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Age related differences in glycaemic control, cardiovascular disease risk factors and treatment in patients with type 2 diabetes: a cross-sectional study from the Australian National Diabetes Audit

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Abstract

Objective: To compare the glycaemic control and cardiovascular risk factor profiles of younger and older patients with type 2 diabetes. Cross-sectional analysis of data from the 2015 Australian National Diabetes Audit (ANDA) was undertaken.

Methods: Data were obtained from adults with type 2 diabetes presenting to Australian secondary/tertiary diabetes centres. Logistic regression examined associations with HbA1c >7% (53 mmol/mol) and cardiovascular risk factors.

Results: Data from 3,492 patients were analysed. Mean (±SD) age was 62.9±12.5 years, mean diabetes duration 13.5±9.4 years and mean HbA1c 8.2±1.8%. Mean HbA1c was 8.6±2.1% and 8.0±1.6% for the younger (<60 years) and older subgroups (≥60 years) respectively (p<0.001). The odds (aOR) of HbA1c above >7.0% was 1.5 times higher (95%CI 1.22-1.84) for younger patients compared with older patients after adjustment for gender, smoking, diabetes duration, renal function and body mass index. Younger patients were also more likely to have dyslipidaemia (aOR 2.02 [1.53-2.68], p<0.001), be obese (aOR 1.25 [1.05-1.49)], p<0.001) and be current smokers (aOR 2.13 [1.64-2.77], p<0.001) than older patients.

Conclusions: Younger age was associated with poorer glycaemic control and adverse cardiovascular risk factor profiles. It is imperative to optimise and monitor treatment in order to improve long-term outcomes.

Strengths and limitations of this study:

- large dataset of patients from a nation-wide survey
- information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control

- We were unable to conduct longitudinal analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.
- Study population may largely represent a specialist referred patient group as the majority of patients were receiving care at tertiary diabetes centres

1. Introduction

Driven by ageing populations, increasing obesity and decreasing physical activity, the prevalence of diabetes is expected to rise by 55% to 592 million individuals worldwide by 2035(1). Traditionally a disease of middle and older age, type 2 diabetes is increasingly diagnosed in younger patients (2, 3). Diabetes and its complications contribute to 10% of Australian deaths (4) and 8.4 % of deaths worldwide (5).

The US National Health and Nutrition Examination Survey (NHANES) indicated that the prevalence of type 2 diabetes has increased by 70% in people aged 20-44 years in the last three decades, making younger adults the fastest growing group of people with type 2 diabetes (6). Diabetes complications are related to duration and degree of glycaemic control (7), thus younger people with diabetes who start their hyperglycaemic exposure at an earlier age may be at highest risk for end-organ damage. However, few studies have compared glycaemic control in younger and older patients with type 2 diabetes (8, 9). Further, these studies were largely conducted within selected trial cohorts (and as such the patients examined may differ from community based cohorts) and have reported variable findings of better glycaemic control in older patients (10), in younger patients (11) or no effect of age (12).

We hypothesised that there may be age-related differences in the management of patients with type 2 diabetes, which may contribute to excess cardiovascular risk in younger patients. This study investigates differences in the achieved levels and management of (1) glycaemic control and (2) cardiovascular risk factors between younger and older patients with type 2 diabetes.

2.Methods

2.1Participants

This national, cross-sectional study examined de-identified data from the 2015 Australian National Diabetes Audit (ANDA) (13). Participants were adult patients with type 2 diabetes, presenting to one of 49 nationally accredited diabetes centres. De-identified data were sourced from a range of diabetes centres located in the community/primary care (n=16) and secondary care (n=33), with patients under the care of endocrinologists, general specialists and local general practitioners. The state and territory location of participating sites is presented in Appendix 1. Information was collected regarding all consecutive patients attending a participating diabetes centre during the one-month survey period (May or June 2015). The Australian National Diabetes Audit has received approval from the Monash Health Human Research Ethics Committee.

2.2 Variables

Pre-specified demographic (gender, date of birth) and clinical variables (diabetes complications, comorbid conditions, blood pressure (BP), glycated haemoglobin A1c (HbA1c), body mass index (BMI), smoking status, medications) were collected for patients with type 2 diabetes. Health professionals from participating centres examined patients, reviewed medical records including pathology results and recorded the information in a standardised data collection form. All missing data, invalid entries and discrepancies were clarified with the patients' treating centres. As per the a priori analysis plan, age at survey was calculated as date of survey (2015) minus date of birth and categorised as <60 years or ≥60 years, diabetes duration was calculated as date of survey minus date of diabetes diagnosis and categorised as <10 years or ≥10 years. Height and weight were measured to calculate BMI. Smoking status was categorised as never, previous or current. Recent

pathology results (within the last 12 months) were recorded for total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), HbA1c and serum creatinine; calculated estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study (MDRD) equation (14).

2.3 Outcomes

The main outcome variables were HbA1c (categorised as >7.0%, 53 mmol/mol), hypertension (defined as >140 and/or 90 mmHg), dyslipidaemia (defined as either TC>4.0 mmol/L, HDL<1.0 mmol/L, LDL>2.0 mmol/L or Tg>2.0 mmol/L), obesity (defined as BMI>30 kg/m^2) and smoker (categorised as never, past or current).

2.4 Statistical analysis

Categorical variables were summarised as percentages and differences between subgroups analysed using χ^2 test. Continuous variables were tested for normality to determine the most appropriate method for statistical analysis (parametric or non-parametric) and reported as means with standard deviations (SD) or as medians with interquartile ranges (IQR). Subgroup analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data as appropriate. Logistic regression was used to examine factors (current age, diabetes duration, gender, smoking, calculated eGFR, BMI) associated with HbA1c, hypertension, dyslipidaemia and obesity (as the categories defined above). The selection of variables was based on identifying all measured clinical variables of known or suspected prognostic importance for the outcomes of interest and/or exhibiting a p value ≤0.10 on univariable analysis. All potential confounding variables were included in the multivariable models. Subgroup analyses were conducted to examine the effect of treatments (yes or no) including insulin, antihypertensive therapy and lipid lowering therapy in patients

above the glycaemic, lipid and BP targets. A prescribing gap was defined as patients who were not prescribed the relevant medications despite being above the recommended targets. A treatment gap was defined as patients who were above the recommended targets despite being on treatment. A sensitivity analysis examined the effect of excluding patients with less than 2 years diabetes duration, who may have not yet had opportunity to modify treatment and achieve targets. Patients were excluded from a particular analysis when data relevant to that analysis were missing, but were not excluded from other analyses where appropriate information was provided. Missing data of variables was less than 10% and not imputed. A two-sided significance level of 0.05 was considered statistically significant. All analyses were performed using Stata software version 14.2 (StataCorp, Texas, USA).

3. Results

3.1 Overall

Data from 3,492 patients (>18 years of age) were analysed. Patients from all states and territories were included (Suppl.Table 1). Younger patients (<60 years) accounted for 38% (n=1,328) of patients. The clinical characteristics of these patients, stratified by age, are shown in Table 1. The mean (±SD) age of the whole group was 62.9±12.5 years and the mean ages of the younger and older age groups were 50.1 ±8.4 years and 70.7 ±7.0 years respectively. Mean diabetes duration was 9.6±7.5 years for the younger age group and 15.9±9.6 years for the older age group (p<0.001). There was a higher proportion of male patients in the older (56.5%) compared with the younger age group (49.5%, p<0.001). The majority of patients (64.9%) were treated at tertiary hospitals followed by community or primary care centres (35.1%). Australian birth was reported by 68.1% of the younger age group and 62.4% of the older age group (p=0.001). Microvascular and macrovascular

complications were prevalent in 35.3% and 21.6% of the younger age group and 49.3% and 43.4% of the older age group respectively (p<0.001 for both).

3.2 Glycaemic control

Mean HbA1c was 8.2±1.8% for the group overall, 8.6±2.1% and 8.0±1.6% for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had an HbA1c above 7.0% compared with the older age group (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking and BMI were all associated with an HbA1c above 7.0%. The unadjusted and adjusted odds ratios [95%CI] for HbA1c above 7.0% were 1.26 [1.07-1.49], p<0.001 and 1.50 [1.22-1.84], p<0.001 respectively for younger patients compared with older patients (Table 2, Figure 1).

Glycaemic management was reported as diet only by 4%, oral agents by 77%, non-insulin injectable therapy by 5% and insulin alone or in combination with oral agents by 61% of patients. Compared with older patients, younger patients were equally likely to not be on insulin treatment despite an HbA1c >8.0%, after adjusting for gender, diabetes duration, renal function and BMI (Suppl. Table 2).

3.3 Hypertension

Mean systolic blood pressure (BP) was 130±18 mmHg and 134±18 mmHg for the younger and older age groups respectively (p<0.001). A smaller proportion of patients in the younger age group were hypertensive compared with the older age group (Table 1, Figure 1). Younger patients were less likely to be hypertensive compared with older patients (unadjusted OR 0.81 [0.70-0.95] p =0.008). However, after adjusting for gender, smoking, renal function and BMI this effect was no longer significant (adjusted OR 0.85 [0.70-1.04], p = 0.119) (Table 2).

The overall study population prescribing and treatment gaps for hypertension were 5% and 25% respectively (Figure 2). Younger patients who were hypertensive were more likely to not be on blood pressure lowering medication (prescribing gap) than older patients who were hypertensive (adjusted OR 1.84 [1.16-2.92], p = 0.002) (Suppl. Table 2).

3.4 Dyslipidaemia

The majority of patients in both age groups had abnormal lipid profiles but a greater proportion of patients in the younger than older age group had dyslipidaemia (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking, BMI and HbA1c were associated with dyslipidaemia. The unadjusted and adjusted odds ratios [95%CI] for dyslipidaemia were 2.41 [1.91-3.03], p<0.001 and 2.02 [1.53-2.68], p<0.001 respectively for younger patients compared with older patients (Table 2).

The overall study population prescribing and treatment gaps for dyslipidaemia were 22% and 60% respectively (Figure 2). Younger patients with dyslipidaemia were more likely to not be on lipid lowering medication (prescribing gap) than older patients with dyslipidaemia after adjustment for diabetes duration, gender, smoking, renal function and vascular disease (adjusted OR 1.48 [1.15-1.90], p = 0.002) (Suppl. Table 2).

3.5 Obesity

Mean BMI was 34.5 ±8.4 kg/m^2 and 32.4 ±6.7 kg/m^2 for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had a BMI in the obese category (>30 kg/m^2) compared with the older age group (Table 1, Figure 2). On univariable analysis, age, gender and smoking were all associated with obesity. The

unadjusted and adjusted odds ratios for obesity were 1.26 [1.09-1.46], p=0.002 and 1.25 [1.05-1.49], p=0.002 respectively for younger patients compared with older (Table 2).

3.6 Smoking

A greater proportion of patients in the younger age group reported being a current smoker compared with older patients (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, BMI and renal function were all associated with current smoking. The unadjusted and adjusted odds ratios for current smoking were 2.60 [2.09-3.22], p<0.001 and 2.13 [1.64-2.77], p<0.001 respectively for younger patients compared with older patients (Table 2).

3.7 Sensitivity analysis

When patients with diabetes duration of 2 years or less were excluded the associations were unchanged. Younger patients were still more likely to have an HbA1c over 7.0% (adjusted OR 1.59 [1.27-2.00], p<0.001), dyslipidaemia (adjusted OR 1.89 [1.41-2.53], p<0.001), be obese (adjusted OR 1.28 [1.06-1.55], p=0.010) and smokers (adjusted OR 2.19 [1.64-2.92], p<0.001) than older patients after adjusting for diabetes duration, gender, renal function, BMI and HbA1c where appropriate (Suppl. Table 3).

4. Discussion

In this large national cross-sectional study of community-living patients with type 2 diabetes, we found that younger patients with significantly shorter disease duration were less likely to achieve recommended targets for glycaemic control, blood pressure and lipids than older patients. Younger patients were also more likely to be obese and to smoke. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger rather than older patients

were more likely to not be on therapy after adjustment for other relevant confounders. These findings remained after exclusion of patients with more recent diabetes onset who may have been relatively new to diabetes services and not yet had opportunity to attain treatment targets.

It is not clear why younger patients demonstrate poorer glycaemic control than older patients. Some evidence suggests that early-onset type 2 diabetes may be a more aggressive phenotype than later-onset type 2 diabetes, representing a greater predisposition to beta cell failure and diagnosis at an earlier age (15). Since younger patients had higher rates of obesity compared with older patients, this may have contributed to worsening insulin resistance, and a need for greater intensification of therapy to achieve optimal glycaemic control. Longer duration of diabetes is also known to be associated with poorer glycaemic control, possibly due to progressive β-cell impairment and reduced insulin secretion (16), which in turn reduces the effectiveness of diet alone or oral agents. However, in our study the younger age group had a shorter diabetes duration than the older age group such that longer disease duration could not explain the poorer glycaemic control.

The high prevalence of poor glycaemic control and adverse cardiovascular risk factors observed in younger patients is of great concern as cardiovascular disease accounts for over half of the mortality among people with type 2 diabetes (17, 18). Given the risk for cardiovascular disease doubles when hypertension is also present in people with diabetes (19) and over a quarter of the patients in the younger age group had either systolic or diastolic hypertension, a review of the intensity of management is in order. This is supported by the larger prescribing and treatment gaps observed in the younger rather than older patients. In contrast, for older patients it is possible that clinicians' concerns regarding hypotension and

postural symptoms due to autonomic neuropathy may appropriately limit antihypertensive use.

Although the absolute differences in the lipid variables were not large between the younger and older age groups, it is noteworthy that among younger patients and in line with other international studies, 89% had abnormal lipids (20). High density cholesterol levels, considered the best lipid predictor of cardiovascular disease (21), were significantly lower and triglyceride levels significantly higher in younger patients compared with older patients suggestive of inadequate lipid management. The relative insulin deficiency seen in type 2 diabetes is known to impair the action of lipoprotein lipase, resulting in lower HDL levels and higher triglyceride levels. However, the lower HDL and higher triglyceride observed in younger patients cannot be attributed solely to the effect of hyperglycaemia as younger age remained independently associated with dyslipidaemia when HbA1c was included in the multivariable model. Another possible explanation is survivor effect bias whereby patients with normal lipid levels have survived longer (and into the older age group) compared with those with dyslipidaemia.

It is recognised that estimates of absolute cardiovascular risk (even for those with diabetes) are driven predominantly by age rather than modifiable risk factors (22). Indeed, in our study the majority of patients in the younger age group would have low absolute cardiovascular risk despite significant risk factor burden. The Global Burden of Disease study reported that the maximum impact in terms of healthy life-years gained or disability adjusted life years averted with cardiovascular preventive therapies would be observed between 55-64 years (23). However, vascular complications develop over many decades from a young age (24), well before presentation with a potentially fatal event. Additionally, younger patients have higher

modifiable risk (risk factors amenable to treatment) and longer future lifetime exposure for any particular absolute risk level when compared to older people. As highlighted by our findings, a major outstanding challenge is how best to implement use of evidence-based preventive therapies in younger patients and to effectively communicate risk of future events. Among newer approaches are the concepts of heart or vascular age (25) and of lifetime or modifiable risk, particularly in younger patients. This is consistent with the American College of Cardiology /American Heart Association (ACC/AHA) guidelines recommending assessment of lifetime risk in younger patients in addition to the traditional absolute risk assessment (26).

