The association of smoking status with glycemic control, metabolic profile and diabetic complications

Title: The association of smoking status with glycemic control, metabolic profile and diabetic complications – Results of the Australian National Diabetes Audit (ANDA).

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Abstract

Background: Tobacco smoking and diabetes mellitus contribute significantly to the overall health burden and mortality of Australians. We aimed to assess the relationship of smoking with glycemic control, metabolic profile and complications in Australian patients living with diabetes.

Methods: We analysed the 2011-2017 biennial Australian National Diabetes Audit cross-sectional data. Patients were classified as current, past or never smokers. Linear (or quantile) and logistic regression models were used to assess for associations.

Results: Data from 15,352 patients were analysed, including 72.2% with type 2 diabetes. Current smokers comprised 13.5% of the study population. Current and past smokers had a median HbA_{1c} that was 0.49% and 0.14% higher than never smokers, respectively, as well as higher triglyceride and lower HDL levels ($p < 0.0001$ for all). Compared to never smokers, current smokers had higher odds of severe hypoglycaemia and current and past smokers had higher odds of myocardial infarction, stroke, peripheral vascular disease, lower limb amputation, erectile dysfunction and peripheral neuropathy (all p values ≤0.001), with no significant change over time.

Conclusion: When compared to never smokers, current and past smokers had poorer glycemic and lipid control and higher odds of macrovascular and microvascular complications. Despite this, current smoking remains prevalent among Australians with diabetes.

Keywords

Diabetes, Smoking, HbA_{1c}, Microvascular, Macrovascular, Complications

1. Background

Diabetes mellitus is a major public health challenge in Australia. An estimated 1.2 million (6%) Australian adults are affected by diabetes, with approximately 85% representing type 2 diabetes (T2DM) and 10% with type 1 diabetes (T1DM).[1, 2] In 2015 diabetes was estimated to contribute to over 1 million hospitalisations per year and 10% of all deaths in Australia.[2, 3] Diabetes also places a substantial economic burden on the Australian population, with over $14.5 billion dollars spent on diabetes-related health expenditure annually.[4]

Tobacco smoking was estimated to be responsible for 9.3% of the disease burden in Australia in 2015; the leading risk factor for both chronic disease and death. In Australia in 2015 it was estimated that smoking contributed to almost 21,000 deaths (13.3% of all deaths), with the most common underlying causes of death being chronic obstructive pulmonary disease, lung cancer, coronary heart disease and stroke.[5] Globally, smoking contributed to over seven million deaths in 2017.[6]

Nicotine deleteriously alters glucose homeostasis through a number of mechanisms, including impaired β cell function, increased insulin resistance[7-9] and hormonally-mediated hyperglycaemia[10, 11]. As such, tobacco smoking has been causally linked with an increased risk of developing type 2 diabetes, which has been observed in a dose-dependent manner and seen in both active and passive smoking[7, 12, 13]. The 2014 Surgeon General's report on the health consequences of smoking, estimated the risk of developing diabetes to be 30-40% higher in smokers than in never smokers.[14] This increased risk was reported to be abrogated or reversed by smoking cessation, such that long-term quitters (>10 years) have a risk almost equivalent to that of the general population.[14, 15] People with diabetes who smoke have worse glycemic control than non-smokers. This may manifest as either hyperglycaemia and its associated complications, with a substantially increased risk of cardiovascular disease (up to 50% greater than that of never smokers) and increased all-cause mortality,[14, 16] or as an increased risk of severe hypoglycaemia.[17]

Guidelines impress the importance of both promoting smoking cessation as a key public health issue in order to control the ever-expanding epidemic of diabetes worldwide,[14] and also as an essential standard of care in the management of people with diabetes.[15, 16, 18] However, efforts to understand contemporary rates of smoking among people with diabetes in Australia and the relationship between smoking and complications, have not yet been reported.

In this study, we aimed to examine the association of smoking status with glycemic control, metabolic profile and diabetic complications among over 15,000 adults living with diabetes in Australia, and to monitor the change in these trends over recent years.

