Impact of Early Diagnosis and Pharmacological Management of Prediabetes and Diabetes on the Middle- and Long-term Outcomes for Patients Attending Australian General Practices

A thesis submitted

by

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Declaration

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I acknowledge the support I have received for my research through the provision of the Faculty of Health and Medical Sciences Divisional Scholarship, Full Fee Scholarship, and Supplementary Scholarship.

Signed:

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Mingyue Zheng (PhD candidate)

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Keywords

General practice

Diabetes mellitus

Prediabetic state

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Big data

Epidemiologic methods

Biostatistics

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Public health informatics

Medical informatics

Population health

Evidence-based medicine

Abbreviations and Acronyms

ABS	Australian Bureau of Statistics
ACR	Albumin-to-creatinine ratio
ADM	Antidiabetic medication
AIPW	Augmented inverse probability weighting
ATE	Average treatment effect
AUSDRISK	Australian Type 2 Diabetes Risk Assessment
BEACH	Bettering the Evaluation and Care of Health
BG	Blood glucose
BMI	Body mass index
BP	Blood pressure
CI	Confidence interval
CKD	Chronic kidney disease
CPRD	Clinical Practice Research Datalink
CVD	Cardiovascular disease
DPP-4	Dipeptidyl peptidase-4
eGFR	Estimated glomerular filtration rate
EHR	Electronic health record
FBG	Fasting blood glucose
GDM	Gestational diabetes mellitus
GLP-1	Glucagon-like peptide-1
GP	General practitioner
HbA1c	Haemoglobin A1c
HDL-C	High-density lipoprotein cholesterol
IHD	Ischaemic heart disease
IRSAD	Index of Relative Socio-economic Advantage and Disadvantage
LDL-C	Low-density lipoprotein cholesterol
MAGNET	Melbourne East Monash General Practice Database
MI	Multiple imputation
MICE	Multivariate imputation by chained equation
OGTT	Oral glucose tolerance test
OR	Odds ratio

PBS	Pharmaceutical Benefits Scheme
PCOS	Polycystic ovary syndrome
RACGP	Royal Australian College of General Practitioners
RBG	Random blood glucose
RCT	Randomised controlled trial
SGLT-2	Sodium-glucose co-transporter 2
T1D	Type 1 diabetes mellitus
T2D	Type 2 diabetes mellitus
UK	United Kingdom
US	United States

Publications and Awards During Candidature

Publications or manuscripts incorporated in the thesis

1. Incorporated as Chapter 4: **Zheng M**, Bernardo C, Stocks N, Gonzalez-Chica D. Diabetes mellitus diagnosis and screening in Australian general practice: a national study. *Journal of Diabetes Research*. 2022;2022:1566408. https://doi.org/10.1155/2022/1566408

2. Incorporated as Chapter 5: **Zheng M**, Bernardo C, Stocks N, Hu P, Gonzalez-Chica D. Diabetes mellitus monitoring and control among adults in Australian general practice: a national retrospective cohort study. *BMJ Open*. 2023; 13(4), p.e069875 http://dx.doi.org/10.1136/bmjopen-2022-069875

3. Incorporated as Chapter 6: **Zheng M**, Begum M, Bernardo C, Stocks N, Gonzalez-Chica D. Comparing the effect of early versus delayed metformin treatment on glycaemic parameters among Australian adults with incident diabetes: evidence using a national general practice database . Under review by *Primary Care Diabetes*

4. Incorporated as Chapter 7. **Zheng M**[#], Soumya S[#], Begum M*, Bernardo C, Stocks N, H Jahan, Gonzalez-Chica D*. Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records. *Diabetic Medicine*. 2023;00:e15170. https://doi.org/10.1111/dme.15170

   * joint corresponding author, # joint first author

Other diabetes-related publications during candidature but not included in the thesis

1. **Zheng M,** Khoja A, Patel A. Luo Y, He Q, Zhao X, Yang S, Hu P, Lin W. Changes in glycaemic control of oral anti-diabetic medications assessed by continuous glucose monitors among patients with type 2 diabetes: a protocol of network meta-analysis. Systematic Reviews. 2022;11:110. https://doi.org/10.1186/s13643-022-01986-5.

2. **Zheng M**, Patel A, Khoja A, Luo Y, Lin W, He Q, Zhao X, Wang J, Yang S, Hu P. Barriers and facilitators of diabetes management by continuous glucose monitoring systems among adults with type 2 diabetes: a protocol of qualitative systematic review. BMJ Open. 2021;11(10):e046050. https://doi.org/10.1136/bmjopen-2020-046050.

3. **Zheng M**, Luo Y, Lin W, Khoja A, He Q, Yang S, Zhao X, Hu P. Comparing effects of continuous glucose monitoring systems (CGMs) and self-monitoring of blood glucose (SMBG) amongst adults with type 2 diabetes mellitus: a systematic review protocol. Systematic Reviews. 2020;9(1):120. https://doi.org/10.1186/s13643-020-01386-7.

4. Lin W[#], **Zheng M[#]**, Chen Y, He Q, Khoja A, Long M, Fan J, Hao Y, Fu C, Hu P, Wang K, Jiang J*, Zhao X*, Dose correlation of *Panax ginseng* and *Atractylodes macrocephala* Koidz. drug pairs in the Chinese medicine prescription based on the copula function. Evidence-Based Complementary and Alternative Medicine. 2021;2021:9933254. https://doi.org/10.1155/2021/9933254 ([#] joint first author, * joint corresponding author)

Conference presentations arising from this thesis

1. **Zheng M,** Bernardo C, Stocks N, Hu P, Gonzalez D (2022). Diabetes mellitus control among adults in Australian general practice: a national study, International Diabetes Federation (IDF) Congress 2022, Lisbon, Portugal (**Oral poster)**. *This conference presentation was awarded the Adelaide Medical School/Biomedicine Research Travel Award by the University of Adelaide (2022).*

2. **Zheng M,** Bernardo C, Begum M, Stocks N, Gonzalez D (2021). Epidemiology of diabetes and prediabetes diagnosis in Australia: a national study using a large general practice database; 2021 Florey Postgraduate Research Conference, Adelaide, Australia (**Oral presentation**).

3. **Zheng M,** Bernardo C, Begum M, Stocks N, Gonzalez D (2021). Diabetes screening for high-risk group among adults attending Australian general practices from 2016 to 2018: a national study; Australian Diabetes Congress, Virtual (**ePoster**). *This conference presentation was awarded the Australasian Diabetes Congress Registration Grant by the Australian Diabetes Society (2021).*

4. **Zheng M,** Luo Y, Khoja A, Lin W, Hu P (2021). Promoting continuous glucose monitoring implementation in comprehensive management of type 2 diabetes; Australian Public Health Conference, Adelaide (**Oral presentation**). *This conference presentation was awarded the Konrad Jamrozik Student Scholarship by the Public Health Association Australia (2021).*

5. **Zheng M**, Bernardo C, Begum M, Stocks N, Gonzalez D (2021). Blood glucose screening profile among adults at high-risk of diabetes attending Australian general practices from 2016 to 2018: a national study; South Australia Population Health Conference, Virtual (**Oral presentation**).

6. **Zheng M,** Luo Y, Khoja A, Lin W, Hu P (2021). Effects of continuous glucose monitoring versus self-monitoring of blood glucose among adults with type 2 diabetes; International Diabetes Federation (IDF) Virtual Congress (**Oral presentation**) https://doi.org/10.1016/j.diabres.2022.109553

Awards and merits arising from this thesis

Date	Type	Title	Institution
2022	Award	Adelaide Medical School/Biomedicine Research Travel Award	The University of Adelaide
2021	Award	Adelaide Medical School HDR Research Support Award	The University of Adelaide
2021	Award	Adelaide Graduate Award	The University of Adelaide
2021	Award	Australasian Diabetes Congress Registration Grant	Australian Diabetes Society
2021	Scholarship	Konrad Jamrozik Student Scholarship	Public Health Association Australia
2020	Award	Adelaide Medical School HDR Research Support Award	The University of Adelaide
2019–2023	Scholarship	Faculty of Health and Medical Sciences Divisional Scholarship	The University of Adelaide
2019–2023	Scholarship	Full-fee Scholarship	The University of Adelaide
2019–2023	Scholarship	Supplementary Scholarship	The University of Adelaide

Reports and media coverage for relevant projects

The University of Adelaide reported research findings from one of my studies (Chapter 4) in 2022.

Entitled 'The ticking time-bomb of diabetes':

https://www.adelaide.edu.au/newsroom/news/list/2022/04/04/the-ticking-time-bomb-of-diabetes

https://medicalxpress.com/news/2022-04-time-bomb-diabetes.html

https://www.miragenews.com/ticking-time-bomb-of-diabetes-757463

Entitled 'Diabetes: are you at higher risk of diabetes and have you been tested?'
https://www.youtube.com/watch?v=GDIU9C0v9Dk

Research grants awarded during candidature and part of this thesis (Chapter 7)

Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using general practice data, Royal Australian College of General Practitioners Foundation and Australia Diabetes Society (AUD57,261).

Abstract

Background

Early diagnosis and management of prediabetes and diabetes have been top priorities for Australian primary care over the past decades. However, there is a lack of national evidence about whether activities undertaken by Australian general practitioners (GPs) regarding screening, diagnosis, and management of prediabetes and diabetes are consistent with current guidelines.

Aims

This thesis investigates (1) the epidemiology of diabetes and prediabetes in general practice and whether people at higher risk of diabetes are more likely to be screened for diabetes than those not at risk; (2) differences in monitoring and control of clinical parameters in patients with past or newly recorded diabetes; (3) whether patients with a recent diabetes diagnosis achieve better glycaemic control with early metformin therapy compared with delayed pharmacological management; and (4) whether patients with prediabetes managed with metformin achieve better glycaemic control than those not receiving that medication.

Methods

The four studies in this thesis used a national electronic health record (EHR) database (MedicineInsight) containing data on diagnoses, laboratory results, and prescriptions, collected between 2011 and 2018 from 662 general practices across Australia. To attend to the first thesis aim, we used a cross-sectional design that projected the prevalence of undiagnosed or diagnosed diabetes and prediabetes in general practice (2016–2018), and explored the sociodemographic and clinical profile of diabetes screening among patients at risk of diabetes. For the second aim, we used a retrospective cohort design that allowed us to identify 101,875 ‘regular’ patients (at least one consultation each year from 2015 to 2018) with past recorded diabetes (diabetes recorded in 2015 and/or 2016) and 9,236 with newly recorded diabetes (diabetes recorded in

2017 but not in previous years). Based on laboratory results reported in 2018, two groups of outcomes were assessed: (1) diabetes monitoring, based on whether a result for HbA1c, blood pressure (BP), total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate, or albumin-to-creatinine ratio was available in the EHR; and (2) 'well-controlled' diabetes, defined as HbA1c ≤7.0%, BP ≤140/90 mmHg, and total cholesterol <4.0 mmol/L. Differences in the frequency of these binary outcomes between those with past or newly recorded diabetes were examined using logistic regression models. For the third aim, we again used a longitudinal cohort design and included data from 27,027 'regular' patients with incident diabetes (at least three consultations, including one the year before and one the year after the first recorded diabetes diagnosis) who were first diagnosed with diabetes between 2012 and 2017. Augmented inverse probability weighting (AIPW) was used to estimate the average treatment effect (ATE) of early (<3 months), timely (3–6 months), delayed (6–12 months), or no metformin prescription within 12 months of diagnosis on glycaemic parameters (HbA1c or fasting blood glucose [FBG] levels). The ATE was estimated at 3–6, 6–12, 12–18, or 18–24 months after exposure or diagnosis. For the fourth aim, we used a similar approach, but the cohort included 4,770 regular patients with incident prediabetes diagnosed between 2012 and 2017. AIPW was used to estimate the ATE of metformin prescription on glycaemic parameters (HbA1c or FBG levels), at 6–12, 12–18, or 18–24 months after exposure.

Results

Paper 1 (addressing thesis aim 1): 7.5% (95%CI 7.3;7.8) of adult patients attending Australian general practices had a recorded diagnosis of diabetes, 0.7% (95%CI 0.6;0.7) of prediabetes, and 0.3% (95%CI 0.3;0.3) had unrecorded diabetes/prediabetes (elevated glucose levels without a recorded diagnosis) during 2016–2018. Patients with unrecorded diabetes/prediabetes had clinical characteristics similar to patients with recorded diabetes, except for a lower prevalence of overweight/obesity among the former (55.5% and 69.9%, respectively).

Dyslipidaemia was 1.8 times higher (36.2% vs 19.7%) and hypertension was 15% more likely (38.6% vs 33.8%) among patients with prediabetes than those with diabetes. The rate of diabetes screening in the past 3 years among people at high risk of diabetes was 55.2% (95%CI 52.7;57.7), with lower rates among young or elderly males, patients with prediabetes, or patients who were prescribed antipsychotics.

Paper 2 (addressing thesis aim 2): In 2018, HbA1c was monitored in 45.2% (95%CI 42.6;47.7) of patients with past diabetes and 39.4% (95%CI 37.1;41.7) of patients with recent diabetes (adjusted odds ratio 0.78, 95%CI 0.74;0.83). Monitoring of HbA1c, BP, and total cholesterol levels was no better among smokers, or patients with hypertension or cardiovascular disease (CVD) than among patients without these risk factors. HbA1c control was achieved by 54.4% (95%CI 53.4;55.4) and 78.5% (95%CI 76.8;80.1) of monitored patients with past and recent diabetes, respectively (adjusted odds ratio 3.11, 95%CI 2.84;3.41). Irrespective of whether they had past or newly recorded diabetes diagnosis, less than 20% of patients had all three clinical parameters controlled (i.e., HbA1c, BP, and total cholesterol levels). Patients with a history of CVD were more likely to have the three clinical parameters controlled than those without a history of CVD, especially among those with newly (adjusted odds ratio 2.43, 95%CI 1.85;3.19) rather than past recorded diabetes (adjusted odds ratio 1.39, 95%CI 1.30;1.49).

Paper 3 (addressing thesis aim 3): Compared with patients with incident diabetes who were not managed with metformin (i.e., the group with the lowest baseline glycaemic levels), the corresponding ATE for HbA1c at 18–24 months was +0.04% (95%CI –0.05;0.10) for early treatment, +0.24% (95%CI 0.11;0.37) for timely treatment, and +0.29% (95%CI 0.20;0.39) for delayed treatment. Similar results were observed for FBG levels.

Paper 4 (addressing thesis aim 4): Despite having higher baseline HbA1c levels, patients with incident prediabetes who were managed with metformin had similar mean HbA1c levels at 6–

12 months (ATE 0.00, 95%CI −0.05;0.05) or 12–18 months (ATE −0.02, 95%CI −0.09;0.06) as patients not managed with antidiabetic medications. However, at 18–24 months, patients with prediabetes who received metformin had lower mean HbA1c levels (ATE −0.09, 95%CI −0.16;0.00) than those who were unexposed. The analysis of FBG levels provided consistent results.

Conclusions and clinical implications

In Australian general practice, diabetes screening among high-risk populations can be improved for patients with prediabetes and those treated with antipsychotics, as these people visit their GP on average five times per year. Moreover, the monitoring of clinical parameters among patients with diabetes is currently suboptimal, as only half of the patients with diabetes had a record of their blood glucose levels being checked over the preceding 12 months. Additionally, 80% of all patients monitored did not reach the recommended HbA1c, BP, and total cholesterol targets. Diabetes screening among high-risk individuals, and monitoring and reaching target levels of critical clinical parameters are essential to minimise the health and economic impact of diabetes progression. International initiatives show it is feasible to improve diabetes screening, monitoring, and management, as these activities could be performed during the annual diabetes 'cycle of care' in general practice.

In primary care settings, early metformin therapy helped patients with diabetes achieve better and more stable glycaemic parameters. Furthermore, metformin therapy for patients with incident prediabetes with high baseline glycaemic levels could help prevent further deterioration of their glycaemic parameters. This finding may influence diabetes and prediabetes management guidelines, as none of them currently recommend using antidiabetic medications to treat prediabetes.

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I acknowledge the traditional custodians of the land where we live and work today.

This thesis represents the work I have done in the Discipline of General Practice over the past 3.5 years. Love, passion, and persistence brought me to the end stage of my PhD candidature. I must admit that this doctoral thesis is not only my research work but also the result of encouragement and support from many people. My PhD journey would not have been possible without them along the way.

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Mingyue Zheng

March 2023

Dedication

This doctoral thesis is dedicated to my loving and loved family, especially my mum.

谨以此博士论文献给我挚爱的母亲

Chapter 1. Introduction

1.1 Preface

This doctoral thesis follows a 'thesis by publication' format. **Chapter 1** gives an overall picture of the burden of diabetes mellitus, introduces the research gaps between current guidelines and clinical practice for diabetes and prediabetes management, and highlights the relevance of using national-level electronic health records (EHRs; also known as electronic medical records – EMRs) to answer the research questions posed by those gaps. **Chapter 2** investigates existing EHR-based research for its capacity to answer the proposed research questions, and identifies research gaps in diabetes screening, monitoring, and pharmacological management. **Chapter 3** presents the methods used in this thesis, including the comprehensive strategy used for data extraction, analysis (i.e., descriptive, cohort analysis, and counterfactual approach), and adjustment when using a national Australian general practice database (MedicineInsight). **Chapters 4 to 7** consist of four publications or manuscripts answering the different research questions that address the main objectives of the thesis. Firstly, **Chapter 4** describes patients with undiagnosed/diagnosed diabetes and prediabetes according to sociodemographic and clinical variables, and the current profile of diabetes screening among people at high risk of diabetes. Using a cohort approach, **Chapter 5** investigates whether patients with diabetes diagnosis had their clinical parameters (i.e., glycaemic parameters, lipid profile and blood pressure [BP]) checked in general practice, and the proportion of those patients that achieved diabetes control. **Chapter 6** uses a longitudinal approach to explore how early or delayed metformin management (Australia's first-line diabetes pharmacological treatment) among patients with a recent diabetes diagnosis impacts changes in blood glucose (BG) levels over 24 months. **Chapter 7** generates evidence of the effects of metformin use on BG levels among patients with prediabetes using longitudinal data and analyses based on a counterfactual approach. **Chapter 8** presents a general discussion of the key findings of the thesis, along with the strengths and limitations of the proposed methodologies, and the overall significance of this

doctoral project. Finally, **Chapter 9** summarises the overall contribution to knowledge and future work directions.

1.2 Investigation of Prediabetes and Diabetes Using General Practice Electronic Health Records

Diabetes mellitus (diabetes) is a lifelong, chronic, and rapidly progressive disease that appears when either the pancreas does not produce adequate insulin levels, or the body does not efficiently use the insulin it delivers.[1] It is generally classified as type 1 diabetes mellitus (T1D), type 2 diabetes mellitus (T2D), gestational diabetes mellitus (GDM; diabetes diagnosed during the second or third trimester of pregnancy, which is not overt diabetes), or another specific type.[2] Diabetes is frequently associated with hypertension and dyslipidaemia, and is a leading contributor to stroke, heart disease, and chronic kidney disease (CKD).[3] Patients with diabetes have a higher risk of these comorbidities than those without diabetes.[3, 4]

In 2020, an estimated nearly 1.3 million Australians – or 1 in 20 people – were living with diabetes (excluding GDM).[5] An accurate national picture of diabetes epidemiology is the first step in developing strategies to mitigate future comorbidities and their impact on society and the health system. The prevalence of diabetes and other chronic disease and their epidemiological profile have traditionally been explored using national health surveys.[6] However, EHRs have emerged as an alternative tool to better understand the frequency and distribution of diabetes. Moreover, EHRs can be used to monitor trends, and to explore preventive activities, management, short- and long-term diabetes-related outcomes, and the epidemiology distribution of diabetes-related comorbidities.[7]

For example, a national study in the United States (US) including approximately 1.3 million patients from the Quintiles EHR research database found that the most commonly associated conditions in patients with T2D were hypertension (82.1%), overweight/obesity (78.2%), dyslipidaemia (77.2%), CKD (24.1%), and cardiovascular disease (CVD; 21.6%).[8] In the United Kingdom (UK), a study of a prominent primary care cohort (N=102,394) from the

Clinical Practice Research Datalink (CPRD) database found that people living in the most disadvantaged areas were more likely to have more than one morbidity present at the time of diagnosis (64% of males and 72% of females) compared to those living in the wealthiest areas (59% of males and 67% of females).[9] In Australia, EHRs have been used to estimate the burden of various chronic diseases over the past decade, but only a few EHR-based studies have focused on diabetes.[10, 11]

Another condition of interest is prediabetes. Also known as impaired glucose tolerance or impaired fasting glucose, prediabetes is a health condition in which BG levels are above normal but below the threshold for the diagnosis of diabetes.[12] Overall, the annual conversion rate from prediabetes to diabetes is 5–10%.[12] Therefore, early screening, regular monitoring, and appropriate prediabetes management are essential to decrease the risk of progression to diabetes and related complications. In Australia, the only national health survey investigating prediabetes was conducted in 2011–2012. Based on BG levels, it was estimated that 3.1% of adults had prediabetes.[13] Limited EHR-based studies have investigated the epidemiology of prediabetes or the pharmacological therapy of this condition in Australia.[14]

General practitioners (GPs) are the health service professionals most often seen by patients. More than 8 out of 10 Australians attend a GP yearly, with over two-thirds receiving a medication prescription from a GP in 2017–2018.[15] Encounters such as prescriptions, diagnoses, clinical measurements, and laboratory results are recorded by Australian GPs using secure digital platforms that, after de-identification, can be used for quality assurance, training, education, and research purposes.[16] Therefore, general practice EHRs represent an excellent opportunity to explore the epidemiology and management of prediabetes and diabetes in countries like Australia, where medical records are routinely collected and electronically recorded.

1.3 Research Gaps Between Guidelines and Clinical Practice

The clinical management of diabetes and prediabetes relies on evidence-based guidelines drawn from research, particularly clinical trials and representative national studies.[17-19] National clinical agencies, non-profit organisations, and government health budgets need up-to-date national research findings on patient behaviours and activities performed by GPs across Australia in real-world settings.[20] However, as the literature review of Chapter 2 demonstrates, there are significant gaps and limitations in our understanding of Australian diabetes and prediabetes epidemiology regarding effective screening, early diagnosis, appropriate management, and short- and long-term control.

Moreover, studies investigating the total burden of undiagnosed diabetes are scarce, mainly because collecting blood samples for national surveys is usually challenging and expensive.[21, 22] Still, it is estimated that nearly half of the people with diabetes or prediabetes are unaware they have these conditions.[23] In Australia, most national surveys use self-reported data, hindering their capacity to investigate this issue. The latest Australian evidence using blood and urine samples was the National Health Measures Survey, the biomedical component of the Australian Health Survey (2011–2013). That study found a further 3.1% of Australian adults were identified as having prediabetes by their biomedical results.[13] Therefore, using pathology results from EHRs is a potentially cost-effective resource to identify undiagnosed patients and describe their sociodemographic and clinical characteristics.

People at higher risk of diabetes (e.g., aged ≥40 years and overweight or obese; with prediabetes; with a history of CVD, GDM or polycystic ovary syndrome [PCOS]; or taking antipsychotic drugs)[24, 25] should have their BG levels checked regularly. For example, a 2020 systematic review of 28 studies involving 170,139 females with GDM found that the incidence rate of T2D after GDM was 26.2% (95% confidence interval [CI] 23.3;29.1) per 1,000 person-years, and the rate was greater among women with a higher baseline body mass index (BMI).[26] According to current guidelines, diabetes screening among these at-risk individuals is a crucial

cost-effective strategy for implementing early interventions, including diabetes education programs and frequent BG monitoring.[27-29] However, diabetes screening can be affected by different factors, including patients' clinical history, current comorbidities, and sociodemographic characteristics (gender, income, education levels).[30-32] Therefore, it is essential to determine whether people at a higher risk of diabetes are more likely to be screened than the general population and what factors influence this outcome. This information is vital for health policymakers, who grapple with medical resource allocation.

Moreover, exploring patterns of clinical practice after diabetes diagnosis, adherence or divergence of diabetes management from clinical guidelines, and changes in antidiabetic medication (ADM) prescriptions is essential to guide health policy and potential interventions. Although Pharmaceutical Benefits Scheme (PBS) data can be used in Australia to investigate patterns of ADM prescriptions and changes over time,[33] that source of information lacks relevant clinical and sociodemographic data to explore potential determinants of change. Once more, EHR databases can be a cost-effective resource for investigating these patterns and possible associations. For example, a large study in the US using EHRs of 1 million adult patients with diabetes who were started on any ADM found that metformin prescriptions increased between 2005 and 2016 (from 60% to 77%), while sulfonylurea prescriptions decreased (from 20% to 8%).[34] The same study reported that patients initiated on metformin were younger than those prescribed sulfonylureas (mean age 57 years vs 64 years), despite both groups having similar HbA1c baseline levels.

Other knowledge gaps exist in terms of diabetes and prediabetes management. For example, should metformin be used from the time of diagnosis without waiting 2–3 months to evaluate whether lifestyle modifications reduce BG levels? Clinical guidelines for early diabetes management differ between countries. Although the International Diabetes Federation (IDF)[35] and US clinical guidelines[36] support the use of metformin as soon as diabetes is diagnosed, guidelines in Australia[37] and China[38] recommend starting with lifestyle modifications for 2–

3 months before considering pharmacological management. On the other hand, some ADMs (i.e., metformin, acarbose, or rosiglitazone) have shown promising results for preventing or postponing the onset of T2D in high-risk people.[17] Currently, metformin use for prediabetes treatment is not recommended in clinical guidelines, as it is assumed that not all patients with prediabetes will develop T2D or its complications over time.[39, 40] Nonetheless, metformin use for diabetes prevention in the US has become more common in recent years (10%, 2015–2018) compared to 15 years ago (4%).[41]

Recently developed epidemiological methods using EHR databases (e.g., cohort analysis, counterfactual analysis, machine learning)[7, 42-44] provide researchers innovative options to address identified research gaps. In addition, general practices have increased the use of clinical information systems and data extraction tools to collect and record patient information (e.g., diagnoses, prescribed medications, and pathology results).[20] Therefore, this thesis aimed to explore whether data or information from an Australian national general practice database (MedicineInsight) can be used to investigate these knowledge gaps and any discrepancies between clinical recommendations and practice.

1.4 Thesis Aims and Research Questions

The main goal of this thesis is to provide a comprehensive real-world profile of diabetes and prediabetes prevalence and treatment using a large general practice database from 662 general practices across Australia (MedicineInsight) (**Objective 1**). This project also aims to identify differences between clinical guidelines and real-world practice (**Objective 2**); assess the occurrence of diabetes-related complications (**Objective 3**); provide the overall profile of patients with past or recent diabetes diagnosis (**Objective 4**), whether they achieve diabetes control (**Objective 5**), and common characteristics among those achieving diabetes management targets (**Objective 6**); evaluate the effects of early pharmacotherapy management on BG levels among patients with recent diabetes (**Objective 7**) or prediabetes diagnosis

(**Objective 8**), as outlined in the critical action objectives or guiding principles of Australian guidelines.[14, 25, 45]

To achieve these objectives, Chapters 4–7 in this thesis correspond to four papers that answer the following research questions:

Chapter 4 (Paper 1, Objectives 1–3): Are people at higher risk of diabetes more likely to be screened for diabetes than those not at risk, and what factors influence this outcome? What are the sociodemographic and clinical profiles of adults with diagnosed or undiagnosed diabetes/prediabetes visiting general practice in Australia? What are the most common risk factors and clinical conditions observed among these patients?

Chapter 5 (Paper 2, Objectives 4–6): Are there any sociodemographic or clinical differences between patients with past or recent diabetes diagnoses among adults attending general practices in Australia? What is the prevalence of well-controlled diabetes? Do sociodemographic or clinical characteristics influence that outcome?

Chapter 6 (Paper 3, Objective 7): Do patients with a recent diabetes diagnosis achieve better glycaemic control with early metformin therapy compared to delayed pharmacological management?

Chapter 7 (Paper 4, Objective 8): Do patients with prediabetes achieve better glycaemic control with metformin therapy than those not receiving that medication?

1.5 Hypotheses of the Project

The hypotheses of the project were developed based on the research questions and existing literature on diabetes screening, diagnosis, monitoring, and management, as follows:

(1) People who are at risk of diabetes are more likely to have their BG screening than those who are not at risk;

(2) Patients with diagnosed diabetes, prediabetes, and undiagnosed diabetes have different sociodemographic and clinical profiles;

(3) Patients with diagnosed diabetes, prediabetes, and undiagnosed diabetes have different risk factors and clinical conditions;

(4) Diabetes monitoring and control are different between patients with past and recent recorded diabetes;

(5) The prevalence of well-controlled diabetes is around 50%;

(6) Gender, age, and diabetes-related comorbidities influence the frequency of well-controlled diabetes;

(7) Early management with metformin can help patients with newly recorded diabetes better control their BG levels, compared to those with delayed metformin management;

(8) Metformin use among patients with prediabetes is beneficial for glycaemic control.

Chapter 2. Literature Review

2.1 Preface

This literature review draws from recent and relevant research to develop a picture of our current understanding of the epidemiology of diabetes diagnosis, management, and control. These topics are mainly explored from a primary care perspective, considering that general practice in Australia is usually the first point of contact for the identification, management, and follow-up of patients with diabetes. After establishing how diabetes is diagnosed and screened for, the chapter addresses the management, control, monitoring, and secondary prevention of diabetes. Subsequent sections then examine the feasibility of using large EHR databases to investigate diabetes screening, diagnosis, and management.

2.2 Epidemiology of Diabetes

2.2.1 Prevalence of Diabetes, Undiagnosed Diabetes, and Prediabetes

It is projected that the global population of patients aged 20–79 with diabetes will reach 642 million by 2040.[46] The predicted increase is multifactorial and has been linked to global ageing, dietary changes, increased obesity, unhealthy lifestyles, restricted access to healthcare services, and socioeconomic adversity.[46-49] T2D is the most common type of diabetes, characterised by β-cell dysfunction and insulin resistance, which can lead to damage and complications in the kidneys, heart, blood vessels, nerves, and eyes over time.[50, 51] The effects of diabetes extend beyond individuals to their families and society, for example, by affecting work productivity and increasing the burden on the healthcare system.[51] On the other hand, prediabetes is a stage of abnormal glucose homeostasis when BG levels are elevated but are not higher than the levels required for diabetes diagnosis.[47] The progression of prediabetes to diabetes is typically caused by an increase in insulin resistance and/or a decline in β-cell function.[52]

Although appropriate tests exist for detecting diabetes and prediabetes, many people are unaware they are affected by these conditions.[53] Population-based studies conducted in many countries (e.g., Vietnam,[54] Canada,[55] China,[56, 57] US,[58, 59] Qatar,[60] and Saudi Arabia[61]) have found the prevalence of undiagnosed diabetes or prediabetes has a direct trend relationship with the prevalence of diagnosed diabetes. In the US in 2019, it was projected that 14.7% (37.1 million) of all adults had diabetes, but 23.0% (8.5 million) of those with diabetes were unaware they had the condition (undiagnosed diabetes).[62] Since socioeconomic background can adversely affect health service use and diabetes diagnosis, it is estimated that the prevalence of undiagnosed diabetes in low-income settings can reach up to 50%.[63] On the other hand, the global prevalence of prediabetes in 2019 was estimated to be 7.5% (374 million) and is expected to increase to 8.0% (454 million) by 2030.[64] However, the actual prevalence of prediabetes is higher if we consider undiagnosed cases. For example, based on BG levels, the National Diabetes Statistics Report in June 2017 estimated that 38.0% (96 million) of US adults had prediabetes,[65] but more than 8 in 10 did not know they had that condition.[66] All these conditions have a substantial economic impact and repercussions for national health systems. In the US, for example, the average annual burden in 2017 was US$13,240 per case for diagnosed diabetes, US$4,250 for undiagnosed diabetes, and US$500 for prediabetes.[21] In Australia, it was estimated that 3.1% of Australian adults had prediabetes (2011–2012).[13] The estimate of the national prevalence of prediabetes has been mainly based on self-report data (with the exception of the Australian national health survey with biomedical results in 2011–2012[13]), and the national prevalence of undiagnosed diabetes has not been reported in Australia since 2013.

In 1990–2000, the Australian Diabetes, Obesity and Lifestyle Study found that around 50% of all diabetes was undiagnosed.[67] The Australian Bureau of Statistics (ABS) Australian Health Survey (2011–2012), which collected BG data at a national level, found that 1 in 5 adults with diabetes were unaware that they had the condition.[5] There is inadequate information on the current rates of undiagnosed diabetes in Australia in recent years, although it is speculated that

the number of people with undiagnosed diabetes may have increased due to higher rates of obesity in the society.[68] Only one small study in South Australia (North-West Adelaide Health Survey, 2014) found that for every 3–4 people with diagnosed diabetes, there was approximately one case of undiagnosed diabetes.[69]

Therefore, opportunistic identification of these individuals is crucial.[70] In Australia, around 82.8% of individuals visited a GP in 2018-19.[15] Among patients with a chronic condition, 94.4% visited a GP annually, while for those without a chronic illness, the proportion was 71.2%.[15] Over 30% of patients with T2D having visited a GP three or more times in the previous 3 months, compared to 16% and 17% of those without diabetes or prediabetes, respectively.[71] Therefore, primary care settings are an ideal environment for the early identification of patients affected by these conditions.

2.2.2 Risk Factors for Prediabetes and Diabetes

The increasing prevalence of prediabetes and diabetes in younger populations and other high-risk groups highlights the need to improve screening, diagnosis, and early management to prevent diabetes-associated complications and comorbidities across a patient's lifetime.[72] Risk factors for prediabetes and diabetes comprise demographic and socioeconomic factors (older age, family history of diabetes, indigenous status), lifestyle factors (physical inactivity, poor sleep, unhealthy diet, smoking, alcohol consumption, being overweight/obese), clinical history (hypertension, dyslipidaemia, GDM, heart disease, stroke, depression, PCOS, acanthosis nigricans, non-alcoholic fatty liver disease), and medications (use of corticosteroids or antipsychotic drugs).[14, 69, 72, 73]

According to Australian guidelines, the following characteristics are considered high-risk factors for T2D: aged ≥40 years with overweight or obesity; being an Australian Aboriginal and/or Torres Strait Islander, Pacific Islander, Hispanic, or Asiatic person; having a strong family history of T2D (first-degree relative with diabetes); or having a clinical history of CVD

(i.e., stroke, angina, acute myocardial infarction, or peripheral vascular disease), prediabetes (impaired glucose tolerance and/or impaired fasting glucose), GDM or PCOS; and taking antipsychotic drugs.[24, 25]

2.2.3 Progression from Prediabetes to Diabetes

T2D is heralded by a long asymptomatic period and generally remains silent during its initial (prediabetes) stage. There is usually a long predetection period (3–7 years) of elevated BG levels, but this is often not diagnosed clinically.[74] People with prediabetes whose BG levels return to normal, either spontaneously or because of intervention, have about half the risk of progressing to T2D compared to those with persistently abnormal BG levels.[75]

Different definitions exist for the diagnosis of prediabetes, which vary in terms of the laboratory test and cut-off points (Table A1, Appendix A).[72] For instance, the World Health Organization (WHO) and International Diabetes Federation (IDF) only consider fasting blood glucose (FBG) levels for prediabetes diagnosis, even though HbA1c is recognised as an alternative diagnosis tool by other organisations. In Australia, the diagnosis of prediabetes can be confirmed by FBG, HbA1c or 75 g oral glucose tolerance test (OGTT): (1) impaired fasting glucose is defined as an FBG level of 6.1–6.9 mmol/L; (2) impaired glucose tolerance is defined as a 2-hour BG of 7.8–11.1 mmol/L by an OGTT; or (3) HbA1c levels of 6.0–6.4%.[2] Indeed, since 2012, the Australian Diabetes Society indicates an HbA1c level of 6.0–6.4% (42–47 mmol/mol) can be used for prediabetes diagnosis.[76] Moreover, annual HbA1c tests for diabetes diagnosis in asymptomatic patients at high risk have been eligible for Medicare Benefits Schedule rebates since November 2014.[77] The rate of progression from prediabetes to diabetes differs depending on the definition of prediabetes, which may have implications for the design and implementation of diabetes prevention programs.[78]

Prediabetes is characterised by mild hyperglycaemia; reducing insulin resistance will reduce the need for β-cell secretion and maintain β-cells functioning longer.[79] If prediabetes is allowed

to progress to diabetes, irreversible complications may occur before treatment begins.[78, 80, 81] It is projected that approximately 75% of patients with impaired glucose tolerance or impaired fasting glucose will progress to T2D over their lifetime.[82]

A large, prospective, occupational cohort study in the UK (n=6,538) found that changes in BG levels, insulin resistance, and insulin secretion in adults were already apparent 3–6 years before the diagnosis of diabetes.[83] Moreover, the progression of pathophysiological changes from prediabetes to diabetes, insulin resistance, and hyperglycaemia that occur in people with prediabetes and diabetes can increase reactive oxygen species, thus triggering intracellular molecular signalling. These changes promote insulin resistance and hyperglycaemia, and contribute to the pathogenesis of CVD and other macrovascular complications.[4]

2.3 A Leading Contributor to Related Comorbidities

2.3.1 Diabetes-related Comorbidities

People with diabetes usually present with many other metabolic abnormalities (e.g., hypertension, dyslipidaemia, obesity) as part of what is known as metabolic syndrome.[4, 84] An extensive range of blood-borne proteins are already altered by the time of diabetes diagnosis, indicating that crucial metabolic syndrome features already exist (e.g., insulin resistance, fatty liver, hypercholesterolaemia, hyperglycaemia).[85] Indeed, evidence shows that the increased risk of CVD in patients with diabetes or prediabetes is primarily due to the presence of multiple metabolic conditions rather than hyperglycaemia itself.[86]

The Australian Institute of Health and Welfare diabetes and disability report (2013) found that patients with diabetes have higher rates of chronic comorbidities (e.g., heart disease, stroke, hypertension, dyslipidaemia, and CKD) than those without diabetes. The same report shows that about 67% of individuals with diabetes aged <60 years and 91% of those aged ≥60 years have another long-term comorbidity.[3] Of these, stroke and heart disease are the leading causes of premature death among patients with T2D.[87, 88] Globally, CVD affects around 32% of people

with T2D and, between 2007 and 2017, accounted for half of all deaths among patients with T2D.[89] Indeed, a meta-analysis of epidemiological studies (2014) found that the risk of a CVD event was 18% higher for each 1% (95%CI 1.10;1.26) increase in HbA1c levels among patients with T2D.[90] Some of the common complications associated with diabetes are detailed below.