Other explanations for our findings include that younger patients may face more hurdles to glucose testing, regular physical activity, healthy diet, and medication adherence whereas older patients may access medical care more frequently, may be more motivated to manage their medical conditions and may be more compliant with diet and medications (27-29). Further research is required to understand the barriers to better glycaemic control and cardiovascular risk profiles faced by younger patients. These data are crucial to inform strategies to assist weight reduction, lifestyle modification and escalation of glycaemic, anti-hypertensive and lipid lowering therapies. Such measures would particularly benefit younger patients with type 2 diabetes, given that the incidence of macrovascular complications and mortality increases with diabetes duration (7) and is reduced with management of glycaemia and cardiovascular risk factors (17, 18). Good glycaemic control earlier in the course of diabetes may also be imperative, as this is demonstrated to reduce complications in the long term (30).

The proportion of patients with hypertension and dyslipidaemia in our study was similar to that reported in the population-based AusDiab study. However, the proportion of patients overall with an HbA1c target ≤7.0% was greater in our study than in the AusDiab study (31) and the community-based Fremantle Diabetes Study (8). In our study younger patients had poorer glycaemic control with a mean diabetes duration approximately half that of older patients. Higher HbA1c levels have previously been independently associated with younger age (8). In contrast, the Australian general practice based NEFRON study, found that younger and more obese patients with a longer duration of diabetes had poor glycaemic control (9). The differences in these studies may be due to the varying sampling frames and population characteristics.

A strength of this analysis is the large dataset of patients from a nation-wide survey. Data were sourced from over half of the centres registered with the National Association of Diabetes centres (NADC) at the time. The participants of our study are likely to be similar to patients attending diabetes clinics throughout Australia. We obtained information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control. Study limitations include that the majority of patients were receiving care at tertiary diabetes centres and may largely represent a specialist referred patient group. Referral bias is also possible. General practitioners may be more likely to refer younger patients whilst managing older patients with shorter diabetes duration. Alternatively, older patients with longer diabetes duration and interrelating co-morbid conditions may also be more likely to be referred to specialist services. Another limitation was the reliance on self/healthcare worker reports as we were unable to independently verify diagnoses and treatments. This is unlikely to change the findings substantively, given previous studies have found approximately 90% of self-reported diabetes information to be valid (32). We were unable to conduct longitudinal

analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.

5. Conclusion

In summary, younger patients with type 2 diabetes attending diabetes centres are burdened by poorer glycaemic control and cardiovascular risk factor profiles compared with older patients. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger patients were significantly more likely to not be on therapy or be above target despite treatment than older patients. Younger patients with diabetes may benefit from more targeted, evidence-based, multi-disciplinary initiatives to achieve and maintain intensive glycaemic control and optimise cardiovascular risk factors. Such measures may minimise the incidence and severity of diabetes related complications in younger patients with type 2 diabetes, thereby reducing morbidity and mortality.

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Authors' Contributions

NN: study design, literature review, statistical analysis, critical discussion, drafting and revision of the manuscript

AG: statistical analysis, critical discussion, revision of the manuscript

SR: statistical analysis and interpretation of the data, revision of the manuscript

WD: critical revision of the manuscript

JF: critical revision of the manuscript

NW: study conception and design, revision of the manuscript

SA: study conception and design, critical revision of the manuscript

SZ: study conception and design, design of analyses, critical revision of the manuscript, supervision of the project.

The authors NN, SR, and SZ had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors have read and approved the final manuscript.

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Data Sharing Statement

Application for datasets generated during and/or analysed during the current study may be considered by the corresponding author on reasonable request.

Competing interests

W. Davis reports past participation in advisory boards and/or receiving honoraria from Novo Nordisk and Eli Lilly Australia. N. Wischer reports past participation in advisory boards and/or receiving honoraria from AstraZeneca Pty Ltd/, Eli Lilly Australia, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk. S Andrikopoulos reports past participation in advisory boards and/or receiving honoraria from GlaxoSmithKline Pty Ltd, Novartis Pty Ltd, AstraZeneca Pty Ltd/Bristol-Myers Squibb Australia Pty Ltd, Eli Lilly Australia, Janssen Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk, Servier Laboratories Pty Ltd S Zoungas reports past participation in advisory boards/contract work on behalf of Monash University with AstraZeneca Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd and Novo Nordisk Pty Ltd. S Zoungas holds a NHMRC senior research fellowship.

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Tables and Figures

Table 1: Characteristics of study participants

Characteristic*	Age		p value
	<60 years n=1328	≥60 years n=2164	
Age to 2015 (years)	50.1 (8.4)	70.7 (7.0)	<0.001
Male	650 (49.5)	1208 (56.5)	<0.001
Age when diabetes first diagnosed (years)	40.6 (9.4)	54.9 (10.6)	<0.001
Diabetes duration (years)	9.6 (7.5)	15.9 (9.6)	<0.001
HbA1c (%)	8.6 (2.1)	8.0 (1.6)	<0.001
Cardiovascular risk factors			
Systolic blood pressure (mmHg)	130.5 (18.1)	134.1 (18.6)	<0.001
Diastolic blood pressure (mmHg)	77.7 (10.5)	72.6 (10.2)	<0.001
Current smoker	235 (20.2)	161 (8.9)	
Past smoker	350 (30.1)	713 (39.4)	<0.001
Never smoker	577 (49.7)	936 (51.7)	
Total cholesterol (mmol/l)	4.6 (1.3)	4.0 (1.1)	<0.001
LDL-cholesterol (mmol/l)	2.4 (1.6)	2.0 (0.9)	<0.001
HDL-cholesterol (mmol/l)	1.1 (0.4)	1.1 (0.4)	0.010
Triglyceride (mmol/l)	2.5 (2.4)	2.1 (1.7)	<0.001
Serum creatinine (µmol/l)	89.5 (91.7)	109.5 (91.3)	<0.001
eGFR ml/min/1.73m^2	89.3 (35.9)	65.9 (27.1)	<0.001
Body Mass Index (kg/m^2)	34.5 (8.4)	32.4 (6.7)	<0.001
Treatments			
Diet alone	65 (4.9)	77 (3.6)	0.052
Oral glucose lowering agents	1050 (79.1)	1634 (75.5)	0.013
Non-insulin injectable glucose lowering agents	94 (7.1)	98 (4.5)	0.003
Insulin	769 (57.9)	1348 (62.3)	0.010
Cardiovascular disease			
Microvascular complications	414 (35.3)	950 (49.3)	<0.001
Macrovascular complications	247 (21.6)	847 (43.4)	<0.001

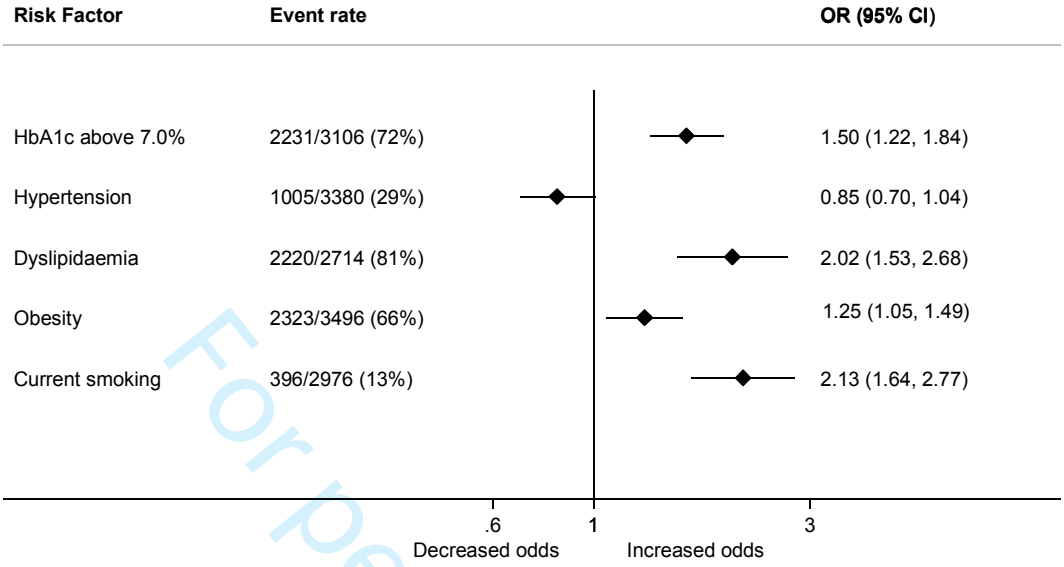
* categorical variables were presented as n (%) and continuous variables as mean (SD) or median (IQR), as appropriate
# categorical variables were assessed with the Chi square test. Continuous variables were tested for normality, analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data
Microvascular complications defined as retinopathy, nephropathy or peripheral neuropathy
Macrovascular complications defined as either cardiovascular, cerebrovascular or peripheral vascular disease

Table 2: Unadjusted and adjusted odds of factors associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.26 (1.07-1.49)	0.005	1.50 (1.22-1.84)	<0.001	0.81 (0.70-0.95)	0.008	0.85 (0.70-1.04)	0.119	2.41 (1.91-3.03)	<0.001	2.02 (1.53-2.68)	<0.001	1.26 (1.09-1.46)	0.002	1.25 (1.05-1.49)	0.011	2.60 (2.09-3.22)	<0.001	2.13 (1.64-2.77)	<0.001
Duration of Diabetes																				
<10 y (ref)																				
≥10 y	2.05 (1.74-2.40)	<0.001	2.51 (2.07-3.03)	<0.001	1.16 (0.99-1.35)	0.067	1.03 (0.85-1.25)	0.735	0.66 (0.53-0.81)	<0.001	0.79 (0.60-1.03)	0.087	1.04 (0.90-1.20)	0.597			0.59 (0.48-0.73)	<0.001	0.82 (0.64-1.06)	0.124
Sex																				
Male (ref)																				
Female	1.18 (1.01-1.38)	0.039	1.16 (0.97-1.39)	0.100	1.02 (0.88-1.18)	0.828	0.87 (0.73-1.04)	0.129	0.76 (0.62-0.92)	0.005	0.70 (0.55-0.90)	0.005	1.34 (1.16-1.54)	<0.001	1.38 (1.16-1.63)	<0.001	0.70 (0.56-0.87)	0.001	0.70 (0.55-0.89)	0.004
Smoking																				
Never (ref)																				
Past	1.09 (0.9-1.32)	0.368			0.93 (0.79-1.10)	0.418	0.90 (0.74-1.09)	0.287	1.10 (0.87-1.38)	0.419	1.01 (0.77-1.32)	0.947	1.44 (1.22-1.71)	<0.001	1.63 (1.35-1.96)	<0.001				
Current	1.09 (0.84-1.42)	0.512			0.65 (0.50-0.84)	0.001	0.72 (0.54-0.96)	0.024	1.73 (1.18-2.52)	0.005	1.32 (0.87-1.99)	0.187	0.93 (0.74-1.17)	0.517	0.92 (0.72-1.18)	0.525				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (0.99-1.00)	0.073	1.00 (1.00-1.01)	0.034	1.00 (0.99-1.00)	0.001	1.00 (0.99-1.00)	0.008	1.00 (1.00-1.01)	0.144			1.00 (1.00-1.00)	0.307			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.001	1.02 (1.01-1.04)	0.004	1.02 (1.00-1.03)	0.077					0.98 (0.97-1.00)	0.017	0.97 (0.95-0.99)	0.001
HbA1c (%) (per unit)					1.03 (0.99-1.07)	0.156			1.18 (1.11-1.26)	<0.001	1.14 (1.05-1.23)	0.001	1.07 (1.03-1.12)	0.001	1.05 (1.00-1.10)	0.049				

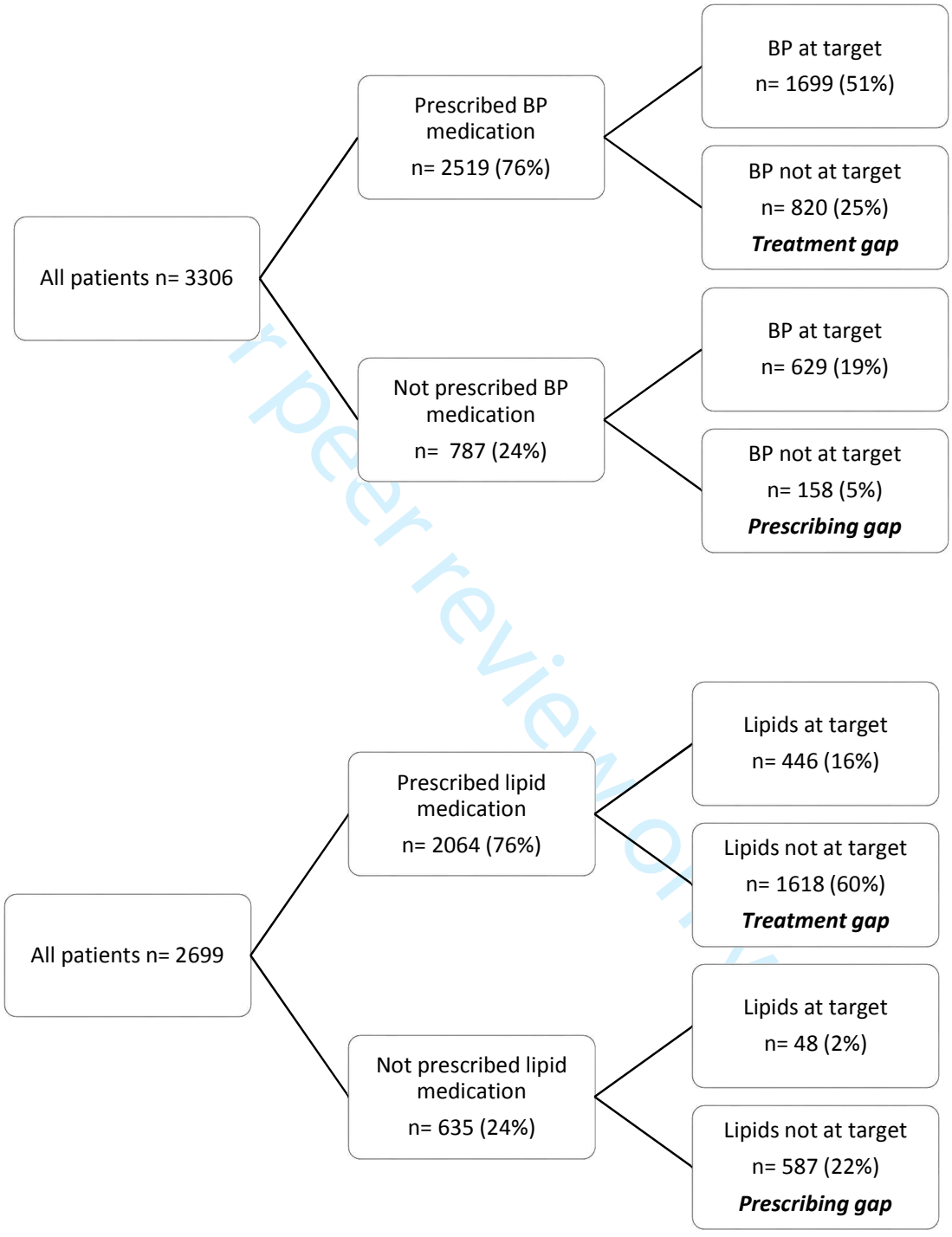
*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group