2. Methods

2.1 Study design, setting and patients

We conducted an observational, cross-sectional study using the Australian National Diabetes Audit (ANDA) data. ANDA is an annual, de-identified, cross-sectional audit performed by over 50 primary, secondary and tertiary health care services throughout Australia. It is facilitated by the National Association of Diabetes Centre (NADC) – a division of the Australian Diabetes Society, with funding provided by the Australian Government Department of Health and Ageing. The data provide both Australian-wide and facility specific information on diabetes management, diabetes complications and the overall wellbeing of patients who are attending diabetes services across every state and territory in Australia. The audit aims to deliver an important basis for quality improvement in the ongoing multi-faceted care of diabetes.[19]

ANDA involves data collection over a four-week period in May to June each year, with an alternating biennial focus on either self-management and quality of life (Australian Quality Self-Management Audit – AQSMA) or clinical management indicators (Australian Quality Clinical Audit – AQCA). In brief, participation is voluntary and formal invitations to participate are sent to all centres registered with the NADC and other interested primary care, community-based or specialist healthcare providers in private practice. Unique site codes are allocated to allow data collection, handling and analysis to be undertaken in a double-blind fashion. Over four weeks (either during May or June) clinicians complete either an electronic or hard copy data collection form for all consecutive patients reviewed at a participating centre. Data were collected during the standard medical consultation by the treating health professional who reviewed medical records and available pathology, in discussion with the patient.[20] The data collection form involves a single page minimal dataset including patient demographics, diabetes history and management, anthropometric measurements, comorbidities and diabetic complications (Supplementary Figure 1).

For the purposes of this study, data were pooled from four consecutive biennial ANDA-AQCA audits: 2011, 2013, 2015 and 2017. All adults with type 1 diabetes, type 2 diabetes and diabetes due to unknown or other aetiologies were included in this study. Those with gestational diabetes and those aged under 18 years were excluded. Given the focus of the effect of smoking in this study, those without information regarding smoking status were excluded.

Ethics approval for our study was provided by the Monash Health Human Research Ethics Committee (Monash Health Reference: RES-17-0000-164L).

2.2 Dependent variable

The pre-specified dependent variable was self-reported smoking status – with never smokers including patients who reported never smoking regularly for longer than a one-month period, past smokers including patients who reported no regular smoking in the preceding one month and current smokers including patients who reported regular smoking.

2.3 Independent variables

Pre-specified independent variables included glycemic control (glycated haemoglobin - HbA_{1c} (%), severe hypoglycaemia (yes if reported having ever had an episode of severe hypoglycaemia requiring the assistance of another person) and number of therapeutics), microvascular complications (retinopathy, peripheral neuropathy, advanced chronic kidney disease (CKD), microalbuminuria, macroalbuminuria and erectile dysfunction), macrovascular complications (peripheral vascular disease, myocardial infarction, coronary artery revascularisation, cerebral stroke, foot ulceration and lower limb amputation), body mass index (BMI) and blood pressure (systolic and diastolic blood pressure).

The most recent pathology results from patients were recorded and included HbA_{1c} (% or mmol/mol), serum creatinine (µmol/L) and lipid profile (total cholesterol, low density lipoprotein (LDL), high density lipoprotein (HDL) and triglycerides – all mmol/L – including both fasting and non-fasting values, depending on availability. Given the large number of services that provided the pathology collected, laboratory values across centres were not able to be standardised. An estimated glomerular filtration rate (eGFR) was calculated using age, sex and serum creatinine as per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Supplementary 1).[21]

Advanced CKD was defined as present if either the calculated eGFR was <30mL/min/1.73m^2; representing stage 4 to 5 CKD, or if the patient had a history of renal replacement therapy or renal transplantation as recorded on the data collection form. The most recent urine collection examining protein or albumin was recorded. The urine

albumin result was used to derive the presence of microalbuminuria or macroalbuminuria.[22] Systolic and diastolic blood pressures were recorded at the time of appointment in mmHg. BMI (kilogram/metre^2) was calculated using measured weight (kg) and height (m) and the formula: weight / (height x height).

The number of glucose lowering therapies was reported in those with type 2 diabetes only, and calculated as the total number of prescribed medications from the following classes; Insulin, Acarbose, Glucagon like peptide 1 (GLP-1) receptor agonist, Glitazone, Sulphonylurea, Metformin, Dipeptidyl peptidase-4 (DPP-4) inhibitor and Sodium-Glucose Co-Transporter 2 (SGLT2) inhibitors.