Heart failure or congestive heart failure appears when the heart muscle is unable to pump blood normally.[91] Diabetes affects the heart muscle, leading to systolic and diastolic heart failure.[92] A meta-analysis of 47 cohorts of 12 million patients found that the excess risk of heart failure associated with diabetes is higher in females than in males. The corresponding pooled risk ratio for heart failure associated with T2D was 1.95 (95%CI 1.70;2.22) in women and 1.74 (95%CI 1.55;1.95) in men.[93]

Ischaemic heart disease (IHD, also known as coronary artery disease or coronary heart disease) is the term given to heart problems caused by narrowed heart (coronary) arteries that supply blood to the heart muscle.[94, 95] Diabetes is a major risk factor for IHD, as long-term hyperglycaemia leads to vascular damage.[94] Diabetes raises the risk of heart disease mortality by 2–4 times.[96] Therefore, glucose control is one of the primary measures that may reduce the risk of IHD among patients with diabetes.

Stroke is a condition that occurs when a blood vessel that supplies blood to the brain becomes blocked or ruptures.[3] A meta-analysis of 39 studies of 359,783 people found that approximately 28% (95%CI 26;31) of stroke patients had diabetes.[97]

Hypertension (BP ≥140/90 mmHg) is a modifiable and strong risk factor for diabetic macrovascular and microvascular complications.[98] It is one of the most common comorbidities of diabetes, and shares similar risk factors (sex, age, ethnicity, and increased BMI).[98, 99] Lowering BP is an effective strategy to prevent diabetes complications.[100] However, established pharmacological interventions have different effects on BP control among people with diabetes, possibly due to their distinct off-target effects. Angiotensin II receptor blockers and

angiotensin-converting enzyme inhibitors have been the most effective treatments for BP control.[101]

Dyslipidaemia is defined by the imbalance of lipids, including high cholesterol levels, elevated triglyceride levels, elevated low-density lipoprotein cholesterol (LDL-C) levels, and/or decreased high-density lipoprotein cholesterol (HDL-C) levels.[102] These changes can be detected many years before the onset of clinically relevant hyperglycaemic conditions.[13, 103] It is estimated that 30–60% of people with T2D have dyslipidaemia.[104] According to current guidelines, individuals with diabetes should have their lipid levels tested every year.[25]

CKD is identified by (1) a measured or estimated glomerular filtration rate (GFR or eGFR) of <60 mL/min/1.73m^2 lasting for ≥90 days with or without evidence of kidney damage; or (2) evidence of kidney damage (i.e., albuminuria, haematuria after exclusion of urological causes, structural abnormalities, or pathological abnormalities) with or without reduced GFR lasting for ≥90 days.[105, 106] Diabetes raises the risk of developing CKD. A systematic review of 71 observational studies indicated that the annual incidence of microalbuminuria and albuminuria ranged from 3.8% to 12.7% for patients with diabetes, and around 2–4% per year developed an eGFR <60 ml/min/1.73m^2 (meeting the definition of CKD).[107] However, the management of diabetes in patients who have CKD can be complex due to their impaired renal function.[106] For instance, metformin is the first-line management strategy for diabetes therapy, but it should be used carefully if the GFR is 30–60 mL/min/1.73m^2 (stages 3a and 3b) and avoided if the GFR is <30 mL/min/1.73m^2 (stage 4).[106]

2.3.2 Potential Effects of Prediabetes and Undiagnosed Diabetes

In the longer term, prediabetes and undiagnosed diabetes also impose substantial health and financial burdens on patients and the health system.[108] Prediabetes is often overlooked in assessments of health and financial burden, even though the impact of its progression appears similar to that of atherosclerotic disease progression (in which coronary anatomy becomes more

complicated, requiring greater numbers of longer stents).[109] This may be because BG regulation impacts CVD progress among patients with prediabetes. A systematic review found that prediabetes was associated with a 13% raised risk of CVD.[110] Furthermore, an American national study reported that CKD prevalence is higher among patients with prediabetes and undiagnosed diabetes than in the general population.[111] Therefore, delayed diagnosis and management of prediabetes and diabetes can cause vascular complications, including CKD, diabetic retinopathy, neuropathies, and macrovascular disease. [57, 83, 112, 113]

2.4 Diabetes Screening

The intention of screening is to identify people with a higher risk of a health condition in an apparently healthy population, so that early intervention or therapy can be provided.[114] Hence, early and timely detection of prediabetes and diabetes is important for proper prevention and management of disease development.[115, 116] However, universal screening of all adults is not a catch-all solution. It is debatable whether diabetes screening based on BG levels among healthy adults can influence short- and long-term outcomes.

From the perspective of the healthcare system, screening for diabetes and prediabetes is generally more cost-effective than not screening. A long period of asymptomatic diabetes increases the risk of developing hyperglycaemia and complications, thus increasing health costs.[117] Therefore, some experts suggest intensive diabetes screening from the age of 20 years should be emphasised to reduce the burden of modifiable CVD risk factors among people with undiagnosed diabetes.[118] Nonetheless, for asymptomatic adults at low risk, screening for prediabetes or diabetes should typically begin with an informal assessment of risk factors or the use of validated tools.[2] For these groups, various risk score tools are recommended for diabetes screening, as they are simple, fast, inexpensive, and non-invasive tools to detect people at high risk of T2D who need further assessment.[119-122] In Australia, the Australian Type 2 Diabetes Risk Assessment (AUSDRISK) tool has been recommended as the national diabetes risk

assessment tool for people aged ≥40 years or Aboriginal and Torres Strait Islander people aged ≥18 years with no other risk factors.[120]

The Australian guidelines for preventive activities in general practice[25] use AUSDRISK in the rubric to help GPs identify people at increased risk of T2D who could therefore benefit from BG tests (Table 2.1). The algorithm for screening people with high risk of T2D is presented in Figure A1, Appendix A. How to calculate the AUSDRISK score is recorded in Figure A2, Appendix A: people who score 6–11 points may be at increased risk of T2D; and people who score ≥12 points may have undiagnosed T2D or be at high risk of developing the condition.[120] According to the guidelines,[25] regular diabetes screening (within 3 years) is recommended for those with an AUSDRISK score ≥12 points, with a clinical history of GDM or PCOS, or those taking antipsychotic medications or who are at higher risk of CVD. Current evidence also suggests that for people aged ≥40 years with overweight or obesity (BMI ≥25 kg/m^2), regular BG screening would also help diagnose prediabetes and diabetes.[138] Moreover, annual monitoring of patients with identified prediabetes is recommended to identify their progression at an earlier stage.[50] Diabetes screening among these individuals at high risk has been found to provide the backbone for detecting undiagnosed diabetes and reducing adverse clinical outcomes (e.g., CVD, retinopathy, renal disease, and all-cause mortality).[108, 123] Screening among these people should be performed frequently using either HbA1c or FBG tests.[14, 25, 124]

Table 2.1. Type 2 diabetes: identifying risk

Who is at risk?[25]	What should be done?	How often?
Increased risk		
Aged ≥40 years Aboriginal and Torres Strait Islander people aged ≥18 years	AUSDRISK	Every 3 years
High risk		
Aged ≥40 years of age and overweight or obese AUSDRISK score ≥12 Consider screening the following groups because they may be at increased risk for diabetes at an earlier age or lower BMI: - first-degree relative with diabetes - high-risk race/ethnicity (Indian subcontinent or Pacific Islander) - people with a history of a previous cardiovascular event - females with a history of GDM - females with PCOS - patients on antipsychotic drugs*	FBG or HbA1c	Every 3 years
Those with impaired glucose tolerance test or impaired fasting glucose (not limited by age)	FBG or HbA1c	Every 12 months

AUSDRISK: Australian Type 2 Diabetes Risk Assessment Tool; BMI: Body mass index; FBG: Fasting blood glucose; HbA1c: Haemoglobin A1c; GDM: Gestational diabetes mellitus; PCOS: Polycystic ovary syndrome; Previous cardiovascular events include: acute myocardial infarction or stroke.

*Antipsychotics listed on the Pharmaceutical Benefits Scheme website (N05A) in 2021 (https://www.pbs.gov.au/browse/body-system?depth=3&codes=n05a#n05a): Phenothiazines with aliphatic side-chain (chlorpromazine); Phenothiazines with piperidine structure (periciazine); Butyrophenone derivatives (haloperidol, haloperidol decanoate); Indole derivatives (lurasidone, ziprasidone); Thioxanthene derivatives (flupentixol decanoate, zuclopenthixol decanoate); Diazepines, oxazepines, thiazepines and oxepines (asenapine, clozapine, olanzapine, quetiapine); Benzamides (amisulpride); Other antipsychotics (aripiprazole, bexpiprazole, paliperidone, risperidone).

Table adapted from Royal Australian College of General Practitioners (2016).

Despite these recommendations, the frequency of diabetes screening in high-risk groups has not been studied at a national level in Australia, likely because filling this research gap requires individualised longitudinal data on the occurrence of risk factors, and BG records. Diabetes screening is influenced by sociodemographic factors (e.g., gender, age, socioeconomic status), clinical factors (pre-existing chronic conditions), and service characteristics (e.g., practice coverage), which need to be taken into consideration during the design of health interventions.[31, 125-127] For example, a recent population-based study conducted in 2022 found that adherence to diabetes screening guidelines (which recommend screening at least once every 3 years for individuals aged 40 years or older) is suboptimal in the US, particularly among

younger men.[123] Additionally, while patients taking antipsychotics are usually considered to be at high risk for diabetes, they receive less screening or monitoring of their BG levels than other high-risk groups. In a large retrospective cohort study of 50,915 participants with severe mental illness diagnoses in the US who were prescribed antipsychotic medications between 2009 and 2011, nearly 70% were not tested for diabetes.[128] In Australia, a national survey investigating 955 responses found that Australian psychiatrists' routine screening for metabolic syndrome in patients on antipsychotics is insufficient.[30]

2.5 Diabetes Management and Control

Because diabetes is a chronic disease, many factors can impact diabetes management and control, including sociodemographic characteristics (e.g., patient's age, gender, ethnicity, education, income, employment, social support, smoking), cardiovascular risks (e.g., high BP, high cholesterol, overweight/obesity), and health status (e.g., diagnosis period, management with ADM, presence of diabetes-related conditions). Early health interventions considering these determinants could reduce the long-term health burden of diabetes and its complications.[19, 129]

Diabetes management has traditionally been seen as the process of keeping BG levels as close to the recommended range as possible through lifestyle changes and/or medications.[35, 36, 129] However, diabetes management goes beyond BG control. According to the Royal Australian College of General Practitioners' (RACGP) guidelines, people with diabetes should have their HbA1c, BP and lipid levels under control to minimise the risk of future complications (Table A2, Appendix A).[129]

2.5.1 Australian Guidelines for Diabetes Management

Lifestyle modifications and pharmacological therapy are the mainstay of diabetes management to prevent and delay diabetes progression and its related complications.[18, 130] Overall, managing patients with diabetes requires the involvement of a multidisciplinary healthcare team,

including medical doctors, practice nurses, allied health professionals, dietitians, diabetes educators, and patients' families, among others.[131] Risk assessment and diabetes management by a multidisciplinary healthcare team has been found to reduce the incidence of microvascular diabetes complications (e.g., non-proliferative diabetic retinopathy, sight-threatening diabetic retinopathy, nephropathy, end-stage renal disease) over a 3-year follow-up.[132]

In Australia, the General Practice Management of Type 2 Diabetes (GPMT2D) guideline (2016–2018) is the most crucial guideline for diabetes management and care in general practice.[129] The GPMT2D guideline recommends assessing the patient's diet, physical activity, smoking, and alcohol consumption, along with monitoring important clinical parameters (e.g., BMI, BG, HbA1c, lipid levels, BP, and kidney function). The diabetes annual cycle of care is an additional simple checklist tool Australian GPs use to check patients' conditions (Table A3, Appendix A). This is considered the minimum level of care that should be provided to patients with diabetes in Australia.[133] Table 2.2 summarises the principles and objectives of all current Australian guidelines and statements (2011–2020) for chronic disease management, particularly diabetes management in primary care settings, as they relate to diabetes prevention, detection, and management. The GPMT2D recommendations for diabetes management and care are examined more thoroughly and compared to EHRs from a national general practice database in Chapter 5.

Table 2.2. Australian guidelines for chronic disease management in primary care

Australian policy or guideline	Publisher (year)	Guiding principles/goals of diabetes care
Diabetes Management in General Practice 2011/2012[134]	RACGP (2011)	The underlying objective is to improve the duration and QoL of patients; Encouraging patients to participate and take an active role in managing their condition; Enabling all other preventive healthcare activities to be included in maintaining diabetes care
A National Diabetes Strategy and Action Plan[135]	Diabetes Australia (2013)	Preventing complications – optimal management and early diagnosis; Preventing more individuals from progressing to T2D; Strengthening prevention, care, and treatment by evidence and knowledge
Australian National Diabetes Strategy (2016–2020)[45]	Australian Government Department of Health (2015)	Coordination and integration of diabetes care across services, settings, technology, and sectors; Reducing health inequalities; Measuring health behaviours and outcomes
General Practice Management of T2D[129]	RACGP (2016)	Targets for optimal management, which encourage all patients with T2D to achieve these targets (diet, exercise, BMI, cigarette and alcohol consumption, BG levels, lipid levels, BP, urine albumin excretion, vaccination)
Guidelines for Preventive Activities in General Practice[25]	RACGP (2016)	The AUSDRISK helps assess the risk of diabetes; Patients at high risk should be tested for diabetes every 3 years from 40 years of age; Aboriginal and Torres Strait Islander people should have their risk of diabetes evaluated every 3 years from 18 years of age
National Strategic Framework for Chronic Conditions[136]	Australian Health Ministers' Advisory Council (2017)	Providing efficient, effective, and appropriate care to support chronic conditions to optimise QoL; Targeting priority populations
Diabetes in Australia: Focus on the Future[137]	Australian Health Ministers' Advisory Council (2017)	Preventing people from developing T2D; Promoting awareness and earlier detection of T1D and T2D; Reducing the occurrence of relevant complications and improving QoL; Strengthening prevention and care through research, evidence, and data
A Position Statement on Screening and Management of Prediabetes in Adults in Primary Care in Australia	Australian Diabetes Society (2020)	Formal screening using the AUSDRISK screening tool is suggested for people with risk factors of prediabetes; Pathological screening (fasting BG, HbA1c, or OGTT) is recommended for those at high risk; Prediabetes treatment should be multi-pronged, including lifestyle modification, psychological support, and pharmacotherapy (as appropriate); No medications are TGA-indicated for prediabetes; The frequency of ongoing monitoring should be personalised; Annual HbA1c testing is recommended, and this test is covered by Medicare

T2D: Type 2 diabetes; RACGP: Royal Australian College of General Practitioners; QoL: Quality of life; T1D: Type 1 diabetes; BMI: Body mass index; BG: Blood glucose; AUSDRISK: Australian Type 2 Diabetes Risk Assessment tool; HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test; BP: Blood pressure; TGA: Therapeutic Goods Administration.

2.5.2 Major Lifestyle Recommendations for Prediabetes and Diabetes

The key driving factors for prediabetes and T2D include being overweight or obese, having a sedentary lifestyle, and/or increased consumption of unhealthy foods (i.e., refined grains, processed meat, and sugar-sweetened beverages).[19, 138] Lifestyle modifications (such as healthy diets, increasing physical activity, weight loss/management, quitting smoking, and reducing alcohol consumption) are recommended for both prediabetes and diabetes management, as these changes can effectively prevent or delay progression.[14, 17, 50, 139, 140]

Healthy diets (e.g., low-carbohydrate, low-fat, and Mediterranean diets) are highly recommended to improve glucose control.[141-143] The principle of healthy eating is following a diet rich in whole grains, vegetables, fruits, legumes, and nuts, and avoiding unhealthy dietary patterns (i.e., increased consumption of refined grains, processed foods, red and processed meats, and sugar-sweetened beverages).[48, 144]

Increasing physical activities and decreasing the amount of time spent in daily sedentary behaviour are crucial components of diabetes management.[145] Increasing physical activity is also a good way to improve BG, BP, and lipid control in people with T2D.[146] The American Diabetes Association suggests that lifestyle interventions among people with prediabetes should follow diabetes prevention programs[147-149] to reach and maintain an initial weight loss of 7%, and improve moderate physical activities (i.e., playing doubles tennis and brisk walking) to at least 150 minutes per week.[50]

Weight management is a crucial component of prediabetes and diabetes management. The increasing rate of obesity is one of the main reasons for the global epidemic of prediabetes and diabetes. Having an excessive amount of body fat raises the risk of insulin resistance and prediabetes, with obese women having a higher likelihood of developing T2D compared to obese men.[140] Furthermore, weight management could effectively help patients with diabetes

keep their diabetes under control and reduce the risk of further comorbidities. The RACGP guideline recommends 5–10% weight loss for patients with overweight/obesity and T2D.[73]

2.6 Pharmacological Therapy

2.6.1 Antidiabetic Medications for Diabetes Prevention and Treatment

The classification, advantages, disadvantages, and mechanisms of the most commonly used ADMs are summarised in Table 2.3.[73, 150] Metformin is the most widely used ADM for diabetes prevention and treatment. The US and IDF guidelines suggest metformin should be started when T2D is diagnosed (unless contraindications exist), combined with lifestyle modifications.[50] However, guidelines in some countries (e.g., Australia and China) recommend that ADM should be started only if a trial of 2–3 months of lifestyle modifications fails to achieve BG control (e.g., HbA1c <7%).[151] However, a systematic review published in 2021 concluded that there was not enough evidence to recommend that management with metformin should be delayed after diabetes diagnosis.[152] Compared with delayed pharmacological therapy, early diabetes management with metformin has been associated with better BG control and a lower risk of intensifying therapy (i.e., need for another oral ADM).[153]

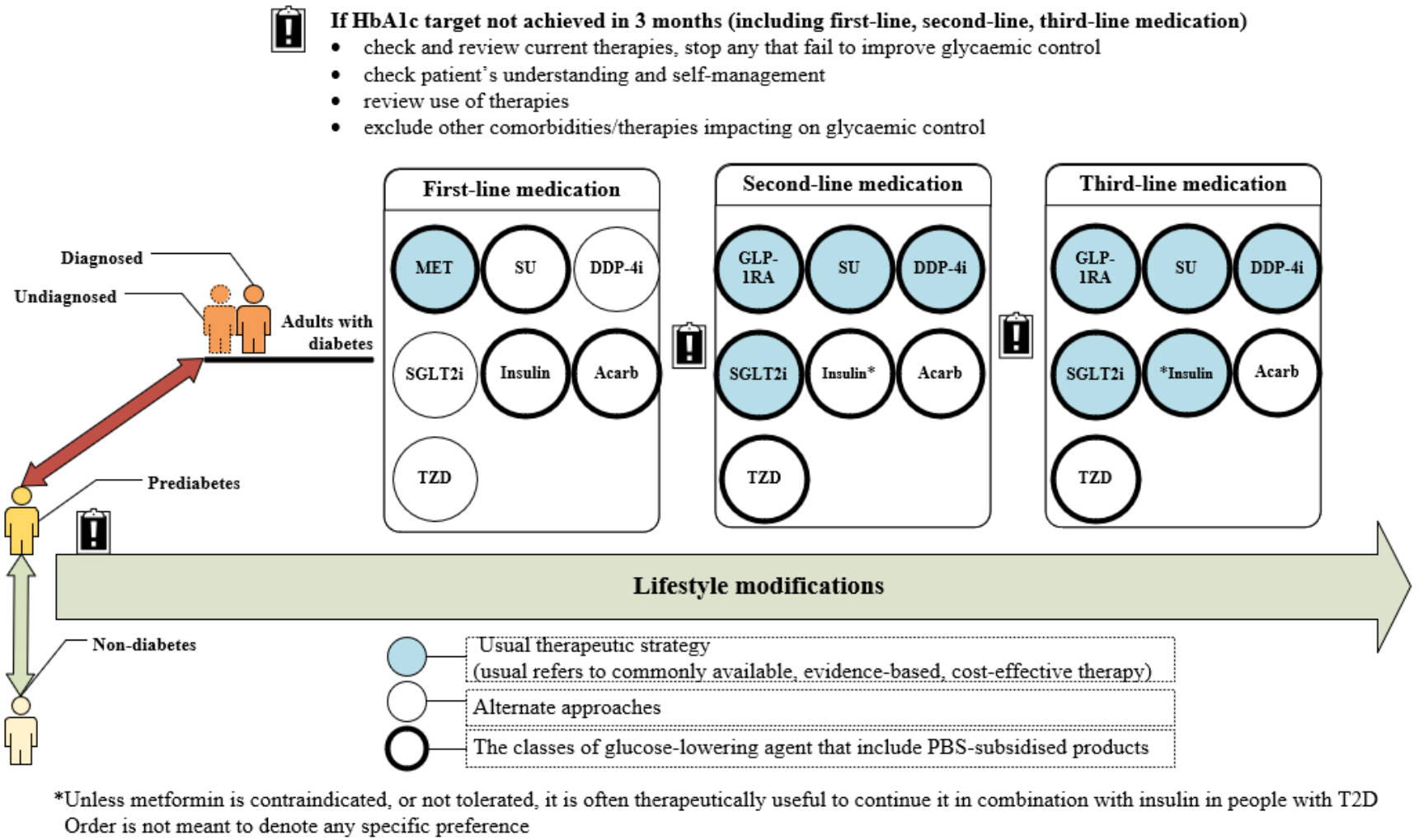
Table 2.3. Advantages, disadvantages, and mechanisms of most commonly used antidiabetic medications

Medicine category	Medicine name	Cost [(a)]	Advantages[(b)36]	Disadvantages	Mechanisms[154-156]
Insulins and analogues	Insulin	High[(a)]	Highest efficacy	Hypoglycaemia Weight gain	Directly activates the insulin receptor
Biguanides	Metformin	Low[(a)]	High efficacy	GI side effects Lactic acidosis	Affects the activity of numerous epigenetic modifying enzymes, mainly by regulating the activation of AMPK
Sulfonylureas	Glibenclamide Gliclazide Glimepiride Glipizide	Low[(a)]	High efficacy	Weight gain	Triggers insulin release in a glucose-independent manner
α-glucosidase inhibitors	Acarbose	Low[(a)]	Not reported	Bloating Flatulence	Slows down the absorption of intestinal carbohydrates and reduces postprandial glucose levels
Thiazolidinediones	Pioglitazone	Low[(a)]	High efficacy	Increased risk of heart failure Weight gain	Reduces circulating fatty acid concentrations and lipid supply in the liver and muscle, and improves insulin sensitivity
DPP-4 inhibitors	Alogliptin Linagliptin Saxagliptin Sitagliptin Vildagliptin	High[(a)]	Intermediate efficacy	Potential risk of heart failure (saxagliptin) GI disturbances	Inhibits DPP-4 activity in peripheral plasma and decreases inactivation of GLP-1 in the peripheral circulation, thereby increasing its availability (GLP-1 stimulates insulin release from β-cells)
GLP-1 analogues	Dulaglutide Exenatide Semaglutide	High[(a)]	High efficacy	Nausea Vomiting Weight loss Increased heart rate	Stimulates insulin release from β-cells and slows gastric emptying
SGLT-2 inhibitors	Dapagliflozin Empagliflozin Ertugliflozin	High[(a)]	Intermediate efficacy Benefit cardiovascular outcomes	Dehydration Dizziness Genitourinary infections Ketoacidosis Weight loss	Inhibits a sodium-glucose co-transporter to induce urinary glucose loss and lower BG levels

DPP-4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; SGLT-2: Sodium-glucose co-transporter 2; GI: Gastrointestinal; AMPK: AMP-activated protein kinase; BG: Blood glucose. (a) Overall, the mentioned antidiabetic medications are available on the general schedule on the Pharmaceutical Benefits Scheme (PBS), but the eligibility of each subsidised drug are different. High: ≥$500 per annum cost to the PBS; Low: $0–499 per annum cost to the PBS. (b) The efficacy rank and cost of drugs were based on practice suggestions from the American Diabetes Association.[36]

In terms of side effects, a systematic review highlighted that the most frequent adverse events of all ADMs were gastrointestinal symptoms, with several cases of hypoglycaemic events. Alogliptin (a DPP-4 inhibitor) has the lowest overall frequency of adverse events compared to other therapy groups.[157] Newer ADMs (e.g., SGLT-2 inhibitors and GLP-1 analogues) were associated with a 14% lower risk of major cardiovascular events among patients with T2D and pre-existing CVD, but a 2% higher risk of major cardiovascular events in those without pre-existing CVD (compared to placebo).[158] Among all these new ADMs (Table A4, Appendix A), semaglutide (a GLP-1 analogue) appears to be the most effective medication for improving HbA1c control.

In Australia, the RACGP suggests that metformin should be selected over other medications for patients with newly diagnosed diabetes, considering its low risk of weight gain and hypoglycaemia.[73] Compared with all other drugs given as monotherapy, metformin was associated with lower or similar HbA1c levels.[130] A UK substudy using the Clinical Practice Research Datalink (CPRD) database indicated that people with T2D who received metformin monotherapy as their primary treatment had longer survival times compared to a control group without diabetes.[159] Sulfonylureas and new ADMs represent the second-line treatment drugs, or first-line pharmacological therapy if metformin is contraindicated (Figure 2.1).[36, 50] Compared to the matched control group and patients receiving metformin monotherapy, the survival rate of patients treated with sulfonylureas was substantially lower, supporting metformin as a first-line treatment.[159] These treatments should be reviewed every 3 months if the patient's glucose levels are uncontrolled.



MET: Metformin; SU: Sulphonylureas; DPP-4i: Dipeptidyl peptidase inhibitor; SGLT2i: Sodium-glucose co-transporter 2 inhibitor; Acarb: Acarbose; TZD: Thiazolidinedione; GLP-1RA: Glucagon-like peptide-1 receptor agonist; PBS: Pharmaceutical Benefits Scheme; T2D: Type 2 diabetes
Source: Adapted from Gunton (2014)[37]

Figure 2.1. Australian algorithm for diabetes management and clinical medication

Another point of contention when considering pharmacological therapy is how to select and add another ADM to metformin. Overall, it has been estimated that all ADMs added to metformin are effective.[130] Nonetheless, when clinicians choose between possible adjunctive agents, they should consider that adding different ADMs to metformin (or sulfonylureas) has different effects on efficacy and safety endpoints.[160] Indeed, starting metformin at different times after diagnosis may cause metformin to be interrupted (adding additional drugs) or to be discontinued (changed into another drug).[153, 161] In the UK, a retrospective cohort study of people with T2D (n=33,849, CPRD data) reported that across oral ADM lines of treatment (mono, dual, or triple treatment), medications classically associated with lower incidence of hypoglycaemia and weight loss were commonly associated with better medication adherence and enhanced glycaemic levels.[162] A systematic review published in 2021 and including 10,974 patients with diabetes at higher risk of CVD found that combination treatment with metformin and SGLT-2 inhibitors is an effective and safe alternative to the combination treatment with metformin and sulfonylureas.[163]

In 2013, prescriptions for metformin reached a peak of 83.6% (95%CI 83.4;83.8) of ADM prescriptions, while the prescription of sulfonylureas achieved a low of 41.4% (95%CI 41.1;41.7);[164] metformin and sulfonylureas were still the most utilised therapies as first-line and add-on therapies. Incretin-based treatments (gliptins and GLP-1 analogues) and thiazolidinediones have also been prescribed as alternative add-on therapies, but they are rarely used in the first-line treatment of T2D.[164] From 2013 to 2016, the pharmacological therapy landscape for diabetes underwent dynamic changes in Australia. More patients started using the newer but more expensive ADMs (i.e., DPP-4 inhibitors, GLP-1 analogues, and SGLT-2 inhibitors) compared to older/classical ADMs (i.e., sulfonylureas, α-glucosidase inhibitors, and thiazolidinediones).[165] However, the new ADMs (DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors) were less commonly prescribed to patients with diabetes living in more deprived areas of Australia, although this difference decreased between 2007 and 2015.[166]

2.6.2 Pharmacological Management of Prediabetes

Despite the recognised benefits of metformin and other ADMs for managing T2D, there are still uncertainties about their use for prediabetes management. Some ADMs (i.e., metformin, α-glucosidase inhibitors, and thiazolidinediones) have been evaluated for their ability to prevent or delay the development of diabetes in people with prediabetes.[14, 139] A Cochrane review published in 2019 showed that, in comparison to placebo (i.e., regular diet and exercise advice), the usage of metformin delayed or reduced the risk of T2D among high-risk groups. However, metformin was not better than intensive exercise and diet in delaying or reducing the risk of T2D.[167] Despite the benefits of intensive lifestyle changes, long-term maintenance of intensive lifestyle changes is challenging for patients,[168] and the use of ADMs represents an alternative for controlling BG and reducing diabetes progression among these patients. For people with glucose intolerance that continues despite lifestyle modification and weight loss methods, using ADMs can reduce the risk of future diabetes by 25–30%.[169] However, there have been no trials exploring the effectiveness of ADMs on clinical outcomes beyond preventing T2D, such as renal failure or myocardial infarction.[14] Therefore, ADMs are currently not recommended by the Food and Drug Administration in the US or the Therapeutic Goods Administration in Australia to manage prediabetes.[14, 169]

2.7 Gaps Between Diabetes Guidelines and Practice

Even when choosing authoritative and widely accepted guidelines, evidence still indicates some gaps between 'real' clinical practice and best clinical practice.[170] A retrospective study in the US involving 305 primary care physicians showed that 38% of them self-reported using national guidelines for diabetes management.[171] However, one-third of these 'compliant' doctors had diabetes management activities registered in patients' EHRs that were inconsistent with current guidelines. Furthermore, while most primary care physicians in that study reported that they were 'very likely' to screen people at higher risk of diabetes, only 76% followed recommendations for diabetes screening. In Australia, a retrospective study using the

Melbourne East Monash General Practice Database (MAGNET, n=10,257 people) indicated that one-third of older people (aged ≥65 years) with T2D had no records of HbA1c levels being tested in the past 2 years.[172]

Moreover, people from disadvantaged groups are less likely to achieve diabetes control than those experiencing less disadvantage, increasing their risk of delayed diagnosis and diabetes complications.[136] For that reason, the Australian National Diabetes Strategy (2016–2020) highlights that reducing health inequalities should also be a guiding principle of diabetes screening and management.[45] In addition, a patient-oriented approach should guide the selection of ADMs to minimise adverse effects, improve medication adherence, and achieve better diabetes control. Considerations should include diabetes-related comorbidities (i.e., IHD, heart failure, and CKD), hypoglycaemia risk, the potential side effects, impact on weight, patient preferences, and costs.[2, 50, 173] However, little analysis has been done in an Australian context to discover the different prescription profiles among patients with diabetes and history of one or more comorbidities.

Finally, ADM non-adherence is another major contributing factor to not achieving diabetes control.[174] Patients with T2D frequently struggle to adhere to therapy for many reasons (e.g., worries about administration, convenience, timing, potential side effects, and costs).[175] Even though the presence of new classes of ADMs and increased efforts in patient education and targeted interventions aimed at improving adherence,[174] the prevalence of medication adherence has ranged from 38.5% to 93.1% in 27 studies.[176] Strategies to improve adherence (patient diabetes education, medication treatment management programs, motivational interviewing, and cooperative management),[175] especially for patients with newly diagnosed diabetes,[177] should be considered.

A systematic review of 56 studies from 20 countries found evidence for the following cost-effective interventions to reduce diabetes progression:[178] (1) intensive lifestyle interventions

and management to prevent T2D among people with prediabetes (vs standard lifestyle suggestions); (2) universal opportunistic screening for undiagnosed T2D in African Americans aged 45–54 years; (3) intensive BG control among people with newly diagnosed T2D, as implemented in the UK Prospective Diabetes Study (vs conventional glycaemic control); and (4) statin therapy for secondary prevention of CVD (vs no statin therapy). Health policymakers should consider giving higher priority to these interventions; however, implementing these strategies needs to consider socioeconomic, cultural, and health system aspects in each country.

To ensure national health budget targets are designated to areas where the greatest benefits to patients can be generated, it is crucial to find evidence of diabetes screening, diagnosis, and management in primary care across Australia.

2.8 Evidence of Diabetes Monitoring and Control

The RACGP guidelines advise patients with diabetes should have their HbA1c, BP, and lipid levels evaluated annually to improve the management and control of these clinical parameters.[129] The goals for optimal management of T2D are presented in Table A2, Appendix A.[129] However, gaps between real-world practice and guideline recommendations for diabetes control have been reported worldwide.[112, 129, 171, 179] Even in the UK, where diabetes prevention programs are carried out on a large scale,[180] the proportion of patients with diabetes not meeting recommended targets is alarmingly high.[108] In 2012, more than 35% of people with diabetes failed to reach HbA1c targets and approximately 50% were unable to achieve BG control.[181]

In Australia, a systematic review including 123 Australian studies found that nearly 50% of patients with diabetes received ‘standard care’ (i.e., assessment of HbA1c, lipids, BP, weight, foot and eye health).[112] Among those evaluated, 40–60% met management goals for HbA1c, BG, or lipid levels, but the study did not report the percentage of patients with the three parameters under control.[112] Most studies included in that review used EHRs to investigate

diabetes control. However, these records were mainly from non-representative samples or used data from specialised centres rather than primary care settings, hindering broader extrapolation of the findings. Furthermore, while some sociodemographic and cardiovascular risk factors, or a history of CVD may influence diabetes control,[94, 101] other potential determinants of diabetes management and control (e.g., sociodemographic and clinical variables) have not been widely investigated. Despite these limitations, the figures in the Australian systematic review[112] are consistent with measured data from the Australian Health Survey (2011–2012), which reported that 54.7% of adults with known diabetes met HbA1c goals, 39% reached BP control, and 38% had cholesterol levels within recommended limits.[13]

Therefore, it is critical to identify key clinical parameters for diabetes monitoring and control, including BG, BP, and lipid levels, and to assess whether sociodemographics, CVD risk factors, or comorbidities influence diabetes monitoring or control.

2.9 Use of Electronic Health Records to Monitor and Prevent Diabetes

2.9.1 Global Use of Electronic Health Records for Diabetes Research

Globally, health research institutions are increasingly looking towards using national EHR databases to investigate diabetes diagnosis and management. This source of real-world information is becoming increasingly important to help healthcare planners manage the diabetes epidemic.[182] Furthermore, using large national databases can reduce bias, comprehensively covering the region or country over a long period and reducing the impact of patient migration and lifetime.[183] This strategy has been used in countries such as England, the US, Germany, Canada, Spain, and Poland to explore the burden of diabetes in terms of diagnosis, management, and outcomes.[28, 184-187] For example, a recent comprehensive analysis of the Polish National Database estimated that the overall prevalence of diabetes was around 7% in Poland.[184] In England, a retrospective cohort study using EHRs from The Health Improvement Network (THIN) database, one of the largest UK general practice databases, estimated that the prevalence of T2D doubled during 2000–2013, although the number of incident diabetes cases

has risen more steadily.[164] Moreover, results from the UK CPRD database indicated that the prevalence of T2D rose from 3.2% in 2004 to 5.3% in 2014.[188] In the US, the percentage of undiagnosed diabetes dropped substantially from 32.8% in 1998 to 17.8% in 2020, indicating substantial improvements in diabetes screening and diagnosis.[189]

Furthermore, real-world evidence from EHRs is increasingly considered and used in making medical decisions.[20, 190] A 2017 comprehensive systematic review summarising recent primary health care data collection projects worldwide suggests that advocating and supporting long-term and extensive primary health care data collection requires robust technical services, and solid academic and government support.[191] Globally, many national general practice databases have been used to investigate diabetes prevention and management. Table 2.4 summarises several leading national databases and prominent GP databases based on available sources.[191-193] The leading databases come from English-speaking countries (US, UK, Australia, and Canada).

Table 2.4. Demographics of landmark primary care databases

Country	Database	Number of general practices (GPs or healthcare professionals)	Number of patients (% population)
UK	CPRD (aka GPRD)[194-196]	600 practices	13 million (20%)
	THIN[125, 164]	562 practices	11.1 million (17%)
US	Veterans Administration – Corporate Data Warehouse[197]	GPs unknown (53,000 healthcare professionals)	17 million
	General Electric Database[198]	7,259 GPs	8.9 million (2.8%)
	Geisinger Health System[199]	41 community practice clinics	400,000 (0.1%)
Australia	MedicineInsight[200]	662 practices (2,700 GPs)	4.4 million
	BEACH[201]	Rotating sample of 1,000 GPs	1.8 million GP–patient encounters
	MAGNET[172, 202]	50 practices	1.1 million
	PATRON[203]	GPs unknown	3.5 million
	POLAR[204, 205]	Over 350 practices	3.1 million
Canada	CPCSSN[206]	200 practices	1.5 million
	EMRALD[207]	54 GPs	0.5 million
Netherlands	IPCI[208]	600 GPs	1.0 million
	Nivel-PCD[209]	500 practices	1.6 million
Spain	SIDIAP[210, 211]	350 practices	17 million
	BIF AP[212]	1,183 GPs	3.2–4.8 million
Belgium	Intego Project[213]	95 practices	285,000 (2.5%)
France	LPD-Cegedim[214]	1,200 GPs (+750 various medical specialists)	1.5 million (2%)
Italy	Health Search Database[215]	900 GPs	2.5 million (4.1%)

CPRD: Clinical Practice Research Datalink; GPRD: General Practice Research Database; THIN: The Health Improvement Network; General Electric database: Centricity Electronic Medical Records Research Database; BEACH: Bettering the Evaluation and Care of Health; MAGNET: Melbourne East Monash General Practice Database; PATRON: PATRON Primary Care Research Data Repository; POLAR: Population Level Analysis and Reporting; CPCSSN: Canadian Primary Care Sentinel Surveillance Network; EMRALD: Electronic Medical Record Administrative Data Linked Database; IPCI: Integrated Primary Care Information Project; Nivel-PCD: Nivel Primary Care Database and Netherlands Information Network of General Practice; SIDIAP: Information System for the Development of Primary Care Research; BIF AP: Database for Pharmacoepidemiology; LPD-Cegedim: Longitudinal Patient Data Network–Cegedim; GP: General practitioner.