The diamonds refer to the odds ratios for patients aged <60 years compared to the reference group of patients aged ≥60 years for each of the outcomes listed
Multivariable analyses are, where appropriate,, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
Obesity is defined as Body Mass Index >30 kg/m^2

Figure 2: Blood pressure (i) and lipid management (ii) gaps in patients with type 2 diabetes



Supplementary Tables

Suppl. Table 1: Number of participating diabetes centres and patients by state or territory

State/Territory	Participating centres	Number of patients included
Australian Capital Territory	1	49
New South Wales	13	1246
Northern Territory	1	91
Queensland	9	758
South Australia	1	44
Tasmania	3	140
Victoria	20	1119
Western Australia	1	45
Total	49	3492

Suppl. Table 2: Unadjusted and adjusted odds of variables associated with prescribing gaps

	HbA1c > 8.0% and not on insulin				Hypertension and not on BP medication				Dyslipidaemia and not on lipid medication			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age (y)												
≥60 (ref)												
<60	1.23 (1.01-1.50)	0.041	0.80 (0.61-1.04)	0.090	2.71 (1.91-3.83)	<0.001	1.84 (1.16-2.92)	0.010	2.17 (1.79-2.63)	<0.001	1.48 (1.15-1.90)	0.002
Duration of Diabetes (y)												
<10 (ref)												
≥10	0.28 (0.23-0.35)	<0.001	0.28 (0.22-0.36)	<0.001	0.39 (0.28-0.56)	<0.001	0.46 (0.29-0.71)	0.001	0.41 (0.34-0.50)	<0.001	0.54 (0.42-0.69)	<0.001
Gender												
Male (ref)												
Female	0.89 (0.73-1.08)	0.239	0.87 (0.69-1.11)	0.260	0.96 (0.68-1.36)	0.818	0.97 (0.62-1.51)	0.890	1.37 (1.13-1.66)	0.001	1.19 (0.93-1.51)	0.160
Smoking												
Never (ref)												
Past	0.83 (0.66-1.05)	0.117			0.57 (0.38-0.86)	0.008	0.66 (0.41-1.09)	0.103	0.71 (0.57-0.90)	0.005	0.76 (0.59-0.99)	0.043
Current	0.97 (0.71-1.33)	0.861			1.57 (0.94-2.64)	0.087	1.40 (0.74-2.65)	0.301	1.06 (0.78-1.44)	0.711	1.03 (0.73-1.46)	0.856
eGFR (ml/min) (per unit)	1.01 (1.00-1.01)	0.001	1.00 (1.00-1.01)	0.049	1.02 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.012	1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.005
BMI (kg/m^2) (per unit)	0.98 (0.97-1.00)	0.021	0.98 (0.96-0.99)	0.004	0.98 (0.96-1.00)	0.100	0.95 (0.93-0.98)	0.002	0.99 (0.98-1.01)	0.238		
HbA1c (%) (per unit)					1.05 (0.95-1.16)	0.331			0.98 (0.93-1.04)	0.497		
Vascular disease												
No (ref)												
Yes					0.37 (0.26-0.53)	<0.001	0.48 (0.31-0.75)	0.001	0.36 (0.29-0.44)	<0.001	0.51 (0.40-0.66)	<0.001

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L

Suppl. Table 3: Unadjusted and adjusted odds of variables associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels, excluding patients with diabetes duration ≤ 2 years.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.47 (1.22-1.77)	<0.001	1.59 (1.27-2.00)	<0.001	0.88 (0.74-1.04)	0.122	0.90 (0.72-1.12)	0.339	2.17 (1.71-2.76)	<0.001	1.89 (1.41-2.53)	<0.001	1.31 (1.11-1.54)	0.001	1.28 (1.06-1.55)	0.010	2.50 (1.96-3.17)	<0.001	2.19 (1.64-2.92	<0.001
Duration																				
<10 y (ref)																				
≥10 y	1.65 (1.37-1.98)	<0.001	2.05 (1.66-2.54)	<0.001	1.10 (0.92-1.31)	0.295			0.80 (0.63-1.01)	0.065	0.93 (0.70-1.25)	0.631	1.02 (0.86-1.21)	0.793			0.71 (0.55-0.92)	0.009	1.00 (0.75-1.35)	0.983
Sex																				
Male (ref)																				
Female	1.18 (0.99-1.40)	0.062	1.18 (0.97-1.44)	0.093	1.05 (0.90-1.23)	0.555	0.96 (0.78-1.17)	0.657	0.75 (0.61-0.92)	0.006	0.70 (0.54-0.90)	0.006	1.29 (1.11-1.50)	0.001	1.35 (1.12-1.62)	0.001	0.74 (0.58-0.94)	0.015	0.77 (0.59-1.01)	0.060
Smoking																				
Never (ref)																				
Past	1.08 (0.88-1.32)	0.484			0.92 (0.77-1.11)	0.387	0.97 (0.78-1.19)	0.748	1.08 (0.85-1.37)	0.539	0.97 (0.74-1.28)	0.853	1.51 (1.26-1.81)	<0.001	1.69 (1.38-2.06)	<0.001				
Current	1.22 (0.89-1.66)	0.215			0.68 (0.51-0.90)	0.006	0.74 (0.53-1.02)	0.062	1.46 (0.99-2.17)	0.058	1.18 (0.77-1.81)	0.446	0.95 (0.74-1.23)	0.712	0.90 (0.69-1.19)	0.468				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (1.00-1.01)	0.002	1.00 (1.00-1.01)	0.014	1.00 (0.99-1.00)	0.005	1.00 (0.99-1.00)	0.011	1.00 (1.00-1.00)	0.655			1.00 (1.00-1.00)	0.175			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.009	1.02 (1.00-1.04)	0.013	1.02 (1.00-1.03)	0.097					0.98 (0.96-1.00)	0.016	0.96 (0.95-0.98)	<0.001
HbA1c (%) (per unit)					1.04 (1.00-1.09)	0.075	1.02 (0.97-1.08)	0.477	1.21 (1.12-1.29)	<0.001	1.14 (1.05-1.23)	0.002	1.09 (1.04-1.14)	<0.001	1.05 (1.00-1.11)	0.040				

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

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Age related differences in glycaemic control, cardiovascular disease risk factors and treatment in patients with type 2 diabetes: a cross-sectional study from the Australian National Diabetes Audit

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Abstract

Objective: To compare the glycaemic control and cardiovascular risk factor profiles of younger and older patients with type 2 diabetes. Cross-sectional analysis of data from the 2015 Australian National Diabetes Audit (ANDA) was undertaken.

Methods: Data were obtained from adults with type 2 diabetes presenting to Australian secondary/tertiary diabetes centres. Logistic regression examined associations with HbA1c >7% (53 mmol/mol) and cardiovascular risk factors.

Results: Data from 3,492 patients were analysed. Mean (±SD) age was 62.9±12.5 years, mean diabetes duration 13.5±9.4 years and mean HbA1c 8.2±1.8%. Mean HbA1c was 8.6±2.1% and 8.0±1.6% for the younger (<60 years) and older subgroups (≥60 years) respectively (p<0.001). The odds (aOR) of HbA1c above >7.0% was 1.5 times higher (95%CI 1.22-1.84) for younger patients compared with older patients after adjustment for gender, smoking, diabetes duration, renal function and body mass index. Younger patients were also more likely to have dyslipidaemia (aOR 2.02 [1.53-2.68], p<0.001), be obese (aOR 1.25 [1.05-1.49)], p<0.001) and be current smokers (aOR 2.13 [1.64-2.77], p<0.001) than older patients.

Conclusions: Younger age was associated with poorer glycaemic control and adverse cardiovascular risk factor profiles. It is imperative to optimise and monitor treatment in order to improve long-term outcomes.

Strengths and limitations of this study:

- large dataset of patients from a nation-wide survey
- information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control

- We were unable to conduct longitudinal analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.
- Study population may largely represent a specialist referred patient group as the majority of patients were receiving care at tertiary diabetes centres

1. Introduction

Driven by ageing populations, increasing obesity and decreasing physical activity, the prevalence of diabetes is expected to rise by 55% to 592 million individuals worldwide by 2035(1). Traditionally a disease of middle and older age, type 2 diabetes is increasingly diagnosed in younger patients (2, 3). Diabetes and its complications contribute to 10% of Australian deaths (4) and 8.4 % of deaths worldwide (5).

The US National Health and Nutrition Examination Survey (NHANES) indicated that the prevalence of type 2 diabetes has increased by 70% in people aged 20-44 years in the last three decades, making younger adults the fastest growing group of people with type 2 diabetes (6). Diabetes complications are related to duration and degree of glycaemic control (7), thus younger people with diabetes who start their hyperglycaemic exposure at an earlier age may be at highest risk for end-organ damage. However, few studies have compared glycaemic control in younger and older patients with type 2 diabetes (8, 9). Further, these studies were largely conducted within selected trial cohorts (and as such the patients examined may differ from community based cohorts) and have reported variable findings of better glycaemic control in older patients (10), in younger patients (11) or no effect of age (12).

We hypothesised that there may be age-related differences in the management of patients with type 2 diabetes, which may contribute to excess cardiovascular risk in younger patients. This study investigates differences in the achieved levels and management of (1) glycaemic control and (2) cardiovascular risk factors between younger and older patients with type 2 diabetes.

2.Methods

2.1Participants

This national, cross-sectional study examined de-identified data from the 2015 Australian National Diabetes Audit (ANDA) (13). Participants were adult patients with type 2 diabetes, presenting to one of 49 nationally accredited diabetes centres. De-identified data were sourced from a range of diabetes centres located in the community/primary care (n=16) and secondary care (n=33), with patients under the care of endocrinologists, general specialists and local general practitioners. The state and territory location of participating sites is presented in Appendix 1. Information was collected regarding all consecutive patients attending a participating diabetes centre during the one-month survey period (May or June 2015). The Australian National Diabetes Audit has received approval from the Monash Health Human Research Ethics Committee.

2.2 Variables

Pre-specified demographic (gender, date of birth) and clinical variables (diabetes complications, comorbid conditions, blood pressure (BP), glycated haemoglobin A1c (HbA1c), body mass index (BMI), smoking status, medications) were collected for patients with type 2 diabetes. Health professionals from participating centres examined patients, reviewed medical records including pathology results and recorded the information in a standardised data collection form. All missing data, invalid entries and discrepancies were clarified with the patients' treating centres. As per the a priori analysis plan, age at survey was calculated as date of survey (2015) minus date of birth and categorised as <60 years or ≥60 years, diabetes duration was calculated as date of survey minus date of diabetes diagnosis and categorised as <10 years or ≥10 years. Height and weight were measured to calculate BMI. Smoking status was categorised as never, previous or current. Recent

pathology results (within the last 12 months) were recorded for total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), HbA1c and serum creatinine; calculated estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study (MDRD) equation (14).

2.3 Outcomes

The main outcome variables were HbA1c (categorised as >7.0%, 53 mmol/mol), hypertension (defined as >140 and/or 90 mmHg), dyslipidaemia (defined as either TC>4.0 mmol/L, HDL<1.0 mmol/L, LDL>2.0 mmol/L or Tg>2.0 mmol/L), obesity (defined as BMI>30 kg/m^2) and smoker (categorised as never, past or current). The targets were based on the current Australian recommendations for people with diabetes as per the Australian Heart Foundation (15).

2.4 Statistical analysis

Categorical variables were summarised as percentages and differences between subgroups analysed using χ^2 test. Continuous variables were tested for normality to determine the most appropriate method for statistical analysis (parametric or non-parametric) and reported as means with standard deviations (SD) or as medians with interquartile ranges (IQR). Subgroup analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data as appropriate. Logistic regression was used to examine factors (current age, diabetes duration, gender, smoking, calculated eGFR, BMI) associated with HbA1c, hypertension, dyslipidaemia and obesity (as the categories defined above). The selection of variables was based on identifying all measured clinical variables of known or suspected prognostic importance for the outcomes of interest and/or exhibiting a p

value ≤0.10 on univariable analysis. All potential confounding variables were included in the multivariable models. Subgroup analyses were conducted to examine the effect of treatments (yes or no) including insulin, antihypertensive therapy and lipid lowering therapy in patients above the glycaemic, lipid and BP targets. A prescribing gap was defined as patients who were not prescribed the relevant medications despite being above the recommended targets. A treatment gap was defined as patients who were above the recommended targets despite being on treatment. A sensitivity analysis examined the effect of excluding patients with less than 2 years diabetes duration, who may have not yet had opportunity to modify treatment and achieve targets and 2) examine the effect of centre type (community/primary and secondary care) or clustering by centre. Patients were excluded from a particular analysis when data relevant to that analysis were missing, but were not excluded from other analyses where appropriate information was provided. Missing data of variables was less than 10% and not imputed. A two-sided significance level of 0.05 was considered statistically significant. All analyses were performed using Stata software version 14.2 (StataCorp, Texas, USA).

2.5 Patient and Public Involvement

This research has been reviewed by the ANDA scientific advisory committee, which consists of clinical and public representatives with an interest in best practice diabetes health care.

3. Results

3.1 Overall

Data from 3,492 patients (>18 years of age) were analysed. Patients from all states and territories were included (Suppl.Table 1). Younger patients (<60 years) accounted for 38% (n=1,328) of patients. The clinical characteristics of these patients, stratified by age, are

shown in Table 1. The mean (±SD) age of the whole group was 62.9±12.5 years and the mean ages of the younger and older age groups were 50.1 ±8.4 years and 70.7 ±7.0 years respectively. Mean diabetes duration was 9.6±7.5 years for the younger age group and 15.9±9.6 years for the older age group (p<0.001). There was a higher proportion of male patients in the older (56.5%) compared with the younger age group (49.5%, p<0.001). The majority of patients (64.9%) were treated at tertiary hospitals followed by community or primary care centres (35.1%). Australian birth was reported by 68.1% of the younger age group and 62.4% of the older age group (p=0.001). Microvascular and macrovascular complications were prevalent in 35.3% and 21.6% of the younger age group and 49.3% and 43.4% of the older age group respectively (p<0.001 for both).

3.2 Glycaemic control

Mean HbA1c was 8.2±1.8% for the group overall, 8.6±2.1% and 8.0±1.6% for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had an HbA1c above 7.0% compared with the older age group (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking and BMI were all associated with an HbA1c above 7.0%. The unadjusted and adjusted odds ratios [95%CI] for HbA1c above 7.0% were 1.26 [1.07-1.49], p<0.001 and 1.50 [1.22-1.84], p<0.001 respectively for younger patients compared with older patients (Table 2, Figure 1).

Glycaemic management was reported as diet only by 4%, oral agents by 77%, non-insulin injectable therapy by 5% and insulin alone or in combination with oral agents by 61% of patients. Compared with older patients, younger patients were equally likely to not be on insulin treatment despite an HbA1c >8.0%, after adjusting for gender, diabetes duration, renal function and BMI (Suppl. Table 2).