Anti-hypertensive therapy use was reported if any medications from the following classes were prescribed; angiotensin-converting enzyme (ACE) inhibitor, angiotensin II receptor blocker (ARB), beta blocker, thiazide, calcium channel blocker or other anti-hypertensive agent. Lipid lowering therapy use was reported if any medications from the following classes were prescribed; statin, fibrate, ezetimibe or fish oil.

Microvascular and macrovascular complications were recorded as present if the patient reported having ever had the disease following direct questioning, or if it was documented as part of their past medical history. Presence of retinopathy, peripheral neuropathy, advanced CKD, erectile dysfunction (males only), peripheral vascular disease, myocardial infarction, coronary artery revascularisation (coronary artery bypass graft surgery (CABG)/angioplasty), cerebral stroke, foot ulceration and lower limb amputation was recorded by the treating specialist at the time of data collection.

2.4 Confounding variables

Pre-specified confounding variables included age (years), sex (male and female), diabetes type (type 1, type 2 and other or unknown type), diabetes duration (years), and ANDA data collection year (2011, 2013, 2015 and 2017).

2.5 Statistical analysis

Patients were categorised by smoking status: never smoker, past smoker or current smoker, and summarised descriptively for the pooled cohort. Categorical variables were presented as percentages and counts (n), and differences in subgroups were analysed using the Chi-square test. Continuous variables were presented as mean (standard deviation) or median (interquartile range (IQR)), and differences in subgroups analysed using Analysis of Variance (ANOVA – for normally distributed data) and Kruskal-Wallis test (for skewed data). Missing data were minimal for most variables, and below the selected cut-off of no more than 20% for the dependent variable. Certain variables that required pre-performed investigations, had a higher level of missing data. No imputation was performed. Data regarding SGLT2 inhibitors were not available in 2011 and 2013 audits (the data collection form is reviewed and updated each year for novel treatments).

Quantile (median) regression was used for non-normally distributed continuous outcome variables; HbA_{1c}, BMI, total cholesterol, LDL, HDL and triglycerides, and unadjusted and adjusted median differences were reported. Ordinal regression was used to assess the relationship between smoking status and the number of therapies, and unadjusted and adjusted Odds Ratios were reported. Linear regression was used for normally distributed continuous outcome variables; systolic and diastolic blood pressure, and unadjusted and adjusted mean differences were reported. Binary logistic regression was used to explore the relationship between smoking status and binary outcome variables: severe hypoglycaemia, retinopathy, peripheral neuropathy, advanced CKD, microalbuminuria, macroalbuminuria, erectile dysfunction, peripheral vascular disease, myocardial infarction, coronary artery revascularisation, stroke, foot ulceration, lower limb amputation, use of anti-hypertensive therapy and use of lipid lowering therapy, and unadjusted and adjusted Odds Ratios were reported. Multivariable models were performed for each outcome, adjusted for age, sex, diabetes type, diabetes duration and year of data collection; as these variables were determined a-priori to be clinically important confounders. The

moderating effect of year of data collection was examined by including an interaction term between year and smoking on each outcome, and the likelihood ratio test was used to evaluate whether the inclusion of this term improved fit of the model. Due to the substantial number of outcome variables and to avoid the issue of multiplicity, a more stringent level of significance ($p < 0.002$) was used to determine statistical significance, using the Bonferroni method. All analyses were performed in Stata Statistical Software (StataCorp, College Station, Texas 77845, USA) version 14.0.

3. Results

3.1 Descriptive Summary

Data from 19,374 patients were reviewed from the 2011, 2013, 2015 and 2017 ANDA-AQCA audits. Of those, 15,352 patients had a valid smoking status and were included in the analysis for this study. Characteristics of study patients are presented in Table 1. Median [IQR] age was 59.9 [46.6, 69.6] and males represented 53.2% of patients. The median [IQR] duration of diabetes was 13 [6, 21] years. The largest proportion of patients (72.2%) had type 2 diabetes. Current and past smokers represented 46.3% of the study population. The median number and type of glucose lowering therapies including insulin was broadly similar among the smoking categories. Compared to never and past smokers, current smokers were less likely to report receiving antihypertensive and lipid lowering therapy ($p<0.0001$ for both).