2.9.2 Use of Pharmaceutical Benefits Scheme (PBS) Data in Australia

Using PBS data to investigate prescription patterns and influencing factors is a cost-effective method to evaluate the gaps between practice and pharmacological therapy guidelines in Australia.[216] According to *Australia's Health* (2018),[217] GPs prescribe the most PBS-subsidised drugs, and about 90% of all drugs dispensed. Published studies from 1987 to 2013 using PBS data generally investigated trends in medication use (33%), GP and clinic prescription (26%), medication use and outcomes (18%), and assessment of intervention effects (17%).[218] From 2003 to 2013, the use of antihypertensive medications, ADMs, and lipid-modifying medications dispensed three or more times per year rose by 8.2%, 17%, and 53%, respectively, among patients with T2D in Australia.[219] Moreover, metformin was Australia's seventh most prescribed medication in 2020–2021, with 5.4 million prescriptions dispensed.[220] Therefore, using Anatomical Therapeutic Chemical (ATC) Classification codes (Table A4, Appendix A) to identify drugs for diabetes treatment in PBS data is practical in Australian primary care settings.

However, little is known about the ADM prescriptions based on the information collected by GPs in Australia. Patients visit their GP often, with more than 8 in 10 Australian individuals attending a GP yearly,[15] making GPs one of the most seen health professionals. In 2017–2018, more than two-thirds (67.4%) of the Australian population received a prescription from a GP.[15] Additionally, general practices collect and electronically store data on prescriptions, laboratory results, and clinical comorbidities.[200] Those kinds of information are not available through PBS data.[218] Therefore, exploring the prescription profile of middle-aged Australians based on the general practice database may be useful in exploring the burden of diabetes, gaps between guidelines and clinical practice, and potential interventions, and identifying which groups would benefit more from strategies targeted at reducing diabetes progression.

2.9.3 National Databases for Diabetes Research in Australia

The Australian Government states that the country's ability to remain competitive in the modern global economy depends on the ability to use national data.[221] In Australia, MedicineInsight information has been used to assist GPs in their therapy and management of patients, and to eventually improve patients' health.[22, 222, 223] However, there are limited primary health care data for use in research in Australia.[224]

Table 2.4 summarises the Australian general practice databases/programs: BEACH (Bettering the Evaluation and Care of Health), MAGNET, PATRON Primary Care Research Data Repository, POLAR (Population Level Analysis and Reporting), and MedicineInsight. BEACH program involved a manual collection of paper-based information on patients seen by randomly selected GPs from 1998 to 2016.[225] Each GP recorded specific details (i.e., Medicare item, reason for visit, referrals, and prescribed medications) of 100 consecutive encounters.[225] This data was manually entered into an electronic database to be used and analysed as a source of GP encounters.[201, 226] Regarding the data extraction tools used by Australian databases based on EHRs, MedicineInsight, POLAR, and PATRON use the GRHANITE™ extraction tool, while MAGNET used PEN-CAT and GRHANITE™ (study ceased). Additionally, there are 31 Primary Health Networks (PHNs) in six states and two territories in Australia, which are independent organisations aiming to increase the effectiveness and efficiency of health services and better coordinate healthcare services to enhance the quality of support for people.[227] PHNs use Primary Sense for data extraction.[228]

It is worth highlighting that Australia's most extensive, nationally representative, general practice database is MedicineInsight, which NPS MedicineWise administered until 2022 with support from the Australian Government Department of Health. The database contains de-identified EHRs from approximately 662 general practices (8.2% of all general practices) in Australia, and over 2,700 GPs (as at 2018).[200] Data extraction algorithms for MedicineInsight can capture diabetes cases and prescribed ADMs, with a sensitivity, specificity, and positive

predictive value of 84%, 99%, and 93%, respectively.[229] Several studies in the field of T2D using MedicineInsight data have explored the association between SGLT-2 inhibitor use and the risk of infection among people with diabetes,[230] as well as management characteristics among patients with T2D and CKD (screening, diagnosis, and prescribing).[231] Another study using MedicineInsight data (2013–2015) indicated that more than 90% of participants with T2D (n=69,718) lived with at least one comorbidity.[11] Nevertheless, investigations into the burden of diabetes in Australian general practice, or whether current guidelines on screening, diagnosis, management, and risk reduction are consistent with GP activities, are lacking.

An additional essential advantage of the MedicineInsight is that patients within each practice have a unique identification number, allowing the development of an ongoing longitudinal database that can be used to generate a partial clinical history.[200] For instance, a paper using MedicineInsight data to investigate chronic musculoskeletal conditions identified that 46% of individuals had available EHRs before the launch of MedicineInsight in 2011.[232] Another study of individuals aged 60–65 years found that 75% of patients (n=259,236) consulted between 2010 and 2017 had visited the same practice at least three times in two consecutive years (i.e., had EHRs with available information on diagnosis, reason for prescription, reason for encounter, and/or immunisations), while 22.6% (n=58,549) patients attended the same practice every year in that period.[233] Therefore, MedicineInsight data can provide national data for exploring patterns over time or causal inference using a longitudinal approach.

2.9.4 Challenges of Using Electronic Health Records for Diabetes Research

The primary purpose of recording information in EHRs is for clinical care and administration activities (billing, scheduling, registration, or reimbursement), not for research.[20] Nowadays, EHRs are gradually being modified to facilitate future research. However, we are still far from having 'complete EHRs'.[20, 43] Overall, the challenges to using EHRs for research purposes are: (1) heterogeneity among systems; (2) data completeness; (3) data quality and validation; and (4) knowledge about the system.[234] Additionally, the use of EHRs requires more focus on the

quality of denominator data to increase the potential benefits of EHRs for patient care, service planning and service improvement, and policy.[235]

Heterogeneity among systems: Three primary sources of bias can result from this challenge: (1) data collected in a variety of health services (e.g., GPs, specialists, hospitals) can differ, leading to selection bias (e.g., patients and measurements obtained in emergency departments are different from those in outpatient settings); (2) due to information bias (i.e., data within the EHR are only collected if they are considered clinically meaningful by the service provider), we can get different results for the same associations depending on where the data are coming from (i.e., data from the same patients seeking care across multiple facilities); and (3) referral encounters can lead to admixture bias (i.e., referral patients may be sicker or have a different distribution of underlying comorbidities).[236] On top of this, different services can use different systems and tools for data entry, which may affect data extraction and completeness of EHRs.

Data completeness: The lack of common health index data (e.g., age, sex, BMI, smoking status, alcohol consumption) in EHRs can affect statistical analysis and the extrapolation of the results.[237] Moreover, unlike clinical trials, data in EHRs are not collected at regular intervals or for all patients attending health services, which may lead to information or selection bias.[236] This challenge needs to be explicitly outlined in the research. A 2015 systematic review found that reporting of missing data had been limited in studies predicting diabetes prevalence, with 62.5% (n=30/48) of included articles not reporting any material on missing data or handling methods; in 43.8% of the included articles, the authors used imputation or case-wise deletion to handle missing predictor values.[238]

Data quality and validation: EHRs reflect real-world data collected for clinical and/or administrative purposes rather than for research. Therefore, the data quality and reliability of the extracted data should be considered by researchers when using these resources.[43, 239, 240] For diabetes research, for example, it may be relevant to exclude cases of T1D (<35 years old and

requiring insulin[241]) when calculating the prevalence and incidence of T2D among younger people. From a longitudinal perspective, management strategies are different in the initial phase of T1D and T2D, but are similar in the final phase when insulin is required.[241, 242] Some algorithms have shown excellent performance in identifying patients with T1D or T2D using national primary care EHRs.[241, 242] In England, a research team using the THIN database validated a two-step approach with 100% sensitivity and 100% specificity to identify individuals with T1D and T2D.[243] Such algorithms can be modified and adapted for other research studies using primary care EHRs.

Knowledge of the system: Insufficient understanding and recognition of the data underlying research leads to poor study design, analysis, and interpretation of research findings. Therefore, it is fundamental that, apart from appropriate statistical and informatics training for investigators, all researchers using EHR data become familiar with the database operation manual, and appropriately report the strengths, limitations, and nuances of the database in their research papers.[234, 240, 244] Different EHR databases have in place data managers, data governance groups, community representatives, and other professionals and stakeholders to certify that all research ethics, data security, and privacy policies are in place, and ensure that the use of EHRs for research is transparent, meaningful, and at expected standards.[43, 234, 244]

2.9.5 Using Full Electronic Health Records for Diabetes Diagnosis and Management

Using patients' full EHRs (e.g., routine information, diagnostic and prescription information, and administrative data) or restricted EHRs (e.g., conventional information along with selected EHR information) is superior to using the conventional covariates alone (e.g., essential predictors and their interactions, such as age, gender, BMI, smoking status, hypertension) to detect patients with diabetes.[245, 246] Generally, the prevalence of chronic diseases can be accurately estimated using EHRs. However, calculating the 'incidence' is challenging because EHRs do not contain the explicit notation distinguishing patients' first onset of the disease from

follow-up visits or disease recurrence.[183] Data linkage or combined use of diagnostics, medical prescriptions, and laboratory results may help minimise this issue.

Algorithms for the identification of diabetes using EHRs have been reported by some national studies in the UK (without reporting validity)[164, 172] and US (for T2D identification, sensitivity 90% and specificity 100%).[247] In Australia, a study utilising the MAGNET database found T2D patients by identifying individuals who met one or more of the following criteria[202]: (1) had at least one diagnosis of T2D in their clinical record; (2) were prescribed ADMs; or (3) had at least two HbA1c records ≥6.5%, or two FBG records ≥7 mmol/L, within the 2 years before their last visit.[172] This database only included 50 practices in the South East of Melbourne and the algorithms were not validated.[202] Furthermore, algorithms using the Australian MedicineInsight database to identify patients with diabetes (i.e., combining diagnosis, prescription, and pathology results) have a sensitivity of 89% and specificity of 100% compared to data obtained from the stored medical records at the practices.[200, 248]

2.10 Chapter Synopsis

International examples and the established literature demonstrate the capacity and significance of using national EHR databases to investigate prediabetes and diabetes. To address knowledge gaps about the prevalence, early treatment, and comprehensive management of prediabetes and diabetes in Australian primary care settings, we used EHRs from the MedicineInsight. Based on that database, Chapters 4–7 of this thesis provide a comprehensive real-world profile of diabetes screening among high-risk groups, diagnosis of undiagnosed diabetes or prediabetes, monitoring and control of key diabetes-related clinical parameters (e.g., BG, BP, lipid levels), and the effects of metformin therapy on BG levels among people with newly diagnosed diabetes and prediabetes. This previously uncaptured picture of diabetes in Australia could provide evidence-based recommendations for further national diabetes prevention and intervention strategies in primary care settings.

Chapter 3. Methodology

3.1 Preface

This chapter discusses data source and design, data generation and extraction, relevant epidemiological concepts (i.e., dealing with confounders and potential bias), and statistical analyses used in the research papers included in this thesis.

3.2 Data Source – MedicineInsight Database

MedicineInsight is an Australian primary care database supported by the Australian Government Department of Health. At the time the thesis was undertaken, MedicineInsight was managed by NPS MedicineWise,[200] but from 1 January 2023,[249] the Australian Commission on Safety and Quality in Health Care (the Commission) became the custodian of the MedicineInsight database. It uses a third-party data extraction tool (GRHANITE™) to identify, extract, and safely transmit entire practice EHRs.[223] It uses confidentiality controls when providing data to researchers, such as removing personal identifiable information (e.g., name and postcodes) and limiting lower-level geographic data to avoid inadvertent identification of patient data.[200]

In 2018, the database contained de-identified EHRs of 3.2 million patients from more than 650 practices (8.2% of all general practices across Australia) and over 2,700 GPs. Data have been collected since 2011. The database covers all Australian states and territories, including practices of different sizes, billing methods, and types of services offered.

The MedicineInsight database includes 15 different datasets (fields) with information recorded in ‘free text’ or ‘coded’ formats (using pre-defined medical codes or imported laboratory values).[250] Table 3.1 describes the six specific datasets and variables used in this doctoral project.

Table 3.1. MedicineInsight datasets used in this doctoral project

Name of dataset	Description	Main variables used from the dataset
Patient	Patients' characteristics	Sex, Year of birth, Aboriginal status, Rurality, IRSAD, Practice ID, Smoking status
Practice	Practice characteristics	Practice ID, Rurality, IRSAD
Diagnosis	Diagnosis	Diagnosis, Visit date
Encounter reason	Reason for encounter	Reason for encounter, Visit date
Prescription reason	Reason for prescription	Reason for prescription, Script date, Medicine name, Medicine active ingredient
Observation	Routine measurements	Observation date, BG, BP, Lipids, Urine records
Pathology results	Laboratory results	Result date, BG, Lipids, Urine records
Script items	Prescription data	Script date, Frequency, Medicine name, Medicine active ingredient

BG: Blood glucose; BP: Blood pressure; IRSAD: Iindex of Relative Socio-economic Advantage and Disadvantage. 'Description' refers to summary of MedicineInsight data tables and fields.[200]

Note: All datasets[250] contain patient ID.

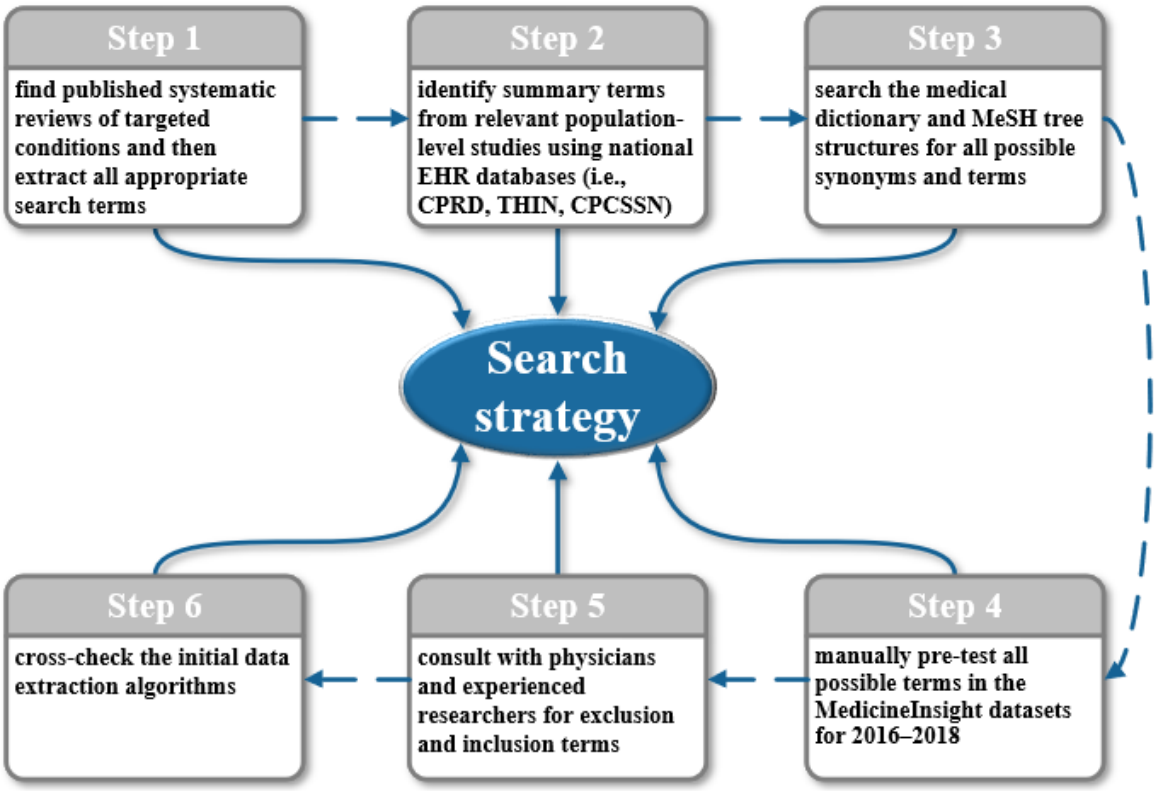
3.3 Data Preparation and Extraction

3.3.1 Dataset Preparation and Variable Definition

Ideally, the definitions of the study population for different studies using EHRs should consider the specificities of the database being used and follow recommendations to improve diagnostic accuracy.[251] For that purpose, only one record per patient and date was considered for analysis in this doctoral project. Moreover, any records related to administrative activities (e.g., emails, paperwork, pathology forms, reminders, or recalls) were excluded as they do not represent 'formal' encounters between patients and GPs. Finally, all analyses were restricted to patients regularly attending MedicineInsight practices. According to the RACGP's Standards for GPs, 'active' patients (i.e., 'regular' patients) are those who attended the service/practice at least three times in the past 2 years.[252] As the three encounters could be consecutive and related to the same condition (e.g., a cold then complicated with sinusitis that required subsequent management with antibiotics, or for wound management that required subsequent assessments), reflecting 'infrequent' rather than regular service users, we added the additional criteria that the

three encounters should include at least one in each of these two consecutive years. The use of 'regular' participant data for research purposes minimises the chance of underestimating health estimates based on EHRs; EHRs of regular patients are more likely to include information about their clinical history, and diagnostic or preventive activities than the EHRs of infrequent patients, who tend to attend a practice for acute or unexpected activities.[22]

For diabetes diagnosis, the annual MedicineInsight report provides reference medical terms to identify diabetes using the Diagnosis, Encounter Reason and Prescription Reason datasets. When extracting diagnostic information from these three datasets, the research team involved in this doctoral project included all possible terms, misspellings, codes, and abbreviations of all possible health conditions based on the MedicineInsight report (2018–2019) (Table B1, Appendix B).[253] Moreover, to minimise the risk of misclassification bias, we developed the following six-step method to identify all possible terms of targeted diseases for data extraction (Figure 3.1): (1) find published systematic reviews of targeted conditions and then extract all appropriate search terms; (2) identify summary terms from relevant population-level studies using national EHRs;[22] (3) search the medical dictionary and MeSH tree structures (https://meshb.nlm.nih.gov/search) for all possible synonyms and terms; (4) manually pre-test all possible terms in the MedicineInsight datasets for 2016–2018; (5) consult with physicians and experienced researchers for exclusion and inclusion terms; and (6) cross-check the initial data extraction algorithms.



HER: Electronic health records; CPRD: Clinical Practice Research Datalink; THIN: The Health Improvement Network; CPCSSN: Canadian Primary Care Sentinel Surveillance Network; MeSH: Medical Subject Headings.

Figure 3.1. The search strategy of possible terms: a six-step method

Although T1D and T2D have different physiopathology and epidemiological profiles, many of the terms recorded in MedicineInsight did not differentiate between these two forms of diabetes and were coded as 'diabetes mellitus' or 'DM' only. Considering that the long-term consequences and management plan for T1D are similar to T2D, we did not make a distinction among the two types for this thesis. However, the thesis focuses primarily on adults (18+ years) with diabetes. The exemption is Paper 3 that estimated the average treatment effect of early versus delayed metformin use in diabetes, for which we limited the analysis to those aged 40 years or older. By adopting this approach, we intended to increase the probability that patients who received a diabetes diagnosis at that age would have T2D (and mainly used metformin, not insulin). Also, this is the recommended age to start regular diabetes screening.[134, 254]

Finally, patients diagnosed with GDM or any other form of transient diabetes were excluded because these health conditions could cause partial or long-term metabolic changes and different treatment plans, which could lead to biased results.

Despite the accuracy of the algorithms developed by MedicineInsight to identify patients with diabetes,[248] they do not consider laboratory results or standardised cut-off points for diabetes or prediabetes diagnosis. Thus, for this thesis, we adapted the data extraction algorithms to facilitate the creation of specific cohorts that would help us answer the proposed research questions. Therefore, results from our research cohort may differ slightly from other studies using the same database.

For data extraction using the laboratory results, we used the recommended cut-off points presented in Table 3.2 for diagnosing diabetes, prediabetes, and other metabolic disturbances investigated in this thesis.[129] Laboratory results and reporting dates were obtained from the pathology results dataset using Logical Observation Identifiers Names and Codes.[223] All units of the recorded pathological results were included to improve data precision.

Table 3.2. Cut-off values and units for diagnosis of diabetes, prediabetes, dyslipidaemia, and chronic kidney disease

Condition	Definition using pathology results	Results value	Results value
Diabetes	1) fasting blood glucose	≥7.0 mmol/L	≥126 mg/dL
	OR 2) random blood glucose	≥11.1 mmol/L	≥200 mg/dL
	OR 3) HbA1c	≥48 mmol/mol	≥6.5%
	OR 4) OGTT	≥11.1 mmol/L	≥200 mg/dL
Prediabetes	1) fasting blood glucose	6.1–6.9 mmol/L	110–124 mg/dL
	AND/OR 2) 2-hour blood glucose in an OGTT	7.8–11.1 mmol/L	140–200 mg/dL
	OR 3) HbA1c	42–47 mmol/mol	6.0–6.4%
Dyslipidaemia	1) Total cholesterol	≥5.5 mmol/L	≥213 mg/dL
	OR 2) HDL cholesterol – for males (for females)	<1.0 (<1.3) mmol/L	<38.7 (<50.3) mg/dL
	OR 3) LDL cholesterol	≥3.5 mmol/L	≥135 mg/dL
	OR 4) Triglycerides	≥2.0 mmol/L	≥177 mg/dL
Chronic kidney disease	1) two eGFR or GFR results	eGFR <60 mL/min/1.73m^2	GFR ≤90 mL/min
	OR 2) presence of albuminuria for >90 days – for males (for females)	albuminuria ≥2.5 (≥3.5) mg/mmol	ACR ≥22.1 (≥31.0) mg/g

HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; ACR: Albumin-to-creatinine ratio.

Note: Valid ranges: for blood glucose levels – 2.6–21.1 as mmol/L OR 50–415 as mg/dL; for HbA1c – 3.3–14 as % OR 15–130 as mmol/mol.

MedicineInsight also captures sufficient data from EHRs to get a picture of prediabetes, but setting diagnostic criteria can be complex using records of diagnosis and laboratory results. According to the diagnostic criteria (Table A1, Appendix A), prediabetes is generally diagnosed by impaired glucose tolerance or impaired fasting glucose and/or borderline HbA1c for at least two tests. Impaired glucose tolerance and impaired fasting glucose are used to describe abnormalities in blood glucose levels that are above normal range but below the threshold for diabetes.[2] In terms of impaired glucose tolerance, it is assessed by the 2-hour plasma glucose value in the 75g OGTT.[2] All guidelines use the same cut-off for impaired glucose tolerance (7.8–11.0 mmol/L). However, WHO, the Australian Diabetes Society (ADS), and the American Diabetes Association (ADA) use different cut-off values for impaired fasting glucose (WHO and ADS: 6.1–6.9 mmol/L; ADA: 5.6–6.9 mmol/L). HbA1c is a reliable indicator of long-term blood glycaemic control over the previous 2–3 months, and also a useful biomarker in the diagnosis and prognosis of patients with diabetes.[255] A 2013 systematic review suggested using a narrow HbA1c range (6.0–6.4%) to diagnose prediabetes,[78] aligning with the current definition of prediabetes recommended in Australian guidelines.[14]

Therefore, the definitions for diabetes and prediabetes diagnosis used in this thesis were based on current guidelines[14, 25] and considered a combination of recorded diagnosis with data reported in other fields (i.e., laboratory results and prescribed medication), as specified in Table 3.3. These definitions were then adapted to answer the specific research questions of the papers within this thesis. The definitions for diagnosed or undiagnosed diabetes and prediabetes (cohort using 2016–2018 data) are presented in Chapter 4 and Table C1, Appendix C. The definitions for past recorded diabetes (i.e., diabetes diagnosis recorded in 2015–2016) or newly recorded diabetes (i.e., diabetes diagnosis recorded in 2017 but not in 2015–2016) are introduced in Chapter 5. Finally, the definitions of 'incident' diabetes and 'incident' prediabetes (using 2012–2017 data) are reported in Chapters 6 and 7, respectively.

Table 3.3. Definitions of diabetes and prediabetes diagnosis

Condition	Definitions
Recorded diabetes	(1) Have a diagnosis of 'diabetes mellitus' in two fields (either in the diagnosis, reason for encounter, or reason for prescription fields) or on two different occasions in the same field, OR (2) They were prescribed insulin (ATC code A10A) AND/OR an oral antidiabetic medication (ATC code A10B, except metformin): glibenclamide, gliclazide, glimepiride, glipizide, acarbose, pioglitazone, alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dulaglutide, exenatide, dapagliflozin, empagliflozin, ertugliflozin, OR (3a) Have a diagnosis of 'diabetes mellitus' in one field (either in the diagnosis, reason for encounter, or reason for prescription fields), AND were prescribed metformin (in the absence of PCOS diagnosis) (3b) Have a diagnosis of 'diabetes mellitus' in one field only (either in the diagnosis, reason for encounter, or reason for prescription fields), AND have one recorded laboratory test with raised glucose levels within the last 24 months (i.e., FBG ≥7.0 mmol/L; RBG ≥11.1 mmol/L; HbA1c ≥6.5%) or OGTT ≥11.1 mmol/L.
Recorded prediabetes	(1) They do not satisfy the criteria for diabetes, AND (2) Have a diagnosis of 'prediabetes' in two fields (either in the diagnosis, reason for encounter, or reason for prescription fields) or on two different occasions in the same field, OR (3a) Have a diagnosis of 'prediabetes' in one field (either in the diagnosis, reason for encounter, or reason for prescription fields), AND were prescribed metformin (in the absence of PCOS diagnosis) (3b) Have a diagnosis of 'prediabetes' in one field only (either in the diagnosis, reason for encounter, or reason for prescription fields), AND have one recorded laboratory test indicating prediabetes within the last 24 months (i.e., FBG 6.1–6.9 mmol/L and/or OGTT 7.8–11.1 mmol/L OR HbA1c 6.0–6.4%)

ATC: Anatomical Therapeutic Chemical classification; PCOS: Polycystic ovary syndrome; HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; RBG: Random blood glucose; OGTT: Oral glucose tolerance test. Study period: 2016–2018.

3.3.2 Data Extraction of Comorbidities and Other Variables

Data extraction of targeted comorbidities combined codes and 'free text' that considered misspellings and synonyms, recorded either in the Diagnosis, Encounter Reason, or Prescription Reason datasets. Furthermore, all available data in MedicineInsight (i.e., 60% of adults in MedicineInsight with EHRs since 2000) was searched to obtain more accurate data about the prevalence of the targeted comorbidities: CVDs (i.e., heart failure, stroke, IHD), dyslipidaemia, CKD, overweight/obesity, or hypertension.

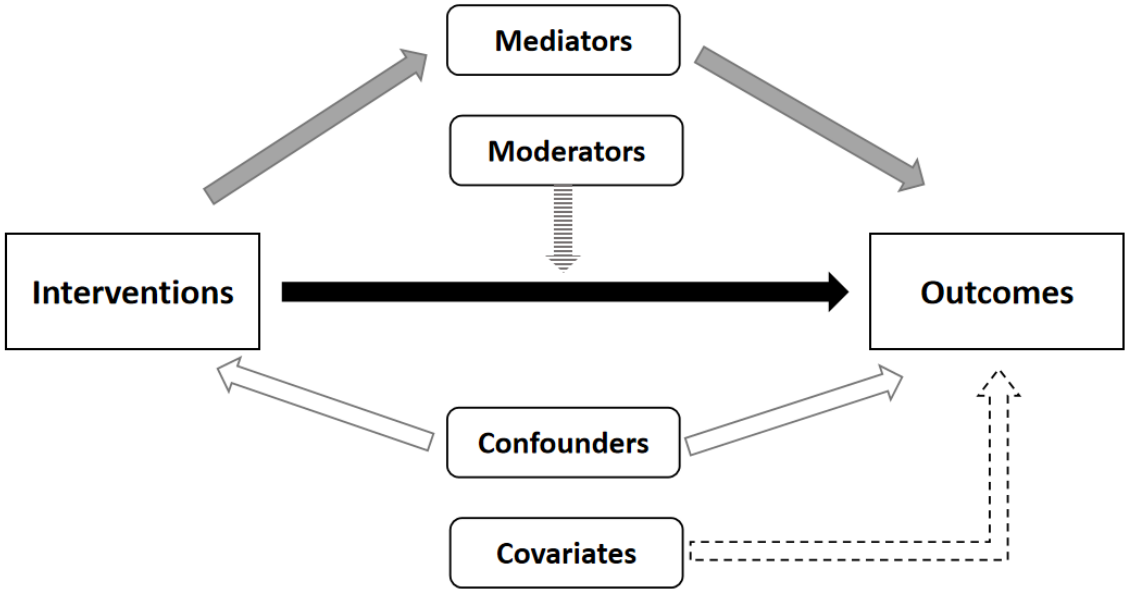
A patient was considered as having any diabetes-relevant comorbidity when that condition was recorded at least twice on different dates, either in the same or different datasets (i.e., diagnosis, reason for encounter, or reason for prescription fields). That approach alone was used for CVD

comorbidities (i.e., heart failure, stroke, IHD),[89, 256] as MedicineInsight does not provide any additional relevant data (e.g., specialists' reference letters, image results) to improve diagnostic accuracy. For other comorbidities, we combined recorded diagnoses with clinical measures and pathology data, using reasonable ranges to account for any reporting and typographical errors. The reasonable values of all clinical parameters (i.e., HbA1c, lipids [total cholesterol, non-HDL, LDL-C, HDL-C, triglycerides], BP, and urine albumin excretion) used in this project are presented in Table 3.2 and Table B2, Appendix B.

Based on laboratory results, patients were also classified as having dyslipidaemia if they had one or more of the following conditions: total cholesterol ≥5.5 mmol/L; HDL-C <1.0 mmol/L for males or <1.3 mmol/L for females; LDL-C ≥3.5 mmol/L; or triglycerides ≥2.0 mmol/L.[13] Patients were classified as having CKD if, apart from the specific diagnosis, they had two eGFR results <60 mL/min/1.73m^2 at least 90 days apart, and/or presence of albuminuria for >90 days of ≥2.5 mg/mmol for males or ≥3.5 mg/mmol for females.[105, 106] Patients were additionally classified as having hypertension if they had at least two BP measurements >140/90 mmHg on different dates, irrespective of whether that diagnosis was reported or not in the EHRs.[100]

3.4 Dealing with Confounding and Potential Bias

Confounders or confounding variables are a crucial concern in epidemiological studies.[257, 258] Ignoring confounders may result in inaccurate estimates of intervention/treatment/exposure–outcome relationships (Figure 3.2).[257] Confounding can be reduced or controlled by many approaches, in either the study design (i.e., randomisation, restriction, and matching[259, 260]) or statistical analytic phase (e.g., stratification and subsequent polling, standardisation, multivariable regression analysis, propensity score, high-dimensional propensity score[261]).

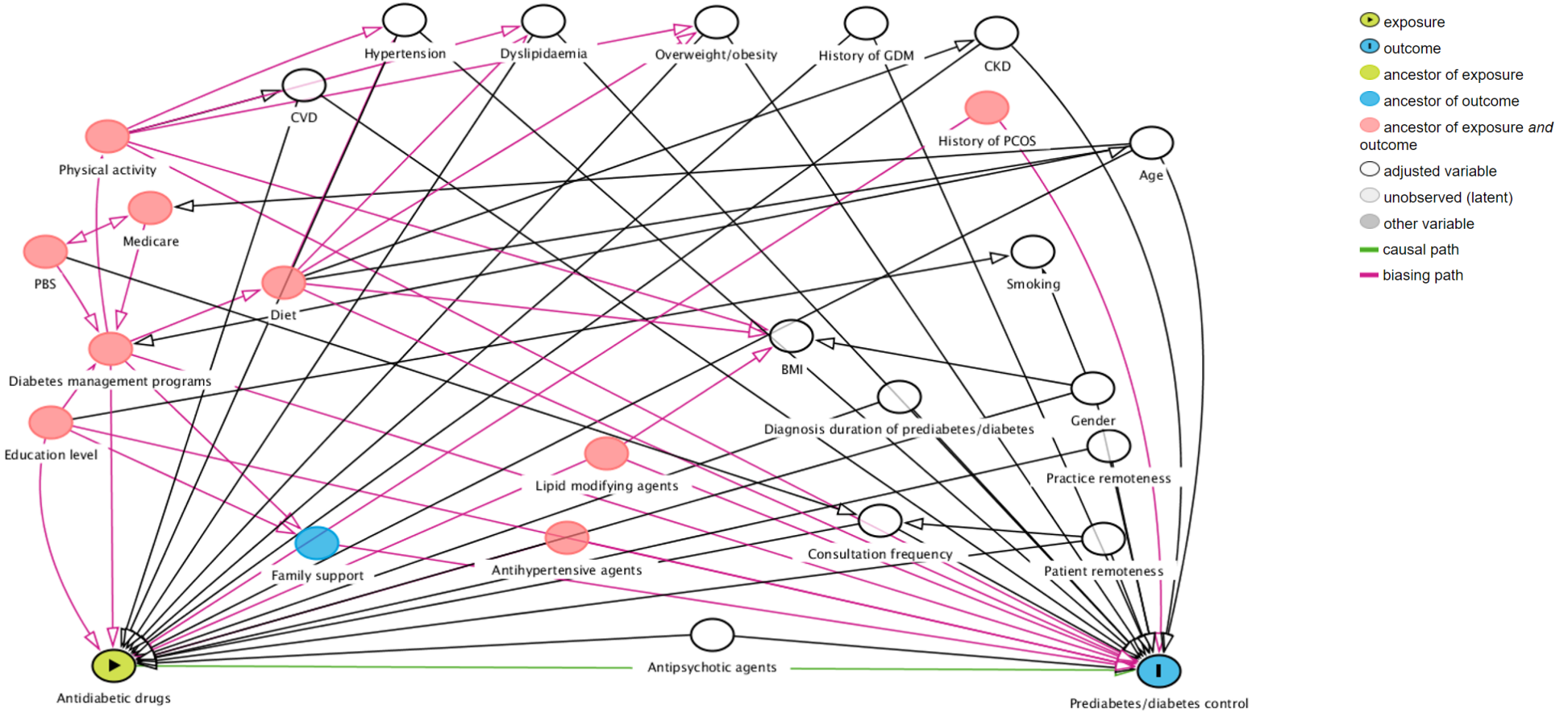


When exploring antidiabetic drug prescription in diabetes treatment, the primary aim is usually in the causal pathway that directly links the intervention to the outcome (black arrow). However, it is critical to consider the impact of moderators and mediators (located on the causal pathway [grey arrows]), and covariates and confounders (not located on the causal path [open arrows]).

Source: Modified from Field-Fote (2019).[258]

Figure 3.2. Effects of mediators, moderators, confounders, and covariates

Therefore, a clear definition of the potential causal relationships between exposure and outcome based on the available literature is fundamental to providing unbiased results. Consequently, these relationships should be clearly defined early during the project design and incorporated into the statistical analyses. One of the recommended methods during the design phase is the generation of the directed acyclic graphs (DAGs) by researchers involved in the study. DAGs are a practical approach for modern epidemiological studies to: (1) hypothesise causal relationships between exposure and outcome,[257, 262, 263] and (2) identify relevant confounders and mediators when estimating causal effects.[260, 264] Based on the literature review (Section 2.6), Figure 3.3 details the potential measured and unmeasured confounders that could affect the association between using ADMs for prediabetes or diabetes management, and achieving management goals. It is an overall guide for future studies using MedicineInsight, emphasizing the importance of identifying potential confounders before analyses.



Measured confounders (i.e., CVD, hypertension, dyslipidaemia, overweight/obesity, history of GDM, CKD, diagnosis duration of prediabetes/diabetes, consultation frequency, antipsychotic agents, patient remoteness, age, BMI, smoking, gender, and practice remoteness); potential unmeasured confounders (e.g., physical activities, PBS, Medicare, diabetes management program, education level, and family support). CVD: Cardiovascular disease; PBS: Pharmaceutical Benefits Scheme (cost of medicines); CKD: Chronic kidney disease; GDM: Gestational diabetes mellitus; PCOS: Polycystic ovary syndrome; BMI: Body mass index.

Figure 3.3. Directed acyclic graphs of confounders for antidiabetic medication use and prediabetes/diabetes management and control

All available variables used in this thesis and extracted from MedicineInsight are reported in Table B2, Appendix B. Practice-level data included remoteness (major city, inner regional, or outer regional/remote/very remote) and Index of Relative Socio-economic Advantage and Disadvantage (IRSAD quintiles – very advantaged, more advantaged, middle, more disadvantaged, very disadvantaged). Remoteness and IRSAD were defined based on postcodes. Remoteness is determined according to the population size and average distance to services, while IRSAD is an area-level measure of socioeconomic status based on combined indicators (i.e., household income, education, and working status). Higher IRSAD scores imply the service is located in a more advantaged area.[265]

Patient variables included remoteness and IRSAD (similar classification as for practice remoteness and IRSAD, respectively); age (continuous variable, 0–109 years old); gender (females, males); smoking status (smoker, ex-smoker, or non-smoker); ethnicity (Aboriginal or Torres Strait Islander, neither Aboriginals nor Torres Strait Islander, not stated); and recorded history of hypertension, dyslipidaemia, CKD, overweight/obesity, or CVD. The recorded history of CVD included records of heart failure, IHD, or stroke. Due to the small percentage of missing data on gender (1%), we only included patients identified as male or female. It was not possible to include patients who identified themselves as non-binary gender because this information was not available in the dataset. Details on the data extraction methods for these variables have been published elsewhere.[248, 266] We also extracted BMI data from the Observation dataset. Based on information about the lowest and highest values recorded for height (32 cm and 223 cm) and weight (0.6 Kg and 248 Kg) in Australia for age groups, all BMI values calculated with height and weight within these intervals were extracted. BMI ranged from 13.0 to 91.9 kg/m^2. We extracted antipsychotic prescriptions from the Script items dataset, using medication names based on ATC Classification N05A.