3.3 Hypertension

Mean systolic blood pressure (BP) was 130±18 mmHg and 134±18 mmHg for the younger and older age groups respectively (p<0.001). A smaller proportion of patients in the younger age group were hypertensive compared with the older age group (Table 1, Figure 1). Younger patients were less likely to be hypertensive compared with older patients (unadjusted OR 0.81 [0.70-0.95] p =0.008). However, after adjusting for gender, smoking, renal function and BMI this effect was no longer significant (adjusted OR 0.85 [0.70-1.04], p = 0.119) (Table 2).

The overall study population prescribing and treatment gaps for hypertension were 5% and 25% respectively (Figure 2). Younger patients who were hypertensive were more likely to not be on blood pressure lowering medication (prescribing gap) than older patients who were hypertensive (adjusted OR 1.84 [1.16-2.92], p = 0.002) (Suppl. Table 2). There were no differences noted in the prescribing and treatment gaps for hypertension when male and female patients were considered separately (data not shown).

3.4 Dyslipidaemia

The majority of patients in both age groups had abnormal lipid profiles but a greater proportion of patients in the younger than older age group had dyslipidaemia (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking, BMI and HbA1c were associated with dyslipidaemia. The unadjusted and adjusted odds ratios [95%CI] for dyslipidaemia were 2.41 [1.91-3.03], p<0.001 and 2.02 [1.53-2.68], p<0.001 respectively for younger patients compared with older patients (Table 2).

The overall study population prescribing and treatment gaps for dyslipidaemia were 22% and 60% respectively (Figure 2). Younger patients with dyslipidaemia were more likely to not be on lipid lowering medication (prescribing gap) than older patients with dyslipidaemia after adjustment for diabetes duration, gender, smoking, renal function and vascular disease (adjusted OR 1.48 [1.15-1.90], p = 0.002) (Suppl. Table 2). There were no differences noted in the prescribing and treatment gaps for dyslipidaemia when male and female patients were considered separately (data not shown).

3.5 Obesity

Mean BMI was 34.5 ±8.4 kg/m^2 and 32.4 ±6.7 kg/m^2 for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had a BMI in the obese category (>30 kg/m^2) compared with the older age group (Table 1, Figure 2). On univariable analysis, age, gender and smoking were all associated with obesity. The unadjusted and adjusted odds ratios for obesity were 1.26 [1.09-1.46], p=0.002 and 1.25 [1.05-1.49], p=0.002 respectively for younger patients compared with older (Table 2).

3.6 Smoking

A greater proportion of patients in the younger age group reported being a current smoker compared with older patients (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, BMI and renal function were all associated with current smoking. The unadjusted and adjusted odds ratios for current smoking were 2.60 [2.09-3.22], p<0.001 and 2.13 [1.64-2.77], p<0.001 respectively for younger patients compared with older patients (Table 2).

3.7 Sensitivity analysis

When patients with diabetes duration of 2 years or less (who may have not yet had opportunity to modify treatment practices and achieve targets) were excluded the associations were unchanged. Younger patients were still more likely to have an HbA1c over 7.0% (adjusted OR 1.59 [1.27-2.00], p<0.001), dyslipidaemia (adjusted OR 1.89 [1.41-2.53], p<0.001), be obese (adjusted OR 1.28 [1.06-1.55], p=0.010) and smokers (adjusted OR 2.19 [1.64-2.92], p<0.001) than older patients after adjusting for diabetes duration, gender, renal function, BMI and HbA1c where appropriate (Suppl. Table 3). Furthermore, the associations were similar when we adjusted the models for centre type (Suppl. Table 4).

4. Discussion

In this large national cross-sectional study of community-living patients with type 2 diabetes, we found that younger patients with significantly shorter disease duration were less likely to achieve recommended targets for glycaemic control, blood pressure and lipids than older patients. Younger patients were also more likely to be obese and to smoke. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger rather than older patients were more likely to not be on therapy after adjustment for other relevant confounders. These findings remained after exclusion of patients with more recent diabetes onset who may have been relatively new to diabetes services and not yet had opportunity to attain treatment targets.

It is not clear why younger patients demonstrate poorer glycaemic control than older patients. Some evidence suggests that early-onset type 2 diabetes may be a more aggressive phenotype than later-onset type 2 diabetes, representing a greater predisposition to beta cell failure and diagnosis at an earlier age (16). Since younger patients had higher rates of obesity compared

with older patients, this may have contributed to worsening insulin resistance, and a need for greater intensification of therapy to achieve optimal glycaemic control. Longer duration of diabetes is also known to be associated with poorer glycaemic control, possibly due to progressive β-cell impairment and reduced insulin secretion (17), which in turn reduces the effectiveness of diet alone or oral agents. However, in our study the younger age group had a shorter diabetes duration than the older age group such that longer disease duration could not explain the poorer glycaemic control.

The high prevalence of poor glycaemic control and adverse cardiovascular risk factors observed in younger patients is of great concern as cardiovascular disease accounts for over half of the mortality among people with type 2 diabetes (18, 19). Given the risk for cardiovascular disease doubles when hypertension is also present in people with diabetes (20) and over a quarter of the patients in the younger age group had either systolic or diastolic hypertension, a review of the intensity of management is in order. This is supported by the larger prescribing and treatment gaps observed in the younger rather than older patients. In contrast, for older patients it is possible that clinicians' concerns regarding hypotension and postural symptoms due to autonomic neuropathy may appropriately limit antihypertensive use.

Although the absolute differences in the lipid variables were not large between the younger and older age groups, it is noteworthy that among younger patients and in line with other international studies, 89% had abnormal lipids (21). High density cholesterol levels, considered the best lipid predictor of cardiovascular disease (22), were significantly lower and triglyceride levels significantly higher in younger patients compared with older patients suggestive of inadequate lipid management. The relative insulin deficiency seen in type 2

diabetes is known to impair the action of lipoprotein lipase, resulting in lower HDL levels and higher triglyceride levels. However, the lower HDL and higher triglyceride observed in younger patients cannot be attributed solely to the effect of hyperglycaemia as younger age remained independently associated with dyslipidaemia when HbA1c was included in the multivariable model. Another possible explanation is survivor effect bias whereby patients with normal lipid levels have survived longer (and into the older age group) compared with those with dyslipidaemia.

It is recognised that estimates of absolute cardiovascular risk (even for those with diabetes) are driven predominantly by age rather than modifiable risk factors (23). Indeed, in our study the majority of patients in the younger age group would have low absolute cardiovascular risk despite significant risk factor burden. The Global Burden of Disease study reported that the maximum impact in terms of healthy life-years gained or disability adjusted life years averted with cardiovascular preventive therapies would be observed between 55-64 years (24). However, vascular complications develop over many decades from a young age (25), well before presentation with a potentially fatal event. Additionally, younger patients have higher modifiable risk (risk factors amenable to treatment) and longer future lifetime exposure for any particular absolute risk level when compared to older people. As highlighted by our findings, a major outstanding challenge is how best to implement use of evidence-based preventive therapies in younger patients and to effectively communicate risk of future events. Among newer approaches are the concepts of heart or vascular age (26) and of lifetime or modifiable risk, particularly in younger patients. This is consistent with the American College of Cardiology /American Heart Association (ACC/AHA) guidelines recommending assessment of lifetime risk in younger patients in addition to the traditional absolute risk assessment (27).

Other explanations for our findings include that younger patients may face more hurdles to glucose testing, regular physical activity, healthy diet, and medication adherence whereas older patients may access medical care more frequently, may be more motivated to manage their medical conditions and may be more compliant with diet and medications (28-30). Further research is required to understand the barriers to better glycaemic control and cardiovascular risk profiles faced by younger patients. These data are crucial to inform strategies to assist weight reduction, lifestyle modification and escalation of glycaemic, anti-hypertensive and lipid lowering therapies. Such measures would particularly benefit younger patients with type 2 diabetes, given that the incidence of macrovascular complications and mortality increases with diabetes duration (7) and is reduced with management of glycaemia and cardiovascular risk factors (18, 19). Good glycaemic control earlier in the course of diabetes may also be imperative, as this is demonstrated to reduce complications in the long term (31).

The proportion of patients with hypertension and dyslipidaemia in our study was similar to that reported in the population-based AusDiab study. However, the proportion of patients overall with an HbA1c target ≤7.0% was greater in our study than in the AusDiab study (32) and the community-based Fremantle Diabetes Study (8). In our study younger patients had poorer glycaemic control with a mean diabetes duration approximately half that of older patients. Higher HbA1c levels have previously been independently associated with younger age (8). In contrast, the Australian general practice based NEFRON study, found that younger and more obese patients with a longer duration of diabetes had poor glycaemic control (9). The differences in these studies may be due to the varying sampling frames and population characteristics.

Similar to other studies investigating gender differences in the management of type 2 diabetes, we found that female patients were more likely to report poorer glycaemic control and higher rates of obesity than males (33). However, contrary to other studies from Germany (34) and Italy (35), male and female patients appeared to experience similar prescribing and treatment gaps of hypertension and dyslipidaemia in Australia. This maybe due to due to cultural, behavioural, psychosocial and/or socio-economic differences between these countries affecting access to healthcare and uptake of preventive measures.

A strength of this analysis is the large dataset of patients from a nation-wide survey. Data were sourced from over half of the centres registered with the National Association of Diabetes centres (NADC) at the time. The participants of our study are likely to be similar to patients attending diabetes clinics throughout Australia. We obtained information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control. Study limitations include that the majority of patients were receiving care at tertiary diabetes centres and may largely represent a specialist referred patient group. Referral bias is also possible. General practitioners may be more likely to refer younger patients whilst managing older patients with shorter diabetes duration. Alternatively, older patients with longer diabetes duration and interrelating co-morbid conditions may also be more likely to be referred to specialist services. Another limitation was the reliance on self/healthcare worker reports as we were unable to independently verify diagnoses and treatments. This is unlikely to change the findings substantively, given previous studies have found approximately 90% of self-reported diabetes information to be valid (36). We were unable to conduct longitudinal analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.

5. Conclusion

In summary, younger patients with type 2 diabetes attending diabetes centres are burdened by poorer glycaemic control and cardiovascular risk factor profiles compared with older patients. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger patients were significantly more likely to not be on therapy or be above target despite treatment than older patients. Younger patients with diabetes may benefit from more targeted, evidence-based, multi-disciplinary initiatives to achieve and maintain intensive glycaemic control and optimise cardiovascular risk factors. Such measures may minimise the incidence and severity of diabetes related complications in younger patients with type 2 diabetes, thereby reducing morbidity and mortality.

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Authors' Contributions

NN: study design, literature review, statistical analysis, critical discussion, drafting and revision of the manuscript

AG: statistical analysis, critical discussion, revision of the manuscript

SR: statistical analysis and interpretation of the data, revision of the manuscript

WD: critical revision of the manuscript

JF: critical revision of the manuscript

NW: study conception and design, revision of the manuscript

SA: study conception and design, critical revision of the manuscript

SZ: study conception and design, design of analyses, critical revision of the manuscript, supervision of the project.

The authors NN, SR, and SZ had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors have read and approved the final manuscript.

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Data Sharing Statement

Application for datasets generated during and/or analysed during the current study may be considered by the corresponding author on reasonable request.

Competing interests

W. Davis reports past participation in advisory boards and/or receiving honoraria from Novo Nordisk and Eli Lilly Australia. N. Wischer reports past participation in advisory boards and/or receiving honoraria from AstraZeneca Pty Ltd/, Eli Lilly Australia, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk. S Andrikopoulos reports past participation in advisory boards and/or receiving honoraria from GlaxoSmithKline Pty Ltd, Novartis Pty Ltd, AstraZeneca Pty Ltd/Bristol-Myers Squibb Australia Pty Ltd, Eli Lilly Australia, Janssen Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk, Servier Laboratories Pty Ltd S Zoungas reports past participation in advisory boards/contract work on behalf of Monash University with AstraZeneca Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd and Novo Nordisk Pty Ltd. S Zoungas holds a NHMRC senior research fellowship.

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Tables and Figures

Table 1: Characteristics of study participants

Characteristic*	Age		p value
	<60 years n=1328	≥60 years n=2164	
Age to 2015 (years)	50.1 (8.4)	70.7 (7.0)	<0.001
Male	650 (49.5)	1208 (56.5)	<0.001
Age when diabetes first diagnosed (years)	40.6 (9.4)	54.9 (10.6)	<0.001
Diabetes duration (years)	9.6 (7.5)	15.9 (9.6)	<0.001
HbA1c (%)	8.6 (2.1)	8.0 (1.6)	<0.001
Cardiovascular risk factors			
Systolic blood pressure (mmHg)	130.5 (18.1)	134.1 (18.6)	<0.001
Diastolic blood pressure (mmHg)	77.7 (10.5)	72.6 (10.2)	<0.001
Current smoker	235 (20.2)	161 (8.9)	
Past smoker	350 (30.1)	713 (39.4)	<0.001
Never smoker	577 (49.7)	936 (51.7)	
Total cholesterol (mmol/l)	4.6 (1.3)	4.0 (1.1)	<0.001
LDL-cholesterol (mmol/l)	2.4 (1.6)	2.0 (0.9)	<0.001
HDL-cholesterol (mmol/l)	1.1 (0.4)	1.1 (0.4)	0.010
Triglyceride (mmol/l)	2.5 (2.4)	2.1 (1.7)	<0.001
Serum creatinine (µmol/l)	89.5 (91.7)	109.5 (91.3)	<0.001
eGFR ml/min/1.73m^2	89.3 (35.9)	65.9 (27.1)	<0.001
Body Mass Index (kg/m^2)	34.5 (8.4)	32.4 (6.7)	<0.001
Treatments			
Diet alone	65 (4.9)	77 (3.6)	0.052
Oral glucose lowering agents	1050 (79.1)	1634 (75.5)	0.013
Non-insulin injectable glucose lowering agents	94 (7.1)	98 (4.5)	0.003
Insulin	769 (57.9)	1348 (62.3)	0.010
Cardiovascular disease			
Microvascular complications	414 (35.3)	950 (49.3)	<0.001
Macrovascular complications	247 (21.6)	847 (43.4)	<0.001

* categorical variables were presented as n (%) and continuous variables as mean (SD) or median (IQR), as appropriate
# categorical variables were assessed with the Chi square test. Continuous variables were tested for normality, analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data
Microvascular complications defined as retinopathy, nephropathy or peripheral neuropathy
Macrovascular complications defined as either cardiovascular, cerebrovascular or peripheral vascular disease

Table 2: Unadjusted and adjusted odds of factors associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels.

