diabetes status. Compared to other developed countries, our prevalence estimate is similar to the 10.7% reported among adults aged ≥20 years in the United States (US) National Health and Nutrition Examination Survey (NHANES) in 2007–2008 [26], despite our considerably higher age bracket, lower than the 14.4% prevalence reported among adults aged ≥45 years in

Canada in 2008–2009 [27], and higher than the estimated prevalence of 8.4% in the UK population aged ≥45 years in 2006.

Studies measuring the incidence of disease over time are the most reliable way to determine growth in disease burden, and incidence itself is most accurately estimated in populations with comprehensive follow-up. Prior to access to linked routinely-collected health datasets, estimates of diabetes incidence were typically reliant on re-engagement of participants [5,9,17], leading to potentially substantial selection bias (usually towards underestimation). This potential for selection bias during repeat active follow-up may in part explain the lower annual incidence of 0.7% reported by the AusDiab study compared to the 1.0% observed here. However, other key differences in study design will also likely play a role [28]. A previous subgroup analysis of the *45 and Up Study* also found a lower person-year incidence rate of 0.4% [17]; however, this study was limited by the absence of biochemical pathology data and likely selection bias due to its reliance on opt-in participation to a second mail survey as part of the *45 and Up Study's* Social Economic and Environmental Factors (SEEF) follow-up study (60.4% response rate) [17].

The annual incidence rate of diabetes among adults ≥45 years remained constant over the course of our linked data period (2006–2014), despite diabetes prevention initiatives being implemented during that time. With the recent introduction of the NSW Diabetes Prevention Framework in 2016 [29], large-scale linked data studies such as the one presented here will be invaluable for efficiently tracking disease incidence over time.

Our study confirms well-known risk factors for type 2 diabetes, including those used in AUSDRISK [18]. This tool was developed in 2010 based on a cohort of 6,060 AusDiab participants aged ≥25 years who attended a second visit between 2004 and 2005. It is used in clinical practice as a simple way of identifying adults at high risk of developing type 2 diabetes. Our findings build upon this work by investigating a similarly broad range of variables using more granular categories, made possible by our study's large sample size. A number of the risk factors identified in this study are also known risk factors of CVD, for example, older age (non-linear association), male gender, clinical history of hypertension, high BMI and smoking [30]. This has important clinical and public health implications, both in terms of the potential double burden of disease in these population subgroups and, conversely, the opportunity to more cost-effectively implement control initiatives that target both diseases.

Being born outside of Australia was independently associated with incident diabetes, with an association found for most of the regions investigated. The exceptions were the US, whose population is relatively similar to that of Australia, and New Zealand and the Pacific Islands, where the number of individuals was limited. Country of birth in South and Central Asia was associated with the greatest risk compared to Australian-born individuals, consistent with previous studies [31–33]. European-born individuals were also at increased risk of developing diabetes compared to those born in Australia. The extent to which migration or ethnicity is driving this association is unclear but our observation of a widespread effect across diverse regions, including Europe where multi-ethnicity is common, suggests that migration itself from these regions might be important. Possible reasons include prior exposure to risk factors in the country of origin, factors related to the migration process or changes in lifestyle behaviours following migration [34]. Moreover, the higher genetic predisposition to diabetes identified in people of Asian descent [35] may amplify the effect of migration on diabetes risk. Further pairwise comparisons between non-Australian-born individuals within Australia-based cohorts might shed light on the relative effects of ethnicity and migration on the risk of diabetes.

We found that individuals living in inner and outer regional areas were less likely to develop diabetes compared to those in major cities, even after adjusting for numerous demographic, socioeconomic and lifestyle factors. This is surprising given that regional populations typically experience higher rates of chronic disease [36]. It is possible that

the observed association may be partly explained by the different lifestyles of rural versus urban dwellers, both in terms of diet and type of work, neither of which have been accounted for in this study. Alternatively, it is possible that the lower incidence in rural populations may reflect poorer access to health services and therefore under-reporting of diabetes in these areas. Further investigation into this is warranted.