Other relevant confounding variables (e.g., family support, diet, physical activity, diabetes management plan) were not included for analysis as they are not systematically recorded in

EHRs by GPs. However, they could bias the results for the associations between diabetes management and control in Paper 3 (Chapter 6) and Paper 4 (Chapter 7).

3.5 Potential Limitations and Bias in this Project

Using EHRs for research can reduce subjective biases that occur in self-reported health surveys, where data sensitivity can be as low as 57.5% for cardiovascular risk factors.[267] Previous studies using EHRs have achieved sensitivity, specificity, and positive predictive values as high as 98% for diabetes diagnosis when different fields were combined (e.g., diagnosis, objective laboratory test results, prescribed medications) and multiple years of data were used.[239, 240, 248]MedicineInsight has overcome some barriers associated with the use of EHRs for research purposes (i.e., ethical, legal, technical, social, and resource-related issues) by involving a data governance committee that is responsible for the ethical, privacy, and security aspects of any research using the MedicineInsight database.[268] Additionally, MedicineInsight has obtained ethical approval from the RACGP and signed agreements from practices, encrypts data, and allows access to de-identified data only. Therefore, the database is a valuable resource for investigating the thesis research objectives in general practice in Australia. Nonetheless, using MedicineInsight to examine the epidemiology of diabetes and prediabetes in Australian general practice has some limitations:[92, 200, 223, 231, 268]

(1) Data completeness: Unlike clinical trials where different strategies are in place to ensure data accuracy and completeness, MedicineInsight uses 'real-world' data entered by clinicians into a clinical information system during their clinical encounters. GPs can choose between recording data using proprietary medical systems or as 'free text'. This may lead to empty fields or recorded data using different medical terms, abbreviations, and misspellings for the same condition. Moreover, not all investigated chronic conditions are recorded at every consultation. The primary reason for the clinical encounter may differ from the investigated conditions (e.g., a patient with diabetes may have visited the GP because of a cold or another comorbidity). These factors may cause under-reporting of clinical information.

(2) Lack of progress notes: Progress notes are not extracted by MedicineInsight for privacy reasons, as they may contain identifiable data. Progress notes may include a range of patient, encounter, diagnosis, and prescription-related information that is not otherwise documented in other fields. This may also result in important information being missed and underestimation of the investigated conditions.

(3) Representativeness of practices: General practices are recruited to MedicineInsight via non-random sampling. Thus, systematic sampling disparities between states and regions cannot be ruled out. Moreover, patients in MedicineInsight cannot be considered representative of the whole Australian population, despite their comparability with census data.

(4) Tracking of patients between practices: Patients are uniquely identified within a practice, but may be duplicated in the database if they attended a different practice in the database. Patients may have also attended for care at practices that do not participate in MedicineInsight.

(5) Prescribed medications differ from medication use: As not all prescriptions and repeats are necessarily dispensed, prescription counts from MedicineInsight may overestimate results compared with dispensed data (e.g., Pharmaceutical Benefits Scheme [PBS] data) or used medications. Prescriptions from hospitals or specialists are also not included in the database.

(6) Information about lifestyle risk factors and other relevant covariates is lacking: Assessment of diabetes diagnosis/management is limited to those variables available in the database. Lifestyle variables (e.g., diet, alcohol consumption, exercise) and other relevant covariates (e.g., eye examination, foot examination, family history of diabetes) are not systematically recorded in MedicineInsight EHRs, which leads to potential residual confounding and limits the analysis of additional outcomes (e.g., health economic analysis, other forms of diabetes management, and complications).

Therefore, the nature of EHRs (secondary data collected in general practices across Australia) may lead to different sources of bias (i.e., selection bias, reporting bias, prevalence-incidence bias, or immortal time bias[269-271]) in this project.

Selection bias is expected due to systematic differences between the baseline characteristics in exposed and unexposed groups.[270] For example, the diagnosis of CVD, CKD, or hypertension is more likely to occur among patients with past recorded diabetes than those with newly recorded diabetes or without diabetes.

Reporting bias is expected due to systematic differences between unreported and reported results. [270, 271] For instance, BMI is more likely to be recorded in patients who are overweight or obese. Additionally, the probability of receiving treatment or diagnosis increases with the number of visits (e.g., older patients or those with multiple chronic conditions are more likely to visit a GP). Therefore, when we run analyses and explain results, we should consider this type of bias. To minimise reporting bias, for example, in Papers 3 and 4, we included the average number of consultations for adjustment as a potential confounder.

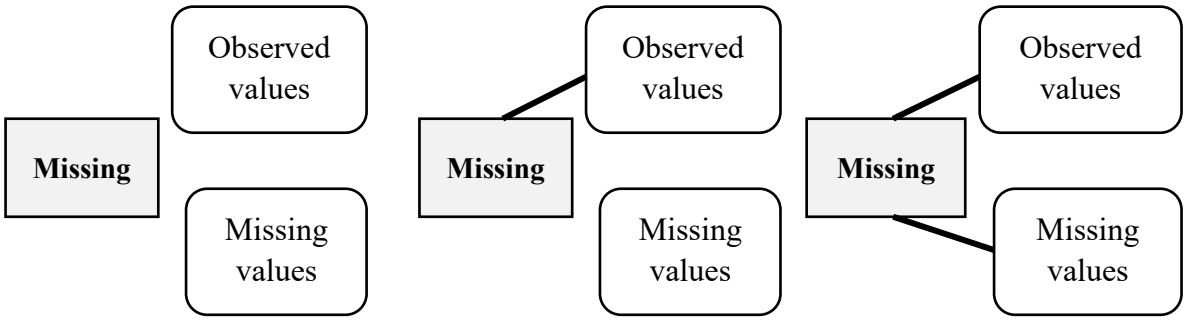
Prevalence-incidence bias (Neyman bias or selective survival bias) can occur as patients with more advanced/severe diabetes may have died as a consequence of advanced aged, CVD or CKD, leaving a higher frequency of patients with mild/moderate diabetes in the database. Thus, it could seem as if advanced age or a history of CVD or CKD are not associated with diabetes outcomes (or show a protective effect).[270, 271]

Immortal time bias is a particular concern for our studies investigating the effects of metformin on BG levels. In observational cohort studies, immortal time bias occurs when participants have not yet been 'exposed' (e.g., to a drug or prevention activity) but are misclassified as having been exposed for that period of time or that time is excluded from analyses.[269, 272, 273] In this case, the beneficial effect of drugs may be ascribed to this bias.[272] In Chapter 7, to account for the immortal time bias (i.e., error introduced by misclassifying a

period of time of individuals as 'exposed' when, in fact, they were not yet exposed), the time from diagnosis until the first metformin prescription was counted as unexposed/untreated.

3.6 Dealing with Missing Data

Missing data (or missing values) is a frequent problem in EHR-based epidemiological studies, and may lead to biased results if people with missing data have unbalanced information regarding exposure and/or outcome compared with people without missing data.[274] There are a very small number of missing data and possible incorrect entries in MedicineInsight data (either due to inaccurate data entered by the provider or due to extraction errors).[275] Thus, handling missing data in the analytical phase is essential for studies using MedicineInsight data. Figure 3.4 presents three types of missing data that should be carefully considered in epidemiological studies: (1) missing completely at random (MCAR), (2) missing at random (MAR), and (3) missing not at random (MNAR).[276-278] MCAR implies no systematic differences occur between the observed and missing values.[278, 279] For instance, BG or BP measurements may be lost due to a malfunction of monitors not related to patient or practice characteristics. MAR indicates that any systematic difference between the observed and missing values can be clarified by differences in the observed/available data.[276, 278] For example, missing BMI data could be less frequent among patients with hypertension or CVD. MNAR indicates systematic differences between the observed and missing values exist even after considering the observed/available data.[278] For example, patients with more advanced/severe diabetes could be more prone to miss outpatient appointments due to accessibility problems (e.g., locomotion problems due to amputation, lack of a carer to take them to their appointments).



(1) MCAR (2) MAR (3) MNAR

MCAR: Missing completely at random; MAR: Missing at random; MNAR: Missing not at random.

Source: Adapted from Pedersen (2017)[280]

Figure 3.4. Three types of missing data

In the statistical analysis stage, five methods can be used to handle different types of missing data (Table 3.4): complete-case analysis, missing indicator approach, sensitivity analyses with worst- and best-case scenarios, single imputation, and multiple imputation (MI). For any of these techniques, it is crucial to understand the mechanism behind missing data to assess the possibility of invalid conclusions.

Table 3.4. Approaches to handling missing data during the analysis phase

Approach	Description	Assumption	Strengths	Limitations
Complete-case analysis (listwise deletion)	Ignore MV and include only people with complete data on all variables of interest	MCAR	-Simplicity -Comparability across analyses	-Data may not be representative -Large SE[(a)] -Discards valuable data
Missing indicator approach	For continuous variables, MV are set to a fixed value (usually zero). Then, an additional binary variable (0/1) is added to the analytic model to indicate whether the variable's value is missing. For categorical variables, MV are grouped into a 'missing' category	None	-Utilises all available information on MV and maintains the entire dataset	-Difficult to predict the magnitude and direction of bias -Small SE[(b)] -Results may be meaningless as the method is theory driven -Biased results due to residual confounding
Sensitivity analyses with worst- and best-case scenarios	MV are replaced with the lowest or highest value observed in the dataset	MCAR	-Simplicity -Maintains the entire dataset	-Small SE[(b)] -Analyses yielding opposite results may be difficult to interpret
Single imputation	Replace MV with a single value (e.g., the mean score of observations, or if the data are measured longitudinally, the most recent available information for that individual)	MCAR, only when estimating mean	-Run analyses as if data are complete -Maintains the entire dataset	-Small SE[(b)] -Potentially biased results -Weakened covariance and correlation estimate in the data (ignores the relationship between variables)
Multiple imputation	MV are imputed based on the distribution of other variables in the dataset	MAR (but can handle MCAR and MNAR)	-The variability of each missing value is more accurate[(c)]	-Room for error when specifying models

MV: Missing values; SE: Standard error; MCAR: Missing completely at random; MAR: Missing at random; MNAR: Missing not at random. Approaches were adapted from Pedersen (2017)[280] and Sterne (2009)[279]. (a) Lack of precision; (b) Overestimated precision; (c) Considers variability due to sampling and imputation (SE close to that of having a whole dataset with true values).

MI was first introduced by Rubin (1987)[281] and is less biased and more efficient than the other four approaches.[277, 282] MI provides valid statistical inference under the assumption of MAR (although it can handle MCAR and MNAR), but its implementation can be complicated.[274, 283] In short, MI removes uncertainty of missing data by following three phases: (1) the imputation phase: creating several (M) copies of the dataset of imputed values (missing values are replaced); (2) the statistical analysis phase: using standard statistical approaches to fit the hypothesised model to each of the M imputed datasets; and (3) the pooling phase: pooling the results across the M imputed datasets to get a final dataset of results based on Rubin's rules.[279, 281, 284, 285] In Papers 3 and 4 in this thesis, MI was used because it provided flexibility for allowing the three types of missing values noted above.

MI can be performed using multivariate normal (MVN) distribution or by multivariate imputation by chained equation (MICE) (also known as fully conditional specification).[286] The MVN method assumes that the variables to be imputed follow a joint MVN distribution, and is accomplished by a data augmentation algorithm that alternates between extracting imputed values for missing data and extracting values of imputation model parameters in an iterative process.[287] MICE uses a series of univariate imputation models to impute missing values one by one, requiring one model for each incomplete variable.[287] When using MICE, it is also important to incorporate the outcome into the imputation model.

Regarding the number of imputations (i.e., copies of the dataset) required, Von Hippel (2020)[288] published the following equation that estimates how many imputations (*M*) should be performed:

$$M = 1 + \tfrac{1}{2}\,(FMI \,/\, \mathrm{CV(SE)})^2$$

where *FMI* is the fraction of missing information and CV(SE) is a coefficient of variation of acceptable standard error (SE) estimates.[288] For example, in Paper 3 of this thesis, the BMI had 60% of missing data (*FMI*=60%) and, if we accept the CV(SE) changing by 10%, we needed

to create at least 19 imputations. FBG and HbA1c at baseline had 55% and 52% missing data, respectively. Assuming a similar CV(SE), then we needed to create at least 15 and 14 imputed copies, respectively. Alternatively, the command '*how_many_imputations*' in Stata (package *how_many_imputations.pkg*) can be used for the same purpose. When there are multiple parameters in the original dataset, it uses the highest FMI to calculate the number of necessary imputations. Following Rubin's recommendations,[281] we decided to use 20 imputations for Papers 3 and 4 for the pooling phase, considering the number of variables with missing data (i.e., FBG, HbA1c, random blood glucose [RBG], OGTT, and BMI).

3.7 Statistical Analyses

All analyses for this thesis were performed in Stata MP 16.1 (StataCorp, Texas, USA). Statistical methods used in each study are described in Table 3.5. The following sections explain the specific analysis and variables used in each paper.

Table 3.5. Summary of study types and statistical methods used in each study

Chapter	Study type	Study period	Research questions	Study sample*	Statistical methods
Chapter 4 (Paper 1)	Cross-sectional study	2016–2018	(1) Are people at a higher risk of diabetes more likely to be screened for diabetes than those not at risk, and what factors influence this outcome? (2) What are the sociodemographic and clinical profiles of adults with diagnosed or undiagnosed diabetes/prediabetes visiting general practice in Australia? (3) What are the most common risk factors and clinical conditions observed among these patients?	'Regular patients' (at least three visits in two consecutive years and at least one consultation each year) aged ≥18 years	-Descriptive analysis -Prevalence -Chi-square tests -Binary logistic regression
Chapter 5 (Paper 2)	Retrospective cohort study	2015–2018	(4) Are there any sociodemographic or clinical differences between patients with past or recent diabetes diagnoses among adults attending general practices in Australia? (5) What is the prevalence of well-controlled diabetes? (6) Do sociodemographic or clinical characteristics influence that outcome?	'Every year patients' (at least one consultation each year from 2015 to 2018) aged ≥18 years	-Descriptive analysis -Prevalence/incidence -Binary or multinomial logistic regression -Linear regression
Chapter 6 (Paper 3)	Causal longitudinal study	2011–2018	(7) Do patients with a recent diabetes diagnosis achieve better glycaemic control with early metformin therapy compared to delayed pharmacological management?	'Regular incident patients' (at least three consultations, including one the year before and one the year after first recorded diabetes diagnosis) aged ≥40 years	-Descriptive analysis -Linear regression -Kaplan–Meier survival curve -Counterfactual approach -Multiple imputation
Chapter 7 (Paper 4)	Causal longitudinal study	2011–2018	(8) Do patients with prediabetes achieve better glycaemic control with metformin therapy than those not receiving that medication?	'Regular incident patients' (at least three consultations, including one the year before and one the year after first recorded prediabetes diagnosis) aged ≥18 years	-Descriptive analysis -Linear regression -Counterfactual approach -Multiple imputation

* All four studies used records from six datasets in MedicineInsight: diagnosis, reason for encounter, reason for prescription, observation, pathology, and scripts datasets.

3.7.1 Descriptive Statistics and Regression Modelling

Descriptive analyses (frequencies) are presented as proportions (%) with their corresponding 95%CI (categorical variables), or as means with their standard deviation (SD) or medians with their interquartile range (numerical variables) in each substudy of the thesis. To reduce selection bias (i.e., the likelihood of receiving diagnosis or treatment increases with the number of consultations), all analyses were weighted to the inverse of the probability of a patient attending a practice in any year. The predicted probability was estimated using a logistic regression model that considered as covariates the number of consultations in the preceding year and sociodemographic variables (i.e., gender, age, IRSAD, remoteness).

Logistic regression models fit under four main assumptions: independence of errors; absence of multicollinearity; linearity of the logit of continuous variables; having no strongly influential outliers.[289, 290] The critical assumption for regression-based models is that independent variables should not be correlated among themselves. Multicollinearity (collinearity) occurs when an independent variable is moderately or highly correlated with one or more other independent variables in regression-based models, leading to unstable and unreliable estimations of regression coefficients.[291] We tested for multicollinearity with variance inflation factors (variance inflation factor ≤5 is considered moderately correlated) before running multinomial or binary logistic regressions. Linear regression predicts the numerical relationship between outcome (dependent) and predictor (independent) variables under four main assumptions (i.e., linearity, homoscedasticity, independence, and normality).[289] Details of the specific regression models used in each study are specified in the corresponding chapter.

3.7.2 Survival Analysis

Time-to-event analysis is also known as survival analysis. Three methods are commonly used: (1) estimating the survival curve using the Kaplan–Meier method (also known as the product-

limit estimate), which is a graphical representation of survival function for a single binary predictor; (2) log-rank test, which provides a statistical comparison of exposed and unexposed groups; and (3) Cox proportional-hazards regression, which allows extra covariates to be included.[292-294] In Paper 3, I estimated the cumulative time to the first metformin prescription after diabetes diagnosis using the Kaplan–Meier method.

3.7.3 Counterfactual Approach

In well-designed randomised controlled trials (RCTs), untreated and treated participants have 'exchangeability'[295] at baseline because untreated and treated groups are assumed to be similar in all measured or unmeasured characteristics because of randomisation. The difference in outcome between the untreated and treated groups is then due to the investigated exposure.[295]

Observed data are susceptible to bias from confounding, selection, and measurement, which can cause underestimation or overestimation of the effect of interest.[296] Furthermore, in observational studies, many characteristics differ between the untreated and treated groups, and participants in each group are unexchangeable because the treatment is not randomly assigned; this can result in a confounding bias in the causal effect estimates.[263, 296] Therefore, it is essential to adjust for confounding bias to gain conditional exchangeability. Different methods are traditionally used to achieve exchangeability in observational studies, including matching, stratification, or adjustment by using regression models. 'Matching' has the disadvantage of reducing the sample size by dropping unmatched observations.[297] 'Stratification' does not allow controlling for multiple confounding covariates, as stratifying by additional layers of each confounder is limited by sample size, and the extrapolation of the results can be difficult.[298] Finally, the adjustment for confounders by using regression models has less transparency for reporting whether an appropriate balance between treatment/exposed and control/reference groups was achieved.[299] Therefore, for Papers 3 and 4, traditional regression models were used

to examine the effect of diabetes medications on glycaemic parameters adjusted for potential confounders, but the potential outcomes (counterfactual) approach (also known as target trial) was also used.[300]

The counterfactual approach is an innovative technique that handles confounding variables by creating a pseudo population where each person is treated as if they were exposed and also unexposed to the investigated exposure/treatment.[263] In other words, this method allows testing what would happen if everyone with diabetes (or prediabetes) received metformin compared to a 'counterfactual' situation where everyone with diabetes (or prediabetes) did not receive metformin. This technique not only applies the first essential principle of causal inference (exchangeability), but also positivity and consistency.[301] Positivity is ensured in the study because, by design, there are people assigned to each level of unexposed and exposed groups.[301] If all people (or subgroups of persons with the same adjustment characteristics) in a study are assigned to the same group, it is not feasible to gain effect estimates without using untestable modelling assumptions.[263] Consistency is related to the counterfactual concept of setting the exposure status as 'exposed' or 'unexposed' through the intervention of interest.[263] Additionally, consistency means that a person's potential outcome under her/his observed exposure history is accurately her/his observed outcome.[302]

For patients with diabetes (or prediabetes), the counterfactual analysis assisted us in quantifying the average treatment effect (ATE) of metformin management of glycaemic parameters, that is, what levels of HbA1c or FBG could be reached at 6, 12, 18, and 24 months if metformin was provided as part of an early management strategy for all patients with diabetes (or prediabetes). ATE can be explained as the average effect of an exposure/treatment when the entire study population is treated with the investigated treatment versus no exposure/treatment (i.e., control).[303] Therefore, the counterfactual approach simulates the findings of a well-designed

RCT, where both the treated and untreated groups are comparable at baseline and free from confounding bias.[304-306]

The counterfactual approach has been used in other international primary care databases to explore the effect of potential treatments or interventions on chronic conditions (e.g., hypertension, diabetes, CVD, and all-cause mortality).[263] For example, a Clinical Practice Research Datalink (CPRD) study first utilised propensity score matching so that characteristics of the intervention and matched control groups were 'comparable'.[307] The matched control group provided a counterfactual for the treatment group without the intervention, and the differences in the models partly eliminated unobserved heterogeneity in the fixed or parallel time trends between groups over time, hence offering a robust estimate. That study found that, after matching, participants had substantial absolute reductions in modelled risk of CVD (−0.21%, 95%CI −0.24;−0.19) and individual risk factors: systolic BP (−2.5 mmHg, 95%CI −2.77;−2.25), diastolic BP (−1.46 mmHg, 95%CI −1.62;−1.29), BMI (−0.27 kg/m^2, 95%CI −0.34;−0.20), and total cholesterol (−0.15 mmol/L, 95%CI −0.18;−0.13).[307] Even if causality cannot be determined using observational data only, these studies using the counterfactual approach have important implications in public health decision-making, being complementary to RCTs, which are not always ethical or practical.[263]

Weighting based on propensity score methods is important and practical for confounding adjustment when using the counterfactual approach for observational data.[263, 299] Augmented inverse probability weighting (AIPW) is a newer approach that allows estimation of the ATE (known as the 'AIPW estimator').[306, 308] In Australia, few population-based linked administrative data studies have used AIPW to estimate ATE.[309, 310]

The AIPW estimator has two practical steps: (1) based on a set of potential covariates, it uses a binary regression model to fit a propensity score model (i.e., the probability that an individual

is either treatment/exposed [category 1] or control/unexposed [category 0]); and (2) it estimates the outcome in control and treatment groups using a regression model (binary or numerical) adjusted for a set of potential confounders and weighted to the inverse of the propensity score obtained in step 1.[309, 311] The AIPW estimator produces a marginal adjusted estimate of the treatment effect, not a conditional estimate.[303] Therefore, AIPW tends to be less biased than traditional regression models because of its double-robustness property: it converges in probability to the true values of the parameters even if only the propensity score model or the outcome model is appropriately specified.[303, 308, 311]

Considering the need for data imputation, I used an updated workflow from Pishgar (2021)[312] to weight multiply imputed datasets using packages/functions in Stata[313] for Papers 3 and 4 (Section 6.3.3 and Section 7.3.3). That workflow required (1) generating *M* (*M*=20) datasets of the cohort of interest with missing values (e.g., BG values, BMI); (2) imputing the missing data into the dataset (MICE method: mi impute chained); (3) weighting the 20 imputed datasets using updated Stata syntax[309] to compute AIPW on imputed data for binary exposure; (4) assessing balance on the weighted dataset (teffects); (5) analysing the weighted datasets (pweight); and (6) pooling the causal effect estimates (used updated Stata syntax[309]). Furthermore, sensitivity analyses were used to determine the robustness of the results.

3.7.4 Sensitivity Analysis

It is crucial to conduct sensitivity analyses to examine the impacts of residual confounding in EHR-based epidemiological research.[282] Sensitivity analysis was used in the four studies of this thesis to determine the robustness of the results: the extent to which these findings would be impacted by changes in the unmeasured variable values, missing data, models, or epidemiological assumptions.[282, 287] Details of the specific sensitivity analyses used in each study are specified in the corresponding chapter.

3.8 Ethical Approval

The first three papers for this project (Chapters 4–6) are part of the project 'Cardiovascular disease in adults: primary and secondary prevention in Australian general practice' coordinated by the Discipline of General Practice at the University of Adelaide. The independent MedicineInsight Data Governance Committee approved the study (Protocol 2016-007). The project only involved the use of de-identified data from the MedicineInsight database and was exempted from ethical review by the Human Research Ethical Committee at the University of Adelaide. The fourth study (Chapter 7) received funding from The RACGP Foundation/Diabetes Australia Research Grant (DIA2021-06). Therefore, a different exemption of ethical review was provided by the Human Research Ethics Committee at the University of Adelaide (No.35601) due to the use of non-identifiable data (Ethical exemption letter, Appendix B). The funding partner did not influence the conduct, analysis, reporting, or interpretation of the findings in that study.

3.9 Consumers involvement

The MedicineInsight Data Governance Committee incorporates consumer representatives responsible for evaluating research proposals seeking access to these records. Entities utilising these EHRs are strongly recommended to involve a consumer advisory/reference group. This participatory approach directly gains insights into user perspectives, thereby enhancing the pertinence and pragmatic utility of research outcomes. Simultaneously, it fosters collaborative efforts and facilitates the real-world application of findings. Therefore, academic GPs involved with the Discipline of General Practice were engaged in discussions regarding study design and result interpretation. Nonetheless, the direct involvement of patients/carers in the study's development occurred later, as the formal constitution of the Primary Care and Health Services Research Group Consumer Reference Group associated with the Discipline of General Practice

occurred in early 2022. Consequently, consumer representatives became actively engaged in the latter phases of the thesis, contributing valuable insights to the reporting and dissemination of research findings.

Chapter 4. Diabetes Screening and Diagnosis (Paper 1 – Published)

4.1 Preface

To answer the first three research questions, Chapter 4 (Paper 1) presents the findings of diabetes screening among adults at high risk of diabetes, and the sociodemographic and clinical profiles of adults with diagnosed or undiagnosed diabetes/prediabetes attending Australian general practice. This paper has been published in *Journal of Diabetes Research* (Appendix G) as:

> Zheng M, Bernardo CD, Stocks N, Gonzalez-Chica D. Diabetes mellitus diagnosis and screening in Australian general practice: a national study. *Journal of Diabetes Research*. 2022;2022:1566408. https://doi.org/10.1155/2022/1566408

This chapter addresses the following research questions of this thesis:

- Are people at a higher risk of diabetes more likely to be screened for diabetes than those not at risk, and what factors influence this outcome?
- What are the sociodemographic and clinical profiles of adults with diagnosed or undiagnosed diabetes/prediabetes visiting general practice in Australia?
- What are the most common risk factors and clinical conditions observed among these patients?

Highlights of Paper 1:

- The prevalence of diabetes derived from the MedicineInsight database resembles figures from national surveys.
- More hypertension and dyslipidaemia were observed among those with prediabetes than those with diabetes.
- Only half of those at high risk of diabetes were screened for diabetes in 3 years.

- Only a quarter of those treated with antipsychotics had their glucose levels tested.
- Diabetes screening was less frequent in young males than in young females, but sex disparities reduced in middle age.

4.2 Statement of Authorship

Title of Paper	Diabetes Mellitus Diagnosis and Screening in Australian General Practice: A National Study
Publication Status	☑ Published ☐ Accepted for Publication ☐ Submitted for Publication ☐ Unpublished and Unsubmitted work written in
Publication Details	Zheng M, Bernardo C, Stocks N, Gonzalez-Chica D. Diabetes mellitus diagnosis and screening in Australian general practice: a national study. Journal of Diabetes Research. 2022;2022:1566408. https://doi.org/10.1155/2022/1566408

Principal Author

Name of Principal Author (Candidate)	Mingyue Zheng		
Contribution to the Paper	MZ contributed to the conception and design of the study and performed the statistical analysis and prepared the manuscript. MZ contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Overall percentage (%)	75%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16 February 2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Carla Bernardo		
Contribution to the Paper	CB assisted in data extraction, analysis, and writing of the manuscript. COB contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	10%	Date	16 February 2023

Name of Co-Author	Stocks Nigel		
Contribution to the Paper	NS contributed to the design and structure of the manuscript. NS contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	17/02/2023

Name of Co-Author	David Gonzalez-Chica		
Contribution to the Paper	DGC contributed to the conception and design of the study and assisted in data extraction, analysis, and writing of the manuscript. DGC contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	10%	Date	16 February 2023

4.3 Publication: Diabetes mellitus diagnosis and screening in Australian general practice: a national study

4.3.1 Abstract

Aims: To investigate the epidemiology of diabetes diagnosis and screening in Australian general practice.

Methods: Cross-sectional study using EHRs of 1,522,622 patients aged 18+ years attending 544 Australian general practices (MedicineInsight database). The prevalence of diagnosed diabetes and diabetes screening was explored using all recorded diagnoses, laboratory results, and prescriptions between 2016 and 2018. Their relationship with patient sociodemographic and clinical characteristics was also investigated.

Results: Overall, 7.5% (95%CI 7.3;7.8) of adults had diabetes diagnosis, 0.7% (95%CI 0.6;0.7) prediabetes, and 0.3% (95%CI 0.3;0.3) unrecorded diabetes/prediabetes (elevated glucose levels without a recorded diagnosis). Patients with unrecorded diabetes/prediabetes had clinical characteristics similar to those with recorded diabetes, except for a lower prevalence of overweight/obesity (55.5% and 69.9%, respectively). Dyslipidaemia was 1.8 times higher (36.2% vs 19.7%) and hypertension 15% more likely (38.6% vs 33.8%) among patients with prediabetes than with diabetes. Diabetes screening (last 3 years) among people at high risk of diabetes was 55.2% (95%CI 52.7;57.7), with lower rates among young or elderly males.

Conclusions: Unrecorded diabetes/prediabetes is infrequent in Australian general practice, but prediabetes diagnosis was also lower than expected. Diabetes screening among high-risk individuals can be improved, especially in men, to enhance earlier diabetes diagnosis and management.

Keywords: Diabetes mellitus, prediabetic state, delayed diagnosis, primary health care, population health, medical records

4.3.2 Introduction

Diabetes mellitus is a major global health problem and one of the fastest-growing chronic conditions.[51] In Australia, the age-standardised ratio of self-reported diabetes has increased from 3.3% in 2001 to 4.4% in 2017–2018.[314] However, diabetes is not always medically diagnosed. Globally, it is estimated that one in two people living with diabetes is unaware of their condition.[64] Several nationwide studies have investigated the actual magnitude of undiagnosed diabetes, either using EHRs[21] or through laboratory tests used as part of national surveys.[315-317] The prevalence of unreported diabetes in the US was estimated at 0.9% in 1988–1994 and 1.2% in 2011–2014,[315] while a French national study found a prevalence of 1.7% in 2014–2016.[317]

Moreover, prediabetes (a condition where the glycaemic parameters are above normal but below the threshold for diabetes [129]) increases the burden of diabetes, with a conversion rate to diabetes of 5–10% per year.[81] Globally, the estimated prevalence of prediabetes was 7.5% in 2019 (~374 million people) and is projected to reach 8.6% (~548 million people) by 2045.[64] In Australia, prediabetes affects 3.1% of adults.[13] Undiagnosed prediabetes is an additional concern, as these individuals are at a higher risk of complications, including CKD, diabetic retinopathy, and macrovascular disease.[50, 248]

Therefore, early detection of prediabetes and diabetes is crucial for appropriate management and prevention of disease progression.[115, 116] According to the Australian Guidelines for Preventive Activities in General Practice,[25] regular (within 3 years) diabetes screening is recommended for those with a clinical history of GDM or PCOS, and those treated with antipsychotics or at higher risk of CVD. Screening among these individuals should be

performed regularly, either through FBG or HbA1c tests.[14, 124, 129] Beyond these groups, non-invasive and straightforward tools such as the Australian Type 2 Diabetes Risk Assessment (AUSDRISK) questionnaire have been developed to identify other individuals at risk of diabetes who require further assessment.[50, 318, 319] For example, the AUSDRISK is a questionnaire that scores the probability of a person developing diabetes mellitus within 5 years or with undiagnosed diabetes.[120] People with a score ≥12 points should then have their BG levels tested.[25]

Diabetes screening in a primary care setting is widely recommended, considering that more than 83% of the population use these services every year,[15] making it an ideal environment for early diabetes diagnosis and management. Despite this, population-based national studies, or data on whether diabetes screening activities are being performed in primary care following current recommendations, are scarce.[318] In this sense, EHRs generated by GPs during medical appointments represent a unique data source for investigating the prevalence of diabetes and prediabetes diagnoses, screening activities, and management of these conditions. In addition, data extracted from EHR databases has been found a cost-effective method for exploring different health outcomes with appropriate accuracy.[10, 21, 248, 320, 321]

In Australia, EHRs have been used in the last decade to estimate the burden of various chronic conditions, but only a few have focused on diabetes.[10, 11, 201, 231, 266, 322] Data from the BEACH (Bettering the Evaluation and Care of Health) program, a national study of general practice activity that included GP-reported data (Nov/2012 to Mar/2016), showed a prevalence of T2D of 9.6% among adults.[323] In Victoria, the POLAR (Population Level Analysis and Reporting) program used recorded pathology results to explore the prevalence of T2D among adults (4.9%), showing results comparable to Australian population-based estimates (5.2%) and with a similar distribution according to sociodemographic characteristics.[10] Finally,

MedicineInsight, a large general practice Australian database, has been used to explore diabetes mellitus, prescriptions, and associated comorbidities.[11, 231, 322] However, none of these studies investigated prediabetes, the magnitude of undiagnosed diabetes/prediabetes, or diabetes screening at a national level.

Therefore, this study is aimed at (1) identifying the prevalence of recorded or unrecorded diabetes and prediabetes among adults in Australian general practice, (2) comparing these groups according to sociodemographic and clinical characteristics, and (3) assessing if diabetes screening was more likely among people at high risk of diabetes.

4.3.3 Methods

Data source

This is a cross-sectional study using MedicineInsight, a large national general practice database managed by NPS MedicineWise. The database contains de-identified EHRs from more than 650 general practices (8.2% of all practices in the country) and over 2,700 GPs from all Australian states and regions. This ongoing longitudinal database includes practices varying in size, billing methods, and type of services.[223] Details of the data collection process and characteristics of the database have been published elsewhere.[200]

Routinely collected data available in MedicineInsight include sociodemographic (i.e., gender, year of birth, postcode of residence) and clinical data (i.e., diagnoses, reasons for consultation, smoking status), prescribed medications and reasons for these prescriptions, laboratory/pathology test results (e.g., BG levels, lipid profile), and clinical measurements (e.g., BP, weight, height).

Study population

Following recommendations for improving data quality,[240, 251, 321] only data from practices established at least 2 years before the end of the analysis period and without interruptions in data greater than 6 weeks was included in the study. Moreover, analysis was restricted to adults (18+ years) considered 'regular' patients (at least three consultations in any two consecutive years [i.e., 'active' patient, as defined by the RACGP to identify frequent users of the service and for reporting purposes],[252] and at least one consultation in each of these two years) and attending a MedicineInsight general practice between Jan/2016 and Dec/2018. Our definition of 'regular' patients takes into account recommendations for improving diagnosis accuracy when using EHRs and the specificities of diabetes diagnosis that requires multiple encounters to request the tests and discuss diagnosis/management with the patient.[240, 251, 321] Administrative contacts (e.g., 'email', 'reminder', 'letter', 'filling forms') were excluded as encounters.

Data extraction

Different fields in MedicineInsight (i.e., 'diagnosis', 'reason for encounter', 'reason for prescription') were searched to identify patients with a recorded diagnosis of diabetes mellitus (either type 1 or type 2) or prediabetes (also recorded as impaired glucose tolerance or impaired fasting glucose), using standard clinical terminology, abbreviations, and misspellings of these words. The algorithm for data extraction also identified all prescriptions of insulin (ATC code A10A) and/or oral ADMs (ATC code A10B: metformin, glibenclamide, gliclazide, glimepiride, glipizide, acarbose, pioglitazone, alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dulaglutide, exenatide, dapagliflozin, empagliflozin, ertugliflozin) during the study period. FBG (mmol/L), RBG (mmol/L), HbA1c (mmol/L or %), and 2-hour OGTT (mmol/L), and date of these tests were obtained from all recorded laboratory results using Logical Observation Identifiers Names and Codes.[223] The MedicineInsight database from 2011 to 2018 has not well-recorded ATC codes; therefore, it is more reliable to use the active ingredient names rather than

only ATC codes. In addition, the use of medications and laboratory results combined with recorded diabetes diagnosis improves the data quality and accuracy of estimates based on EHRs.[321]

Patients were considered as having diabetes when (1) diabetes diagnosis was recorded ('diagnosis', 'reason for encounter', 'reason for prescription') on two different occasions between 2016 and 2018, or (2) a patient was prescribed an ADM (ATC A10A or A10B; metformin considered only in the absence of PCOS diagnosis), or (3) diabetes diagnosis was recorded only once but the patient had in the preceding 24 months at least one laboratory result (FBG, HbA1c, or OGTT) above the threshold for diabetes diagnosis[25] (Table C1, Appendix C). A similar approach was used to identify patients with prediabetes, considering a combination of (1) two records of prediabetes diagnosis, or (2) only one record plus metformin prescription (i.e., in the absence of PCOS or diabetes diagnosis) or laboratory results consistent with impaired glucose levels. Patients with at least two laboratory results above recommended thresholds (either FBG or HbA1c) and/or a positive OGTT, but without any record of diabetes or prediabetes diagnosis or any prescribed ADM, were classified as 'unrecorded' diabetes or 'unrecorded' prediabetes. When only one abnormal FBG or HbA1c laboratory result was recorded, but no diabetes/prediabetes diagnosis was recorded or ADM prescribed, patients were classified as having 'insufficient data' (Figure 4.1 and Table C1, Appendix C).

Additional data extracted from the dataset included risk factors for diabetes (age 40+ years and overweight/obesity, AUSDRISK score ≥12 points, clinical history of CVD [including IHD and stroke], GDM, PCOS, or current use of antipsychotics [ATC N05A; 2018 only]) and other clinical conditions related to diabetes or prediabetes (hypertension, dyslipidaemia, CKD, atrial fibrillation, heart failure).[25] Data extraction was performed based on algorithms used in previous studies.[200, 248, 266] Overweight/obesity diagnosis used records of these terms as a

'diagnosis', 'reason for encounter', or 'reason for prescription', and BMI data (i.e., ≥25.0 kg/m^2) recorded in the same fields or as a clinical measure in the 'observation' field. The AUSDRISK score among patients without recorded diabetes diagnosis was calculated based on six of the 13 recommended variables: age, gender, Aboriginal status, smoking status, the antecedent of high BG (i.e., FBG levels), and the prescription of antihypertensive medications (Table C2, Appendix C).[120] Vegetable or fruit intake, physical activity levels, a family history of diabetes, or waist circumference values were not used to estimate the AUSDRISK score as they are not consistently recorded in MedicineInsight.[200] Data extraction algorithms used in this study are available under request.