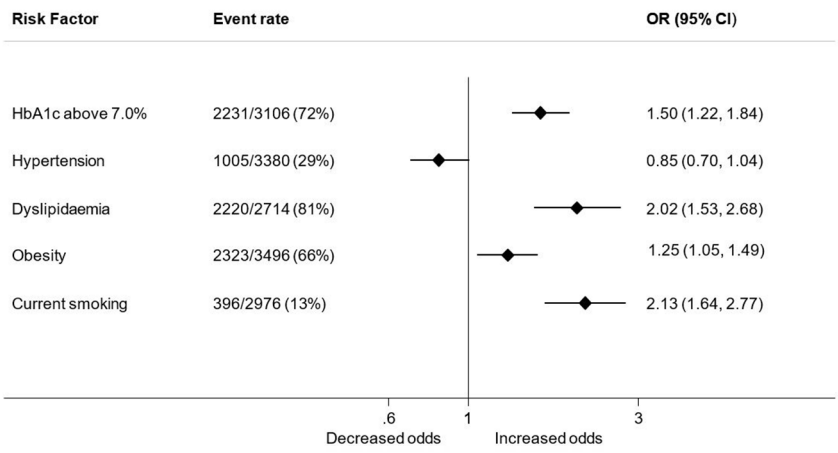
	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.26 (1.07-1.49)	0.005	1.50 (1.22-1.84)	<0.001	0.81 (0.70-0.95)	0.008	0.85 (0.70-1.04)	0.119	2.41 (1.91-3.03)	<0.001	2.02 (1.53-2.68)	<0.001	1.26 (1.09-1.46)	0.002	1.25 (1.05-1.49)	0.011	2.60 (2.09-3.22)	<0.001	2.13 (1.64-2.77)	<0.001
Duration of Diabetes																				
<10 y (ref)																				
≥10 y	2.05 (1.74-2.40)	<0.001	2.51 (2.07-3.03)	<0.001	1.16 (0.99-1.35)	0.067	1.03 (0.85-1.25)	0.735	0.66 (0.53-0.81)	<0.001	0.79 (0.60-1.03)	0.087	1.04 (0.90-1.20)	0.597			0.59 (0.48-0.73)	<0.001	0.82 (0.64-1.06)	0.124
Sex																				
Male (ref)																				
Female	1.18 (1.01-1.38)	0.039	1.16 (0.97-1.39)	0.100	1.02 (0.88-1.18)	0.828	0.87 (0.73-1.04)	0.129	0.76 (0.62-0.92)	0.005	0.70 (0.55-0.90)	0.005	1.34 (1.16-1.54)	<0.001	1.38 (1.16-1.63)	<0.001	0.70 (0.56-0.87)	0.001	0.70 (0.55-0.89)	0.004
Smoking																				
Never (ref)																				
Past	1.09 (0.9-1.32)	0.368			0.93 (0.79-1.10)	0.418	0.90 (0.74-1.09)	0.287	1.10 (0.87-1.38)	0.419	1.01 (0.77-1.32)	0.947	1.44 (1.22-1.71)	<0.001	1.63 (1.35-1.96)	<0.001				
Current	1.09 (0.84-1.42)	0.512			0.65 (0.50-0.84)	0.001	0.72 (0.54-0.96)	0.024	1.73 (1.18-2.52)	0.005	1.32 (0.87-1.99)	0.187	0.93 (0.74-1.17)	0.517	0.92 (0.72-1.18)	0.525				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (0.99-1.00)	0.073	1.00 (1.00-1.01)	0.034	1.00 (0.99-1.00)	0.001	1.00 (0.99-1.00)	0.008	1.00 (1.00-1.01)	0.144			1.00 (1.00-1.00)	0.307			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.001	1.02 (1.01-1.04)	0.004	1.02 (1.00-1.03)	0.077					0.98 (0.97-1.00)	0.017	0.97 (0.95-0.99)	0.001
HbA1c (%) (per unit)					1.03 (0.99-1.07)	0.156			1.18 (1.11-1.26)	<0.001	1.14 (1.05-1.23)	0.001	1.07 (1.03-1.12)	0.001	1.05 (1.00-1.10)	0.049				

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group

Figure 2: Blood pressure (i) and lipid management (ii) gaps in patients with type 2 diabetes

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group



The diamonds refer to the odds ratios for patients aged <60 years compared to the reference group of patients aged ≥60 years for each of the outcomes listed
Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
Obesity is defined as Body Mass Index >30 kg/m²

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group

111x68mm (300 x 300 DPI)

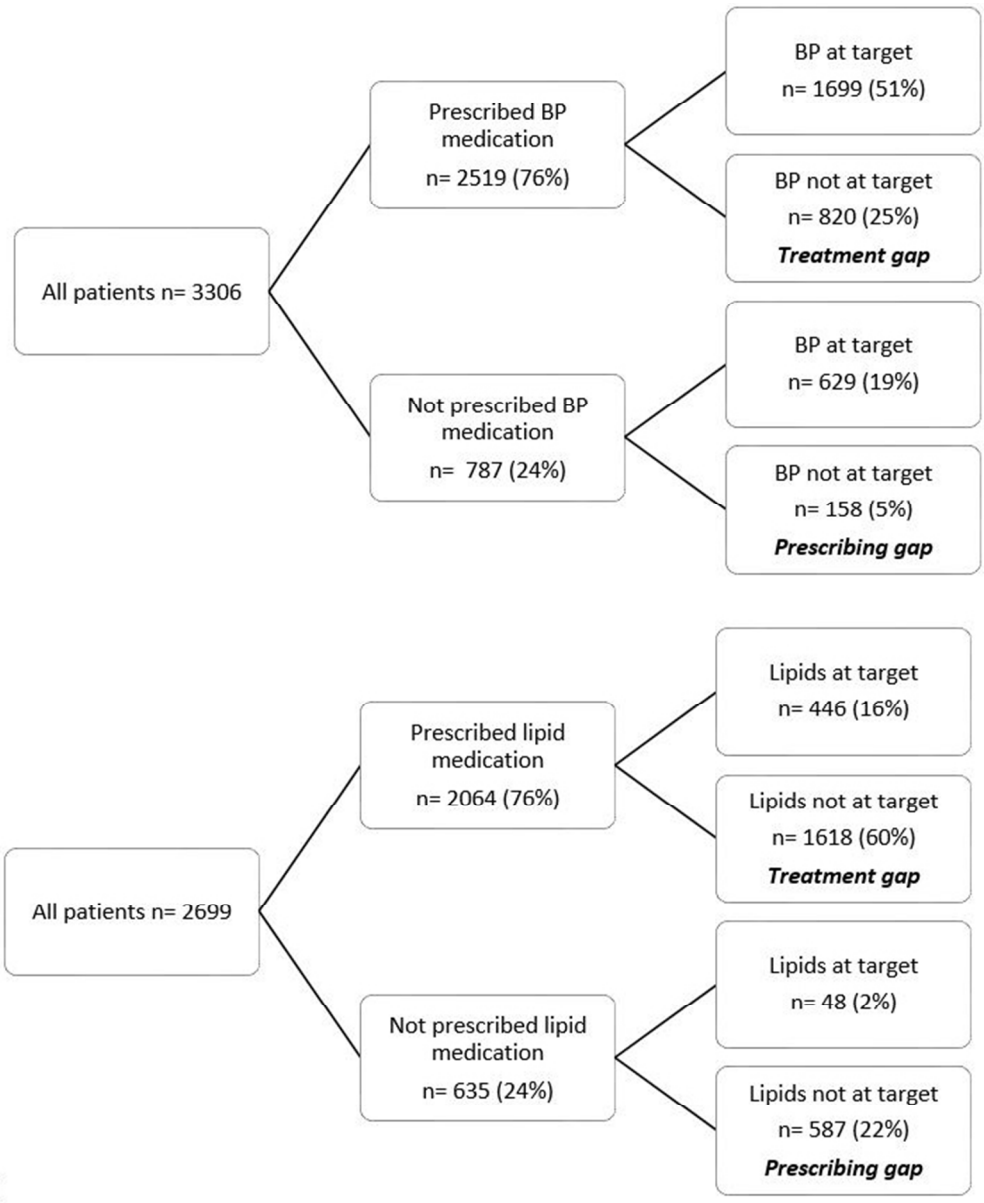


Figure 2: Blood pressure and lipid management gaps in patients with type 2 diabetes

59x72mm (300 x 300 DPI)

Supplementary Tables

Suppl. Table 1: Number of participating diabetes centres and patients by state or territory

State/Territory	Participating centres	Number of patients included
Australian Capital Territory	1	49
New South Wales	13	1246
Northern Territory	1	91
Queensland	9	758
South Australia	1	44
Tasmania	3	140
Victoria	20	1119
Western Australia	1	45
Total	49	3492

Suppl. Table 2: Unadjusted and adjusted odds of variables associated with prescribing gaps

	HbA1c > 8.0% and not on insulin				Hypertension and not on BP medication				Dyslipidaemia and not on lipid medication			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age (y)												
≥60 (ref)												
<60	1.23 (1.01-1.50)	0.041	0.80 (0.61-1.04)	0.090	2.71 (1.91-3.83)	<0.001	1.84 (1.16-2.92)	0.010	2.17 (1.79-2.63)	<0.001	1.48 (1.15-1.90)	0.002
Duration of Diabetes (y)												
<10 (ref)												
≥10	0.28 (0.23-0.35)	<0.001	0.28 (0.22-0.36)	<0.001	0.39 (0.28-0.56)	<0.001	0.46 (0.29-0.71)	0.001	0.41 (0.34-0.50)	<0.001	0.54 (0.42-0.69)	<0.001
Gender												
Male (ref)												
Female	0.89 (0.73-1.08)	0.239	0.87 (0.69-1.11)	0.260	0.96 (0.68-1.36)	0.818	0.97 (0.62-1.51)	0.888	1.37 (1.13-1.66)	0.001	1.19 (0.93-1.51)	0.160
Smoking												
Never (ref)												
Past	0.83 (0.66-1.05)	0.117			0.57 (0.38-0.86)	0.008	0.66 (0.41-1.09)	0.103	0.71 (0.57-0.90)	0.005	0.76 (0.59-0.99)	0.043
Current	0.97 (0.71-1.33)	0.861			1.57 (0.94-2.64)	0.087	1.40 (0.74-2.65)	0.301	1.06 (0.78-1.44)	0.711	1.03 (0.73-1.46)	0.856
eGFR (ml/min) (per unit)	1.01 (1.00-1.01)	0.001	1.00 (1.00-1.01)	0.049	1.02 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.014	1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.005
BMI (kg/m^2) (per unit)	0.98 (0.97-1.00)	0.021	0.98 (0.96-0.99)	0.004	0.98 (0.96-1.00)	0.100	0.95 (0.93-0.98)	0.001	0.99 (0.98-1.01)	0.238		
HbA1c (%) (per unit)					1.05 (0.95-1.16)	0.331			0.98 (0.93-1.04)	0.497		
Vascular disease												
No (ref)												
Yes					0.37 (0.26-0.53)	<0.001	0.48 (0.31-0.75)	0.001	0.36 (0.29-0.44)	<0.001	0.51 (0.40-0.66)	<0.001

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.5 mmol/L

Suppl. Table 3: Unadjusted and adjusted odds of variables associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels, excluding patients with diabetes duration ≤ 2 years.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.47 (1.22-1.77)	<0.001	1.59 (1.27-2.00)	<0.001	0.88 (0.74-1.04)	0.122	0.90 (0.72-1.12)	0.339	2.17 (1.71-2.76)	<0.001	1.89 (1.41-2.53)	<0.001	1.31 (1.11-1.54)	0.001	1.28 (1.06-1.55)	0.010	2.50 (1.96-3.17)	<0.001	2.19 (1.64-2.92	<0.001
Duration																				
<10 y (ref)																				
≥10 y	1.65 (1.37-1.98)	<0.001	2.05 (1.66-2.54)	<0.001	1.10 (0.92-1.31)	0.295			0.80 (0.63-1.01)	0.065	0.93 (0.70-1.25)	0.631	1.02 (0.86-1.21)	0.793			0.71 (0.55-0.92)	0.009	1.00 (0.75-1.35)	0.983
Sex																				
Male (ref)																				
Female	1.18 (0.99-1.40)	0.062	1.18 (0.97-1.44)	0.093	1.05 (0.90-1.23)	0.555	0.96 (0.78-1.17)	0.657	0.75 (0.61-0.92)	0.006	0.70 (0.54-0.90)	0.006	1.29 (1.11-1.50)	0.001	1.35 (1.12-1.62)	0.001	0.74 (0.58-0.94)	0.015	0.77 (0.59-1.01)	0.060
Smoking																				
Never (ref)																				
Past	1.08 (0.88-1.32)	0.484			0.92 (0.77-1.11)	0.387	0.97 (0.78-1.19)	0.748	1.08 (0.85-1.37)	0.539	0.97 (0.74-1.28)	0.853	1.51 (1.26-1.81)	0.001	1.69 (1.38-2.06)	<0.001				
Current	1.22 (0.89-1.66)	0.215			0.68 (0.51-0.90)	0.006	0.74 (0.53-1.02)	0.062	1.46 (0.99-2.17)	0.058	1.18 (0.77-1.81)	0.446	0.95 (0.74-1.23)	0.712	0.90 (0.69-1.19)	0.468				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (1.00-1.01)	0.002	1.00 (1.00-1.01)	0.014	1.00 (0.99-1.00)	0.005	1.00 (0.99-1.00)	0.011	1.00 (1.00-1.00)	0.655			1.00 (1.00-1.00)	0.175			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.009	1.02 (1.00-1.04)	0.013	1.02 (1.00-1.03)	0.097					0.98 (0.96-1.00)	0.016	0.96 (0.95-0.98)	<0.001
HbA1c (%) (per unit)					1.04 (1.00-1.09)	0.075	1.02 (0.97-1.08)	0.477	1.21 (1.12-1.29)	<0.001	1.14 (1.05-1.23)	0.002	1.09 (1.04-1.14)	0.001	1.05 (1.00-1.11)	0.040				

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

Suppl. Table 4: Unadjusted and adjusted odds of variables associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels, adjusted for diabetes centre type.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.26 (1.07-1.49)	0.005	1.51 (1.23-1.86)	*<0.001*	0.81 (0.70-0.95)	0.008	0.86 (0.70-1.05)	0.133	2.41 (1.91-3.03)	<0.001	2.05 (1.55-2.72)	*<0.001*	1.26 (1.09-1.46)	0.002	1.26 (1.06-1.50)	*0.009*	2.60 (2.09-3.22)	<0.001	2.09 (1.61-2.72)	*<0.001*
Duration of Diabetes																				
<10 y (ref)																				
≥10 y	2.05 (1.74-2.40)	<0.001	2.52 (2.08-3.05)	*<0.001*	1.16 (0.99-1.35)	0.067	1.04 (0.86-1.26)	0.702	0.66 (0.53-0.81)	<0.001	0.80 (0.61-1.05)	0.115	1.04 (0.90-1.20)	0.591			0.59 (0.48-0.73)	<0.001	0.81 (0.63-1.04)	0.099
Sex																				
Male (ref)																				
Female	1.18 (1.01-1.38)	0.039	1.15 (0.96-1.38)	0.119	1.02 (0.88-1.18)	0.828	0.87 (0.72-1.04)	0.121	0.76 (0.62-0.92)	0.005	0.70 (0.55-0.90)	*0.005*	1.34 (1.16-1.54)	<0.001	1.37 (1.16-1.63)	*<0.001*	0.70 (0.56-0.87)	0.001	0.71 (0.55-0.90)	*0.005*
Smoking																				
Never (ref)																				
Past	1.09 (0.9-1.32)	0.368			0.93 (0.79-1.10)	0.418	0.90 (0.74-1.09)	0.281	1.10 (0.87-1.38)	0.419	1.01 (0.78-1.32)	0.920	1.44 (1.22-1.71)	<0.001	1.63 (1.35-1.97)	*<0.001*				
Current	1.09 (0.84-1.42)	0.512			0.65 (0.50-0.84)	0.001	0.72 (0.54-0.96)	*0.025*	1.73 (1.18-2.52)	0.005	1.34 (0.89-2.02)	0.164	0.93 (0.74-1.17)	0.517	0.93 (0.73-1.19)	0.562				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (0.99-1.00)	0.073	1.00 (1.00-1.01)	*0.040*	1.00 (0.99-1.00)	0.001	1.00 (0.99-1.00)	*0.007*	1.00 (1.00-1.01)	0.144			1.00 (1.00-1.00)	0.301			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	*0.001*
BMI (kg/m^2) (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	*<0.001*	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	*0.001*	1.02 (1.01-1.04)	0.004	1.02 (1.00-1.03)	0.088					0.98 (0.97-1.00)	0.017	0.97 (0.96-0.99)	*0.001*
HbA1c (%) (per unit)					1.03 (0.99-1.07)	0.156			1.18 (1.11-1.26)	<0.001	1.13 (1.05-1.22)	*0.001*	1.07 (1.03-1.12)	0.002	1.05 (1.00-1.09)	0.054				
Centre type^	1.06 (0.83-1.36)	0.617	1.25 (0.94-1.67)	0.122	1.18 (0.96-1.45)	0.115	1.07 (0.85-1.35)	0.576	1.04 (0.79-1.36)	0.802	1.25 (0.88-1.78)	0.203	1.15 (0.94-1.41)	0.186	1.18 (0.93-1.50)	0.170	0.17 (0.15-0.18)	*<0.001*	0.75 (0.53-1.07)	0.113

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2
^ Tertiary care centres (reference group) compared with primary and secondary care centres

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Age related differences in glycaemic control, cardiovascular disease risk factors and treatment in patients with type 2 diabetes: a cross-sectional study from the Australian National Diabetes Audit

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Abstract

Objective: To compare the glycaemic control and cardiovascular risk factor profiles of younger and older patients with type 2 diabetes. Cross-sectional analysis of data from the 2015 Australian National Diabetes Audit (ANDA) was undertaken.