Higher education was negatively associated with diabetes incidence in our study, consistent with previous findings [37,38]. As reported previously, this is likely explained by a combination of unmeasured lifestyle factors, health literacy and socioeconomic factors [37,39–41]. We also found that having an annual household pre-tax income of AU \$50,000 or higher was associated with a lower rate of diabetes compared to an income of less than AU\$5,000. However, the absence of an association for lower income categories must be interpreted with caution, as the older age of our cohort may mean that household income is a limited indicator of socioeconomic status among participants above retirement age [40]. Nevertheless, our findings suggest a complex interplay between different socioeconomic indicators in the role of diabetes development.

All modifiable lifestyle factors investigated in the present study, except physical activity, were independently associated with incident diabetes. This is particularly concerning given that, in high-income countries like Australia, the prevalence of modifiable risk factors is disproportionately high in disadvantaged groups [42,43]. Increasing BMI was a particularly strong risk factor, with individuals with a BMI >40.0 kg/m² having a 6.5-fold risk of developing diabetes compared to individuals whose BMI was in the range of 18.0–24.9 kg/m². This is consistent with previous studies. With the Australian obesity epidemic expected to rise [44], carefully planned diabetes prevention initiatives that are designed specifically for overweight and obese individuals will be increasingly important, together with appropriate healthcare resourcing for the potential increases in diabetes burden.

Smoking (either currently or formerly) was also independently associated with incident diabetes, similar to previous findings [17]. Notably, whilst a higher risk of developing diabetes still existed in ex-smokers, the effect was considerably stronger in current smokers, indicating that smoking cessation at any point might prevent diabetes development and should be encouraged. Clinical trials of smoking cessation interventions among individuals with diabetes will help to clarify this.

Sleep time is an emerging lifestyle behavior that has been found to be associated with diabetes. A 2015 meta-analysis of 10 prospective observational studies found a U-shaped dose–response relationship between self-reported sleep time and diabetes risk [45], with prolonged sleep having a greater effect on risk than short sleep time. In the present study, we found that long sleep time (≥ 10 h), but not short sleep time (< 7 h), was associated with a higher rate of diabetes. The mechanism for this association is unclear, but previous research has shown that long sleep duration may indicate other underlying morbidities [46].

A key strength of this study is its large size (at least ten times that of earlier studies), providing sufficient power to adjust for a broad range of risk factors and overcoming a common limitation of association models for type 2 diabetes. In addition, the use of multiple data sources, including laboratory results and glucose-lowering drug prescription claims, to ascertain diabetes status reduces the chances of cases being missed. Indeed, it has been shown that such an approach improves the sensitivity of disease ascertainment without compromising on positive predictive value [47]. Our breakdown of the contribution of the different linked data sources in the identification of diabetes highlights the number of cases that would have been missed through using only self-report. Finally, our study did not rely on the active and repeated participation by study participants over its long follow-up time of seven years, thereby reducing the extent of potential healthy volunteer bias.

Limitations of this study include its limited generalisability to younger age groups due to its selection of people aged over 45 years. However, given the higher burden of diabetes in older age groups, our

findings remain policy-relevant. We were not able to distinguish between type 1 and type 2 diabetes, although given the age cut-offs, the study results are most likely applicable to type 2 diabetes. The initial, unsolicited invitation for participation in the *45 and Up Study* was distributed to a random sample of the general community and resulted in an uptake of 18% [10]. This could have resulted in the selection of a slightly healthier cohort than the general population, potentially leading to frequency estimates being underestimated. However, the potential for healthy volunteer bias in our study only applies at initial enrolment. This is because follow-up did not require repeat attendance by participants, unlike conventional longitudinal cohort studies. While the oversampling of people in rural areas and those aged ≥ 80 years in the *45 and Up Study* could have caused frequency estimates to be overestimated, these populations represented $< 1.0\%$ and 2.4% of the total included cohort, respectively. Any impact on the overall prevalence and incidence estimates is therefore likely to be small. Our study inclusion criterion of at least one linked laboratory record (any test) in the EXTEND45 dataset could have (i) introduced an indication bias, leading to diabetes prevalence being overestimated, or (ii) resulted in cases who would have otherwise met our PBS criterion for diabetes being missed. Nevertheless, this criterion ensures that all included participants are covered by all of the linked datasets, making disease ascertainment consistent for everyone. Many of these limitations are not unique to our study and, in fact, our use of real-world data, and our ability to compare included individuals with those who did not meet our inclusion criteria, allows greater transparency around potential sources of bias in our estimates compared to conventional longitudinal cohort studies. Moreover, these potential issues of non-representativeness do not apply to our risk factor findings, as these have been previously shown to be generalisable in the presence of selection bias [48]. Finally, information on the majority of the risk factors investigated was derived from the *45 and Up Study* baseline questionnaire and therefore may be subject to recall or information bias [10]. Most of the risk factors were measured using validated instruments, thereby minimising such bias.