Outcomes and covariates

The first investigated outcome was the prevalence of recorded diabetes, recorded prediabetes, and unrecorded diabetes/prediabetes, presented as a proportion of 'regular' adult patients in the database. The second outcome was the prevalence of recorded diabetes screening (i.e., at least one laboratory result of any BG test recorded between 2016 and 2018) among patients at high risk of diabetes (i.e., patients without a diabetes diagnosis, but with some of the conditions listed above, including prediabetes). Current guidelines recommend that individuals at high risk of diabetes should have their glucose levels checked at least every 3 years (every 12 months for prediabetes), preferably by testing FBG or HbA1c.[25] Diabetes screening was defined as having at least one recorded BG test result (FBG, HbA1c, random levels, OGTT, or finger-prick test), irrespective of the reported value.

Covariates included patient data (gender [male, female]; age [categorised as 18–29, 30–39, 40–49, 50–59, 60–69, 70–79, 80–89, 90+ years]; comorbidities; median number of consultations) and practice data (practice remoteness [major cities, inner regional, or outer regional/remote]; IRSAD [in quintiles]). IRSAD is a macroeconomic indicator of socioeconomic status based on

postcodes and generated by the ABS based on a range of census variables.[265] A higher IRSAD score indicates the practice is located in a more advantaged area. The investigated comorbidities included overweight/obesity, hypertension, dyslipidaemia, CKD, ischaemic heart disease, atrial fibrillation, heart failure, and stroke.[25]

Statistical analyses

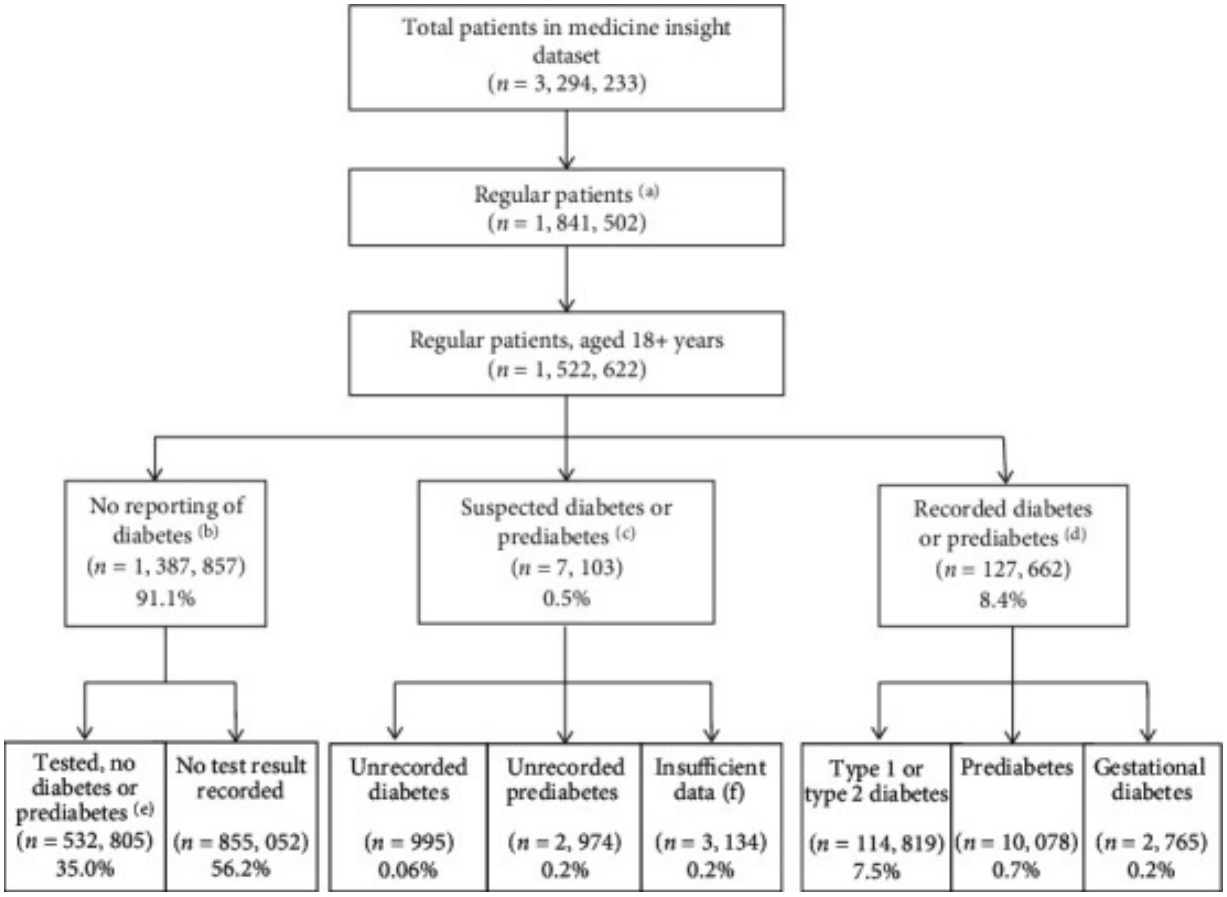
All analyses were conducted in Stata MP 16.1 (StataCorp, Texas, USA), with the practice as a cluster, using robust standard errors and conditioned to the number of visits to the practice. The sociodemographic profile of those with unrecorded prediabetes/diabetes was compared to those with recorded diabetes or recorded prediabetes using Chi-square tests. The same procedure was used to compare the prevalence of risk factors (i.e., overweight/obesity, hypertension, dyslipidaemia, CKD) and coexisting CVD (i.e., ischaemic heart disease, atrial fibrillation, heart failure, stroke) among those with recorded or unrecorded diabetes/prediabetes. The results were presented graphically with the corresponding 95%CI.

The prevalence of diabetes screening among those at high risk of diabetes was estimated overall (at least one of these risk factors) and for each risk factor. Furthermore, to assess how screening was performed over the lifespan, the prevalence of diabetes screening according to age and gender was presented graphically, separately for those at high risk (i.e., at least one risk factor) or not at high risk of diabetes. Differences in diabetes screening according to age, gender, and risk status were assessed using Chi-square tests.

This study followed the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement.[240] The independent MedicineInsight Data Governance Committee approved the study (protocol 2016-007). The Human Research Ethics Committee of the University of Adelaide exempted the study of an ethical review as it used only existing and non-identifiable data.

4.3.4 Results

The sample included 1,522,622 'regular' patients aged 18+ years (41.9% males; mean age 49.8±19.1 years) attending 544 general practices (Figure 4.1 and Table 4.1). The prevalence of recorded diabetes was 7.5% (95%CI 7.3;7.8), recorded prediabetes 0.7% (95%CI 0.6;0.7), and unrecorded diabetes/prediabetes 0.3% (95%CI 0.3;0.3). Supplementary Figures C1 and C2 (Appendix C) show the prevalence of these outcomes according to sociodemographic characteristics.



(a) At least three consultations in two consecutive years and at least one in each year. (b) No recording of diabetes, either as a diagnosis, reason for encounter, reason for prescription, or receiving an antidiabetic medication over the 3-year period. (c) One or more positive laboratory results for diabetes or prediabetes (details in Supplementary Table C1, Appendix C) but no recorded diagnosis of diabetes or prediabetes or prescription of antidiabetic medication. (d) Diagnosis (diabetes, prediabetes, gestational diabetes) recorded on at least two different occasions either as a diagnosis, reason for encounter, reason for prescription, or patient was prescribed antidiabetic medication, or the diagnosis was recorded only once but the patient had a positive laboratory result consistent with diabetes or prediabetes.(e) At least one laboratory test recorded, all results negative for diabetes or prediabetes. (f) Only one positive blood test for diabetes/prediabetes.

Figure 4.1. Flowchart of the distribution of patients included in the study, their screening status, and diagnosis of diabetes or prediabetes in Australian general practice, MedicineInsight, 2016–2018

Table 4.1. Sociodemographic profile of the study population (regular patients aged 18+ years) according to diabetes diagnosis status (2016–2018)

Characteristics	All patients, aged 18+ years (%)	Recorded diabetes (%)	Recorded prediabetes (%)	Unrecorded diabetes/ prediabetes (%)
Number of consultations in 2018, median (IQR)	3 (2–7)	7 (3–13)[(b)**]	5 (3–10)[(c)**]	7 (3–12)
Age, mean ± SD	49.8 ± 19.1	63.5 ± 15.6[(b)**]	60.3 ± 13.4[(c)**]	68.5 ± 13.3
Gender: males	41.9	52.2	54.8	53.7
Age group (years)				
18–29	17.9	3.1[(b)**]	1.5[(c)**]	0.5
30–39	17.1	5.6[(b)**]	6.2[(c)**]	2.8
40–49	16.1	9.7[(b)**]	13.6[(c)**]	5.4
50–59	16.0	17.1[(b)**]	23.8[(c)**]	14.0
60–69	15.1	25.6[(b)*]	29.4	27.5
70–79	11.2	24.8[(b)**]	19.5[(c)**]	29.6
80–89	5.5	12.4[(b)**]	5.6[(c)**]	17.1
90+	1.1	1.7[(b)**]	0.4[(c)**]	3.0
Practice remoteness				
Major cities	64.5	60.3	64.5	57.9
Inner regional	23.5	26.2	23.7	27.2
Outer regional/remote	12.0	13.5	11.8	14.9
Practice IRSAD quintile[(a)]				
Very high	25.3	19.1[(b)**]	23.0	23.1
High	19.4	17.0	19.3	17.3
Middle	22.8	24.6	23.2	23.1
Low	16.3	18.3	16.2	15.9
Very low	15.5	20.3	17.6	20.1

IQR: Interquartile range; SD: Standard deviation; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

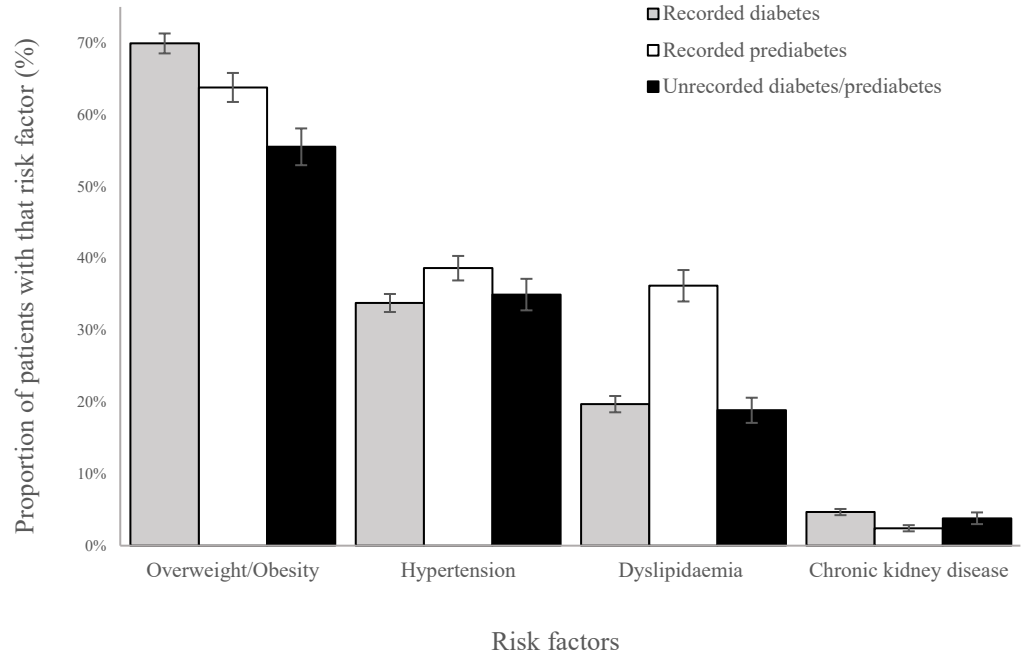
(a) IRSAD had 0.8% of missing data; high quintiles indicate greater advantage, and low quintiles indicate greater disadvantage. (b) P-value for the difference between people with recorded diabetes and unrecorded diabetes/prediabetes. (c) P-value for the difference between people with recorded prediabetes and unrecorded diabetes/prediabetes.

P-value *<0.01, **<0.001.

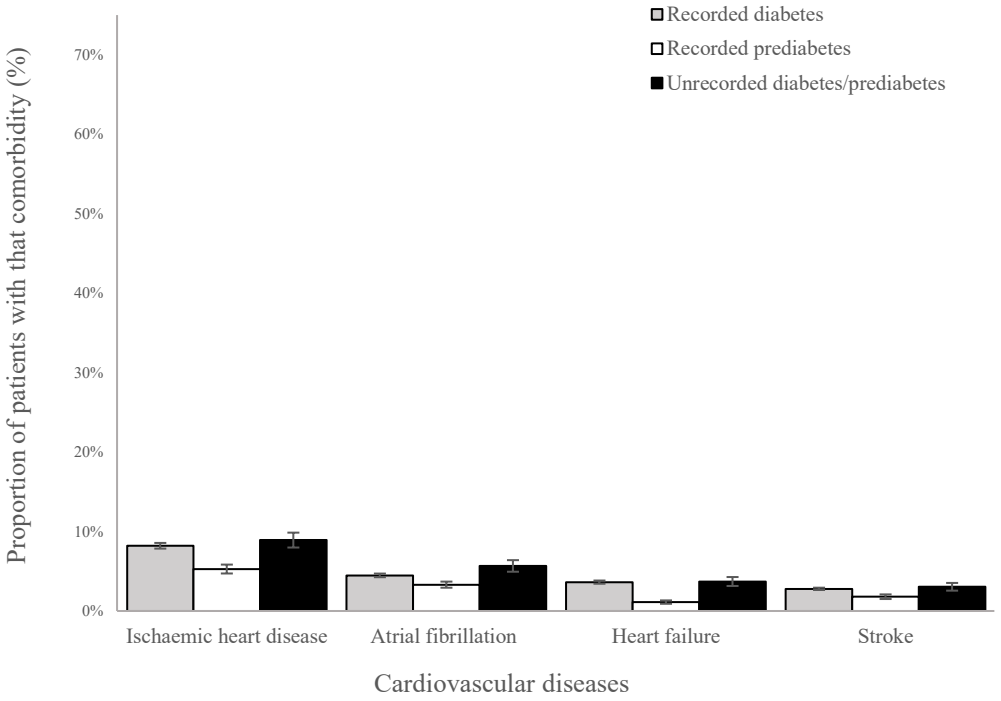
Table 4.1 shows that the median number of consultations was lower among those with recorded prediabetes than in the other two groups. The mean age of patients with unrecorded

diabetes/prediabetes (68.5 ± 13.3 years) was higher than those with recorded diabetes (63.5 ± 15.6 years) or recorded prediabetes (60.3 ± 13.4 years). Still, the distribution according to gender, practice remoteness, and practice IRSAD quintile was similar. Table C3 (Appendix C) presents further details on these comparisons (i.e., proportions with the corresponding 95%CI).

Figure 4.2 shows the prevalence of risk factors for CVD (Figure 4.2a) or established CVD (Figure 4.2b) according to diabetes/prediabetes diagnosis status. Overweight/obesity was the most prevalent risk factor, affecting 69.9% of patients with diabetes, 63.8% of those with prediabetes, and 55.5% of those with unrecorded diabetes/prediabetes. Dyslipidaemia was around twice higher (36.2% vs 19.7%) and hypertension 15% more likely (38.6% vs 33.8%) among patients with prediabetes than with diabetes. In contrast, all cardiovascular conditions were less frequent among those with recorded prediabetes. Except for the lower prevalence of overweight/obesity, patients with unrecorded diabetes/prediabetes had a similar clinical profile to those with recorded diabetes.



(2a)



(2b)

Figure 4.2. Prevalence of diabetes-related comorbidities: (2a) Risk factors for cardiovascular disease; (2b) Cardiovascular disease among regular patients (aged 18+ years) with recorded diabetes, recorded prediabetes, and unrecorded diabetes/prediabetes (Australia, 2016–2018)

Table 4.2 presents the results for diabetes screening among patients with no diabetes diagnosis. The prevalence of diabetes screening was 71% more likely among those with at least one risk factor for diabetes (55.2%, 95%CI 52.7;57.7) than those not at high risk of diabetes (32.3%, 95%CI 30.5;34.1). In addition, diabetes screening was slightly higher among those with a higher AUSDRISK score (61.3%), CVD (57.1%,) or aged 40+ years and overweight/obese (56.6%). The lowest prevalence of diabetes screening was for those treated with antipsychotics (27.0%) or with prediabetes diagnosis (45.5%).

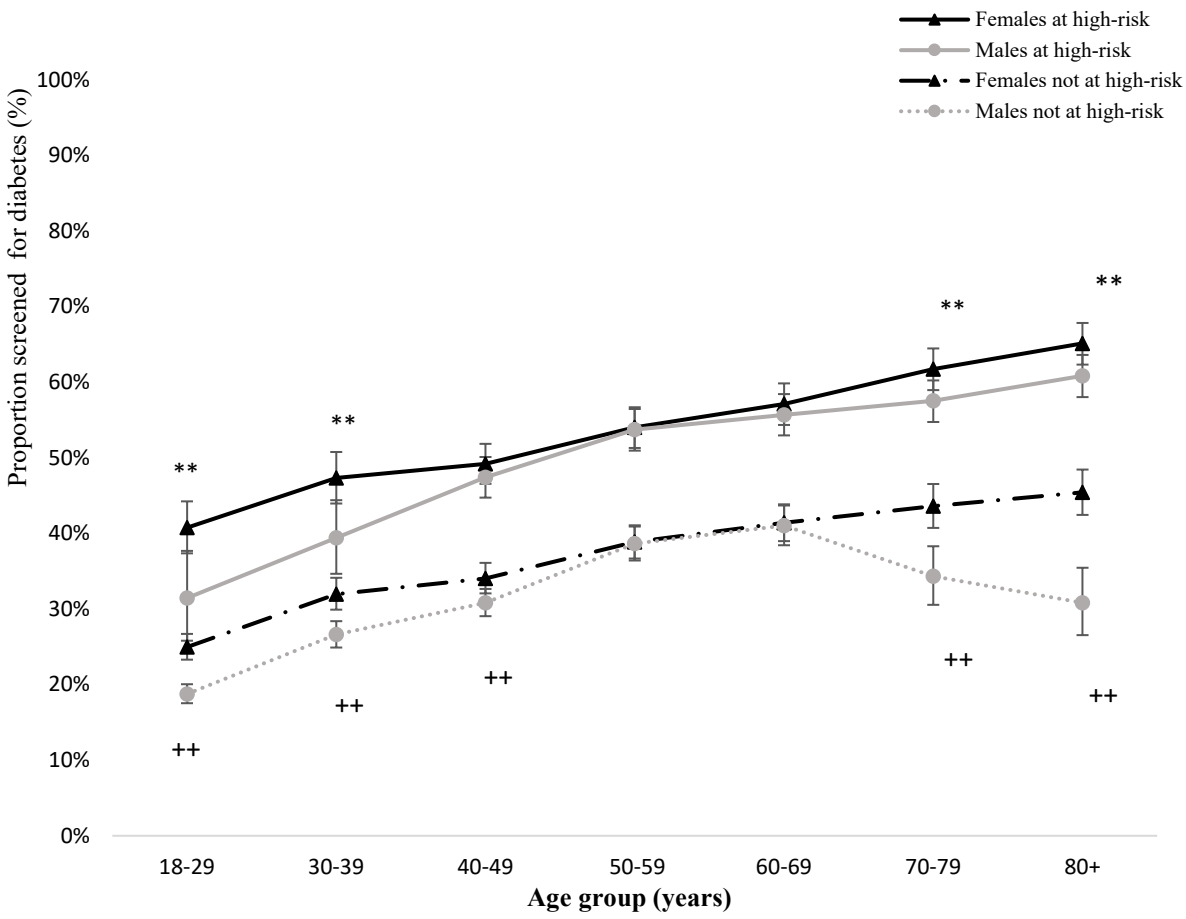
Table 4.2. Proportion of diabetes screening according to the presence or not of risk factors for diabetes. Regular patients aged 18+ years (n=1,407,803)

		Screened for diabetes (2016–2018)		Consultations in 2018
Risk factor for diabetes	**N[(a)]**	**n[(b)]**	**% (95%CI)**	**median (IQR)**
None of them	999,352	322,302	32.3 (30.5–34.1)	2 (1–5)
At least one risk factor	408,451	225,620	55.2 (52.7–57.7)	5 (2–10)
Aged 40+ years and overweight/obesity	300,939	170,352	56.6 (53.9–59.2)	5 (2–10)
AUSDRISK score ≥12	117,406	71,921	61.3 (58.8–63.7)	6 (3–11)
Prediabetes[(c)]	10,078	4,582	45.5 (42.8–48.2)	5 (3–10)
Cardiovascular disease	40,542	23,142	57.1 (54.4–59.7)	8 (3–14)
History of gestational diabetes mellitus	2,765	1,505	54.4 (49.7–59.1)	4 (2–9)
Polycystic ovary syndrome	6,253	2,885	46.1 (42.9–49.4)	3 (2–7)
Antipsychotics[(c)]	27,692	7,492	27.0 (25.3–28.8)	8 (4–16)

AUSDRISK: Australian Type 2 Diabetes Risk Assessment tool; CI: Confidence interval; IQR: Interquartile range.
(a) Regular patients aged 18+ years in each subgroup, excluding those with recorded diabetes diagnosis (n=114,819).
(b) Patients with at least one record of any blood glucose test in the last 3 years (2016–2018).
(c) Patients with at least one record of any blood glucose test in the last 12 months (2018).

The prevalence of diabetes screening according to gender, age, and presence of risk factors for diabetes is shown in Figure 4.3. Overall, the prevalence of diabetes screening increased with the age of the patients, but the association with gender varied across age groups. Diabetes screening was less frequent in younger males (18–39 years) than females, with a more pronounced difference among those at high risk of diabetes. However, gender differences were less evident among those aged 40–69 years, whether they were or were not at high risk of

diabetes. After that age, diabetes screening was again less frequent in men, showing a decline among those not at high risk of diabetes.



P-value for the difference between males and females at high risk: *<0.01, **<0.001.
P-value for the difference between males and females not at high risk: +<0.01, ++<0.001.

Figure 4.3. Prevalence of having a record of diabetes screening in males and females according to age and presence or not of risk factors for diabetes

4.3.5 Discussion

Five main findings can be highlighted based on our results. First, the prevalence and distribution of diabetes according to age and gender was consistent with national figures. Second, patients with prediabetes showed a higher prevalence of hypertension and dyslipidaemia than those with diabetes. Third, the prevalence of prediabetes diagnosis was lower than expected, but unrecorded diabetes/prediabetes was also infrequent. Fourth, the last finding probably under-

represents actual figures, as 45% of patients at high risk of diabetes were not screened for diabetes over 3 years. Those treated with antipsychotics had the lowest frequency of diabetes screening. Finally, diabetes screening increased with age and was lower in males. Still, the gender difference lessened among those aged 40–69 years, whether they were or were not at high risk of diabetes.

According to the Australian national health survey, the prevalence of diabetes among adults was 5.1% in 2011–2012 (combining self-reported and laboratory results) and 6.2% in 2017–2018 (self-reported data only).[324] The lower prevalence observed in the most recent national health survey compared to our study (7.5%) may reflect the use of a community-based sample in that survey compared to people seeking medical care in MedicineInsight, as well as the use of self-reported data and misclassification error of those with undiagnosed diabetes.[324]

Globally, it is estimated that one in two people living with diabetes do not know they have diabetes [64]. However, these proportions are lower in high-income countries. In the US, data from the National Health and Nutrition Examination Survey (NHANES, 2011–2014) showed that between 23% and 35% of people with diabetes were undiagnosed (using either FBG/HbA1c or 2-hour OGTT, respectively).[115] A French national survey conducted between 2014 and 2016 found that 23% of people living with diabetes were undiagnosed (FBG results), with a prevalence three times higher in males than females.[317] In Australia, data from the national health survey in 2011–2012 showed that 18% of adults living with diabetes were undiagnosed (FBG and HbA1c results), increasing the estimated prevalence of diabetes from 4.2% (known diabetes) to 5.1% (total diabetes).[13]

According to our findings, once a patient has tested positive for diabetes or prediabetes, it is more likely their status will be updated in the EHRs (i.e., only 0.26% of adults had unrecorded diabetes/prediabetes). As well as reducing misclassification bias due to undiagnosed diabetes,

another advantage of studies based on EHRs is that they can help monitor annual changes in the prevalence of diabetes and other chronic conditions.[200]

Our results are slightly different from other Australian studies that used medical records. POLAR found 4.9% of adults attending practices in urban Victoria had diabetes in 2016 (recorded diagnosis only).[10] Still, using GP-reported data, BEACH found 10.4% of adults in Australia had a diagnosis of diabetes (2012–2016).[323] The discrepancy across studies is probably related to the different methodological approaches used to identify patients with diabetes.

In this regard, analyses based on EHR databases rely on proper data recording and data extraction. In our study, one result that is lower than expected is the prevalence of prediabetes (0.7% compared to 3.1% in the Australian national health survey from 2011–2012).[13] Most Australian general practices use automatic methods to download the laboratory results (Logical Observation Identifiers Names and Codes, values, date, and limits of the results) into the EHRs,[223] making data extraction a less likely source of information bias. Nonetheless, 4 in 10 patients at risk of diabetes had no record of a glucose test in the last 3 years, suggesting the prevalence of prediabetes and undiagnosed diabetes is higher than observed.

Current Australian guidelines recommend regular laboratory diabetes screening only for those at high risk of diabetes.[25, 319] Nonetheless, compliance with these recommendations was suboptimal, as one-half of individuals at increased risk of diabetes were screened for diabetes in 3 years (one-third among those not at high risk of diabetes). This finding is consistent with results from the NHANES in the US, where 46% of adults at high risk of diabetes reported diabetes screening, compared to 30% among those for whom screening was not recommended.[325] In a recent South Australian survey including a population-based sample of individuals aged 35+ years, diabetes screening in the last 12 months was reported by 69% of

those with cardiometabolic conditions, 75% of those with CVD, and 51% of those with none of these conditions.[326]

In our study, less than half of patients with prediabetes were screened for diabetes in the last 12 months, which is a concern, as the conversion rate to diabetes among them is 5–10% per year.[25, 81] Moreover, patients with recorded prediabetes showed a higher prevalence of dyslipidaemia and hypertension than those with diabetes. The last finding is counterintuitive, as we expected a better metabolic profile among patients with prediabetes when compared to those with diabetes, as the former were younger (mean age of 60.3 vs 63.5 years) and had a lower prevalence of obesity (63.8% vs 69.9%). Moreover, a national cross-sectional study involving 69,974 middle-aged Chinese people showed the prevalence of dyslipidaemia was higher in patients with T2D than with prediabetes (59.3% vs 46.8%).[327] It is possible the worst metabolic profile observed among patients with prediabetes resulted from different sources of error, including detection bias (i.e., GPs were more likely to test, diagnose, and/or record hypertension and dyslipidaemia to reduce diabetes progression; hypertension/dyslipidaemia diagnosis leading to the diagnosis of 'asymptomatic' prediabetes), survival bias (i.e., patients with diabetes in the database represent 'survivor' cases with a better metabolic profile), and/or underdiagnosis of patients with less complicated forms of prediabetes. Therefore, our findings require cautious interpretation, and further longitudinal studies using primary data collection would be necessary to verify these results.

An even lower screening rate was found for patients treated with antipsychotics, at just over a quarter in 2018, which is worrying as antipsychotics have severe effects on BG levels.[328] Tests outside general practice (i.e., hospital or mental health services) are not captured in MedicineInsight, which may explain these lower numbers. However, a large retrospective cohort study in the US using comprehensive data of all performed tests (FBG or HbA1c, either

in primary care or mental health services) found that only 30% of non-diabetic patients treated with antipsychotics were screened for diabetes over 12 months.[128] Moreover, that study also reported that patients that had visited a primary care doctor in addition to mental health services were twice more likely to be screened than those who did not. Another possible explanation for the lower screening rates among patients treated with antipsychotics in our study is their younger age (median 50 years; interquartile range 37–67 years) compared to those with other risk factors for diabetes (median 63 years; interquartile range 51–73 years). The lower prevalence of diabetes screening among younger individuals has been reported in other studies.[31, 128, 325, 326]

Regardless of being at risk or not of diabetes, screening was lower among males, which is also consistent with previous studies.[128, 325] This finding is likely related to more frequent health-service-seeking behaviour in females.[329, 330] Nonetheless, men and women aged 40–69 years showed similar diabetes screening rates, which may reflect the influence of current chronic disease screening programs in midlife (e.g., 45–49 Year Old Health Check program).[25, 331]

This study used a large national database including general practices from all states and geographic regions to provide a comprehensive profile of diabetes diagnosis and screening in Australia. The study design incorporated methodological recommendations from previous studies using large datasets to improve data quality.[240, 251, 321]

However, this study is not free of limitations. First, data in MedicineInsight was recorded by GPs as part of their daily clinical activities, which may affect the completeness and accuracy of recorded data. Second, patients who visit multiple general practices or who are not 'regular' patients may have had their BG levels tested in other settings (e.g., hospitals or specialists) or not tested at all. This selection bias is an additional limitation that probably contributed to the low prevalence of prediabetes and unrecorded diabetes/prediabetes when compared to national

figures. Third, due to ethical issues that restrict the access to fields with potentially identifiable information, it was not possible to get access to the 'progress notes' of an appointment, which may contain relevant clinical data. Moreover, the accuracy of the extracted information is another limitation. This limitation is mitigated by data-checking: compared to the original EHRs available at the participating practices, data extracted from MedicineInsight had a sensitivity of 89% and specificity of 100% in identifying patients with diabetes.[248]

4.3.6 Conclusion

MedicineInsight represents a valuable resource for monitoring and providing a comprehensive diabetes diagnosis and diabetes screening profile in Australian general practice, considering that unrecorded diagnosis among those tested is uncommon. However, the rate of diabetes screening among patients at high risk of diabetes can be substantially improved, as these individuals have an average of five encounters per year with their GP. Specific interventions should target diabetes screening among patients with prediabetes and those treated with antipsychotics. National strategies such as the 45–49 Year Old Health Check program[331] seem to have reduced gender disparities for diabetes screening in midlife. Expanding that program to younger and older individuals at high risk of diabetes may be beneficial for improving early diagnosis and reducing further complications, especially in men.

Funding statement

MZ received a PhD Scholarship from the University of Adelaide to complete this study. The study did not receive any funding.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Data used in this study was obtained from a third party (MedicineInsight) for this specific project and cannot be released. Information about MedicineInsight data and how they can be accessed is available on the website (https://www.nps.org.au/medicine-insight). The data extraction algorithms used in this study are available from the corresponding author upon request.

Author contributions

MZ and DGC contributed to the conception and design of the study. MZ performed the statistical analysis and prepared the manuscript. COB and DGC assisted in data extraction, analysis, and writing the manuscript. NS contributed to the design and structure of the manuscript. All authors contributed to critically revising the text and provided intellectual contributions to strengthen the manuscript. All authors approved the final version for publication.

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_____End of published paper_____

4.4 Chapter Synopsis

Chapter 4 identified the prevalence of diabetes (7.5%) and prediabetes (0.7%) between 2016 and 2018. It also indicated undiagnosed diabetes/prediabetes is infrequent among patients attending Australian general practices. This provided the basis for further studies focusing on

newly recorded diabetes and prediabetes, as initial monitoring and management are crucial in the early stages. This chapter also calls for greater public awareness of diabetes screening among high-risk populations, as only half of those at risk for diabetes had been screened for diabetes within the past 3 years. In particular, only a quarter of those taking antipsychotic medications had had their glucose levels tested. This chapter found that hypertension was 15% more likely and dyslipidaemia 1.8 times higher among patients with prediabetes than with diabetes. Therefore, in addition to diabetes screening, the next chapter further compares diabetes monitoring and control among patients at an early stage (incident cases in 2017) and at a later stage (prevalent cases between 2015 and 2016) of diabetes.

Chapter 5. Diabetes Monitoring and Control (Paper 2 – Published)

5.1 Preface

Chapter 5 (Paper 2) presents details of comprehensive diabetes monitoring and control of key clinical parameters (i.e., BG, BP, lipid levels) recorded in EHRs, among patients with past recorded diabetes (first diagnosis in 2015–2016) or newly recorded diabetes (first diagnosis in 2017), in Australian general practices, and compares current practice to guideline recommendations. This chapter also investigates the sociodemographic or clinical characteristics of control of those critical clinical parameters. This paper has been published in *BMJ Open* (Appendix G) during the thesis examination:

Zheng M, Bernardo C, Stocks N, Hu P, Gonzalez-Chica D. Diabetes mellitus monitoring and control among adults in Australian general practice: a national retrospective cohort study. BMJ Open. 2023; 13(4), p.e069875 http://dx.doi.org/10.1136/bmjopen-2022-069875

It addresses the following research questions of this thesis:

- Are there any sociodemographic or clinical differences between patients with past or recent diabetes diagnoses among adults attending general practices in Australia?
- What is the prevalence of well-controlled diabetes?
- Do sociodemographic or clinical characteristics influence that outcome?

Highlights of Paper 2:

- Only 4 out of 10 people with diabetes had their HbA1c monitored over 12 months.
- Monitoring of clinical parameters was lower among people with newly recorded diabetes.
- Monitoring was not better in smokers, or adults with hypertension or CVD.
- HbA1c control was higher in patients with newly recorded rather than past recorded diabetes.

- Only 17–19% of adults with diabetes had HbA1c, total cholesterol, and BP well controlled.

5.2 Statement of Authorship

Title of Paper	Glycaemic management of initial metformin treatment for newly diagnosed diabetes attending Australian general practices: a longitudinal national study
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Zheng M, Bernardo C, Begum M, Stocks N, Gonzalez-Chica D. Glycaemic management of initial metformin treatment for newly diagnosed diabetes attending Australian general practices: a longitudinal national study. Under review by Diabetes Research and Clinical Practice.

Principal Author

Name of Principal Author (Candidate)	Mingyue Zheng		
Contribution to the Paper	MZ contributed to the conception and design of the study and performed the statistical analysis and prepared the manuscript. MZ contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16 February 2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Carla Bernardo		
Contribution to the Paper	CB assisted in data extraction and analysis. CB contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	10%	Date	16 February 2023

Name of Co-Author	Stocks Nigel		
Contribution to the Paper	NS contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	17 February 2023

Name of Co-Author	Peng Hu		
Contribution to the Paper	PH contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	3%	Date	16 February 2023

Name of Co-Author	David Gonzalez-Chica		
Contribution to the Paper	DGC contributed to the conception and design of the study and assisted in the data extraction of the manuscript. DGC contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	10%	Date	16 February 2023

5.3 Manuscript: Diabetes mellitus monitoring and control among adults in Australian general practice: a national retrospective cohort study

5.3.1 Abstract

Objectives: This study investigated whether the monitoring and control of clinical parameters are better among patients with newly compared to past recorded diabetes diagnosis.

Design: Retrospective cohort study.

Setting: MedicineInsight, a national general practice database in Australia.

Participants: 101,875 'regular' adults aged 18+ years with past (2015-2016) and 9,236 with newly recorded (2017) diabetes diagnosis.

Main outcome measures: Two different groups of outcomes were assessed in 2018. The first group of outcomes was the proportion of patients with clinical parameters (i.e., HbA1c, blood pressure [BP], total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate-eGFR, albumin-to-creatinine ratio) monitored at least once in 2018. The second group of outcomes were those related to diabetes control in 2018 (HbA1c ≤7.0%, (BP) ≤140/90mmHg, total cholesterol <4.0mmol/L, and LDL-C <2.0mmol/L). Adjusted odds ratios (ORadj) and adjusted probabilities (%) were obtained based on logistic regression models adjusted for practice variables and patients' sociodemographic and clinical characteristics.

Results: The study included 111,111 patients (51.7% males; mean age 65.3±15.0 years) with recorded diabetes diagnosis (11.0% of all 1,007,714 adults in the database). HbA1c was monitored in 39.2% (95%CI 36.9;41.6) of patients with newly and 45.2% (95%CI 42.6;47.8) with past recorded diabetes (ORadj 0.78, 95%CI 0.73;0.82). HbA1c control was achieved by 78.4% (95%CI 76.7;80.0) and 54.4% (95%CI 53.4;55.4) of monitored patients with newly or

past recorded diabetes, respectively (ORadj 3.11, 95%CI 2.82;3.39). Less than 20% of patients with newly or past recorded diabetes had their HbA1c, BP, and total cholesterol levels controlled (ORadj 1.08, 95%CI 0.97;1.21).

Conclusions: The monitoring of clinical parameters was lower among patients with newly than past recorded diabetes. However, diabetes control was similarly low in both groups, with only one in five monitored patients achieving control of all clinical parameters.

Keywords: Epidemiological monitoring, evidence-based practice, population health

Strengths and limitations of this study

- This retrospective cohort used a large sample of patients attending primary healthcare services across all Australian states and territories.
- A wide range of sociodemographic and clinical variables related to diabetes monitoring and control were included for adjustment.
- Lifestyle variables were not included for adjustment, as they are not consistently recorded in the electronic medical records.
- Patients may have had their diabetes parameters monitored somewhere else (e.g., different practices or by specialists).