Methods: Data were obtained from adults with type 2 diabetes presenting to Australian secondary/tertiary diabetes centres. Logistic regression examined associations with HbA1c >7% (53 mmol/mol) and cardiovascular risk factors.

Results: Data from 3,492 patients were analysed. Mean (±SD) age was 62.9±12.5 years, mean diabetes duration 13.5±9.4 years and mean HbA1c 8.2±1.8%. Mean HbA1c was 8.6±2.1% and 8.0±1.6% for the younger (<60 years) and older subgroups (≥60 years) respectively (p<0.001). The odds (aOR) of HbA1c above >7.0% was 1.5 times higher (95%CI 1.22-1.84) for younger patients compared with older patients after adjustment for gender, smoking, diabetes duration, renal function and body mass index. Younger patients were also more likely to have dyslipidaemia (aOR 2.02 [1.53-2.68], p<0.001), be obese (aOR 1.25 [1.05-1.49)], p<0.001) and be current smokers (aOR 2.13 [1.64-2.77], p<0.001) than older patients.

Conclusions: Younger age was associated with poorer glycaemic control and adverse cardiovascular risk factor profiles. It is imperative to optimise and monitor treatment in order to improve long-term outcomes.

Strengths and limitations of this study:

- large dataset of patients from a nation-wide survey
- information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control

- We were unable to conduct longitudinal analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.
- Study population may largely represent a specialist referred patient group as the majority of patients were receiving care at tertiary diabetes centres

1. Introduction

Driven by ageing populations, increasing obesity and decreasing physical activity, the prevalence of diabetes is expected to rise by 55% to 592 million individuals worldwide by 2035(1). Traditionally a disease of middle and older age, type 2 diabetes is increasingly diagnosed in younger patients (2, 3). Diabetes and its complications contribute to 10% of Australian deaths (4) and 8.4 % of deaths worldwide (5).

The US National Health and Nutrition Examination Survey (NHANES) indicated that the prevalence of type 2 diabetes has increased by 70% in people aged 20-44 years in the last three decades, making younger adults the fastest growing group of people with type 2 diabetes (6). Diabetes complications are related to duration and degree of glycaemic control (7), thus younger people with diabetes who start their hyperglycaemic exposure at an earlier age may be at highest risk for end-organ damage. However, few studies have compared glycaemic control in younger and older patients with type 2 diabetes (8, 9). Further, these studies were largely conducted within selected trial cohorts (and as such the patients examined may differ from community based cohorts) and have reported variable findings of better glycaemic control in older patients (10), in younger patients (11) or no effect of age (12).

We hypothesised that there may be age-related differences in the management of patients with type 2 diabetes, which may contribute to excess cardiovascular risk in younger patients. This study investigates differences in the achieved levels and management of (1) glycaemic control and (2) cardiovascular risk factors between younger and older patients with type 2 diabetes.

2.Methods

2.1Participants

This national, cross-sectional study examined de-identified data from the 2015 Australian National Diabetes Audit (ANDA) (13). Participants were adult patients with type 2 diabetes, presenting to one of 49 nationally accredited diabetes centres. De-identified data were sourced from a range of diabetes centres located in the community/primary care (n=16) and secondary care (n=33), with patients under the care of endocrinologists, general specialists and local general practitioners. The state and territory location of participating sites is presented in Supplementary Data. Information was collected regarding all consecutive patients attending a participating diabetes centre during the one-month survey period (May or June 2015). The Australian National Diabetes Audit has received approval from the Monash Health Human Research Ethics Committee.

2.2 Variables

Pre-specified demographic (gender, date of birth) and clinical variables (diabetes complications, comorbid conditions, blood pressure (BP), glycated haemoglobin A1c (HbA1c), body mass index (BMI), smoking status, medications) were collected for patients with type 2 diabetes. Health professionals from participating centres examined patients, reviewed medical records including pathology results and recorded the information in a standardised data collection form. All missing data, invalid entries and discrepancies were clarified with the patients' treating centres. As per the a priori analysis plan, age at survey was calculated as date of survey (2015) minus date of birth and categorised as <60 years or ≥60 years, diabetes duration was calculated as date of survey minus date of diabetes diagnosis and categorised as <10 years or ≥10 years. Height and weight were measured to calculate BMI. Smoking status was categorised as never, previous or current. Recent

pathology results (within the last 12 months) were recorded for total cholesterol (TC), low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TG), HbA1c and serum creatinine; calculated estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease Study (MDRD) equation (14).

2.3 Outcomes

The main outcome variables were HbA1c (categorised as >7.0%, 53 mmol/mol), hypertension (defined as >140 and/or 90 mmHg), dyslipidaemia (defined as either TC>4.0 mmol/L, HDL<1.0 mmol/L, LDL>2.0 mmol/L or Tg>2.0 mmol/L), obesity (defined as BMI>30 kg/m^2) and smoker (categorised as never, past or current). The targets were based on the current Australian recommendations for people with diabetes as per the Australian Heart Foundation (15).

2.4 Statistical analysis

Categorical variables were summarised as percentages and differences between subgroups analysed using χ^2 test. Continuous variables were tested for normality to determine the most appropriate method for statistical analysis (parametric or non-parametric) and reported as means with standard deviations (SD) or as medians with interquartile ranges (IQR). Subgroup analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data as appropriate. Logistic regression was used to examine factors (current age, diabetes duration, gender, smoking, calculated eGFR, BMI) associated with HbA1c, hypertension, dyslipidaemia and obesity (as the categories defined above). The selection of variables was based on identifying all measured clinical variables of known or suspected prognostic importance for the outcomes of interest and/or exhibiting a p

value ≤0.10 on univariable analysis. All potential confounding variables were included in the multivariable models. Subgroup analyses were conducted to examine the effect of treatments (yes or no) including insulin, antihypertensive therapy and lipid lowering therapy in patients above the glycaemic, lipid and BP targets. A prescribing gap was defined as patients who were not prescribed the relevant medications despite being above the recommended targets. A treatment gap was defined as patients who were above the recommended targets despite being on treatment. A sensitivity analysis examined the effect of excluding patients with less than 2 years diabetes duration, who may have not yet had opportunity to modify treatment and achieve targets and 2) examine the effect of centre type (community/primary and secondary care) or clustering by centre. Patients were excluded from a particular analysis when data relevant to that analysis were missing, but were not excluded from other analyses where appropriate information was provided. Missing data of variables was less than 10% and not imputed. A two-sided significance level of 0.05 was considered statistically significant. All analyses were performed using Stata software version 14.2 (StataCorp, Texas, USA).

2.5 Patient and Public Involvement

This research has been reviewed by the ANDA scientific advisory committee, which consists of clinical and public representatives with an interest in best practice diabetes health care.

3. Results

3.1 Overall

Data from 3,492 patients (>18 years of age) were analysed. Patients from all states and territories were included (Suppl.Table 1). Younger patients (<60 years) accounted for 38% (n=1,328) of patients. The clinical characteristics of these patients, stratified by age, are

shown in Table 1. The mean (±SD) age of the whole group was 62.9±12.5 years and the mean ages of the younger and older age groups were 50.1 ±8.4 years and 70.7 ±7.0 years respectively. Mean diabetes duration was 9.6±7.5 years for the younger age group and 15.9±9.6 years for the older age group (p<0.001). There was a higher proportion of male patients in the older (56.5%) compared with the younger age group (49.5%, p<0.001). The majority of patients (64.9%) were treated at tertiary hospitals followed by community or primary care centres (35.1%). Australian birth was reported by 68.1% of the younger age group and 62.4% of the older age group (p=0.001). Microvascular and macrovascular complications were prevalent in 35.3% and 21.6% of the younger age group and 49.3% and 43.4% of the older age group respectively (p<0.001 for both).

3.2 Glycaemic control

Mean HbA1c was 8.2±1.8% for the group overall, 8.6±2.1% and 8.0±1.6% for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had an HbA1c above 7.0% compared with the older age group (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking and BMI were all associated with an HbA1c above 7.0%. The unadjusted and adjusted odds ratios [95%CI] for HbA1c above 7.0% were 1.26 [1.07-1.49], p<0.001 and 1.50 [1.22-1.84], p<0.001 respectively for younger patients compared with older patients (Table 2, Figure 1).

Glycaemic management was reported as diet only by 4%, oral agents by 77%, non-insulin injectable therapy by 5% and insulin alone or in combination with oral agents by 61% of patients. Compared with older patients, younger patients were equally likely to not be on insulin treatment despite an HbA1c >8.0%, after adjusting for gender, diabetes duration, renal function and BMI (Suppl. Table 2).

3.3 Hypertension

Mean systolic blood pressure (BP) was 130±18 mmHg and 134±18 mmHg for the younger and older age groups respectively (p<0.001). A smaller proportion of patients in the younger age group were hypertensive compared with the older age group (Table 1, Figure 1). Younger patients were less likely to be hypertensive compared with older patients (unadjusted OR 0.81 [0.70-0.95] p =0.008). However, after adjusting for gender, smoking, renal function and BMI this effect was no longer significant (adjusted OR 0.85 [0.70-1.04], p = 0.119) (Table 2).

The overall study population prescribing and treatment gaps for hypertension were 5% and 25% respectively (Figure 2). Younger patients who were hypertensive were more likely to not be on blood pressure lowering medication (prescribing gap) than older patients who were hypertensive (adjusted OR 1.84 [1.16-2.92], p = 0.002) (Suppl. Table 2). There were no differences noted in the prescribing and treatment gaps for hypertension when male and female patients were considered separately (data not shown).

3.4 Dyslipidaemia

The majority of patients in both age groups had abnormal lipid profiles but a greater proportion of patients in the younger than older age group had dyslipidaemia (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, smoking, BMI and HbA1c were associated with dyslipidaemia. The unadjusted and adjusted odds ratios [95%CI] for dyslipidaemia were 2.41 [1.91-3.03], p<0.001 and 2.02 [1.53-2.68], p<0.001 respectively for younger patients compared with older patients (Table 2).

The overall study population prescribing and treatment gaps for dyslipidaemia were 22% and 60% respectively (Figure 2). Younger patients with dyslipidaemia were more likely to not be on lipid lowering medication (prescribing gap) than older patients with dyslipidaemia after adjustment for diabetes duration, gender, smoking, renal function and vascular disease (adjusted OR 1.48 [1.15-1.90], p = 0.002) (Suppl. Table 2). There were no differences noted in the prescribing and treatment gaps for dyslipidaemia when male and female patients were considered separately (data not shown).

3.5 Obesity

Mean BMI was 34.5 ±8.4 kg/m^2 and 32.4 ±6.7 kg/m^2 for the younger and older age groups respectively (p<0.001). A greater proportion of patients in the younger age group had a BMI in the obese category (>30 kg/m^2) compared with the older age group (Table 1, Figure 2). On univariable analysis, age, gender and smoking were all associated with obesity. The unadjusted and adjusted odds ratios for obesity were 1.26 [1.09-1.46], p=0.002 and 1.25 [1.05-1.49], p=0.002 respectively for younger patients compared with older (Table 2).

3.6 Smoking

A greater proportion of patients in the younger age group reported being a current smoker compared with older patients (Table 1, Figure 1). On univariable analysis, age, diabetes duration, gender, BMI and renal function were all associated with current smoking. The unadjusted and adjusted odds ratios for current smoking were 2.60 [2.09-3.22], p<0.001 and 2.13 [1.64-2.77], p<0.001 respectively for younger patients compared with older patients (Table 2).

3.7 Sensitivity analysis

When patients with diabetes duration of 2 years or less (who may have not yet had opportunity to modify treatment practices and achieve targets) were excluded the associations were unchanged. Younger patients were still more likely to have an HbA1c over 7.0% (adjusted OR 1.59 [1.27-2.00], p<0.001), dyslipidaemia (adjusted OR 1.89 [1.41-2.53], p<0.001), be obese (adjusted OR 1.28 [1.06-1.55], p=0.010) and smokers (adjusted OR 2.19 [1.64-2.92], p<0.001) than older patients after adjusting for diabetes duration, gender, renal function, BMI and HbA1c where appropriate (Suppl. Table 3). Furthermore, the associations were similar when we adjusted the models for centre type (Suppl. Table 4).

4. Discussion

In this large national cross-sectional study of community-living patients with type 2 diabetes, we found that younger patients with significantly shorter disease duration were less likely to achieve recommended targets for glycaemic control, blood pressure and lipids than older patients. Younger patients were also more likely to be obese and to smoke. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger rather than older patients were more likely to not be on therapy after adjustment for other relevant confounders. These findings remained after exclusion of patients with more recent diabetes onset who may have been relatively new to diabetes services and not yet had opportunity to attain treatment targets.

It is not clear why younger patients demonstrate poorer glycaemic control than older patients. Some evidence suggests that early-onset type 2 diabetes may be a more aggressive phenotype than later-onset type 2 diabetes, representing a greater predisposition to beta cell failure and diagnosis at an earlier age (16). Since younger patients had higher rates of obesity compared

with older patients, this may have contributed to worsening insulin resistance, and a need for greater intensification of therapy to achieve optimal glycaemic control. Longer duration of diabetes is also known to be associated with poorer glycaemic control, possibly due to progressive β-cell impairment and reduced insulin secretion (17), which in turn reduces the effectiveness of diet alone or oral agents. However, in our study the younger age group had a shorter diabetes duration than the older age group such that longer disease duration could not explain the poorer glycaemic control.