The most frequently reported complications were erectile dysfunction among men (29.5%), microalbuminuria (28.4%), peripheral neuropathy (24.9%) and retinopathy (22.1%). The proportion of patients with complications (i.e. peripheral neuropathy, microalbuminuria, macroalbuminuria, erectile dysfunction, peripheral vascular disease, myocardial infarction, coronary artery revascularisation, stroke, foot ulcer, lower limb amputation and severe hypoglycaemia) was higher among current and past smokers than never smokers ($p<0.0001$ for all).

Table 1: Characteristics of patients participating in the Australian National Diabetes Audit (2011, 2013, 2015 and 2017), stratified by smoking status

		Smoking status			
	All **% (N)** **n=15,352**	**Never** **% (n)** **53.7%** **n=8,241**	**Past** **% (n)** **32.8%** **n=5,033**	**Current** **% (n)** **13.5%** **n=2,078**	**p-value**
Age (years) α	59.9 [46.6, 69.6]	59.1 [42.9, 69.7]	63.7 [54.3, 71.4]	52.7 [41.8, 62.2]	0.0001
Sex (male)	53.2 (8,111)	43.2 (3,533)	67.0 (3,350)	59.6 (1,228)	<0.0001
Diabetes type					<0.0001
Type 1	24.8 (3,804)	28.2 (2,325)	17.1 (861)	29.7 (618)	
Type 2	72.2 (11,087)	68.7 (5,665)	80.2 (4,034)	66.8 (1,388)	
Other	3.0 (461)	3.1 (251)	2.7 (138)	3.5 (72)	
Diabetes duration α	13 [6, 21]	13 [7, 21]	14 [7, 21]	10 [4, 18]	0.0001
Diabetes therapeutics type					<0.0001
Diet only	3.6 (552)	3.8 (316)	3.4 (169)	3.2 (67)	
Tablets and non-insulin injectables only	23.7 (3,638)	23.4 (1,931)	24.1 (1,212)	23.8 (495)	
Insulin only	36.5 (5,605)	39.4 (3,245)	30.8 (1,549)	39.0 (811)	
Tablets + insulin	30.9 (4,744)	28.3 (2,332)	36.2 (1,822)	28.4 (590)	
Other/unstated	5.3 (813)	5.1 (417)	5.6 (281)	5.5 (115)	
Insulin-treated	70.6 (10,675)	70.8 (5,740)	70.3 (3,489)	70.4 (1,446)	0.803
Insulin duration (years) α*	7 [2, 15]	8 [3, 15]	6 [2, 15]	6 [2, 15]	0.0001
Glycemic control					
HbA_{1c} (%) α	7.9 [7.0, 9.0]	7.8 [6.9, 8.9]	7.9 [7.0, 9.0]	8.4 [7.2, 9.7]	0.0001
Severe hypoglycaemia	8.7 (1,286)	8.3 (654)	8.8 (425)	10.4 (207)	0.010
Number of glucose lowering therapies α±	2 [1, 2]	2 [1, 2]	2 [1, 2]	2 [1, 2]	0.156
BMI α	30.4 [26.2, 35.5]	29.8 [25.7, 34.9]	31.7 [27.5, 36.7]	29 [24.7, 34.6]	0.0001
Complications					
Retinopathy	22.1 (2,886)	21.5 (1,520)	24.3 (1,043)	19.0 (323)	<0.0001
Peripheral neuropathy	24.9 (3,761)	21.2 (1,721)	31.1 (1,543)	24.4 (497)	<0.0001
Advanced CKD	7.4 (1,092)	7.0 (556)	9.1 (442)	4.7 (94)	<0.0001
Microalbuminuria	28.4 (2,737)	26.4 (1,387)	31.8 (1,004)	28.5 (346)	<0.0001
Macroalbuminuria	12.9 (1,242)	11.1 (583)	14.7 (466)	15.9 (193)	<0.0001
Erectile dysfunction×	29.5 (2,220)	24.5 (814)	35.8 (1,106)	27.0 (300)	<0.0001
Peripheral vascular disease	11.0 (1,649)	7.7 (624)	15.5 (766)	12.8 (259)	<0.0001
Myocardial infarction	12.4 (1,820)	8.8 (692)	18.6 (903)	11.3 (225)	<0.0001
Coronary artery revascularisation	13.1 (1,936)	9.7 (771)	20.0 (981)	9.4 (184)	<0.0001
Stroke	6.2 (925)	5.1 (407)	8.3 (405)	5.6 (113)	<0.0001
Foot ulcer	8.2 (1,215)	6.6 (520)	10.6 (516)	9.0 (179)	<0.0001
Lower limb amputation	3.0 (443)	2.2 (178)	4.0 (195)	3.5 (70)	<0.0001
Lipids					
Cholesterol α	4.2 [3.5, 5.0]	4.2 [3.6, 5.0]	4.0 [3.4, 4.8]	4.4 [3.6, 5.3]	0.0001
LDL α	2.1 [1.6, 2.8]	2.1 [1.6, 2.8]	2.0 [1.5, 2.6]	2.3 [1.7, 2.9]	0.0001
HDL α	1.1 [0.9, 1.4]	1.2 [1.0, 1.5]	1.1 [0.9, 1.4]	1.1 [0.9. 1.3]	0.0001
Triglycerides α	1.6 [1.0, 2.4]	1.5 [1.0, 2.2]	1.7 [1.1, 2.5]	1.7 [1.1, 2.7]	0.0001
Blood pressure					
Systolic BP β	130.8 (±17.9)	130.3 (±17.9)	132.5 (±17.9)	128.2 (±17.9)	0.980
Diastolic BP β	74.8 (±10.7)	74.7 (±10.6)	74.6 (±10.7)	75.7 (±11.0)	0.075
Antihypertensive therapy	64.7 (9,501)	60.8 (4,779)	75.4 (3,650)	54.2 (1,072)	<0.0001
Lipid lowering therapy	64.7 (9,657)	60.8 (4,851)	74.1 (3,648)	57.5 (1,158)	<0.0001