5.3.2 Introduction

Diabetes mellitus is a lifelong disease that requires regular monitoring and control to reduce the risk of diabetes-related complications.[35, 101, 170, 332, 333] Micro- and macrovascular complications of uncontrolled diabetes (e.g., hypertension, dyslipidaemia, chronic kidney disease-CKD, cardiovascular disease-CVD) increase the health burden worldwide.[19] Blood glucose control is the most critical clinical goal of diabetes management, but other clinical variables also require regular monitoring.[35] The Royal Australian College of General Practitioners (RACGP)

guidelines recommend patients with diabetes should have their haemoglobin A1c (HbA1c), blood pressure (BP), and lipid levels evaluated annually to improve management and control of these clinical parameters.[129] Treatment options may vary depending on individual characteristics (e.g., age, gender, presence of comorbidities)[129, 334] and the stage of diabetes progression (i.e. recent or past diagnosis, presence of diabetes complications).[335]

Maintaining optimal levels of diabetes control with a combination of drug monotherapy and lifestyle changes is often possible for several years, after which a combination therapy may be necessary. The evaluation and modification of treatment plans in diabetes hinge on the information obtained from close monitoring of clinical parameters.[32] However, gaps between real-world practice and guideline recommendations for diabetes management have been reported worldwide.[112, 170, 171, 179] For instance, a survey of 305 primary care physicians in the US showed that only 38% of clinicians use guidelines in the management of diabetes.[171]

A systematic review of 123 Australian studies found that approximately 50% of patients with diabetes received 'standard care' (i.e., assessment of HbA1c, BP, lipids, weight, eye health, foot health). Among those assessed, 40-60% met management targets for HbA1c, BP, or lipid levels, but the study did not report the proportion that had all three parameters under control.[112] Most studies included in that review used electronic health records (EHRs) to investigate diabetes control. However, these studies also tended to source data from specialised centres rather than primary healthcare settings, and used non-representative samples, hindering the generalisability of the results at a national level. Additionally, other potential determinants of diabetes management and control (e.g., sociodemographic and clinical variables) were not widely investigated. Despite these limitations, figures in the review were consistent with measured data from the Australian Health Survey (AHS) (2011-2012), which reported that 54.7%

of adults with known diabetes met HbA1c targets, 39% met recommended BP levels, and 38%, total cholesterol targets.[13]

Despite concerns about the completeness and feasibility of using EHR-based primary care databases in research, studies conducted in countries such as the United States, Canada, the United Kingdom, France, Sweden, India and Australia have shown EHRs can provide accurate information on diabetes prevalence,[229, 248, 336] management and control.[92, 112, 240, 337] EHR-based research can improve diabetes management without increasing overall treatment costs.[338, 339] Moreover, EHR databases minimise self-report bias by providing information on doctor-reported diagnoses, objective laboratory results, and prescribed medications.[200, 229, 248]

Thus, this study used retrospective data from a national general practice database to investigate if (1) the monitoring of clinical parameters for diabetes management (HbA1c, BP, total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides (HDL), estimated glomerular filtration rate (eGFR), albumin-to-creatinine ratio (ACR)) is better among patients with newly than past recorded diabetes diagnosis, and (2) the proportion of those monitored who achieved diabetes control (i.e., HbA1c, BP, total cholesterol, LDL-C) is higher in patients with newly compared to those with past recorded diabetes diagnosis.

5.3.3 Methods

Data source

We used retrospective data from an open cohort database (MedicineInsight) that includes de-identified EHRs from approximately 662 general practices (8.2% of all Australian practices) and over 2,700 general practitioners (GPs) across Australia.[200] Details of data extraction and database characteristics have been published elsewhere.[200] Although practices in MedicineInsight were selected using a non-random process, all Australian states and territories,

urban and rural settings and socioeconomic settings are represented in the database. Diagnostic algorithms used for identifying patients with chronic disease using MedicineInsight have been validated, showing sensitivity of 89% against the recording of diabetes in the original EHR.[248]

Study sample

This study was reported according to the REporting of studies Conducted using Observational Routinely-collected Data (RECORD) statement.[240] Only data from practices with regular data provision (i.e., no gap of more than 6-weeks in data provision in the previous two years) was included. The sample was adults (18+ years) who regularly attended the practice (i.e., those with at least one consultation per year between 2015 and 2018) and who had a diagnosis of diabetes mellitus (either type 1 or type 2). Data from consultations between January 2015 and December 2017 were used to identify the level of exposure: patients with past (i.e., diabetes diagnosis recorded in 2015 or 2016) or newly recorded diabetes (i.e., first diagnosis recorded in 2017, but not during appointments in 2015 or 2016). The outcome was assessed using data from January to December 2018, considering all recordings of clinical parameters related to diabetes monitoring and control in that year.[129]

Three fields ('diagnosis', 'reason for encounter', 'reason for prescription') were initially searched to identify patients with recorded diabetes diagnoses. The original search was based on the methods for data extraction used by MedicineInsight.[200, 248] It included standard clinical terminology, misspellings, and abbreviations, and then expanded to include prescribed medications and laboratory results. Using as much information as possible from EHRs (i.e., observations, medications, diagnostic information) can provide a more accurate picture for identifying diabetes.[245] Besides, including laboratory results from EHRs are associated with higher rates of diabetes ascertainment.[340, 341]

Patients were classified as having past recorded diabetes (i.e., past diabetes) if between January 2015 and December 2016: (1) 'diabetes' was recorded in two different fields; or (2) antidiabetic medications were prescribed (Anatomical Therapeutic Chemical A10A or A10B;[342] metformin was considered only in the absence of polycystic ovary syndrome diagnosis); or (3) a diabetes diagnosis was recorded only once but there was at least one recorded laboratory result (fasting blood glucose, HbA1c or 2-hour oral glucose tolerance test) above the diabetes diagnosis threshold within the same timeframe.[129] Patients were classified as having newly recorded diabetes (i.e., recent diabetes) if: (1) they did not meet the criteria for past recorded diabetes (i.e. attended the practice in 2015 and 2016 but diabetes was not recorded) and (2) between January 2017 and December 2017 they presented any of the three criteria mentioned above for diabetes diagnosis (i.e., 'diabetes' recorded in two fields, antidiabetic medications were prescribed OR 'diabetes' was recorded once only but there was at least one abnormal glycaemic result recorded in 2017).

Outcomes

The outcome was assessed considering data related to diabetes monitoring and control reported between January and December 2018. The first group of outcomes was the proportion of patients with diabetes who had their clinical parameters for diabetes management monitored at least once in 2018 (i.e., HbA1c, BP, total cholesterol, LDL-C, HDL-C, triglycerides, eGFR, or ACR).[129] These clinical parameters were obtained from the fields 'observations' and 'laboratory results' using Logical Observation Identifiers Names and Codes.[343]

According to the RACGP guidelines, patients with diabetes should achieve recommended targets for all clinical parameters (i.e. HbA1c, lipids [total cholesterol, HDL-C, LDL-C, non-HDL, triglycerides], BP, and urine albumin excretion).[129] However, three key parameters (HbA1c, BP, and total cholesterol) can be used to define 'well-controlled' diabetes, since they

indicate that patients can comprehensively manage their diabetes and reduce the risk of complications.[112, 179] Therefore, the second group of outcomes was the proportion of patients that achieved in 2018, among those checked, generally recommended targets (HbA1c≤7.0%, BP≤140/90mmHg, and total cholesterol <4.0mmol/L). Considering LDL-C is also commonly used to monitor cardiovascular risk[335], we performed additional analysis reporting the proportion of patients who achieved well-controlled LDL-C (<2.0mmol/L). When multiple results were reported in 2018 for the same parameter and patient, the mean of these results was estimated and used for analysis.

'Well-controlled' diabetes was then explored using two different approaches. First, we analysed each clinical parameter as a different outcome: (1) controlled HbA1c, (2) controlled BP, or (3) controlled total cholesterol or LDL-C. Second, based on whether each of these three parameters was controlled or not, we created an outcome variable with eight categories to explore the most frequent combination of parameters that were under control: (1) none controlled, (2) HbA1c only, (3) BP only, (4) total cholesterol only, (5) HbA1c and BP controlled, (6) HbA1c and total cholesterol controlled, (7) BP and total cholesterol controlled, or (8) all controlled. The same combination was analysed considering LDL-C rather than total cholesterol and results were reported as supplementary material.

Covariates

Covariates included a group of sociodemographic and cardiovascular risk factors/history of CVD that may affect diabetes control.[101, 344] Practice data included practice remoteness (major cities, inner regional, or outer regional/remote/very remote] and practice Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD quintiles). Remoteness and IRSAD were defined based on postcodes. Remoteness is determined according to the population size and average distance to services, while IRSAD is an area-level measure of socioeconomic status

based on combined indicators (i.e., household income, education, and working status). Higher IRSAD scores indicate a more advantaged area.[265] Patient variables included age (18-39, 40-64, 65+), gender (females, males), smoking status (smoker, ex-smoker or non-smoker), recorded history of hypertension, and recorded history of CVD (including heart failure, ischemic heart disease, or stroke), dyslipidaemia, CKD, liver disease, and depressive symptoms during 2015-2017. Details on the data extraction methods for these variables have been published elsewhere.[248, 266]

Statistical analysis

All analyses were performed in Stata 16.1 (StataCorp, Texas, USA), considering the practices as clusters, using robust standard errors and conditioned to the number of visits to the practice.

The distribution of sociodemographic and clinical characteristics among patients with past or newly recorded diabetes were presented as proportions with their corresponding 95% confidence intervals (95%CI) (categorical variables), or as means with their standard deviation or median with their interquartile range (numerical variables).

Logistic regression models were used to assess differences in diabetes monitoring or diabetes control in 2018 (binary outcomes: each parameter controlled) between patients with past (i.e., diagnosis recorded in 2015 or 2016, reference group) or newly recorded diabetes (i.e. first diagnosis recorded in 2017). All results were adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), or clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, and depressive symptoms. We reported adjusted odds ratios (OR_{adj}) with their corresponding 95%CI, following recommendations of the American Statistical Association.[345] Furthermore, results from the adjusted logistic regression models were also used

to estimate adjusted predicted probabilities (i.e., adjusted proportions) of the investigated outcomes using the command 'margins' in Stata.

Multinomial logistic regression models were used to compare whether the most frequent combination of parameters under control differed between patients with past or newly recorded diabetes, using a similar approach for adjustment and then obtaining the OR_{adj} and adjusted probabilities for each category of the outcome.

Patient and public involvement

No patient involved.

5.3.4 Results

Population characteristics

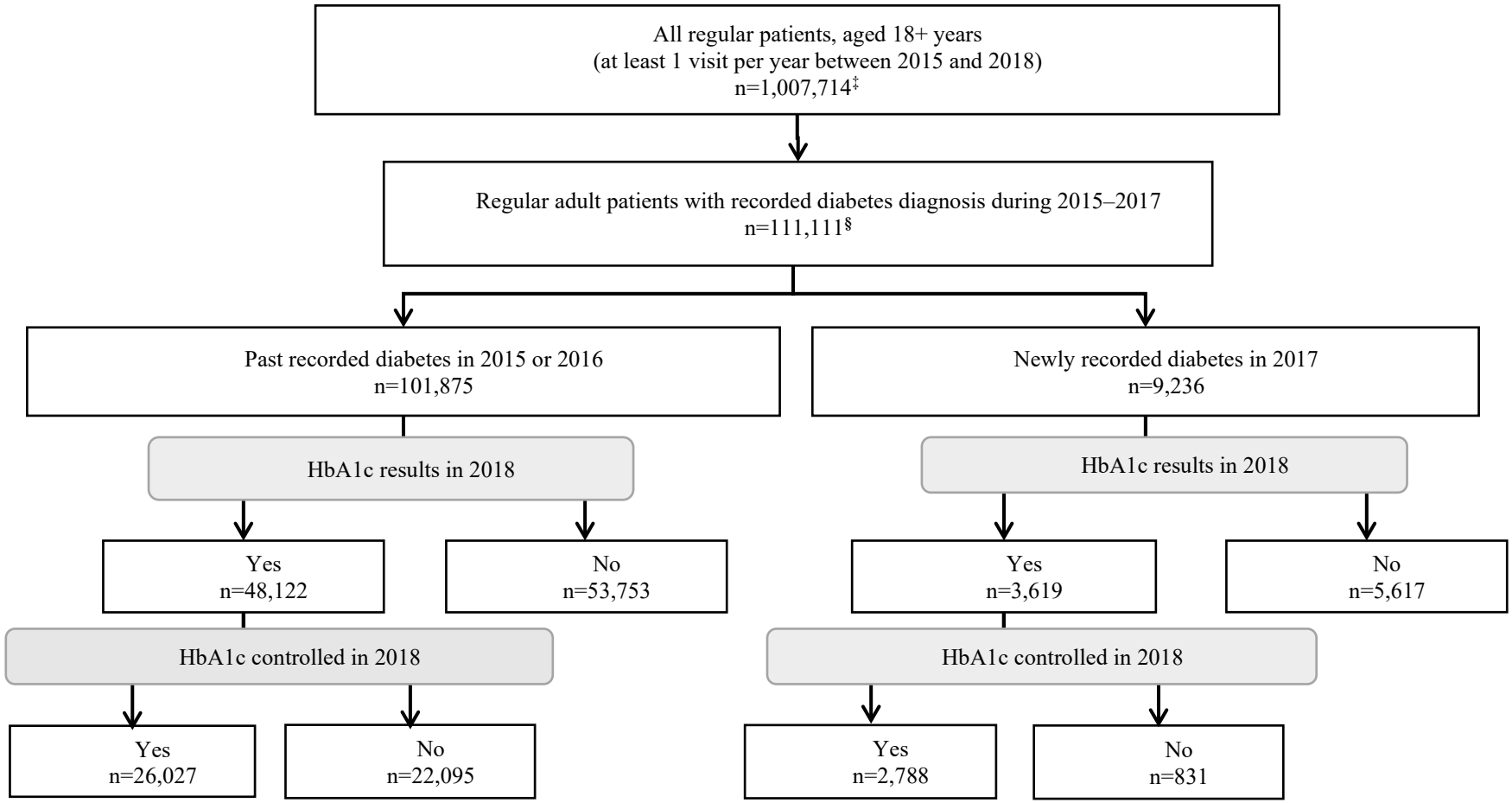
The database included 1,007,714 regular patients (at least one visit per year between 2015 and 2018) aged 18+ years attending 541 practices (Figure 5.1 and Table 5.1). Of these, 111,111 individuals (11.0%) had recorded diabetes diagnosis (51.7% males; mean age 65.3±15.0 years): 101,875 with past and 9,236 with newly recorded diabetes. Table 5.1 shows that patients with past recorded diabetes were older (mean 65.9±14.6 vs. 58.1±17.1 years), and had a higher proportion of males (52.4% vs. 44.0%), and history of CKD (4.7% vs. 2.9%) than those with newly recorded diabetes. However, diagnosis of hypertension (35.0% vs. 36.8%), dyslipidaemia (17.6% vs. 20.2%), or depressive symptoms (18.4% vs. 20.9%) was less frequent in patients with past recorded diabetes. The distribution according to remoteness, IRSAD, smoking status, history of CVD or history of liver disease was similar in both groups.

Diabetes monitoring

Table 5.1. Sociodemographic and clinical profile of regular patients† aged 18+ years in the database

	All adults in MedicineInsight (N = 1,007,714)	Patients with diabetes	
Variables		Past recorded diabetes (n = 101,875) % (95%CI)	Newly recorded diabetes (n = 9,236) % (95%CI)
Practice characteristics			
Geographical area of GP			
Major cities	63.8 (59.4–68.2)	59.4 (54.6–64.2)	62.3 (57.2–67.4)
Inner regional	24.8 (20.6–28.9)	27.4 (22.8–32.1)	25.0 (20.4–29.7)
Outer regional/remote/very remote	11.4 (8.5–14.4)	13.2 (9.8–16.5)	12.6 (9.1–16.0)
GP IRSAD			
More disadvantaged	33.8 (32.4–35.2)	39.2 (34.0–44.4)	38.3 (33.0–43.7)
Middle	23.7 (22.4–25.1)	25.0 (20.3–29.6)	24.6 (19.8–29.4)
More advantaged	43.8 (42.5–45.1)	36.6 (32.1–41.0)	38.1 (33.5–42.8)
Patient's characteristics			
Gender			
Male	40.4 (39.9–40.9)	52.4 (51.9–53.0)	44.0 (42.7–45.4)
Age, mean ± SD	54.0 ± 19.1	65.9 ± 14.6	58.1 ± 17.1
Age group (years)			
18–39	26.2 (25.1–27.2)	5.8 (5.4–6.2)	15.8 (14.6–17.1)
40–64	40.9 (40.4–41.4)	34.9 (34.0–35.7)	43.0 (41.7–44.4)
65+	33.0 (31.7–34.2)	59.4 (58.2–60.5)	41.2 (39.5–42.9)
Smoking status			
Smoker	12.0 (11.6–12.4)	10.5 (10.1–10.8)	10.8 (10.0–11.5)
History of hypertension			
Yes	19.0 (18.5–19.5)	35.0 (33.9–36.2)	36.8 (35.4–38.3)
History of CVD			
Yes	5.3 (5.2–5.4)	13.2 (12.8–13.5)	12.5 (11.7–13.3)
History of dyslipidaemia			
Yes	11.0 (10.5–11.4)	17.6 (16.7–18.6)	20.2 (19.0–21.3)
History of CKD			
Yes	1.3 (1.2–1.4)	4.7(4.3–5.1)	2.9 (2.5–3.4)
History of liver disease			
Yes	0.2 (0.2–0.2)	0.5 (0.5–0.6)	0.6 (0.5–0.8)
History of depressive symptoms			
Yes	20.7 (20.1–21.4)	18.4 (17.6–19.1)	20.9 (19.9–22.0)
Consultations in 2018, median (IQR)	4 (2–8)	7 (4–13)	6 (3–11)

GP: General practice; 95%CI: 95% Confidence interval; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; IQR: Interquartile range; SD: Standard deviation; CVD: Cardiovascular diseases, including heart failure, ischemic heart disease, and stroke; CKD: Chronic kidney disease.
All results were adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), or clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, and depressive symptoms. † People had at least one visit per year between 2015 and 2018.



† Results are shown as absolute numbers from the dataset without adjusting or weighting. ‡ At least one consultation per year between 2015 and 2018. § Patients were classified as recorded diabetes when (1) 'diabetes' was recorded on two different occasions (as a 'diagnosis', 'reason for encounter', or 'reason for prescription', or (2) antidiabetic medications were prescribed (Anatomical Therapeutic Chemical A10A or A10B; metformin was considered only in the absence of polycystic ovary syndrome diagnosis), or (3) diabetes diagnosis was recorded only once, but there was at least one laboratory result (fasting blood glucose, HbA1c or 2-hour oral glucose tolerance test) above the diabetes threshold.

Figure 5.1. Flowchart of the identification of 'regular' adult patients with recorded diabetes and HbA1c control†

Diabetes Monitoring

Table 5.2 reports the proportion and OR_{adj} of individuals who had their clinical parameters monitored in 2018, according to whether they had past or newly recorded diabetes. The most frequently monitored parameter was BP (past diabetes, 84.3% [95%CI 83.3;85.3]; newly diagnosed diabetes, 81.4% [95%CI 80.0;82.8]). The least monitored parameter was ACR (past diabetes, 17.4% [95%CI 16.8;18.0]; newly recorded diabetes, 13.5% [95%CI 12.6;14.3]). Although 45.2% (95% CI 42.6;47.8) of those with past diabetes and 39.2% (95%CI 36.9;41.6) with newly recorded diabetes had their HbA1c levels monitored in 2018 (Table 5.2), an additional 15 percentage points in each group (absolute difference) had their glycaemic parameters checked through fasting and/or random glucose levels (Table D1, Appendix D).

Table 5.2 also shows that OR_{adj} of monitoring of any parameter (i.e., HbA1c, BP, total cholesterol, HDL-C, LDL-C, triglycerides, eGFR, or ACR) was lower among patients with newly than past recorded diabetes, especially HbA1c (OR_{adj} 0.78, 95%CI 0.73;0.82) and ACR (OR_{adj} 0.74, 95%CI 0.69;0.79). Table D2 (Appendix D) presents the ORadj of distribution of patients with all three clinical parameters nontiered (HbA1c, blood pressure, and total cholesterol) according to sociodemographic and clinical characteristics among those with past or newly recorded diabetes.

Table 5.2. Clinical parameters monitored in 2018 according to whether patients had past (2015–2016) or newly recorded diabetes (2017)

	Past recorded diabetes (n = 101,875)	Newly recorded diabetes (n = 9,236)	
Clinical parameters monitored	**% (95%CI)**	**% (95%CI)**	**Adjusted† odds ratio (95%CI)**
HbA1c	45.2 (42.6–47.8)	39.2 (36.9–41.6)	0.78 (0.73–0.82)
Blood pressure¶	84.3 (83.3–85.3)	81.4 (80.0–82.8)	0.81 (0.75–0.87)
Total cholesterol	42.3 (39.8–44.8)	38.9 (36.4–41.4)	0.86 (0.82–0.91)
HDL-C	38.0 (35.7–40.2)	34.5 (32.2–36.7)	0.86 (0.81–0.91)
LDL-C	35.8 (33.6–37.9)	32.9 (30.5–34.8)	0.87 (0.82–0.92)
Triglycerides	41.3 (38.9–43.7)	37.8 (35.4–40.1)	0.86 (0.81–0.90)
Any type of kidney function#	26.9 (26.3–27.5)	25.5 (24.4–26.4)	0.93 (0.88–0.98)
eGFR	26.5 (25.9–27.1)	25.1 (24.1–26.2)	0.93 (0.88–0.98)
ACR	17.4 (16.8–18.0)	13.5 (12.6–14.3)	0.74 (0.69–0.79)

95%CI: 95% Confidence interval; HbA1c: Haemoglobin A1C; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; eGFR: Estimated glomerular filtration rate; ACR: Urine albumin-to-creatinine ratio; CVD: Cardiovascular diseases, including heart failure, ischemic heart disease, and stroke; CKD: Chronic kidney disease.
† Past recorded diabetes was used as the reference category. Results adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and CVD risk factors (smoking status, history of hypertension or CVD, CKD, dyslipidaemia, liver disease, and depressive symptoms using logistic regression models.

Well-controlled Diabetes

Table 5.3 shows the proportion of patients that achieved clinical goals for diabetes management in 2018 among those with available results for each of the three key parameters. Patients with newly recorded diabetes had higher chance of having their HbA1c controlled than those with past diabetes (OR_{adj} 3.11, 95%CI 2.82;3.39). Nevertheless, the odds of having diastolic BP (OR_{adj} 0.72, 95%CI 0.63;0.82), total cholesterol (OR_{adj} 0.63, 95%CI 0.57;0.69), and LDL-C (OR_{adj} 0.58, 95%CI 0.53;0.63) controlled were lower among those with newly recorded diagnosis than their peers. Systolic BP control was not different across groups.

Table 5.3. Clinical parameters controlled in 2018 according to whether patients had past (2015-2016) or newly recorded diabetes (2017) among those with available results for the three key parameters (HbA1c, blood pressure, and total cholesterol/LDL-C)

	Past recorded diabetes n = 40,008	Newly recorded diabetes n = 2,912	
Clinical parameter controlled	% (95%CI)	% (95%CI)	Adjusted† odds ratio (95%CI)
HbA1c (≤7.0% or ≤53 mmol/mol)	54.4 (53.4–55.4)	78.4 (76.7–80.0)	3.11 (2.82–3.39)
Systolic blood pressure (≤140mmHg)	70.6 (69.5–71.6)	71.4 (69.6–73.3)	1.04 (0.96–1.14)
Diastolic blood pressure (≤90mmHg)	94.6 (94.2–94.9)	92.8 (91.9–93.6)	0.72 (0.63–0.82)
Total cholesterol (<4.0mmol/L)	43.9 (43.0–44.9)	33.8 (31.9–35.6)	0.63 (0.57–0.69)
LDL-C (<2.0mmol/L)	47.1 (46.1–48.1)	34.7 (32.7–36.6)	0.58 (0.53–0.63)

95%CI: 95% Confidence interval; HbA1c: Haemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; CVD: Cardiovascular diseases, including heart failure, ischemic heart disease, and stroke; CKD: Chronic kidney disease.
† Past recorded diabetes was used as the reference category. Results adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and CVD risk factors (smoking status, history of hypertension or CVD, CKD, dyslipidaemia, liver disease, and depressive symptoms using logistic regression models.

Table 5.4 shows the combination of the three key parameters that were more frequently controlled in 2018. The proportion of individuals that met the three recommended targets was clinically similar, whether they had past (17.4%, 95%CI 16.7;18.1) or newly recorded diabetes (18.8%, 95%CI 17.2;20.3). Patients with newly recorded diabetes were more likely to have their HbA1c controlled, either alone (OR_{adj} 1.62, 95%CI 1.40;1.87) or in combination with BP controlled (OR_{adj} 1.64, 95%CI 1.45;1.86) than their peers. In contrast, the odds of total cholesterol being controlled (either alone or with BP) was ~65% lower among those with newly recorded diabetes than their counterpart. Analyses using LDL-C rather than total cholesterol showed similar results to those presented above (Table D3, Appendix D).

The association between sociodemographic and clinical variables with the monitoring of the three key parameters (HbA1c, BP and total cholesterol or LDL-C) are presented as supplementary materials (Tables D4 and D5, Appendix D).

Table 5.4. Combination of clinical parameters controlled in 2018 according to whether patients had past (2015–2016) or newly recorded diabetes (2017) among those with available results for all three parameters (HbA1c, blood pressure, and total cholesterol)

		Past recorded diabetes (n = 40,008)		Newly recorded diabetes (n = 2,912)	Adjusted† odds ratio (95%CI)
Parameter(s) controlled	**n**	**% (95%CI)**	**n**	**% (95%CI)**	
None controlled	3,521	8.8 (8.3–9.3)	149	5.1 (4.3–5.9)	0.54 (0.45–0.66)
Only HbA1c	3,961	9.9 (9.4–10.4)	492	16.9 (15.4–18.3)	1.62 (1.40–1.87)
Only BP	6,761	16.9 (16.3–17.5)	259	8.9 (7.9–9.9)	0.49 (0.42–0.57)
Only total cholesterol	2,360	5.9 (5.5–6.2)	61	2.1 (1.6–2.6)	0.33 (0.25–0.43)
HbA1c and BP	8,202	20.5 (19.8–21.1)	1,031	35.4 (33.5–37.3)	1.64 (1.45–1.86)
HbA1c and total cholesterol	2,641	6.6 (6.2–7.0)	210	7.2 (6.1–8.4)	1.02 (0.84–1.24)
BP and total cholesterol	5,601	14.0 (13.6–14.5)	163	5.6 (4.7–6.5)	0.37 (0.30–0.45)
All controlled	6,961	17.4 (16.7–18.1)	547	18.8 (17.2–20.3)	1.08 (0.97;1.21)

95%CI: 95% Confidence interval; HbA1c: Glycated haemoglobin; BP: Blood pressure; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular diseases, including heart failure, ischemic heart disease, and stroke; CKD: Chronic kidney disease.

† Past recorded diabetes was used as the reference category. Past recorded diabetes was used as the reference category. Results adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and CVD risk factors (smoking status, history of hypertension or CVD, CKD, dyslipidaemia, liver disease, and depressive symptoms using multinomial logistic regression models.

5.3.5 Discussion

General findings

Based on a large retrospective cohort study of the national general practice database, this paper highlighted three main findings. Less than half of patients with diabetes had their HbA1c levels assessed over 12 months, and the monitoring of HbA1c or other clinical parameters was less frequent among patients with newly than past recorded diabetes. Although patients with newly recorded diabetes were less likely to be monitored, 8 out of 10 of these patients achieved HbA1c control. In general, less than 20% of patients with diabetes who were monitored in 2018 had their HbA1c, BP and total cholesterol within targeted levels considered well-controlled.

Comparison with literature

Current Australian guidelines recommend annual monitoring of clinical parameters for all patients with diabetes.[129] Nonetheless, we found that only 45.2% of those with past diabetes and 39.4% of those with newly recorded diabetes had their HbA1c levels monitored in 2018. Our results are consistent with the 'Rule of Halves' discussed in an Australian review, showing that half of patients with diabetes receive appropriate diabetes care/monitoring.[112] On the other hand, another recent Australian retrospective study not included in that review and using EHRs from patients attending 50 practices in the inner eastern region of Melbourne (MAGNET database, period 2009–2014) found a higher proportion of monitoring. Findings showed that 66.5% of patients aged 65+years with T2D had their HbA1c checked within the last two years.[172] However, it is important to note that the population in that study was older, probably triggering a more frequent monitoring.

Among other clinical parameters, BP was the most frequently monitored regardless of having past (84.3%) or newly recorded diabetes (81.4%). In fact, having a newly recorded diagnosis of diabetes does not seem to affect BP monitoring in comparison with the general population,

as a population-based study in South Australia found that 81.8% of individuals without diabetes, hypertension, or CVD had their BP measured by a GP in the last 12 months.[326]

People with past recorded diabetes had a slightly higher proportion of kidney function monitoring than newly recorded diabetes. However, it is concerning that only 1 in 4 patients had these results reported in the last 12 months, even among those with past diabetes, considering that diabetes is one of the most important causes of CKD and annual kidney health checks (eGFR and urine ACR) are strongly recommended for patients living with diabetes.[106]

It is also concerning that a history of smoking or CVD did not affect the monitoring of the three main parameters (HbA1c, BP and total cholesterol) in any of the groups (past or newly recorded diabetes). These health conditions contribute to absolute CVD risk, diabetes-related comorbidities and, consequently, mortality.[35] However, it is plausible that healthcare professionals have monitored these patients in other settings, such as smoking cessation programs or CVD secondary prevention[129, 346] that would not be captured by our study.

Although patients with newly recorded diabetes were less likely to have their HbA1c monitored, 8 out of 10 of those monitored achieved HbA1c control. Patients with newly recorded diabetes were, on average, eight years younger than those with past diabetes, which suggests their condition was at an earlier stage when complications are less frequent and diabetes control is more likely to be achieved with first-line medications.[35, 333] Additionally, medication adherence among patients with newly diagnosed diabetes can be as high as 65% then reduce over time, which, in turn, has been found to impact diabetes control.[177] A previous study using the MedicineInsight database showed that greater regularity and continuity of care was associated with an increased likelihood of HbA1c monitoring, but it did not influence HbA1c control among patients with diabetes.[347] Our results differ substantially from the findings of a longitudinal study carried out with newly diagnosed patients (within 6 months before screening)

from 81 hospitals in China.[348] The investigation found only 36.8% of HbA1c control (< 7.0%),[348] but it is important to consider the different settings and patients characteristics in each study, as patients in hospital or specialised centres tend to need extra care or have a deteriorated health condition. Nonetheless, the possibility of information bias introduced by the less frequent HbA1c monitoring among those with newly recorded diabetes in our study cannot be discounted as an alternative explanation.

Despite the known effect of behavioural aspects[349] such as denial or anxiety in the patient's ability to monitor and manage their HbA1c when diabetes is diagnosed, according to our results, the management tend to weaken years after the diagnosis. The literature indicates that it happens due to the distress of living with diabetes and the high level of self-care needed to manage blood glucose, but also the lack of appropriate support or patient willpower over time.[332, 349-352] In our study, 54.4% of patients with past recorded diabetes achieved HbA1c control, very similar to results from the AHS (2011-2012), which reported 54.7% of control (HbA1c ≤7.0%) among adults with known diabetes.[13] Results from the MAGNET database, 2009 to 2014, found that among patients monitored for HbA1c, 42.4% achieved control (i.e., levels ≤7.0% in the most recent laboratory result).[172]

On the other hand, control of other clinical parameters in our study was better among patients with past than those with newly recorded diabetes. This could be related to the fact that patients with past diabetes were older (almost 60% were 65+ years compared to 41% among newly recorded diabetes), and older patients were at least twice more likely to achieve diabetes control than younger patients (Table 5.4). Results from the AHS (2011-2012)[13] also found that the proportion of patients with well-controlled diabetes increased with age. The reason might be that older patients visit their GP more frequently, allowing more opportunities to have disease management monitored.

Our findings showed that among patients who had the three key parameters monitored (HbA1c, BP and total cholesterol or LDL-C), only 1 in 5 achieved targeted goals for the three parameters. A British EHR-based study indicated that despite optimal control of different CVD risk factors (HbA1c, systolic-BP, total cholesterol, triglycerides, smoking), patients with diabetes still had a 21% higher CVD risk than those without diabetes, reinforcing the need to monitor and control these parameters.[353] Patients with a history of CVD were more likely to achieve well-controlled parameters, especially when they had newly recorded diabetes diagnosis. This finding might be related to the co-administration of antihypertensive and lipid-lowering therapy among patients with a history of CVD to reduce the risk of new CVD events.[354] And the fear of own mortality increases the chances of compliance to medication in the short-term. Besides, this may be because patients with history of CVD were given more intensive treatments or combined use of antidiabetic medications.[355] Discrepancies between patients with past or newly recorded diabetes diagnosis could result from prevalence-incidence bias, and prospective studies would be necessary to elucidate these findings.

Strengths and limitations

The study has significant strengths, such as the use of a large sample of patients attending primary healthcare services across all Australian states and territories. Furthermore, we explored sociodemographic and clinical variables related to diabetes monitoring and control that were not included in the most recent Australian studies on the same topic. Nonetheless, some other relevant covariates (e.g., diet and exercise) were not explored, as they are not consistently recorded in EHRs, or are recorded in the progress notes which cannot be extracted because of confidentiality issues. This is a common limitation of EHR-based studies, as data from progress notes may affect completeness of information used for analysis. Additionally, patients may have had their diabetes parameters monitored somewhere else (e.g., different

practices or specialists). To minimise the effect of this, we used different fields to identify laboratory results that were not requested and automatically reported to the practice by the laboratories. Despite using widely accepted target levels for the clinical parameters investigated, they may be adjusted and tailored to individual characteristics, which may not be feasible to differentiate in large epidemiological studies. Finally, prevalence-incidence bias may have affected some of the investigated associations (e.g., history of CVD and hypertension) among patients with past or newly recorded diabetes.

5.3.6 Conclusion

In Australia, monitoring and achieving clinical targets for diabetes management appears to be suboptimal. Consistent with previous research, we found half of the patients with diabetes had a record of their glycaemic levels being checked over 12 months. However, 80% of all those monitored did not achieve all targets of HbA1c, BP, and total cholesterol recommended by the RACGP guidelines, regardless of the time of diabetes diagnosis. Multi-component interventions for early detection and management of risk factors and complications, intensive glycaemic control and education on self-monitoring of blood glucose in persons with newly diagnosed diabetes, monitoring diabetes distress as part of routine care since the initial diagnosis, statin therapy for secondary CVD prevention, and intensive hypertension control with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers to prevent end-stage renal disease are some of the cost-effective strategies highlighted in the literature that could be incorporated and emphasized in standard diabetes care programs.[178, 349, 351, 352, 356] Further studies are necessary to examine whether systematic implementation of these strategies in Australian primary healthcare settings, in addition to the continuous promotion of behaviour changes through clear and engaged communication within health professionals and patients, can optimise diabetes management in line with guidelines.

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We are grateful to the general practices that participate in MedicineInsight, and the patients who allow the use of their de-identified information. We also thank all colleagues at the Discipline of General Practice, especially Dr Jessica Edwards and Dr Mumtaz Begum.

Data availability statement

Data used in this study was obtained from a third party (MedicineInsight) for this specific project and cannot be released. Information about MedicineInsight data and how they can be accessed is available on the website (https://www.nps.org.au/medicine-insight). The data extraction algorithms used in this study are available from the corresponding author upon request.

Contributors

MZ and DGC contributed to the conception and design of the study. MZ performed the statistical analysis and prepared the manuscript. CB and DGC assisted with data extraction, analysis, and manuscript writing. NS and PH contributed to the design and structure of the manuscript. All authors critically revised the manuscript and provided intellectual support to enhance the manuscript. All authors approved the final version for publication.

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Competing interests

The authors declare no conflict of interest.

Funding resources

MZ received a PhD Scholarship from the University of Adelaide for this study. Research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics approval statement

The independent MedicineInsight Data Governance Committee approved the study (protocol 2016-007). The Human Research Ethics Committee of the University of Adelaide exempted the study from an ethical review as it used de-identified data.

_____End of manuscript_____

5.4 Chapter Synopsis

Chapter 5 highlighted that diabetes monitoring and care appear suboptimal in primary care settings, although regular checks of key clinical parameters are recommended as part of annual diabetes standard care. All three key clinical parameters (i.e., HbA1c, BP, total cholesterol) were 'well-controlled' in only 20% of patients, which may cause further diabetes-related complications. BG is still the key component of diabetes control, and this chapter also indicated that HbA1c control was higher in patients with newly recorded diabetes rather than past recorded diabetes. This may be because diabetes interventions (lifestyle modifications and/or pharmacological therapy) work well in the beginning stage of diabetes. Therefore, the next chapter investigates the mean HbA1c effects of metformin use in patients with newly recorded diabetes.

Chapter 6. Early Metformin Therapy for Newly Diagnosed Diabetes (Paper 3 – Under peer review)

6.1 Preface

To answer the seventh research question, Chapter 6 (Paper 3) uses an advanced approach (augmented inverse probability weighting [AIPW]) to calculate the average treatment effect (ATE) of early or delayed metformin prescription on glycaemic control at 3–6, 6–12, 12–18 or 18–24 months after exposure or diagnosis among patients with newly recorded diabetes. This chapter is presented in the format of a manuscript submitted for publication, which is under peer review by *Primary Care Diabetes*.

It addresses the following research questions of this thesis:

- Do patients with a recent diabetes diagnosis achieve better glycaemic control with early metformin therapy compared to delayed pharmacological management?

Highlights of Paper 3:

- One-third of patients were prescribed metformin within 3 months of diabetes diagnosis
- Baseline glycaemic levels were higher among those with early metformin treatment
- Early metformin treatment also included more men, smokers, and people from more disadvantaged areas
- Early metformin treatment improved glycaemic parameters within 3–6 months
- They also reached better glycaemic parameters over 24 months than other treatment groups

6.2 Statement of Authorship

Title of Paper	Glycaemic management of initial metformin treatment for newly diagnosed diabetes attending Australian general practices: a longitudinal national study
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Zheng M, Begum M, Bernardo C, Stocks N, Gonzalez-Chica D. Comparing the effect of early versus delayed metformin treatment on glycaemic parameters among Australian adults with incident diabetes: evidence using a national general practice database. Under review by Diabetes Research and Clinical Practice.

Principal Author

Name of Principal Author (Candidate)	Mingyue Zheng		
Contribution to the Paper	MZ contributed to the conception and design of the study and performed the statistical analysis and prepared the manuscript. MZ contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Overall percentage (%)	80%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16 February 2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate in include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Begum M		
Contribution to the Paper	BM assisted in data extraction and cross-checked Stata syntax. BM contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	17 Feb 2023

Name of Co-Author	Carla Bernardo		
Contribution to the Paper	CB assisted in study design and data extraction. CB contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	16 February 2023

Name of Co-Author	Stocks Nigel		
Contribution to the Paper	NS contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	17/02/2023

Name of Co-Author	Gonzalez-Chica David		
Contribution to the Paper	DGC contributed to the conception and design of the study and assisted in the data extraction of the manuscript. DGC contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	5%	Date	16 February 2023

6.3 Manuscript: Comparing the effect of early versus delayed metformin treatment on glycaemic parameters among Australian adults with incident diabetes: evidence using a national general practice database

6.3.1 Abstract

Aims: To compare the effect of early versus delayed metformin treatment for glycaemic management among patients with incident diabetes.