The high prevalence of poor glycaemic control and adverse cardiovascular risk factors observed in younger patients is of great concern as cardiovascular disease accounts for over half of the mortality among people with type 2 diabetes (18, 19). Given the risk for cardiovascular disease doubles when hypertension is also present in people with diabetes (20) and over a quarter of the patients in the younger age group had either systolic or diastolic hypertension, a review of the intensity of management is in order. This is supported by the larger prescribing and treatment gaps observed in the younger rather than older patients. In contrast, for older patients it is possible that clinicians' concerns regarding hypotension and postural symptoms due to autonomic neuropathy may appropriately limit antihypertensive use.

Although the absolute differences in the lipid variables were not large between the younger and older age groups, it is noteworthy that among younger patients and in line with other international studies, 89% had abnormal lipids (21). High density cholesterol levels, considered the best lipid predictor of cardiovascular disease (22), were significantly lower and triglyceride levels significantly higher in younger patients compared with older patients suggestive of inadequate lipid management. The relative insulin deficiency seen in type 2

diabetes is known to impair the action of lipoprotein lipase, resulting in lower HDL levels and higher triglyceride levels. However, the lower HDL and higher triglyceride observed in younger patients cannot be attributed solely to the effect of hyperglycaemia as younger age remained independently associated with dyslipidaemia when HbA1c was included in the multivariable model. Another possible explanation is survivor effect bias whereby patients with normal lipid levels have survived longer (and into the older age group) compared with those with dyslipidaemia.

It is recognised that estimates of absolute cardiovascular risk (even for those with diabetes) are driven predominantly by age rather than modifiable risk factors (23). Indeed, in our study the majority of patients in the younger age group would have low absolute cardiovascular risk despite significant risk factor burden. The Global Burden of Disease study reported that the maximum impact in terms of healthy life-years gained or disability adjusted life years averted with cardiovascular preventive therapies would be observed between 55-64 years (24). However, vascular complications develop over many decades from a young age (25), well before presentation with a potentially fatal event. Additionally, younger patients have higher modifiable risk (risk factors amenable to treatment) and longer future lifetime exposure for any particular absolute risk level when compared to older people. As highlighted by our findings, a major outstanding challenge is how best to implement use of evidence-based preventive therapies in younger patients and to effectively communicate risk of future events. Among newer approaches are the concepts of heart or vascular age (26) and of lifetime or modifiable risk, particularly in younger patients. This is consistent with the American College of Cardiology /American Heart Association (ACC/AHA) guidelines recommending assessment of lifetime risk in younger patients in addition to the traditional absolute risk assessment (27).

Other explanations for our findings include that younger patients may face more hurdles to glucose testing, regular physical activity, healthy diet, and medication adherence whereas older patients may access medical care more frequently, may be more motivated to manage their medical conditions and may be more compliant with diet and medications (28-30). Further research is required to understand the barriers to better glycaemic control and cardiovascular risk profiles faced by younger patients. These data are crucial to inform strategies to assist weight reduction, lifestyle modification and escalation of glycaemic, anti-hypertensive and lipid lowering therapies. Such measures would particularly benefit younger patients with type 2 diabetes, given that the incidence of macrovascular complications and mortality increases with diabetes duration (7) and is reduced with management of glycaemia and cardiovascular risk factors (18, 19). Good glycaemic control earlier in the course of diabetes may also be imperative, as this is demonstrated to reduce complications in the long term (31).

The proportion of patients with hypertension and dyslipidaemia in our study was similar to that reported in the population-based AusDiab study. However, the proportion of patients overall with an HbA1c target ≤7.0% was greater in our study than in the AusDiab study (32) and the community-based Fremantle Diabetes Study (8). In our study younger patients had poorer glycaemic control with a mean diabetes duration approximately half that of older patients. Higher HbA1c levels have previously been independently associated with younger age (8). In contrast, the Australian general practice based NEFRON study, found that younger and more obese patients with a longer duration of diabetes had poor glycaemic control (9). The differences in these studies may be due to the varying sampling frames and population characteristics.

Similar to other studies investigating gender differences in the management of type 2 diabetes, we found that female patients were more likely to report poorer glycaemic control and higher rates of obesity than males (33). However, contrary to other studies from Germany (34) and Italy (35), male and female patients appeared to experience similar prescribing and treatment gaps of hypertension and dyslipidaemia in Australia. This maybe due to due to cultural, behavioural, psychosocial and/or socio-economic differences between these countries affecting access to healthcare and uptake of preventive measures.

A strength of this analysis is the large dataset of patients from a nation-wide survey. Data were sourced from over half of the centres registered with the National Association of Diabetes centres (NADC) at the time. The participants of our study are likely to be similar to patients attending diabetes clinics throughout Australia. We obtained information on a broad range of variables with potential impact on glycaemic, blood pressure and lipid control. Study limitations include that the majority of patients were receiving care at tertiary diabetes centres and may largely represent a specialist referred patient group. Referral bias is also possible. General practitioners may be more likely to refer younger patients whilst managing older patients with shorter diabetes duration. Alternatively, older patients with longer diabetes duration and interrelating co-morbid conditions may also be more likely to be referred to specialist services. Another limitation was the reliance on self/healthcare worker reports as we were unable to independently verify diagnoses and treatments. This is unlikely to change the findings substantively, given previous studies have found approximately 90% of self-reported diabetes information to be valid (36). We were unable to conduct longitudinal analyses as the data were de-identified and the cross-sectional nature of the analysis precluded investigation of causality.

5. Conclusion

In summary, younger patients with type 2 diabetes attending diabetes centres are burdened by poorer glycaemic control and cardiovascular risk factor profiles compared with older patients. Of patients not achieving glycaemic, blood pressure, and lipid targets, younger patients were significantly more likely to not be on therapy or be above target despite treatment than older patients. Younger patients with diabetes may benefit from more targeted, evidence-based, multi-disciplinary initiatives to achieve and maintain intensive glycaemic control and optimise cardiovascular risk factors. Such measures may minimise the incidence and severity of diabetes related complications in younger patients with type 2 diabetes, thereby reducing morbidity and mortality.

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Authors' Contributions

NN: study design, literature review, statistical analysis, critical discussion, drafting and revision of the manuscript

AG: statistical analysis, critical discussion, revision of the manuscript

SR: statistical analysis and interpretation of the data, revision of the manuscript

WD: critical revision of the manuscript

JF: critical revision of the manuscript

NW: study conception and design, revision of the manuscript

SA: study conception and design, critical revision of the manuscript

SZ: study conception and design, design of analyses, critical revision of the manuscript, supervision of the project.

The authors NN, SR, and SZ had full access to the data and take responsibility for the integrity of the data and accuracy of the analysis. All authors have read and approved the final manuscript.

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Data Sharing Statement

Application for datasets generated during and/or analysed during the current study may be considered by the corresponding author on reasonable request.

Competing interests

W. Davis reports past participation in advisory boards and/or receiving honoraria from Novo Nordisk and Eli Lilly Australia. N. Wischer reports past participation in advisory boards and/or receiving honoraria from AstraZeneca Pty Ltd/, Eli Lilly Australia, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk. S Andrikopoulos reports past participation in advisory boards and/or receiving honoraria from GlaxoSmithKline Pty Ltd, Novartis Pty Ltd, AstraZeneca Pty Ltd/Bristol-Myers Squibb Australia Pty Ltd, Eli Lilly Australia, Janssen Cilag Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd, Sanofi Aventis Pty Ltd, Novo Nordisk, Servier Laboratories Pty Ltd S Zoungas reports past participation in advisory boards/contract work on behalf of Monash University with AstraZeneca Pty Ltd, Merck Sharp & Dohme (Australia) Pty Ltd and Novo Nordisk Pty Ltd. S Zoungas holds a NHMRC senior research fellowship.

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Tables and Figures

Table 1: Characteristics of study participants

Characteristic*	Age		p value
	<60 years n=1328	≥60 years n=2164	
Age to 2015 (years)	50.1 (8.4)	70.7 (7.0)	<0.001
Male	650 (49.5)	1208 (56.5)	<0.001
Age when diabetes first diagnosed (years)	40.6 (9.4)	54.9 (10.6)	<0.001
Diabetes duration (years)	9.6 (7.5)	15.9 (9.6)	<0.001
HbA1c (%)	8.6 (2.1)	8.0 (1.6)	<0.001
Cardiovascular risk factors			
Systolic blood pressure (mmHg)	130.5 (18.1)	134.1 (18.6)	<0.001
Diastolic blood pressure (mmHg)	77.7 (10.5)	72.6 (10.2)	<0.001
Current smoker	235 (20.2)	161 (8.9)	
Past smoker	350 (30.1)	713 (39.4)	<0.001
Never smoker	577 (49.7)	936 (51.7)	
Total cholesterol (mmol/l)	4.6 (1.3)	4.0 (1.1)	<0.001
LDL-cholesterol (mmol/l)	2.4 (1.6)	2.0 (0.9)	<0.001
HDL-cholesterol (mmol/l)	1.1 (0.4)	1.1 (0.4)	0.010
Triglyceride (mmol/l)	2.5 (2.4)	2.1 (1.7)	<0.001
Serum creatinine (µmol/l)	89.5 (91.7)	109.5 (91.3)	<0.001
eGFR ml/min/1.73m^2	89.3 (35.9)	65.9 (27.1)	<0.001
Body Mass Index (kg/m^2)	34.5 (8.4)	32.4 (6.7)	<0.001
Treatments			
Diet alone	65 (4.9)	77 (3.6)	0.052
Oral glucose lowering agents	1050 (79.1)	1634 (75.5)	0.013
Non-insulin injectable glucose lowering agents	94 (7.1)	98 (4.5)	0.003
Insulin	769 (57.9)	1348 (62.3)	0.010
Cardiovascular disease			
Microvascular complications	414 (35.3)	950 (49.3)	<0.001
Macrovascular complications	247 (21.6)	847 (43.4)	<0.001

* categorical variables were presented as n (%) and continuous variables as mean (SD) or median (IQR), as appropriate
# categorical variables were assessed with the Chi square test. Continuous variables were tested for normality, analyses were performed using ANOVA for normally distributed data and Mann-Whitney U tests for non-normally distributed data
Microvascular complications defined as retinopathy, nephropathy or peripheral neuropathy
Macrovascular complications defined as either cardiovascular, cerebrovascular or peripheral vascular disease

Table 2: Unadjusted and adjusted odds of factors associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels.

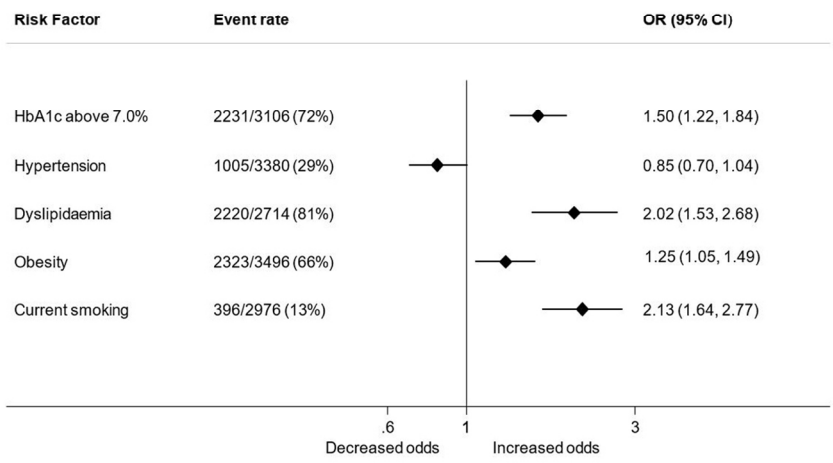
	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.26 (1.07-1.49)	0.005	1.50 (1.22-1.84)	<0.001	0.81 (0.70-0.95)	0.008	0.85 (0.70-1.04)	0.119	2.41 (1.91-3.03)	<0.001	2.02 (1.53-2.68)	<0.001	1.26 (1.09-1.46)	0.002	1.25 (1.05-1.49)	0.011	2.60 (2.09-3.22)	<0.001	2.13 (1.64-2.77)	<0.001
Duration of Diabetes																				
<10 y (ref)																				
≥10 y	2.05 (1.74-2.40)	<0.001	2.51 (2.07-3.03)	<0.001	1.16 (0.99-1.35)	0.067	1.03 (0.85-1.25)	0.735	0.66 (0.53-0.81)	<0.001	0.79 (0.60-1.03)	0.087	1.04 (0.90-1.20)	0.597			0.59 (0.48-0.73)	<0.001	0.82 (0.64-1.06)	0.124
Sex																				
Male (ref)																				
Female	1.18 (1.01-1.38)	0.039	1.16 (0.97-1.39)	0.100	1.02 (0.88-1.18)	0.828	0.87 (0.73-1.04)	0.129	0.76 (0.62-0.92)	0.005	0.70 (0.55-0.90)	0.005	1.34 (1.16-1.54)	<0.001	1.38 (1.16-1.63)	<0.001	0.70 (0.56-0.87)	0.001	0.70 (0.55-0.89)	0.004
Smoking																				
Never (ref)																				
Past	1.09 (0.9-1.32)	0.368			0.93 (0.79-1.10)	0.418	0.90 (0.74-1.09)	0.287	1.10 (0.87-1.38)	0.419	1.01 (0.77-1.32)	0.947	1.44 (1.22-1.71)	<0.001	1.63 (1.35-1.96)	<0.001				
Current	1.09 (0.84-1.42)	0.512			0.65 (0.50-0.84)	0.001	0.72 (0.54-0.96)	0.024	1.73 (1.18-2.52)	0.005	1.32 (0.87-1.99)	0.187	0.93 (0.74-1.17)	0.517	0.92 (0.72-1.18)	0.525				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (0.99-1.00)	0.073	1.00 (1.00-1.01)	0.034	1.00 (0.99-1.00)	0.001	1.00 (0.99-1.00)	0.008	1.00 (1.00-1.01)	0.144			1.00 (1.00-1.00)	0.307			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	0.001	1.02 (1.01-1.04)	0.004	1.02 (1.00-1.03)	0.077					0.98 (0.97-1.00)	0.017	0.97 (0.95-0.99)	0.001
HbA1c (%) (per unit)					1.03 (0.99-1.07)	0.156			1.18 (1.11-1.26)	<0.001	1.14 (1.05-1.23)	0.001	1.07 (1.03-1.12)	0.001	1.05 (1.00-1.10)	0.049				

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group

Figure 2: Blood pressure (i) and lipid management (ii) gaps in patients with type 2 diabetes

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group



The diamonds refer to the odds ratios for patients aged <60 years compared to the reference group of patients aged ≥60 years for each of the outcomes listed
Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
Obesity is defined as Body Mass Index >30 kg/m²

Figure 1: Risks of adverse cardiovascular risk factor levels in patients with type 2 diabetes by age group

116x76mm (300 x 300 DPI)