*Insulin duration and SGLT2 inhibitor use were not available for 2011 and 2013 data. **α** median [interquartile range] reported, differences analysed with Kruskal Wallis test. **β** mean (standard deviation) reported, differences analysed with ANOVA. Number of treatments (±) includes the total number of medication classes of: insulin, acarbose GLP-1 agonist, glitazone, sulphonylurea, metformin, DPP-4 inhibitor and SGLT2 inhibitor in those with type 2 diabetes only. ×data collected and analysed in males only.

3.2 The association between smoking status and clinical outcomes

The results of unadjusted and adjusted analyses (for age, sex, diabetes type, diabetes duration and study year) examining the relationship of smoking status with glycemic control, metabolic profile and microvascular and macrovascular complications are presented in Table 2, Figure 1 and Figure 2.

Table 2: The association of smoking status with glycemic and metabolic outcomes in Australian patients living with diabetes

	Past smokers				**Current smokers**					
	Median difference (unadjusted)	**p-value**	**Median difference (adjusted)**	**p-value**	**Median difference (unadjusted)**	**p-value**	**Median difference (adjusted)**	**p-value**	**Likelihood Ratio test (interaction of year)**	**Pairwise comparison of coefficient p-value**
HbA_{1c} (%)	0.10 [0.03, 0.17]	0.004	0.14 [0.07, 0.21]	<0.001	0.60 [0.51, 0.69]	<0.001	0.49 [0.40, 0.59]	<0.001	0.6542	<0.0001
BMI	1.91 [1.61, 2.21]	<0.001	1.57 [1.27, 1.87]	<0.001	-0.63 [-1.04, -0.22]	0.003	-0.78 [-1.18, -0.37]	<0.001	0.4244	<0.0001
Cholesterol	-0.20 [-0.25, -0.15]	<0.001	-0.06 [-0.11, -0.01]	0.043	0.20 [0.13, 0.27]	<0.001	0.09 [0.02, 0.16]	0.018	0.1508	0.0003
LDL	-0.16 [-0.21, -0.11]	<0.001	-0.07 [-0.12, -0.02]	0.004	0.16 [0.09, 0.23]	<0.001	0.03 [-0.03, 0.10]	0.319	0.9323	0.0040
HDL	-0.10 [-0.11, -0.09]	<0.001	-0.04 [-0.05, -0.02]	<0.001	-0.10 [-0.11, -0.09]	<0.001	-0.08 [-0.11, -0.06]	<0.001	0.1782	0.0003
Triglycerides	0.20 [0.14, 0.26]	<0.001	0.12 [0.08, 0.16]	<0.001	0.20 [0.12, 0.29]	<0.001	0.26 [0.20, 0.32]	<0.001	0.2137	<0.0001
	Mean difference (unadjusted)	**p-value**	**Mean difference (adjusted)**	**p-value**	**Mean difference (unadjusted)**	**p-value**	**Mean difference (adjusted)**	**p-value**	**Likelihood Ratio test (interaction of year)**	**Pairwise comparison of coefficient p-value**