Methods: Cohort study using EHRs of regular patients (i.e., at least one visit per year in three consecutive years) aged 40+ years with 'incident' diabetes (i.e., newly recorded diagnosis) attending Australian general practices (MedicineInsight, 2011–2018). The effect of early (<3 months after diagnosis), timely (3–6 months), and delayed (6–12 months after diagnosis) start of metformin treatment versus no management with metformin (i.e., within 12 months of diagnosis) on HbA1c and FBG levels at 3–6, 6–12, 12–18 or 18–24 months after diagnosis was compared using linear regression and augmented inverse probability of treatment (AIPW) models.

Results: Of the 18,856 investigated patients with incident diabetes, 38.8% were prescribed metformin within 3 months, 3.9% between 3–6 months, and 6.2% between 6–12 months after diagnosis. Baseline glycaemic parameters for those on early treatment (mean HbA1c 7.64%; FBG 8.83 mmol/L) were higher than other groups, reaching controlled levels at 3–6 months (mean HbA1c 6.45%; FBG 6.86 mmol/L) that persisted over the 24-month follow-up. Compared to those not managed with metformin (i.e., group with the lowest glycaemic levels at baseline and follow-ups), the corresponding ATE for HbA1c at 18–24 months was +0.04% (95%CI –0.05;0.10) for early treatment, +0.24% (95%CI 0.11;0.37) for timely treatment, and +0.29% (95%CI 0.20;0.39) for delayed treatment. Similar patterns were found for FBG levels.

Conclusion: Early metformin therapy helped patients achieve better and more stable glycaemic parameters.

Keywords: Evidence-based practice, drug prescriptions, hypoglycaemic agents, electronic health records, epidemiologic methods, general practice, population health management

6.3.2 Introduction

Type 2 diabetes mellitus (T2D) is a lifelong disease mainly diagnosed and managed in primary care settings.[164, 336] Guidelines recommendations vary on whether patients should start ADMs combined with lifestyle modifications (e.g., healthy diet, exercise, or weight control) soon after diagnosis, or only when glycaemic goals were not achieved after a few months of non-pharmacological management based on lifestyle modifications.[35, 37, 131, 357]

Lifestyle modifications for diabetes management are challenging in routine care,[146] and it remains debated whether patients with newly diagnosed diabetes should start medication management immediately.[35] Indeed, earlier metformin therapy after diabetes diagnosis has been found to provide better glycaemic control.[35, 152, 153, 358] A large US study including 2,925 patients with T2D and new users of metformin found that each additional month of delayed metformin therapy after diagnosis of diabetes was linked with an increased HbA1c level of 0.005% (95% CI 0.003;0.006).[153] Early metformin treatment was also associated with a more pronounced weight decrease and a lower risk for therapy intensification than those with delayed pharmacological treatment.[153]

Despite the recognised evidence of early ADM therapy for treating diabetes and preventing complications, only half of the patients with incident diabetes and attending primary care settings in the US are treated with metformin within the first year of diagnosis.[36, 359] Of those

treated, 68% received metformin within the first month and 13% at least 4 months after diagnosis.[358]

In Australia, metformin is the preferred first-line ADM considering its low risk of hypoglycaemia and weight gain,[37, 73] and the number of dispensed drugs containing metformin doubled in Australia between 2003 and 2019.[33] Using Pharmaceutical Benefits Scheme (PBS) data, it was estimated that 86% of Australian adults with T2D initiating a non-insulin T2D medication were started on metformin as monotherapy.[360] However, PBS data do not include follow-up laboratory results to investigate the effect of early or delayed medication administration on glycaemic parameters. EHR databases have been used to estimate the longitudinal effect of ADM prescription on glycaemic parameters in the UK and US.[153, 164, 358, 361] Australia's primary care data is a reliable resource to improve our understanding of the management of diabetes and other chronic conditions,[22, 200, 248] but no EHR-based studies have evaluated this topic at a national level. Therefore, this study aimed to investigate the effect of different treatment times (receiving metformin treatment within 3 months, 3–6 months, 6–12 months, or no metformin treatment within 12 months of diagnosis) on glycaemic parameters over 24 months among patients attending Australian general practices.

6.3.3 Methods

Data source

This longitudinal study used data from MedicineInsight (2011–2018), a large-scale primary care database containing routinely collected de-identified EHRs from approximately 2,700 GPs and 622 general practices across Australia, comprising about 8.2% of all Australian practices.[200]

We used EHRs from practices that provided regular data, did not have gaps of data provision of more than 6 weeks in the past 2 years, and had a consistent number of consultations over time (i.e., ratio of the highest to lowest total number of consultations per year <5).

Administrative contacts and duplicated records were excluded.[200, 248, 336] This study was reported according to The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies.[362]

Study population

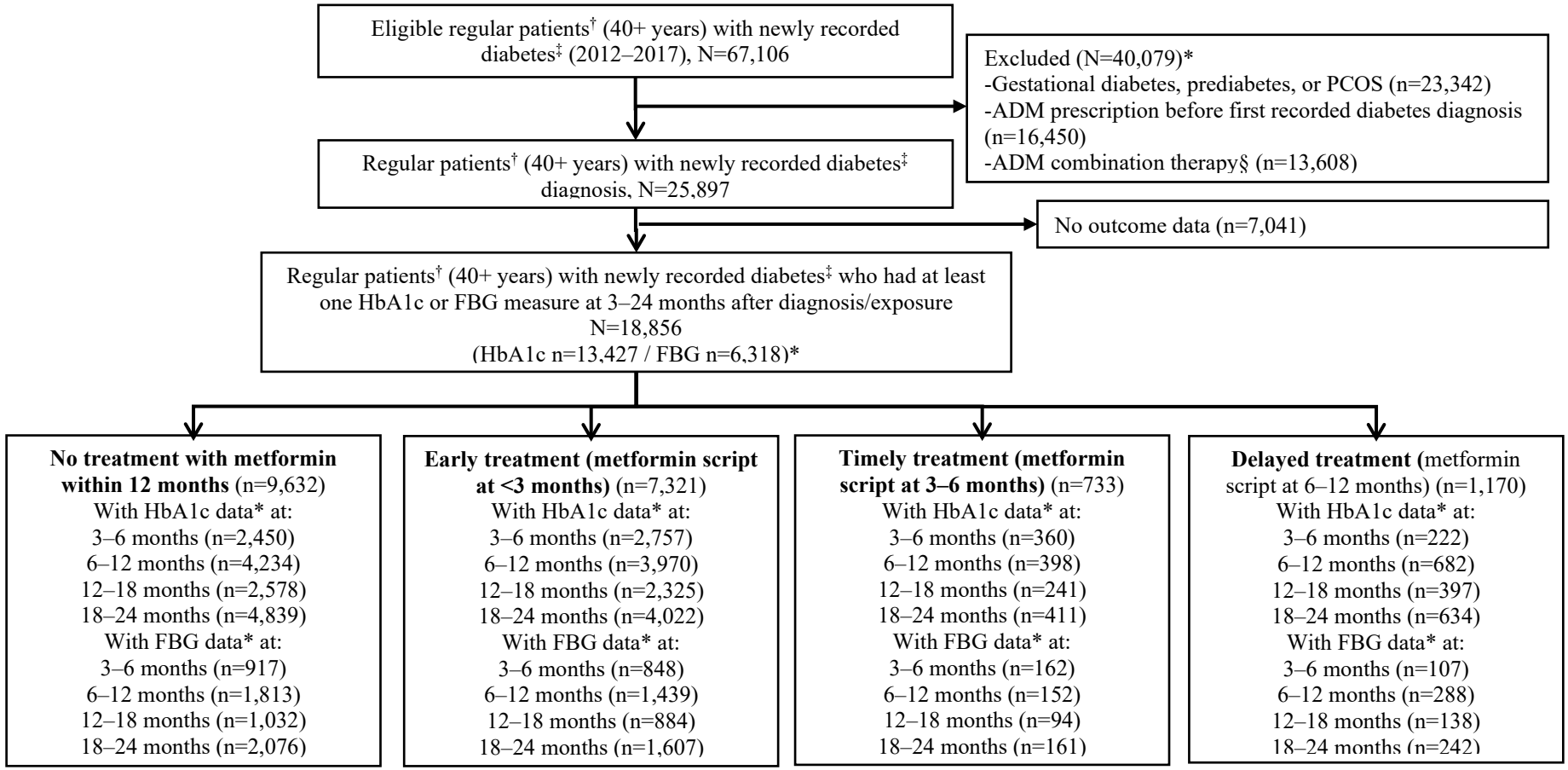
The study sample included 'regular patients' (i.e., at least one visit per year in three consecutive years) aged ≥40 years with 'newly' recorded diabetes diagnosed between 1 January 2012 and 31 December 2017. Information on diabetes diagnosis was extracted from six different datasets/fields of the MedicineInsight database ('diagnosis', 'reason for encounter', 'reason for prescription', 'scripts', 'observation' and 'pathology results'). Algorithms used by MedicineInsight to identify patients with diabetes in the database have a sensitivity of 89% and specificity of 100% compared to data directly obtained from the original medical record extracted at the practice.[248]

The search terms included pre-coded terms, synonyms, and misspellings related to diabetes diagnosis. Further details on the used terms and methods are described elsewhere.[200, 336] The prescriptions of ADMs (Anatomical Therapeutic Chemical code A10A and A10B) were extracted from the 'scripts' dataset using ingredients and brand names. Valid BG results recorded in the observation and pathology datasets were used to identify baseline (i.e., HbA1c, FBG, OGTT, RBG) and outcomes (i.e., HbA1c, FBG) variables.

To identify individuals with 'newly' recorded diabetes (i.e., incident diabetes), we included only patients with at least 12 months of medical data before the first recording of diabetes diagnosis (i.e., no recording of diabetes in the previous 12 months to exclude 'prevalent' diabetes). Moreover, only patients with at least one encounter 12 months after the first recorded diabetes diagnosis were selected. Therefore, patients with newly recorded diabetes were defined as those with 'diabetes' recorded at least twice (i.e., in two different datasets, or on different

dates in the same dataset), or with 'diabetes' was recorded only once but with at least one abnormal glycaemic result (i.e., HbA1c ≥6.5%, FBG ≥7.0 mmol/L, or OGTT ≥11.1 mmol/L) recorded within the 3 months before the recorded diagnosis.

Patients were excluded if they (1) were managed with any ADM prior to the first recorded diabetes diagnosis, (2) were initially managed with non-metformin medications, (3) received metformin with another ADM within the first 30 days (ADM combination therapy), or (4) had a recorded history of other conditions that could impact glycaemic changes and/or management decisions (i.e. GDM, prediabetes, or PCOS[35, 129]) (Figure 6.1).



ADM: Antidiabetic medication; PCOS: Polycystic ovary syndrome; FBG: Fasting blood glucose

† Patients have at least one visit per year for three consecutive years since the year before the first diagnosis of diabetes.

‡ Patients with newly recorded diabetes were defined as: (1) they did not have any diagnosis of diabetes or ADM prescriptions first period of recorded diabetes AND (2) they had at least two diabetes diagnoses (i.e., 'diabetes' recorded on two different fields), OR one diagnosis of diabetes plus at least one abnormal glycaemic result (i.e., HbA1c ≥6.5%, fasting blood glucose ≥7.0 mmol/L, or oral glucose tolerance test ≥11.1 mmol/L) recorded within the previous 3 months of the diagnosis.

§ ADM combination therapy: patients who received metformin with other ADM(s) on the same day or within up to 30 days of metformin prescription.

* Numbers are not mutually exclusive. Results are shown as absolute numbers from the dataset without adjusting or weighting.

Figure 6.1. Flowchart of the identification of regular patients (aged 40+) with newly recorded diabetes (2012–2017)

Exposures

The exposure variable was defined based on the time of metformin commencement after the first recorded diabetes diagnosis (within the first 12 months of diagnosis) based on previous literature.[153, 358] Thus, patients were classified as early treatment (metformin prescription started within the first 3 months of diagnosis), timely treatment (metformin started between 3 and 6 months), delayed treatment (metformin started between 6 and 12 months), or no treatment with metformin within 12 months of diagnosis (reference category for comparison).

Outcome

Two glycaemic parameters (HbA1c and FBG levels) were assessed as the study's primary outcomes. They were assessed during four different time periods: 3–6 months (T1), 6–12 months (T2), 12–18 months (T3), and 18–24 months (T4) after the first diabetes diagnosis (T0). For patients with multiple glycaemic measurements during the corresponding timeframe, we used the most recent values of HbA1c or FBG – that is, values measured closest to the date of diabetes diagnosis (for unexposed) or closest to the date of starting metformin (for exposed). Patients who received other ADMs prior to each follow-up point were excluded because this study focused only on metformin treatment, so we attempted to exclude the effect of other ADM. For example, at 18–24 months, patients who had received another ADM up to 24 months were excluded from the final analysis. Considering the principle of intention to treat analysis, we reported the results of the analyses without excluding other ADMs at each timeframe in supplementary materials.

Confounding

Confounders of the association between the time of metformin treatment started and the glycaemic measures were defined based on the literature.[35, 153, 358] The assumed relationship between these variables was presented as a directed acyclic graph (Figure E1, Appendix E).

These confounders included the practice variables such as remoteness of location – major cities, inner regional, or outer regional/remote/very remote – and the IRSAD quintiles – (1) more disadvantaged (lower two quintiles), (2) middle, (3) more advantaged (upper two quintiles).[265] Remoteness is a classification used by the ABS to measure the distance and level of access of the postcode to main services in a physical location. IRSAD is another regional-level socioeconomic measure established by the ABS and based on postcodes that considers information (e.g., income, housing, and education).[200] A higher IRSAD indicates a more advantaged region. Patient data included patient's IRSAD (in quintiles), gender (males, females), age (in years), pre-existing comorbidities (hypertension, dyslipidaemia, CVD, CKD), smoking status (non-smoker/ex-smoker, current smoker), baseline BMI (continuous variable), the average number of consultations per year (during 2012–2017), and the prescription of antipsychotics before diabetes diagnosis. Details on the algorithms used for the extraction of these variables from MedicineInsight have been published elsewhere.[22, 200, 336]

Additionally, the baseline glyacemic level was included as a confounder, as it could have influenced the decision of starting medication management. However, only 48% of patients had baseline HbA1c and/or 35% had FBG values at the date of first recorded diabetes diagnosis. To minimise data loss, we used multiple parameters (HbA1c, FBG, OGTT, RBG) and measures recorded over an extended period (up to 365 days before or 30 days after the first recorded diabetes diagnosis). When multiple measurements were available within this timeframe, we chose the closest value to T0. Considering these variables have different units, they were transformed into categorical variables (i.e., classified as normal, prediabetic, or diabetic range), so that they could be combined into a unique baseline glycaemic indicator variable.[22, 358] Using this approach, 79.9% of the investigated patients had a baseline glycaemic indicator available.

Statistical analysis

All analyses were performed in Stata MP 16.1 (StataCorp, Texas, USA), considering general practices as clusters. The description of characteristics of the regular patients (aged 40+ years) with incident diabetes and with baseline glycaemic measure and follow-up data (HbA1c or FBG) in the baseline according to sociodemographic or clinical characteristics was presented as % for categorical variables or as means with their SE for numerical variables.

Linear regression and AIPW[303] models were used to estimate the effects of early, timely, or delayed metformin prescription on HbA1c and FBG compared to no metformin treatment. Analyses using linear regression models were adjusted for all potential confounders and presented graphically as predicted adjusted means (estimated using the command 'margins' in Stata) with their corresponding 95% CIs. For the AIPW analyses, two models were specified.[299, 311] First, the treatment model (multinomial regression) was used to calculate the probability of exposure to metformin (no treatment within 12 months vs early, timely, or delayed treatment). Second, the reciprocal of this predicted probability was used as a weighting variable (AIPW) in the outcome model (linear regression) for the specific outcome (HbA1c or FBG). The entire set of confounders were used in the treatment and outcome (without the average number of consultations during 2012–2017) models. additionally AIPW is a doubly robust approach, which can produce unbiased estimates if either the treatment model or the outcome model is correctly specified.[311]

In the final cohort, missing data was less than 0.02% for most confounders, except for baseline glycaemic measures (21.1% missing) and BMI (32.1% missing). We imputed the missing data for all confounders using multivariate imputation by chained equation (MICE).[279] All confounders and auxiliary variables (including the practiceid) were used to impute the missing confounders. Exposure and outcome variables were not imputed. Twenty datasets were generated by multiple imputations, and Rubin's rules[303] were followed to combine the estimates

from the 20 datasets. All results for the linear regressions and AIPW models presented in this study are based on imputed data. The Stata syntax used to calculate the AIPW in imputed data has been described elsewhere.[309]

Additionally, sensitivity analyses were conducted and are presented as supplementary materials, considering complete-case scenarios.

6.3.4 Results

Characteristics of participants

Figure 6.1 and Table E1 (Appendix E) show the baseline data for the 25,897 eligible regular patients (aged 40+ years) with newly recorded diabetes diagnosed between 2012 and 2017 (52.3% men, mean age 64.0±11.4 years). Of these, 18,856 (72.8% of the original cohort) had available data on at least one of the outcomes. The original cohort and the investigated sample were comparable according to all sociodemographic and clinical variables (Table E1, Appendix E), including the baseline levels of HbA1c (mean 7.0±1.5% for both) and FBG (mean 7.7±2.7 mmol/L and 7.8±2.7 mmol/L, respectively). Half the investigated sample (51.1%) were not treated with metformin within 12 months of diagnosis, 38.8% were prescribed metformin within 3 months, 3.9% between 3 and 6 months and 6.2% in 6–12 months after diagnosis. Figure E2 (Appendix E) shows the time of starting metformin prescription during the first year of diagnosis, stratified by gender.

Table 6.1 compares the baseline sociodemographic and clinical characteristics of the investigated sample according to the time when metformin was first prescribed (imputed data). The lowest baseline HbA1c and FBG levels were observed in the untreated group, and the highest among those in the early treatment group. Individuals in the early treatment group were more likely to live and attend practices located in more disadvantaged areas or more remote settings. That treatment group also included a higher proportion of males, smokers, younger

individuals, and patients with a higher BMI than the untreated group. Similar patterns were observed when the available number of patients at each follow-up timeframe was investigated (Tables E3 and E4, Appendix E).

Table 6.1. Baseline characteristics of the regular patients (aged 40+ years) with newly recorded diabetes and with baseline glycaemic measure and follow-up data (N=18,856)* (imputed data)

	No treatment with metformin within 12 months (unexposed) n=9,632 (%)	Early treatment (metformin script <3 months) n=7,321 (%)	Timely treatment (metformin script at 3–6 months) n=733 (%)	Delayed treatment (metformin script at 6–12 months) n=1,170 (%)
Practice characteristics				
Geographical area of GP				
Major cities	55.1	49.7	51.7	51.9
Inner regional	30.5	29.2	32.6	33.2
Outer regional/remote/very remote	14.4	21.1	15.7	14.9
GP IRSAD				
More disadvantaged	38.6	47.0	41.2	39.8
Middle	24.1	22.6	25.2	26.6
More advantaged	37.1	30.0	33.2	33.3
Patients' demographic characteristics				
Gender: Male	51.0	54.7	49.5	52.9
Age, mean ± SE	66.4 ± 0.1	62.3 ± 0.1	62.7 ± 0.4	62.0 ± 0.3
Patients' IRSAD				
More disadvantaged	39.9	47.1	43.0	40.9
Middle	24.3	23.6	24.8	26.9
More advantaged	35.3	28.3	31.5	31.6
Aboriginal and/or Torres Strait Islander (% Yes)	1.8	3.1	3.7	2.7
Smoking status (% Yes)	8.3	13.5	12.0	12.1
Patients' clinical characteristics				
Baseline BMI (kg/m^2), mean ± SE	31.8 ± 0.1	33.8 ± 0.1	33.4 ± 0.3	33.6 ± 0.2
Baseline HbA1c (%), mean ± SE	6.4 ± 0.0	7.6 ± 0.0	7.1 ± 0.1	6.8 ± 0.0
Baseline FBG (mmol/L), mean ± SE	6.9 ± 0.0	8.8 ± 0.1	7.8 ± 0.2	7.4 ± 0.1
History of hypertension (% Yes)	14.2	15.8	12.4	14.9
History of dyslipidaemia (% Yes)	3.9	4.8	3.1	4.4
History of CVD (% Yes)	2.5	2.6	3.1	2.8
History of CKD (% Yes)	0.3	0.1	0.3	No observations
Antipsychotics (% Yes)	3.0	4.6	4.5	5.2

GP: General practitioner; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; SE: Standard error; BMI: Body mass index; HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; SE: Standard error; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease.

Metformin effects on glycaemic parameters

Table 6.2 and Figure 6.2a compare the effects of early, timely, delayed or no metformin commencement within 12 months of diagnosis on HbA1c levels at 3–6, 6–12, 12–18, and 18–24 months after diabetes diagnosis. The baseline HbA1c of those in the early treatment group (mean HbA1c 7.64%; FBG 8.83 mmol/L) was higher than other groups. However, it reached lower HbA1c levels at 3–6 months, becoming closer to the untreated group (β=0.22, 95%CI 0.17;0.28; ATE=0.21, 95%CI 0.16;0.27) than the timely treatment group (β=1.04, 95%CI 0.89;1.20; ATE=0.91, 95%CI 0.74;1.10) or the delayed treatment group (β=0.58, 95%CI 0.47;0.70; ATE=0.58, 95%CI 0.46;0.70). Differences in the HbA1c levels between those in the early treatment and untreated groups became practically null in subsequent periods, remaining steady over the 24 months of follow-up. Individuals in the timely or delayed metformin groups also reached better HbA1c parameters in the months after pharmacological management was started, although the best trajectory was for those in the early treatment group.

A similar pattern was observed when the FBG levels were assessed as the investigated outcome (Table 6.3 and Figure 6.2b), or when we used complete-case data for sensitivity analyses (Tables E5–E8, Appendix E).

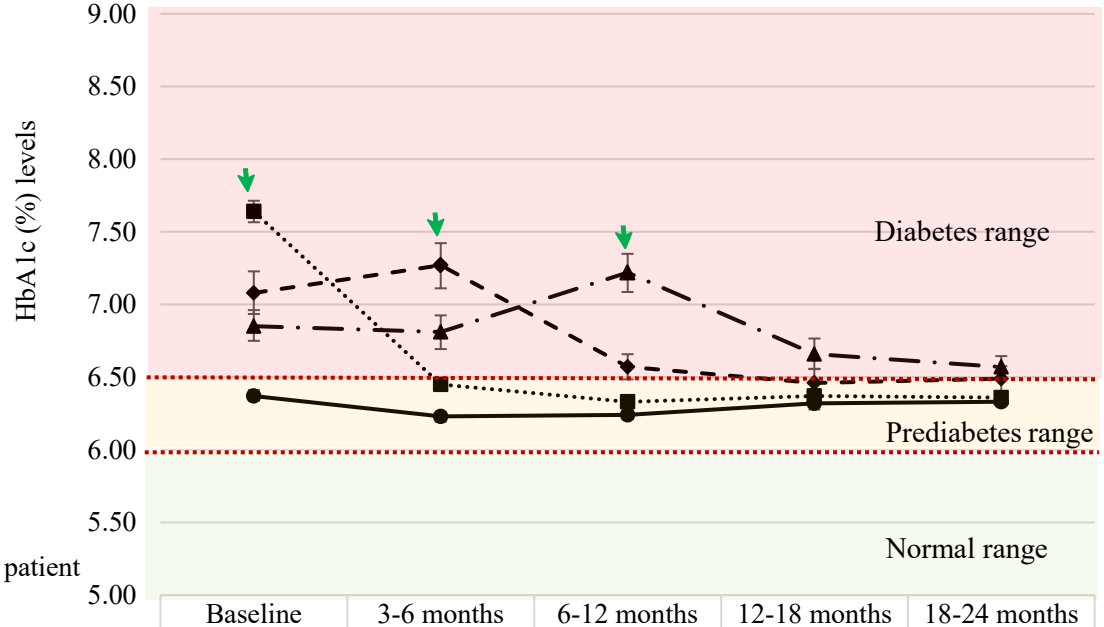
Table 6.2. Average treatment effect of early or delayed metformin commencement on HbA1c levels among regular patients (aged 40+ years) with newly recorded diabetes (N=13,427) (imputed data)

		Crude results	Linear regression	ATE using AIPW*
	N	Mean (SE)	β (95%CI)	ATE (95%CI)
HbA1c (%) at 3–6 months	**n=5,411**			
No treatment within 12 months	2,397	6.2 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	2,454	6.5 (0.0)	0.22 (0.17 to 0.28)	0.21 (0.16 to 0.27)
Timely treatment (3–6 months)	338	7.3 (0.1)	1.04 (0.89 to 1.20)	0.91 (0.74 to 1.10)
Delayed treatment (6–12 months)	222	6.8 (0.1)	0.58 (0.47 to 0.70)	0.58 (0.46 to 0.70)
HbA1c (%) at 6–12 months	**n=8,399**			
No treatment within 12 months	4,105	6.2 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	3,331	6.4 (0.0)	0.08 (0.04 to 0.13)	0.09 (0.04 to 0.14)
Timely treatment (3–6 months)	327	6.6 (0.0)	0.33 (0.24 to 0.42)	0.33 (0.24 to 0.43)
Delayed treatment (6–12 months)	636	7.2 (0.1)	0.98 (0.84 to 1.11)	0.91 (0.77 to 1.05)
HbA1c (%) at 12–18 months	**n=4,894**			
No treatment within 12 months	2,476	6.3 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	1,875	6.4 (0.0)	0.06 (–0.02 to 0.12)	0.02 (−0.05 to 0.09)
Timely treatment (3–6 months)	195	6.5 (0.0)	0.15 (0.05 to 0.25)	0.15 (0.04 to 0.26)
Delayed treatment (6–12 months)	348	6.6 (0.0)	0.34 (0.23 to 0.46)	0.37 (0.23 to 0.540)
HbA1c (%) at 18–24 months	**n=8,357**			
No treatment within 12 months	4,557	6.3 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	2,993	6.4 (0.0)	0.03 (–0.18 to 0.07)	0.04 (−0.05 to 0.10)
Timely treatment (3–6 months)	294	6.5 (0.0)	0.16 (0.06 to 0.25)	0.24 (0.11 to 0.37)
Delayed treatment (6–12 months)	513	6.6 (0.0)	0.23 (0.15 to 0.32)	0.29 (0.20 to 0.39)

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; SE: Standard error; CI: Confidence interval; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

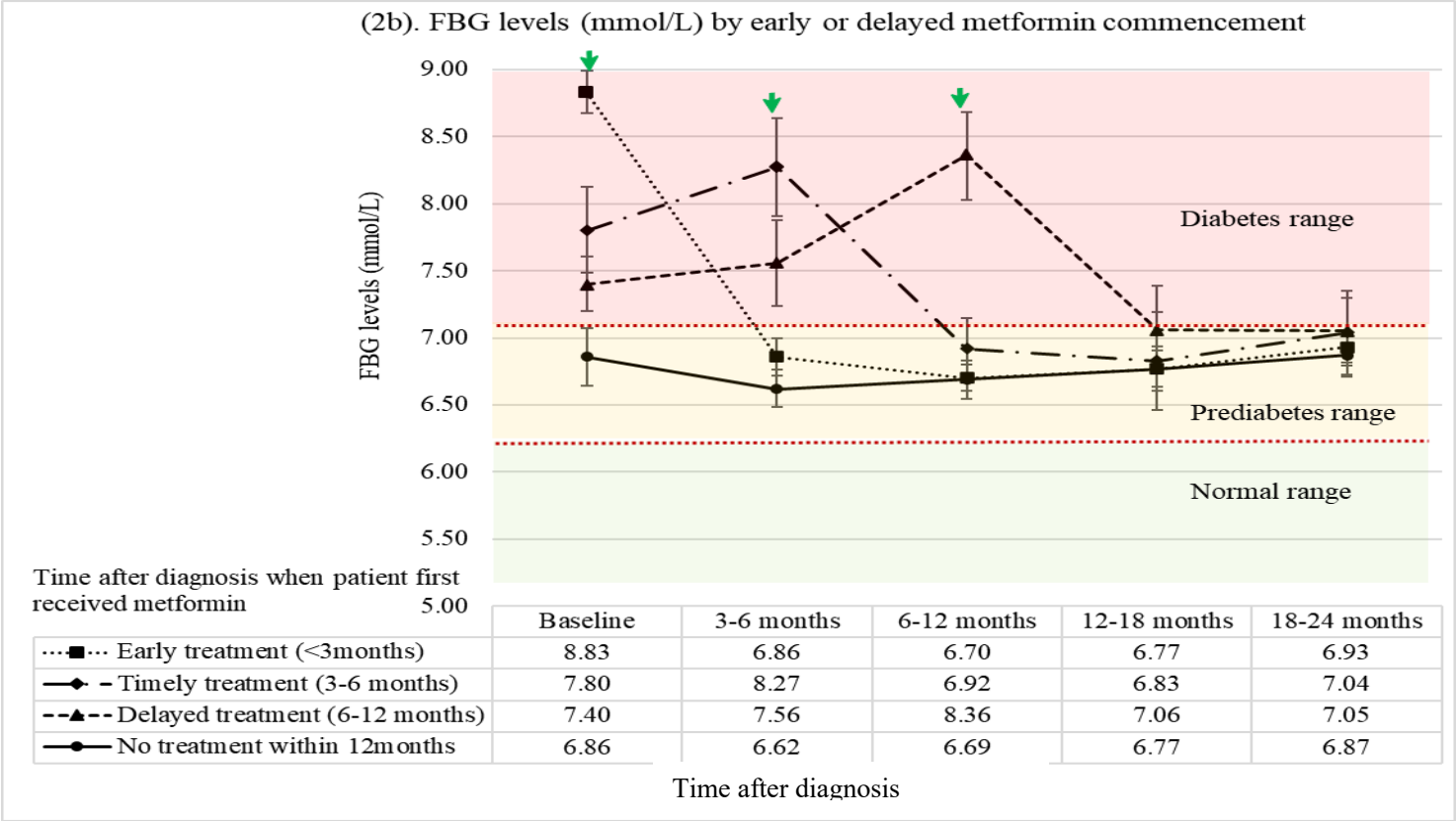
* Adjusted for practice characteristics (remoteness, practice IRSAD) and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, and previous history of heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.

(2a). HbA1c levels (%) by early or delayed metformin commencement



Time after diagnosis when patient first received metformin	Baseline	3-6 months	6-12 months	12-18 months	18-24 months
Early treatment (<3months)	7.64	6.45	6.33	6.37	6.36
Timely treatment (3-6 months)	7.08	7.27	6.57	6.46	6.49
Delayed treatment (6-12 months)	6.85	6.81	7.22	6.66	6.57
No treatment within 12months	6.37	6.23	6.24	6.32	6.33

Time after diagnosis



HBA1c: Haemoglobin A1c; FBG: Fasting blood glucose; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

Results based on linear regression models adjusted for practice characteristics (remoteness, practice IRSAD) and patient characteristics (baseline glycaemic levels, age, gender, smoking status, ethnicity, patients' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and the average number of consultations in 2012–2017). Vertical lines represent 95% confidence intervals. Green arrows indicate the first time of metformin prescription for each group.

Reference values for HbA1c – normal range: ≤5.9%; prediabetes range: 6.0–6.4%; diabetes range: ≥6.5%.

Reference values for FBG – normal range: ≤6.0 mmol/L; prediabetes range: 6.1–6.9 mmol/L; diabetes range: ≥7.0 mmol/L.

Figure 6.2. Predicted adjusted mean of HbA1c levels (2a) and fasting blood glucose levels (2b) at baseline, 3–6, 6–12, 12–18, and 18–24 months by early or delayed metformin commencement

Table 6.3. Average treatment effect of early or delayed metformin commencement on fasting blood glucose levels among regular patients (aged 40+ years) with newly recorded diabetes (N=6,318) (imputed data)

		Crude results	Linear regression	ATE using AIPW*
	N	Mean (SE)	β (95%CI)	ATE (95%CI)
FBG (mmol/L) at 3–6 months	**n=1,925**			
No treatment within 12 months	902	6.5 (0.0)	**Ref**	Ref
Early treatment (<3 months)	764	7.0 (0.1)	0.24 (0.05 to 0.42)	0.21 (0.00 to 0.41)
Timely treatment (3–6 months)	152	8.3 (0.2)	1.65 (1.26 to 2.03)	1.12 (0.74 to 1.64)
Delayed treatment (6–12 months)	107	7.5 (0.2)	0.93 (0.59 to 1.23)	1.11 (0.35 to 1.86)
FBG (mmol/L) at 6–12 months	**n=3,395**			
No treatment within 12 months	1,775	6.6 (0.0)	**Ref**	Ref
Early treatment (<3 months)	1,217	6.9 (0.0)	0.02 (–0.14 to 0.17)	0.01 (–0.13 to 0.15)
Timely treatment (3–6 months)	128	6.9 (0.1)	0.23 (–0.05 to 0.51)	0.29 (0.05 to 0.54)
Delayed treatment (6–12 months)	275	8.4 (0.2)	1.67 (1.34 to 2.00)	1.56 (1.10 to 2.04)
FBG (mmol/L) at 12–18 months	**n=1,957**			
No treatment within 12 months	1,006	6.6 (0.1)	**Ref**	Ref
Early treatment (<3 months)	748	6.9 (0.1)	0.00 (–0.20 to 0.20)	–0.33 (–0.63 to –0.03)
Timely treatment (3–6 months)	78	6.8 (0.2)	0.06 (–0.36 to 0.47)	–0.47 (–1.00 to 0.05)
Delayed treatment (6–12 months)	125	7.1 (0.2)	0.29 (–0.08 to 0.66)	0.43 (–0.32 to 1.18)
FBG (mmol/L) at 18–24 months	**n=3,529**			
No treatment within 12 months	1,977	6.7 (0.0)	**Ref**	Ref
Early treatment (<3 months)	1,229	7.1 (0.1)	0.06 (–0.12 to 0.24)	–0.04 (–0.22 to 0.14)
Timely treatment (3–6 months)	123	7.0 (0.1)	0.17 (–0.17 to 0.52)	0.22 (–0.12 to 0.56)
Delayed treatment (6–12 months)	200	7.0 (0.1)	0.18 (–0.87 to 0.45)	0.28 (–0.17 to 0.72)

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; SD: Standard deviation; CI: Confidence interval; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

* Adjusted for practice characteristics (remoteness, practice IRSAD) and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, and previous history of heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.

6.3.5 Discussion

This open cohort study estimated the effect of early, timely, or delayed metformin therapy versus no treatment with metformin within 12 months of diagnosis on glycaemic parameters in patients with newly recorded diabetes diagnosed between 2012 and 2017. Four main findings can be highlighted based on our results. First, only half of the individuals with newly diagnosed diabetes were managed with metformin within the first year of recorded diagnosis, and most of them were started on that medication within the first 3 months. Second, early treatment with metformin was more frequent among males, smokers, patients from more disadvantaged or remote areas, and those with higher baseline glycaemic levels. Third, patients in the early treatment group achieved better glycaemic parameters over 24 months than those who received metformin at 3–6 or 6–12 months after diagnosis. Finally, glycaemic levels decreased substantially once metformin monotherapy started, regardless of when that treatment was initiated.

Half of the patients with incident diabetes were not started on metformin within the first 12 months after diagnosis, but this group presented the lowest glycaemic parameters at baseline and follow-up, although above recommended limits. For those managed with metformin, the time of initiation seems to be related to the underlying glycaemic levels. For example, those prescribed metformin soon after diagnosis had a worse glycaemic profile at baseline, and this could have influenced the GP decision to start earlier metformin rather than waiting to see if lifestyle changes would improve BG levels. This is consistent with the recommendation that pharmacological treatment of T2D requires an individualised approach that takes into account factors such as efficacy, cost, side effects, adherence and treatment burden, and comorbidities,[357, 363] where clinician and patient share the decision about the timing and type of diabetes treatment.[153]

Approximately 80% of those managed with metformin were prescribed metformin within 3 months of diagnosis. Currently, Australian guidelines recommend starting ADM after 2–3 months of lifestyle modifications when glycaemic goals are not met (i.e., HbA1c<7%).[73] We found that early treatment with metformin was more frequent among patients who were males, smokers, or from more disadvantaged or remote areas. This could be because males and those from socioeconomically deprived areas were more likely to have T2D [164] and were less likely to visit a GP.[22] However, guidelines in the US[36] and the International Diabetes Federation[35] recommend that patients should start ADM immediately, in conjunction with lifestyle modification. This finding is consistent with another US EHR-based study of adult patients with incident diabetes (age ≥18 years) that used propensity score matching to compare early management (metformin prescribed within 6 months of diagnosis) with delayed management (receiving metformin >6 months after diagnosis; n=1072, in each group). That study reported earlier treatment with metformin was associated with better HbA1c levels over an average of approximately 12 months, than delayed treatment (–0.36%, 95%CI –0.44;–0.27),[153] but it did not contain a no treatment group for comparison.

We found that glycaemic levels decreased substantially once metformin monotherapy started, regardless of when that treatment was initiated. However, avoiding the delay of pharmacological treatment and motivating patients with T2D to adhere to ADM use can prevent the risk of CVD and other complications.[131, 152, 359] This is because persistently elevated HbA1c levels during the first years after diagnosis of T2D have been associated with microvascular complications over time, even when glycaemic parameters are eventually controlled.[364] Another population-based study in Denmark found that a substantial initial reduction in HbA1c within 6 months of starting metformin was associated with a lower risk of cardiovascular events and death among adult patients with T2D.[365]

This large longitudinal study used a national general practice database with up to 8 years of follow-up. We applied multiple statistical approaches to improve data quality and provide consistent and reliable results comparable to clinical trials (i.e., intention to treat analyses), but with a substantially lower cost. However, a few limitations need to be recognised. First, despite using validated algorithms for data extraction, the completeness of the recorded information may vary across practices and variables related to lifestyle modification are not systematically recorded.[200] Second, some subgroups were analysed with small samples due to missing data on laboratory parameters, which reduced the overall sample by 30%. Nonetheless, the results were consistent regardless of the method used, and there were no systematic differences between eligible participants and the analysed cohort. Third, this study used information on metformin prescriptions rather than medication use, which may have biased the results. Nonetheless, the expected bias would be toward the nullity of the associations. Finally, the database did not capture patients who visited other practices or specialists for diagnosis or follow-up.