Conclusions

The prevalence of diabetes is increasing in Australia, associated with rapid lifestyle changes and improvements in healthcare. This study represents, to date, the largest comprehensive investigation of the burden of diabetes in Australian adults and the associated risk factors of incident diabetes. We identified a combination of independent modifiable (e.g. BMI, sleeping, smoking) and non-modifiable (e.g. family history of diabetes, country of birth) risk factors. A detailed understanding of these risk factors may inform predictions of the future burden of diabetes and inform the development of effective health interventions. Large real-world linked datasets such as the EXTEND45 Study will be useful for efficiently examining how diabetes prevention initiatives affect its burden over time.

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Authors' contributions

H.Z. contributed to the design, interpretation of the data and writing of the manuscript. K.R. contributed to the design, statistical analysis, interpretation of the data and critical review of the manuscript. L.S., M. Ju., A.K., T.Y., A.Cam. all contributed to the design and critical review of the manuscript. A.Cas., C.K.C., E.C., M.G., J.K., B.L., T.L., M.M., D.P., C. P., D.S., G.W., S.Z. all contributed to the critical review of the manuscript. C.F. contributed to the acquisition of data and critical review of the manuscript. M.Ja. contributed to the design, acquisition of data, interpretation of the data, supervision, writing and critical review of the manuscript. CH contributed to the interpretation of the data, supervision and management of the research, writing and critical review of the manuscript.

All authors affirm that authorship is merited based on the International Committee of Medical Journal Editors authorship criteria. K.R., M.Ja. and C.H. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

MJu has received unrestricted grant support from VentureWise (a wholly own commercial subsidiary of NPS MedicineWise) to conduct a commissioned project funded by AstraZeneca. CKC is the Asia Pacific Scientific Leader for Vertis, has received sponsorship from Merck Sharp & Dohme and has been a speaker for Bayer. MG has received honoraria from Shire Pharmaceuticals and Amgen Pty Ltd. CP is the current Chair of: Kidney Health Australia, NSW Bureau Health Information and the NSW Cardiovascular Research Network; is a member of the International Advisory Board for AstraZeneca; is a member of Local Advisory Boards for Vifor, Merck Sharpe & Dohm, Boehringer Ingelheim and Otsuka; serves on the Scientific Advisory Board of Pharmaxis; has received travel and accommodation support from Amgen, AstraZeneca and Roche; and has received speaker support from Amgen, AstraZeneca, Novartis and Vifor. DS has received research support from Amgen, Sanofi, Pfizer, Regeneron, Amrin, AstraZeneca and Novartis and provided consultancy services to Amgen, Arrowhead Pharmaceuticals and Sanofi. SZ has participated in the Advisory Board, expert committees, or educational meetings for Boehringer Ingelheim, Eli Lilly, Sanofi, Servier, AstraZeneca, Novo Nordisk, and Merck Sharp & Dohme on behalf of Monash University, with no direct financial compensation. MJa is supported by a Medical Research Future Fund Next Generation Clinical Researchers Program Career Development Fellowship; is responsible for research

projects that have received unrestricted funding from Gambro, Baxter, CSL Behring, Amgen, Eli Lilly, and Merck; has served on advisory boards sponsored by Akebia, Baxter, Boehringer Ingelheim and Vifor, spoken at scientific meetings sponsored by Janssen, Amgen and Roche; with any consultancy, honoraria or travel support paid to her institution. HZ, KR, LS, AK, TY, ACam, ACas, EC, CF, JK, BL, TL, MM, DP, GW and CH have no competing interests to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jcte.2020.100240>.

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