Systolic blood pressure	2.21 [1.58, 2.85]	<0.0001	-0.06 [-0.69, 0.58]	0.864	-2.09 [-2.96, -1.21]	<0.001	-1.15 [-20.1, -0.29]	0.009	0.8794	0.0193
Diastolic blood pressure	-0.10 [-0.48, 0.28]	0.611	-0.15 [-0.53, 0.24]	0.462	1.01 [0.49, 1.53]	<0.001	0.08 [-0.44, 0.60]	0.764	0.3665	0.4288
	Odds ratio (unadjusted)	**p-value**	**Odds ratio (adjusted)**	**p-value**	**Odds ratio (unadjusted)**	**p-value**	**Odds ratio (adjusted)**	**p-value**	**Likelihood Ratio test (interaction of year)**	**Pairwise comparison of coefficient p-value**
Severe hypoglycaemia	1.07 [0.94, 1.21]	0.313	1.21 [1.05, 1.39]	0.008	1.29 [1.09, 1.52]	0.002	1.49 [1.25, 1.78]	<0.001	0.0557	0.0284
Number of glucose lowering therapies	1.08 [0.99, 1.16]	0.058	1.08 [0.99, 1.17]	0.054	1.01 [0.91, 1.13]	0.825	1.03 [0.92, 1.16]	0.596	0.7785	0.4442
Antihypertensive therapy	1.98 [1.83, 2.15]	<0.0001	1.35 [1.22, 1.48]	<0.001	0.77 [0.69, 0.85]	<0.001	0.97 [0.86, 1.10]	0.648	0.0917	<0.0001
Lipid lowering therapy	1.85 [1.71, 2.00]	<0.0001	1.27 [1.16, 1.39]	<0.001	0.87 [0.79, 0.97]	0.009	1.13 [1.00, 1.27]	0.045	0.2523	0.0721

Reference category is non-smokers. Adjusted for age (continuous), sex (male or female), diabetes type (type 1, type 2, other), diabetes duration (years) and year (2011, 2013, 2015, 2017)
p-values significance set at 0.05/22(outcomes) = 0.002

3.3 Glycemic and Metabolic Profile

The median HbA_{1c} was 0.49% higher among current smokers (median difference 0.49, [0.40, 0.59], p <0.0001), and 0.14% higher among past smokers (0.14, [0.07, 0.21], p <0.0001) when compared to never smokers. There was no relationship between smoking status and the number of glucose lowering therapies used. Current smokers (aOR=1.49 [1.25, 1.78], p <0.0001) had higher odds of severe hypoglycaemia than never smokers.

Current smokers had a lower median BMI (-0.78 [-1.18, -0.37], p <0.0001) and past smokers had a higher median BMI (1.57 [1.27, 1.87], p <0.0001) than never smokers. Total cholesterol, LDL cholesterol and systolic and diastolic blood pressure differences between smoking groups were not significant. HDL cholesterol levels were 0.08 mmol/L (-0.08, [-0.11, -0.06], p <0.0001) lower in current smokers and 0.04 mmol/L (-0.04, [-0.05, -0.02], p <0.0001) lower in past smokers, compared to never smokers. Triglyceride levels were 0.26 mmol/L (0.26, [0.20, 0.32], p <0.0001) higher in current smokers and 0.12 mmol/L (0.12 [0.08, 0.16], p <0.0001) higher in past smokers, compared to never smokers.

Insert figures 1 and 2 in this area.

3.4 Microvascular complications

Compared to never smokers, the odds of peripheral neuropathy were higher in current (aOR=1.54 [1.36, 1.74], p <0.0001) and past smokers (aOR=1.38 [1.26, 1.51], p <0.0001). The odds of macroalbuminuria (aOR=1.53 [1.28, 1.84], p <0.0001) were also higher in current compared to never smokers. Smoking status was not significantly associated with retinopathy, microalbuminuria and advanced CKD.