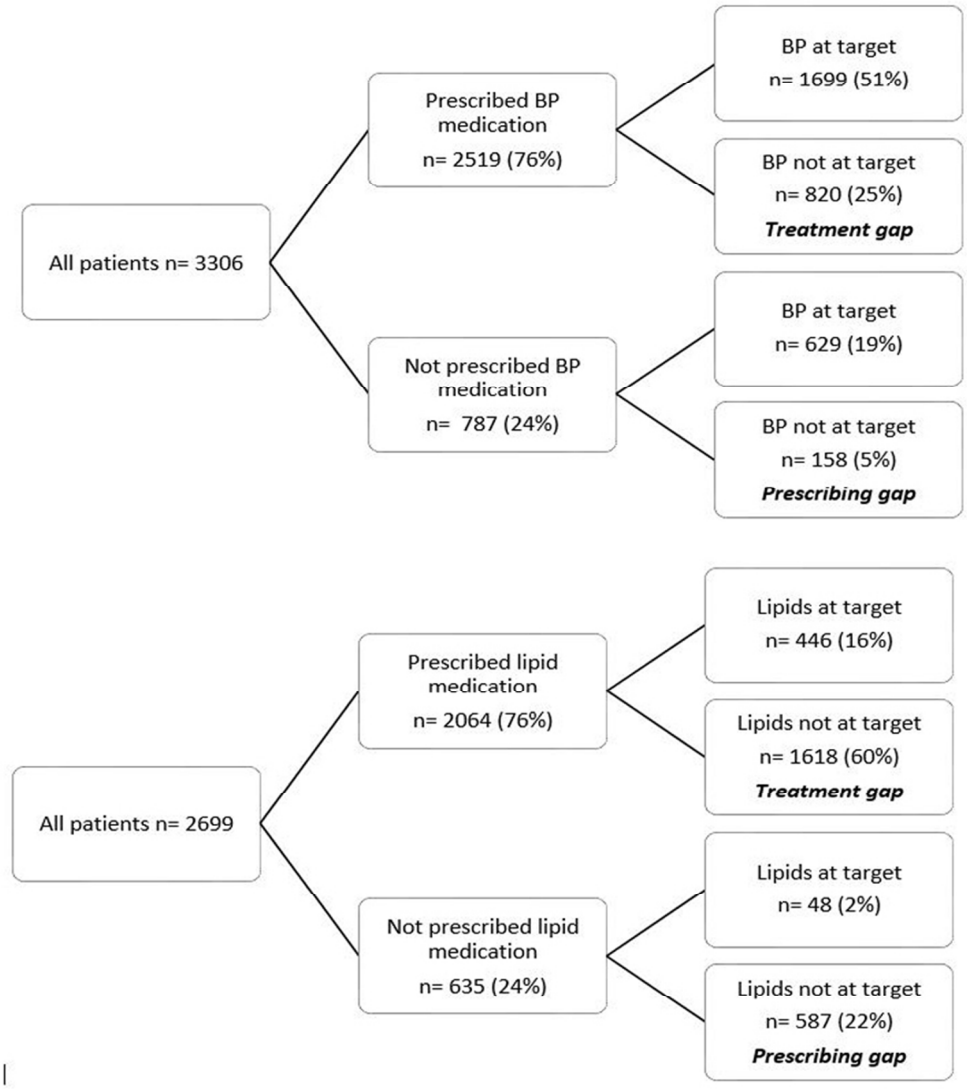


Figure 2: Blood pressure and lipid management gaps in patients with type 2 diabetes

76x85mm (300 x 300 DPI)

Supplementary Tables

Suppl. Table 1: Number of participating diabetes centres and patients by state or territory

State/Territory	Participating centres	Number of patients included
Australian Capital Territory	1	49
New South Wales	13	1246
Northern Territory	1	91
Queensland	9	758
South Australia	1	44
Tasmania	3	140
Victoria	20	1119
Western Australia	1	45
Total	49	3492

Suppl. Table 2: Unadjusted and adjusted odds of variables associated with prescribing gaps

	HbA1c > 8.0% and not on insulin				Hypertension and not on BP medication				Dyslipidaemia and not on lipid medication			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age (y)												
≥60 (ref)												
<60	1.23 (1.01-1.50)	0.041	0.80 (0.61-1.04)	0.090	2.71 (1.91-3.83)	<0.001	1.84 (1.16-2.92)	0.010	2.17 (1.79-2.63)	<0.001	1.48 (1.15-1.90)	0.002
Duration of Diabetes (y)												
<10 (ref)												
≥10	0.28 (0.23-0.35)	<0.001	0.28 (0.22-0.36)	<0.001	0.39 (0.28-0.56)	<0.001	0.46 (0.29-0.71)	0.001	0.41 (0.34-0.50)	<0.001	0.54 (0.42-0.69)	<0.001
Gender												
Male (ref)												
Female	0.89 (0.73-1.08)	0.239	0.87 (0.69-1.11)	0.260	0.96 (0.68-1.36)	0.818	0.97 (0.62-1.51)	0.888	1.37 (1.13-1.66)	0.001	1.19 (0.93-1.51)	0.160
Smoking												
Never (ref)												
Past	0.83 (0.66-1.05)	0.117			0.57 (0.38-0.86)	0.008	0.66 (0.41-1.09)	0.103	0.71 (0.57-0.90)	0.005	0.76 (0.59-0.99)	0.043
Current	0.97 (0.71-1.33)	0.861			1.57 (0.94-2.64)	0.087	1.40 (0.74-2.65)	0.301	1.06 (0.78-1.44)	0.711	1.03 (0.73-1.46)	0.856
eGFR (ml/min) (per unit)	1.01 (1.00-1.01)	0.001	1.00 (1.00-1.01)	0.049	1.02 (1.01-1.02)	<0.001	1.01 (1.00-1.01)	0.014	1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.005
BMI (kg/m^2) (per unit)	0.98 (0.97-1.00)	0.021	0.98 (0.96-0.99)	0.004	0.98 (0.96-1.00)	0.100	0.95 (0.93-0.98)	0.001	0.99 (0.98-1.01)	0.238		
HbA1c (%) (per unit)					1.05 (0.95-1.16)	0.331			0.98 (0.93-1.04)	0.497		
Vascular disease												
No (ref)												
Yes					0.37 (0.26-0.53)	<0.001	0.48 (0.31-0.75)	0.001	0.36 (0.29-0.44)	<0.001	0.51 (0.40-0.66)	<0.001

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.5 mmol/L

Suppl. Table 3: Unadjusted and adjusted odds of variables associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels, excluding patients with diabetes duration ≤ 2 years.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.47 (1.22-1.77)	<0.001	1.59 (1.27-2.00)	<0.001	0.88 (0.74-1.04)	0.122	0.90 (0.72-1.12)	0.339	2.17 (1.71-2.76)	<0.001	1.89 (1.41-2.53)	<0.001	1.31 (1.11-1.54)	0.001	1.28 (1.06-1.55)	0.010	2.50 (1.96-3.17)	<0.001	2.19 (1.64-2.92	<0.001
Duration																				
<10 y (ref)																				
≥10 y	1.65 (1.37-1.98)	<0.001	2.05 (1.66-2.54)	<0.001	1.10 (0.92-1.31)	0.295			0.80 (0.63-1.01)	0.065	0.93 (0.70-1.25)	0.631	1.02 (0.86-1.21)	0.793			0.71 (0.55-0.92)	0.009	1.00 (0.75-1.35)	0.983
Sex																				
Male (ref)																				
Female	1.18 (0.99-1.40)	0.062	1.18 (0.97-1.44)	0.093	1.05 (0.90-1.23)	0.555	0.96 (0.78-1.17)	0.657	0.75 (0.61-0.92)	0.006	0.70 (0.54-0.90)	0.006	1.29 (1.11-1.50)	0.001	1.35 (1.12-1.62)	0.001	0.74 (0.58-0.94)	0.015	0.77 (0.59-1.01)	0.060
Smoking																				
Never (ref)																				
Past	1.08 (0.88-1.32)	0.484			0.92 (0.77-1.11)	0.387	0.97 (0.78-1.19)	0.748	1.08 (0.85-1.37)	0.539	0.97 (0.74-1.28)	0.853	1.51 (1.26-1.81)	0.001	1.69 (1.38-2.06)	<0.001				
Current	1.22 (0.89-1.66)	0.215			0.68 (0.51-0.90)	0.006	0.74 (0.53-1.02)	0.062	1.46 (0.99-2.17)	0.058	1.18 (0.77-1.81)	0.446	0.95 (0.74-1.23)	0.712	0.90 (0.69-1.19)	0.468				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (1.00-1.01)	0.002	1.00 (1.00-1.01)	0.014	1.00 (0.99-1.00)	0.005	1.00 (0.99-1.00)	0.011	1.00 (1.00-1.00)	0.655			1.00 (1.00-1.00)	0.175			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	0.001
BMI (kg/m^2) (per unit)	1.03 (1.02-1.05)	<0.001	1.03 (1.02-1.05)	<0.001	1.02 (1.01-1.03)	<0.001	1.02 (1.00-1.03)	0.009	1.02 (1.00-1.04)	0.013	1.02 (1.00-1.03)	0.097					0.98 (0.96-1.00)	0.016	0.96 (0.95-0.98)	<0.001
HbA1c (%) (per unit)					1.04 (1.00-1.09)	0.075	1.02 (0.97-1.08)	0.477	1.21 (1.12-1.29)	<0.001	1.14 (1.05-1.23)	0.002	1.09 (1.04-1.14)	0.001	1.05 (1.00-1.11)	0.040				

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2

Suppl. Table 4: Unadjusted and adjusted odds of variables associated with suboptimal glycaemic control and adverse cardiovascular risk factor levels, adjusted for diabetes centre type.

	HbA1c above target (7.0%, 53 mmol/mol)				Hypertension				Dyslipidaemia				Obesity				Current Smoker			
	Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis		Univariable Analysis		Multivariable Analysis	
	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value	OR (95%CI)	p value
Age																				
≥60 y (ref)																				
<60 y	1.26 (1.07-1.49)	0.005	1.51 (1.23-1.86)	*<0.001*	0.81 (0.70-0.95)	0.008	0.86 (0.70-1.05)	0.133	2.41 (1.91-3.03)	<0.001	2.05 (1.55-2.72)	*<0.001*	1.26 (1.09-1.46)	0.002	1.26 (1.06-1.50)	*0.009*	2.60 (2.09-3.22)	<0.001	2.09 (1.61-2.72)	*<0.001*
Duration of Diabetes																				
<10 y (ref)																				
≥10 y	2.05 (1.74-2.40)	<0.001	2.52 (2.08-3.05)	*<0.001*	1.16 (0.99-1.35)	0.067	1.04 (0.86-1.26)	0.702	0.66 (0.53-0.81)	<0.001	0.80 (0.61-1.05)	0.115	1.04 (0.90-1.20)	0.591			0.59 (0.48-0.73)	<0.001	0.81 (0.63-1.04)	0.099
Sex																				
Male (ref)																				
Female	1.18 (1.01-1.38)	0.039	1.15 (0.96-1.38)	0.119	1.02 (0.88-1.18)	0.828	0.87 (0.72-1.04)	0.121	0.76 (0.62-0.92)	0.005	0.70 (0.55-0.90)	*0.005*	1.34 (1.16-1.54)	<0.001	1.37 (1.16-1.63)	*<0.001*	0.70 (0.56-0.87)	0.001	0.71 (0.55-0.90)	*0.005*
Smoking																				
Never (ref)																				
Past	1.09 (0.9-1.32)	0.368			0.93 (0.79-1.10)	0.418	0.90 (0.74-1.09)	0.281	1.10 (0.87-1.38)	0.419	1.01 (0.78-1.32)	0.920	1.44 (1.22-1.71)	<0.001	1.63 (1.35-1.97)	*<0.001*				
Current	1.09 (0.84-1.42)	0.512			0.65 (0.50-0.84)	0.001	0.72 (0.54-0.96)	*0.025*	1.73 (1.18-2.52)	0.005	1.34 (0.89-2.02)	0.164	0.93 (0.74-1.17)	0.517	0.93 (0.73-1.19)	0.562				
eGFR (ml/min/1.73m^2) (per unit)	1.00 (0.99-1.00)	0.073	1.00 (1.00-1.01)	*0.040*	1.00 (0.99-1.00)	0.001	1.00 (0.99-1.00)	*0.007*	1.00 (1.00-1.01)	0.144			1.00 (1.00-1.00)	0.301			1.01 (1.01-1.01)	<0.001	1.01 (1.00-1.01)	*0.001*
BMI (kg/m^2) (per unit)	1.03 (1.02-1.04)	<0.001	1.03 (1.02-1.04)	*<0.001*	1.02 (1.01-1.03)	<0.001	1.02 (1.01-1.03)	*0.001*	1.02 (1.01-1.04)	0.004	1.02 (1.00-1.03)	0.088					0.98 (0.97-1.00)	0.017	0.97 (0.96-0.99)	*0.001*
HbA1c (%) (per unit)					1.03 (0.99-1.07)	0.156			1.18 (1.11-1.26)	<0.001	1.13 (1.05-1.22)	*0.001*	1.07 (1.03-1.12)	0.002	1.05 (1.00-1.09)	0.054				
Centre type^	1.06 (0.83-1.36)	0.617	1.25 (0.94-1.67)	0.122	1.18 (0.96-1.45)	0.115	1.07 (0.85-1.35)	0.576	1.04 (0.79-1.36)	0.802	1.25 (0.88-1.78)	0.203	1.15 (0.94-1.41)	0.186	1.18 (0.93-1.50)	0.170	0.17 (0.15-0.18)	*<0.001*	0.75 (0.53-1.07)	0.113

*Multivariable analyses are, where appropriate, adjusted for gender, diabetes duration, smoking, estimated glomerular filtration rates, body mass index and HbA1c.
#Hypertension is defined as systolic blood pressure >140mmHg and/or diastolic blood pressure >90 mmHg
†Dyslipidaemia is defined as either total cholesterol >4.0 mmol/L, high density lipoprotein <1.0 mmol/L, low density lipoprotein >2.0 mmol/L or triglycerides >2.0 mmol/L
‡Obesity is defined as Body Mass Index >30 kg/m^2
^ Tertiary care centres (reference group) compared with primary and secondary care centres

STROBE Statement—Checklist of items that should be included in reports of ***cross-sectional studies***

	Item No	Recommendation	Page No
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	4
Objectives	3	State specific objectives, including any prespecified hypotheses	4
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	5
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*5,6*
Bias	9	Describe any efforts to address potential sources of bias	15
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	5
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6,7
		(*b*) Describe any methods used to examine subgroups and interactions	6,7
		(*c*) Explain how missing data were addressed	6,7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	7
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	5
		(c) Consider use of a flow diagram	N/A
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	21
		(b) Indicate number of participants with missing data for each variable of interest	7
Outcome data	15*	Report numbers of outcome events or summary measures	7-10,21
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear	7-10,23

		which confounders were adjusted for and why they were included	
		(*b*) Report category boundaries when continuous variables were categorized	7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	10,28
Discussion			
Key results	18	Summarise key results with reference to study objectives	11
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	15
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	12-14
Generalisability	21	Discuss the generalisability (external validity) of the study results	15
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.