3.5 Macrovascular complications

Current and past smokers had higher odds of myocardial infarction (aOR=1.74 [1.47, 2.06] and aOR=1.76 [1.57, 1.98]), cerebral stroke (aOR=1.47 [1.18, 1.85] and aOR=1.35 [1.16, 1.57]) and peripheral vascular disease (aOR=2.50 [2.11, 3.00] and aOR=1.75 [1.55, 1.97]), when compared to never smokers (all p <0.001). In addition, past smokers (aOR=1.70 [1.53, 1.91], p <0.0001) had higher odds of having undergone coronary artery revascularisation procedures, when compared to never smokers.

3.6 Other complications

Both current and past smokers had higher odds of foot ulceration (aOR=1.59 [1.32, 1.91] and aOR=1.36 [1.19, 1.55]), lower limb amputation (aOR=1.73 [1.28, 2.33] and aOR=1.42 [1.14, 1.78]) and erectile dysfunction (aOR=1.49 [1.26, 1.76] and aOR=1.37 [1.22, 1.53]) when compared to never smokers (all p <0.0001).

3.7 Annual trends (effect of study year)

The association of smoking status with glycemic control, metabolic risk factors and diabetic complications did not significantly change over the 6-year study interval.

4. Discussion

We explored the association between smoking status and glycemic control, metabolic risk factors and microvascular and macrovascular complications in over 15,000 Australian adults living with diabetes. We observed that current smoking was associated with worse glycemic control as demonstrated by a higher median HbA_{1c} and higher odds of severe hypoglycaemia, despite this sub-group being on average younger and having had diabetes for a shorter period of time. Current and past smoking were also associated with higher odds of dyslipidaemia, peripheral neuropathy, erectile dysfunction, peripheral vascular disease, myocardial infarction, cerebral stroke, foot ulceration and lower limb amputation. The odds associated with current and past smoking were considerably higher for macrovascular, compared with microvascular complications.

The results of our study are consistent with the growing evidence on the detrimental effects of smoking in diabetes.[14, 16, 23, 24] Similarly, the long-standing associations seen between smoking and micro- and macrovascular complications[25-27] have also been reported in more recent literature.[28-31] We build on this evidence by also reporting a significant association between current smoking and worse glycemic control and metabolic profile and an increased risk of a range of diabetic complications including severe hypoglycaemia, among a large group of patients attending diabetes centres across Australia.

We observed that the prevalence of smoking in our cohort with diabetes (13.5%) was similar to that among the general Australian population (13.8%) in 2017-18.[1] This suggests suboptimal adherence to primary and/or secondary prevention recommendations on smoking cessation in this high-risk population. Furthermore, the potential for weight gain in the initial period of smoking cessation[32] should not deter patients from making efforts given the substantial improvements in metabolic parameters,[33] and the lower risk of microvascular and

macrovascular complications and mortality[34] that accompany smoking cessation. Given the ongoing high rates of smoking, assessment of tobacco use and counselling or treatments that aid smoking cessation, as recommended by guidelines, should be considered as an imperative for improving outcomes among people with diabetes.[15, 18] Further research on interventions that promote smoking cessation among people with diabetes would also be useful.

Among current smokers, treatment with antihypertensive and lipid lowering therapy was significantly lower, whilst use of glucose lowering therapies was similar, compared to past and never smokers, despite their greater risk profile. This highlights the need for continued review and re-evaluation of clinical guidelines and optimal patient-specific targets, so that timely intensification of therapy occurs and clinical inertia is avoided.[15, 35]

A strength of the use of the ANDA data is that it provides information regarding a large population of patients with both type 1 and type 2 diabetes, throughout all states and territories of Australia. We believe these data describe for the first time the prevalence of smoking and its relationship with diabetic outcomes among an Australian population of individuals with diabetes. There are limitations to the use of the ANDA dataset. All data collected are cross-sectional in nature with no current linked follow up of the de-identified patients from one audit to another. In that setting, we are able to only discuss associations rather than causal interactions, and there is also no capacity to collect mortality data. However, there is scope to add linked longer-term assessments in future years, with the addition of a longitudinal component to the audit that will be commencing with the 2019 ANDA AQCA data collection. There was a high prevalence of missing data for the albumin and lipid profile variables, therefore these variables should be interpreted with caution as a larger proportion of participants were excluded from their analysis, which has the potential to introduce selection bias for these outcomes. Another limitation is that a larger proportion of patients are from tertiary diabetes services rather than primary care practices, which may also introduce referral bias. More complicated patients with multiple complications tend to

be referred for further specialist management, therefore our cohort may not be entirely comparable to the population with diabetes that is managed in general practice. There is also reliance on the patient or the healthcare worker to accurately complete the data collection form, as the de-identified data cannot be further independently validated, which may contribute to missed or incorrect diagnoses.

5. Conclusion

In an adult Australian population of patients with diabetes, current and past smoking was associated with worse glycemic and lipid control, and higher odds of macrovascular and microvascular complications, when compared to never smoking. The prevalence of complications has not improved over recent years, even with the introduction of newer therapeutic agents. Despite this increased risk, smoking remains prevalent among the diabetic population. Smoking cessation should be a major focus of care among people with diabetes. This, together with addressing physician- patient- and healthcare-related factors that contribute to lack of timely initiation and intensification of appropriate treatment, may help improve glycemic and metabolic control and prevent or halt the progression of micro- and macrovascular complications.

Abbreviations

ACE – Angiotensin-Converting Enzyme

ARB – Angiotensin II Receptor Blocker

ANDA – Australian National Diabetes Audit

ANOVA – Analysis of Variance

aOR – Adjusted Odds Ratio

AQCA – Australian Quality Clinical Audit

AQSMA – Australian Quality Self-Management Audit

BMI – Body Mass Index

BP – Blood Pressure

CABG – Coronary Artery Bypass Graft

CKD – Chronic Kidney Disease

CKD-EPI – Chronic Kidney Disease Epidemiology Collaboration

DDP-4 – Dipeptidyl Peptidase-4

eGFR – Estimated Glomerular Filtration Rate

ESKD – End Stage Kidney Disease

GLP-1 – Glucagon Like Peptide 1

HbA_{1c} – Haemoglobin A1C

HDL – High Density Lipoprotein

IQR – Interquartile Range

LDL – Low Density Lipoprotein

NADC – National Association of Diabetes Centre

SGLT2 – Sodium-Glucose Co-Transporter 2

T1DM – Type 1 Diabetes Mellitus

T2DM – Type 2 Diabetes Mellitus

Declarations

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Data sharing statement: Applications for datasets generated and/or analysed during the current study may be considered by corresponding with the ANDA secretariat on reasonable request in line with research data enquiry procedures.

Part of this study has been presented during the 2019 Australasian Diabetes Congress (August 21st-23rd 2019, Sydney, Australia

Supplementary Appendix

Supplementary 1: eGFR formula

eGFR (mL/min/1.73m^2) = 175 x [Serum Creatinine (µmol/L) x 0.0113] - 1.154 x Age(years) - 0.203 (x 0.742 if female)

Supplementary Table 1: Missing Data Table

	Number missing (of total, 15,352)	**Percentage (%)**
Smoking status	0	0
Age	56	0.4
Sex	118	0.8
Diabetes type	0	0
Diabetes duration	203	1.3
Diabetes therapy	74	0.5
Insulin therapy	230	1.5
Insulin duration	2,863(/10,675)	26.8
HbA_{1c} (%) α	1,077	7.0
Severe hypoglycaemia	624	4.1
Number of Glucose Lowering Therapies	71	0.5
BMI	1,167	7.6
Retinopathy	2,294	15.0
Peripheral neuropathy	227	1.5
Advanced CKD	536	3.5
Microalbuminuria	5,717	37.2
Macroalbuminuria	5,717	37.2
Erectile dysfunction	690 (/8,111)	8.5
Peripheral vascular dis.	286	1.9
Myocardial infarction	625	4.1
Coronary artery revascularisation	530	3.5
Stroke	513	3.4
Foot ulceration	604	3.9
Lower limb amputation	539	3.5
Cholesterol α	3,624	23.6
LDL α	5,615	36.6
HDL α	5,214	33.9
Triglycerides α	3,927	25.6
Systolic BP	412	2.7
Diastolic BP	413	2.7
Antihypertensive therapy	668	4.4
Lipid lowering therapy	418	2.7

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