6.3.6 Conclusion

GP's decision to prescribe metformin early is made when patients' glycaemic levels were well above recommended limits, or among patients at a higher risk. This study suggests that starting metformin therapy early after diagnosis can help patients achieve better and more steady glycaemic levels over 24 months, which would help reduce the risk of further complications. Nonetheless, patients who started metformin later also improved their glucose parameters, but the progression over 24 months was better for those on early metformin treatment. Further studies are needed to evaluate early versus delayed metformin therapy's long-term effects on diabetes complications.

Funding statement

MZ received a PhD Scholarship from the University of Adelaide to complete this study. The study did not receive any funding.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Data used in this study was obtained from a third party (MedicineInsight) for this specific project and cannot be released. Information about MedicineInsight data and how they can be accessed is available on the website (https://www.nps.org.au/medicine-insight). The data extraction algorithms used in this study are available from the corresponding author upon request.

Author contributions

MZ and DGC contributed to the conception and design of the study. MZ performed the statistical analysis and prepared the manuscript. COB and DGC assisted in data extraction. MB assisted in data analysis and critically reviewing the draft. NS contributed to the structure of the manuscript. All authors contributed to the critical review of the text and provided intellectual contributions to strengthen the manuscript. All authors approved the final version for publication.

Ethical approval

The independent MedicineInsight Data Governance Committee approved the study (protocol 2016-007). The Human Research Ethics Committee of the University of Adelaide exempted the study from an ethical review as it used de-identified data.

Acknowledgements

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_____End of manuscript_____

6.4 Chapter Synopsis

This chapter has detailed the benefits of immediately starting the metformin with lifestyle modification once patients are diagnosed with diabetes, to help patients achieve stable and better glycaemic control to reduce the further cardiovascular events. The findings indicate that GPs' decisions about prescribing metformin were consistent with current recommendations to start pharmacological treatment when patients' glycaemic levels cannot be controlled by lifestyle changes alone. The next chapter extends the evaluation of metformin use from early diabetes therapy to prediabetes therapy and diabetes prevention.

Chapter 7. Using Metformin for Prediabetes Therapy (Paper 4 – Published)

7.1 Preface

To answer the last research question, Chapter 7 (Paper 4) uses the counterfactual approach to evaluate the effectiveness of metformin use for prediabetes prevention.

This paper has been published in Diabetic Medicine (Appendix G) during the thesis examination:

Zheng M#, Soumya S#, Begum M*, Bernardo C, Stocks N, H Jahan, Gonzalez-Chica D*. Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records. Diabetic Medicine. 2023;00:e15170. https://doi.org/10.1111/dme.15170

It addresses the following research questions of this thesis:

- Do patients with prediabetes achieve better glycaemic control with metformin therapy than those not receiving that medication?

Highlights of Paper 4:

- During 2012–2017, over 1 in 10 adults with incident prediabetes were prescribed metformin.
- Higher baseline glycaemic levels in prediabetes probably influenced GPs' decisions to start metformin.
- Patients with prediabetes managed with metformin achieved glycaemic control at 6–12 months similar to those not managed with metformin, despite having higher baseline HbA1c.
- Beneficial effects were found later, with slightly better HbA1c levels in patients managed with metformin at 18–24 months.

- Metformin therapy for incident prediabetes with high baseline glycaemic levels is a good strategy to prevent further deterioration of glycaemic levels.

Novelty statement of Paper 4:

What is already known?

- Metformin is used in some large diabetes prevention programs, but the use of metformin for prediabetes treatment in real-world practice is largely unknown.

What this study found?

- In Australia, GPs prescribed metformin to over 1 in 10 adults with incident prediabetes. Despite having higher baseline HbA1c levels, patients managed with metformin reduced their glycaemic parameters within 6–12 months.
- HbA1c levels at 6–12 months were similar among those who were managed with metformin and those who were not, but were slightly better at 18–24 months in the treatment group.

What are the implications of the study?

- Metformin therapy for incident prediabetes with high baseline glycaemic levels could help prevent further deterioration of glycaemic parameters.

7.2 Statement of Authorship

Title of Paper	Short- and long-term outcomes of initial Metformin treatment for newly diagnosed diabetes attending Australian general practices: a longitudinal national study
Publication Status	☐ Published ☐ Accepted for Publication ☑ Submitted for Publication ☐ Unpublished and Unsubmitted work written in manuscript style
Publication Details	Zheng M#, Soumya S#, Begum M*, Bernardo C, Stocks N, H Jahan, Gonzalez-Chica D*. Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records. Under review by Diabetic Medicine.

Principal Author

Name of Principal Author (Candidate)	Mingyue Zheng		
Contribution to the Paper	MZ contributed to the conception and design of the study. MZ prepared the introduction and conclusion of the manuscript. MZ contributed to critically revising the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Overall percentage (%)	55%		
Certification:	This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.		
Signature		Date	16 February 2023

Co-Author Contributions

By signing the Statement of Authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);
ii. permission is granted for the candidate in include the publication in the thesis; and
iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of Co-Author	Soumya Soumya			
Contribution to the Paper	SS prepared the discussion draft of the manuscript. SS contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.			
Signature	15%		Date	21 02 2023

Name of Co-Author	Mumtaz Begum		
Contribution to the Paper	MB performed the statistical analysis and helped write and edit the draft. MB contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	15%	Date	23 February 2023

Name of Co-Author	Carla Bernardo		
Contribution to the Paper	CB contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	3%	Date	16 February 2023

Name of Co-Author	Stocks Nigel		
Contribution to the Paper	NS contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	3%	Date	17/02/2023

Name of Co-Author	Habiba Jahan		
Contribution to the Paper	HJ contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	2%	Date	21/02/2023

Name of Co-Author	David Gonzalez-Chica		
Contribution to the Paper	DGC contributed to the conception and design of the study. DGC supervised this study and edited the manuscript. GCD contributed to the critical review of the text, provided intellectual contributions to strengthen the manuscript, and approved the final version for publication.		
Signature	7%	Date	16 February 2023

7.3 Manuscript: Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records

Novelty Statement

What is already known?

- Metformin is used in some large diabetes prevention programs, but the use of metformin for prediabetes treatment in real-world practice is largely unstudied.

What this study found?

- In Australia, general practitioners prescribed metformin to over one in 10 adults with incident prediabetes. Despite having higher baseline HbA1c levels, patients managed with metformin reduced their glycaemic parameters within 6-12 months.
- HbA1c levels at 6-12 months were similar among those who were managed with metformin and those who were not, but were slightly better at 18-24 months in the treatment group.

What are the implications of the study?

- Metformin therapy for incident prediabetes with high baseline glycaemic levels could help prevent further deterioration of glycaemic parameters.

7.3.1 Abstract

Aims: To estimate the effectiveness of metformin on glycaemic parameters among patients with incident prediabetes attending Australian general practices.

Methods: This retrospective cohort study used electronic health records of regular patients (3+ visits in two consecutive years) attending 383 Australian general practices (MedicineInsight). Patients with ‘incident’ prediabetes (newly recorded diagnosis between 2012 and 2017) and

their glycaemic parameters (HbA1c or fasting blood glucose (FBG)) at 6-, 12-, and 18-24 months post diagnosis (unexposed) or post-management with metformin (treatment) were identified from the database. We estimated the average treatment effect (ATE) of metformin management on glycaemic parameters using both linear regression and augmented inverse probability weighting (AIPW).

Results: Of the 4,770 investigated patients with 'incident' prediabetes, 10.2% were managed with metformin. Patients on metformin had higher HbA1c levels at the baseline than those unexposed [mean 45 mmol/mol (6.2%) and 41 mmol/mol (5.9%), respectively], but no differences were observed at 6–12 months (mmol/mol ATE 0.0, 95%CI -0.4;0.7) or 12-18 months (ATE -0.3, 95%CI -1.2;0.3). However, patients on metformin had lower mean HbA1c mmol/mol at 18-24 months (ATE -1.1, 95%CI -2.0;0.1) than those unexposed. Consistent results were observed for FBG [ATE at 6-12 months -0.14 (95%CI -0.25;-0.04), 12-18 months 0.02 (95%CI -0.08;0.13), and 18-24 months -0.07 (95%CI -0.25;0.12)].

Conclusion: The higher HbA1c and FBG baseline levels among patients with 'incident' prediabetes managed with metformin improved after 6-12 months of starting pharmacological management, and the effect persisted for up to 24 months. Management with metformin could prevent further deterioration of glycaemic levels.

Keywords: Prediabetic state, drug prescriptions, hypoglycaemic agents, electronic health records, epidemiologic methods, general practice, population health

7.3.2 Introduction

Prediabetes is a condition characterised by elevated blood glucose levels [i.e. fasting blood glucose (FBG) 6.1-6.9mmol/L, hemoglobin A1c (HbA1c) 6.0-6.4% and/or oral glucose tolerance tests (OGTT) 7.8-11.0mmol/L].[14] Similar to diabetes mellitus, prediabetes also

increases the risk of complications such as diabetes retinopathy, chronic kidney disease and cardiovascular disease.[14, 50] It is estimated that prediabetes affects about 16.4% (3.3 million) of Australian adults,[14] with up to 75% potentially progressing to diabetes over their lifetime.[82] Managing prediabetes through lifestyle modifications is crucial to prevent its progression to diabetes and avoid relevant complications.[2, 14] However, long-term adherence to lifestyle modifications is challenging.[366-368] Managing prediabetes with antidiabetic medications (ADMs) could provide long-term benefits for diabetes prevention, but their use to treat prediabetes in clinical practice is still controversial.[2, 14, 129]

The role of some ADMs (e.g., metformin, α-glucosidase inhibitors, thiazolidinediones, and acarbose) in reducing the risk of diabetes progression has been previously investigated.[14, 366, 369] Overall, these studies have reported the beneficial impact of ADMs on glycaemic levels and diabetes progression (especially metformin), with effect and cost-effectiveness results comparable to lifestyle modifications.[27, 367, 370-373] One of the first randomised controlled trials (RCTs) to compare metformin and lifestyle for diabetes prevention was conducted in the United States (US) between 1996 and 2001 using a sample of 3,234 adults with prediabetes. Compared to placebo, metformin and lifestyle intervention substantially reduced progression to diabetes by 31% and 58%, respectively.[367] The Diabetes Prevention Program Outcomes Study (N = 2,276) in the US also found that metformin and lifestyle intervention reduced the incidence of diabetes by 18% and 27%, respectively, compared to placebo, after 15 years of follow-up.[373] Further studies have demonstrated that lifestyle modifications can reduce by up to 50% the risk of diabetes progression compared to a 36% risk reduction among those on medication management.[366, 374-376]

People with prediabetes are already being prescribed metformin (off-label prescribing) in many countries, including Australia, the US, and the United Kingdom (UK).[369-371] However, in

Australia the use of ADM for prediabetes management is not yet recommended in current guidelines.[14, 129] This may be attributed to the lack of implementation studies that consider cost-effectiveness profiles for different diagnostic-treatment combinations, equity of healthcare provision and specificities of the national health system.

In Australia, adults with prediabetes visit their general practitioners (GP) on average five times per year,[336] with data on the prescriptions they received and laboratory results systematically recorded and stored electronically.[200] Thus, using electronic health records (EHRs) from general practices represents an excellent opportunity to investigate the effect of ADM prescribing on diabetes prevention in Australia. Other international primary care databases, such as the Clinical Practice Research Datalink in the UK, have been used previously to explore the effect of potential interventions on chronic disease prevention (e.g., hypertension, diabetes, cardiovascular disease) using a counterfactual approach.[303, 307] Confounding in these studies (i.e., longitudinal observational data) was handled by creating a pseudo population that considers every patient as if they were both exposed (i.e., prescribed metformin) and unexposed (i.e., not prescribed metformin), subsequently estimating the average treatment effect (ATE) of the potential intervention.[303] Therefore, by using a large Australian general practice database (MedicineInsight), we aimed to investigate whether patients with recent prediabetes diagnosis who received metformin achieved better glycaemic levels (HbA1c and FBG) within the first two years than their peers, not on metformin.

7.3.3 Methods

Study design and data source

In this observational retrospective cohort study, we used deidentified EHRs of adult patients from general practices included in the Australian primary care database MedicineInsight, with data recorded between 2011 and 2018. In 2018, MedicineInsight comprised more than 2,700

GPs from 662 general practices across Australia (~8.2% of all practices in Australia). MedicineInsight extracts monthly data on the reason for encounters, reason for prescriptions, diagnoses, scripts, clinical and sociodemographic data, and pathology results from participating general practices.[200]

Study population

We used EHRs from practices with consistent data provision over time [i.e. established at least two years before the end of the analysis period, gap lower than six weeks in data provided during the last two years, issue an average of at least 30 prescriptions per week, stable number of annual consultations (ratio <5 between the maximum and minimum number of yearly consultations between 2011 and 2018)].[200] A total of 383 practices were included. Additionally, we only included 'regular' patients [i.e., with a minimum of three visits in any two consecutive years (e.g., three consultations between 2016 and 2017) and at least one visit in each of these two years (e.g., at least one consultation in 2016 and 2017)]. This approach was used to consider the longitudinal design of the study and minimise the risk of bias (e.g., unavailability of prescription and laboratory data among non-regular patients). Administrative contacts (i.e., phone calls and reminders) were not counted as a consultation.

Information on recorded prediabetes diagnosis was extracted from five datasets within MedicineInsight (reason for encounter, diagnosis, reason for prescription, scripts, and pathology results). Patients were classified with prediabetes if they had (1) prediabetes recorded in at least two different datasets (reason for encounter, diagnosis, reasons for prescription) or in the same dataset on two different dates; (2) prediabetes was recorded only once, but a positive laboratory result consistent with prediabetes [i.e., FBG 6.1-6.9mmol/L; HbA1c 42-46 mmol/mol (6.0-6.4%); or OGTT 7.8-11.0mmol/L][14] was reported up to four weeks before or up to two weeks after the recorded diagnosis. We included only patients with their first recorded

prediabetes diagnosis (i.e., 'incident') between Jan/2012 and Dec/2017 and who had at least 12 months of data before and after the first diagnosis in any of the five datasets included in this study (not only from laboratory results). This allowed us to 1) differentiate prevalent from 'incident' prediabetes, 2) identify potential exclusion criteria, 3) obtain baseline information on the glycaemic parameters and other confounders, and 4) allow enough follow-up time to assess outcome data.

The start of follow-up for each patient commenced with the first recorded diagnosis of prediabetes (T0) and ended at the earliest of 1) 24 months after diagnosis, 2) on the 30th December 2018, or 3) the appointment before diabetes diagnosis. The final investigated cohort sample consisted of 4,770 regular adult patients with 'incident' recorded prediabetes who had an outcome (HbA1c or FBG) measured within 6 to 24 months after the diagnosis of prediabetes (for unexposed) or the start of metformin management (for exposed; Figure 7.1).

The sample excluded those who 1) received metformin before prediabetes diagnosis, 2) had a diagnosis of diabetes, gestational diabetes, or polycystic ovary syndrome preceding prediabetes diagnosis where metformin was specifically used for managing their gestational diabetes or polycystic ovary syndrome rather than prediabetes,[336, 372, 377] or 3) had a diagnosis of diabetes within 90 days of being diagnosed with prediabetes. The methodology used to identify patients with diabetes has been previously described.[336]

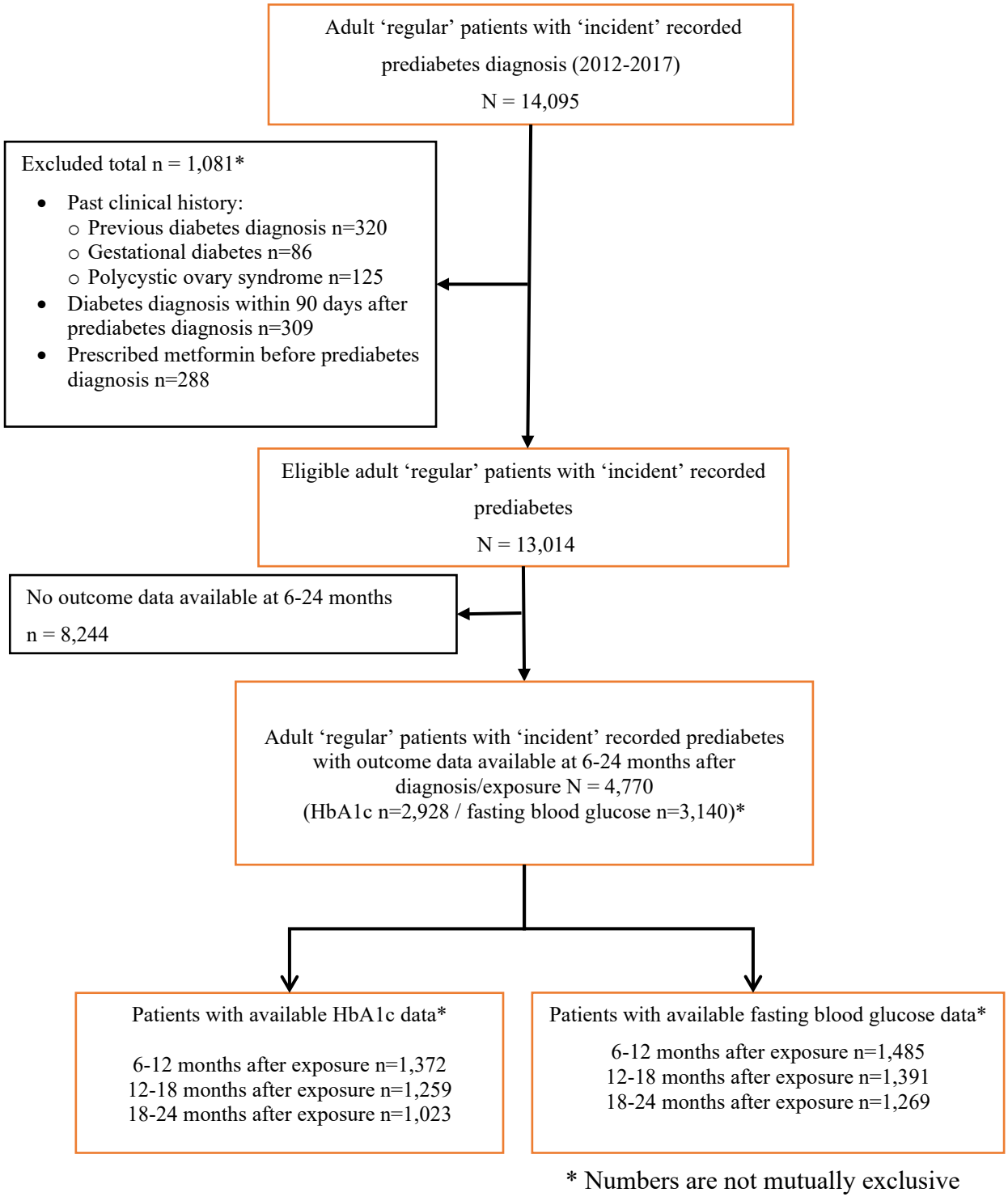


Figure 7.1. Flow chart of the study sample

Exposure

Information on whether or not a patient received metformin prescriptions and when these prescriptions started were obtained from the 'script' dataset. Not all cases managed with metformin were prescribed that medication from the date of prediabetes diagnosis. To account for the immortal time bias (i.e., error introduced by misclassifying a period as time spent as 'exposed' when, in fact, an individual was not yet exposed),[273] these individuals were counted as unexposed from diagnosis until the consultation before metformin's first prescription. Therefore, some individuals (n=488) were counted twice, as 'unexposed' from the date of diagnosis to metformin prescription (mean waiting time=139 days), and then as 'exposed' from the date of the first metformin prescription until 24 months from starting medication (because we have used HbA1c and FBG measured within 24 months as an outcome). We did not assess for how long patients were prescribed metformin after the first prescription, similar approach to the intention to treat analysis in RCTs.

Outcome

Three timeframes were considered for each glycaemic parameter [HbA1c in IFCC units (mmol/mol) and DCCT units (%) and FBG in mmol/L]: measurements were taken at 6-12, 12-18, and 18-24 months after prediabetes diagnosis/or after starting metformin (T0). For those with multiple measurements for the same parameter in a specific timeframe (e.g., HbA1c between 6 and 12 months), we used the closest measurement to T0 within that time window, for both exposed and unexposed individuals. This excludes any measurements made after the patient was diagnosed with diabetes.

Confounders

Confounders were identified a priori based on background knowledge[14, 336, 375] and their relationships assessed using a directed acyclic graph (Figure F1, Appendix F). These confounders included practice level and patient variables. Practice level variables were

remoteness or accessibility to the services – major cities, inner regional, outer regional/remote/very remote, and IRSAD [Index of Relative Socio-economic Advantage and Disadvantage: 1) more advantaged (upper two quintiles), 2) middle, 3) more disadvantaged (lower two quintiles)]. Remoteness is defined as a measure of the level of access to services. IRSAD is an indicator of the socio-economic advantage/disadvantage of people and households within an area, based on income, housing and education, established by the Australian Bureau of Statistics.[200, 248] Higher IRSAD scores indicate that people are in more advantaged areas.

Patients' characteristics included age (continuous variable), gender (males, females), body mass index (BMI, continuous variable), smoking status (current smoker, non-smokers, ex-smokers, not stated/recorded), ethnicity (Aboriginal or Torres Strait Islanders, neither Aboriginals nor Torres Strait Islanders, not stated), and patients IRSAD (similar classification as for practice IRSAD). Moreover, the clinical history of heart failure, stroke, dyslipidaemia, ischaemic heart disease, or hypertension before the first recorded prediabetes at the baseline, and the prescription of antipsychotic medications within the two years preceding prediabetes diagnosis were also considered as potential confounders (all included as yes/no binary variables). Details on the data extraction process for these variables are available elsewhere.[200]

Finally, baseline levels of HbA1c, FBG and OGTT within the 12 months preceding prediabetes diagnosis were also included as a confounder. When multiple measures for these parameters were available, we used the closest value before diagnosis.

Statistical analysis

A linear regression model was used to estimate the crude and adjusted effect of metformin prescription (yes/no) on each specific outcome (HbA1c or FBG at 6–12, 12–18 or 18–24 months). Then, to estimate the ATE of metformin management on the same glycaemic parameters (mentioned above), we specified two consecutive models: (1) the treatment model (logistic regression), and (2) the outcome model (linear regression) using augmented inverse

probability weightings (AIPW).[303] The treatment model (taking metformin or not as the outcome variable) was used to compute the probability of being exposed to metformin given all potential confounders, mentioned above, and the total number of consultations in the study period. The reciprocal of this probability was then used as the weight in the outcome regression (linear model) for the specific outcome. All confounders were also included in the outcome model. ATEs in this study are interpreted as the marginal difference in HbA1c or FBG levels between patients with 'incident' prediabetes managed with metformin compared to those not prescribed that medication. AIPW is a doubly robust method, which can produce consistent estimates if either the 'treatment' or 'outcome' model is correctly specified.[303] To obtain reliable estimates of the ATE of metformin management on glycaemic parameters in patients with incident prediabetes, we used linear regression and AIPW models, incorporating key assumptions (i.e., exchangeability, positivity, no interference, consistency).[303, 378, 379] Regarding exchangeability, we included a wide range of potential confounders and indicator variables (e.g., socioeconomic and clinical characteristics such as smoking and comorbidities), with exposed and unexposed groups being comparable according to most listed confounders, except for gender, dyslipidaemia, and hypertension. Moreover, the possibility of unmeasured confounding cannot be discarded, as some relevant confounders (i.e., family history of diabetes, diet, physical activity, health insurance) were not available in Medicineinsight. Therefore, we performed different sensitivity analyses to minimise the potential impact of unmeasured confounders. Second, to ensure that all patients had a non-zero probability of receiving metformin management (i.e. positivity),[378] we explored for extremely large or small weights (0.7%), which were discarded before weighting. Third, minimal interference was achieved by considering the clustering of patients within practices (i.e. intragroup correlation) in our analyses. Fourth, we assumed consistency[379] in that the potential outcomes were the same as those actually observed regardless of whether metformin was prescribed.

Missing data represented less than 1% for most confounders, except for the baseline glycaemic measures (i.e., at least one record of HbA1c, FBG, or OGTT, 35% missing). As baseline glycaemic level is an important confounder, we imputed missing data for all confounders using multiple imputations by chained equation.[279] Based on current literature regarding the use of multiple imputation, we included the outcome in the imputation model to avoid biased estimates.[380, 381] Apart from all confounders mentioned in Table 7.1, the total number of consultations and the practice were included as auxiliary variables for imputation. Twenty datasets were generated during multiple imputations. We used Stata syntax for computing AIPW in imputed data.[309] Rubin's rules[281] were applied to estimate the mean ATE, between imputation variance, within imputation variance, and to combine the estimates from the imputed datasets.

Analyses were conducted on Stata 16.1 (StataCorp, Texas, USA), and all models considered the clustering of patients within the practice. Using a cluster variable specifies that the standard errors of estimators consider intragroup correlations (i.e., observations are independent across sites but not necessarily within practices). All analyses were repeated using complete-case data with and without adjustment for BMI, considering the high proportion of missing data for BMI (43%). These sensitivity analyses are presented as supplementary material.

7.3.4 Results

Of the 13,014 eligible regular adult patients with 'incident' recorded prediabetes between 2012 and 2017 (51.7% males, mean age 63.9±12.7 years), 4,770 (51.9% males, mean age 65.9 years) had data available about at least one of the investigated outcomes at one of the assessed time points (Figure 7.1 and Table 7.1). The final analysed cohort had sociodemographic and clinical characteristics compared similar to the original eligible sample, except for a higher proportion of patients attending practices located in outer regional/remote/very remote areas. Moreover,

no systematic differences were observed when those with available outcome data at 6-12, 12-18, or 18-24 months were considered (Table F1, Appendix F). Overall, 10.2% of the analysed cohort was managed with metformin.

Table 7.1. Characteristics of the eligible sample and the final cohort included in our study. Patients with 'incident' recorded diabetes between 2012 and 2017.

	Eligible sample † N = 13,014 Initial data (%)	Final Cohort ‡ N = 4,770 Imputed data (%)
Practice characteristics		
Geographical area of GP		
Major Cities	60.1	53.0
Inner Regional	25.5	27.2
Outer/Remote/Very Remote	14.4	19.8
GP IRSAD		
More advantaged	40.4	40.1
Middle	21.4	22.0
More disadvantaged	38.3	38.0
Patients' demographic characteristics		
Gender: Male	51.7	51.9
Age, mean ± SD	63.9±12.7	65.9 (SE=0.2)
Patients' IRSAD		
More advantaged	38.8	38.1
Middle	22.4	23.9
More disadvantaged	38.8	38.0
Smoking status (% Yes)	10.0	8.8
Aboriginal and/or Torres Strait Islander (% Yes)	1.6	1.6
Patients' clinical characteristics		
Heart failure (% Yes)	1.2	1.3
Stroke (% Yes)	2.5	2.9
Dyslipidaemia (% Yes)	36.8	37.4
Ischaemic heart disease (% Yes)	6.8	7.7
Hypertension (% Yes)	43.8	46.4
Antipsychotic scripts (% Yes)	2.7	2.5
Baseline Hba1c (%): Mean ± SD	6.1± 0.7	5.9 (SE 0.01)
Baseline FBG (mmol/L): Mean ± SD	6.2± 0.8	6.1 (SE 0.01)
Exposed to metformin (%)	12.4%	10.2%

GP: General practitioner; IRSAD: Index of Relative Socio-Economic Advantage and Disadvantage; SE: Standard error; SD: Standard deviation; HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose.
† Eligible sample (regular adult patients with 'incident' recorded prediabetes)
‡ Final cohort (regular adult patients with 'incident' recorded prediabetes, with outcome data available at 6-24 months after diagnosis/exposure)

Table 7.2 shows a comparison of the baseline sociodemographic and clinical characteristics of the cohort sample according to whether they were prescribed metformin or not (imputed data). Patients with 'incident' prediabetes who were prescribed metformin were more likely to be females, live in more socioeconomically disadvantaged areas, or have a history of hypertension than those unexposed to metformin. However, they were comparable in terms of age, smoking status, baseline HbA1c and FBG levels, and most of the other clinical characteristics. Similar patterns were observed when the original non-imputed data was analysed (Table F2, Appendix F).

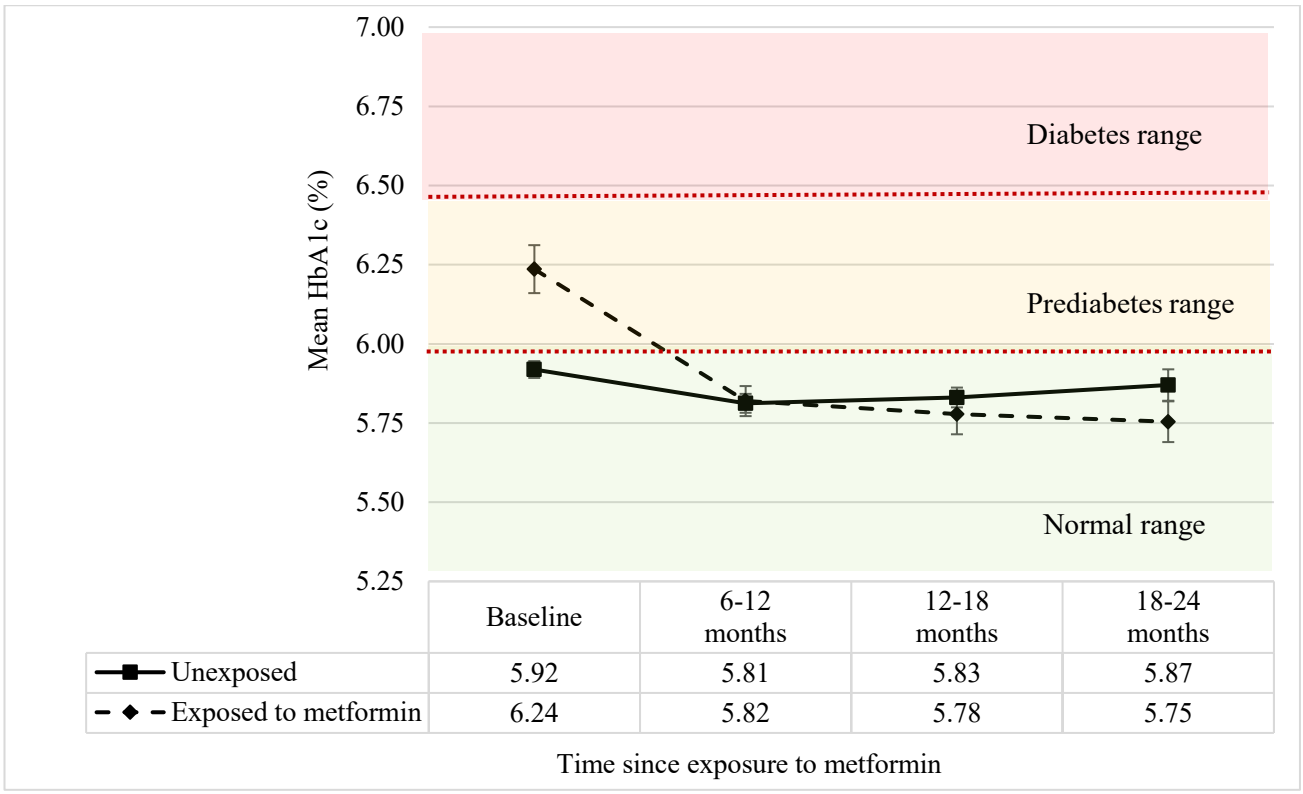
Table 7.2. Baseline characteristics of the regular adult patients (18+) with 'incident' recorded prediabetes included for analysis according to exposure and outcome variables (imputed data, unadjusted results).

	HbA1c as an outcome N = 2,928		**FBG as an outcome N = 3,140**	
	Unexposed n = 2,526 (%)	Exposed to metformin n = 402 (%)	Unexposed n =2,860 (%)	Exposed to metformin n = 280 (%)
Practice characteristics				
Geographical area of GP				
Major Cities	59.4	51.7	47.7	55.7
Inner Regional	23.4	29.4	29.8	32.5
Outer/Remote/Very Remote	17.1	18.9	22.6	11.8
GP IRSAD				
More advantaged	44.2	34.7	37.6	33.5
Middle	18.5	18.8	25.7	25.6
More disadvantaged	37.3	46.5	36.7	40.9
Patients' demographic characteristics				
Gender: Male	51.8	43.5	53.7	43.6
Age, mean (SE)	65.7 (0.2)	64.6 (0.6)	66.6 (0.2)	64.0 (0.7)
Patients' IRSAD				
More advantaged	42.0	34.0	36.2	33.1
Middle	21.6	20.9	26.3	26.7
More disadvantaged	36.4	45.0	37.5	40.0
Smoking status (% Yes)	9.0	9.7	7.9	8.2
Aboriginal and/or Torres Strait Islander (% Yes)	1.5	3.0	1.3	2.5
Patients' clinical characteristics				
Baseline HbA1c, mean (SE), mmol/mol	41 (0.11)	42 (0.33)	41 (0.22)	41 (0.44)
mean (SE), %	5.9 (0.01)	6.0 (0.03)	5.9 (0.02)	5.9 (0.04)
Baseline FBG, mean (SE)	6.2 (0.02)	6.3 (0.05)	6.1 (0.01)	6.2 (0.04)
BMI, mean (SE)	31.5 (0.25)	32.7 (0.60)	31.1 (0.17)	33.3 (0.57)
Heart failure (% Yes)	1.5	1.5	1.0	0.4

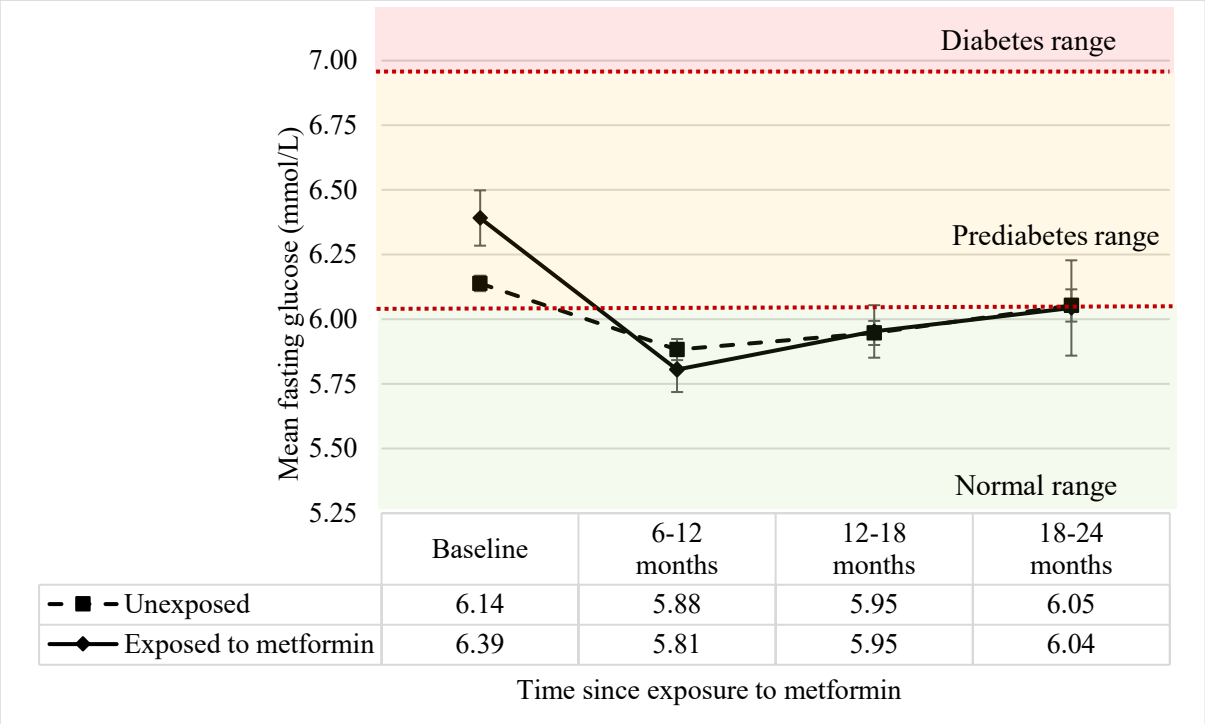
Stroke (% Yes)	2.8	3.0	3.0	3.2
Dyslipidaemia (% Yes)	39.1	35.3	37.2	33.2
Ischaemic heart disease (% Yes)	8.0	9.0	7.1	6.8
Hypertension (% Yes)	47.2	52.2	45.2	48.9
Antipsychotic scripts (% Yes)	2.7	4.0	2.4	3.2

GP: General practitioner; IRSAD: Index of Relative Socio-Economic Advantage and Disadvantage; HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; SE: Standard error.

Figure 7.2 depicts that HbA1c (2a) and FBG levels (2b) at baseline were higher among patients with 'incident' prediabetes who were prescribed metformin than their peers (imputed adjusted data). Patients who received metformin experienced considerable attenuation in their HbA1c and FBG levels at 6–12 months after exposure to metformin, following a similar curve of no difference (FBG) or slightly lower glycaemic levels (HbA1c) within 24 months than patients not managed with metformin.



(2a)



(2b)

Figure 7.2. Predicted adjusted mean of HbA1c (2a) or fasting blood glucose (2b) at baseline, 6-12, 12-18, and 18-24 months after diagnosis/exposure (imputed data).

Results based on linear regression models adjusted for practice characteristics (remoteness, and practice IRSAD) and patient characteristics (baseline glycaemic levels, age, gender, smoking status, ethnicity, patients' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, number of consultations, and wait time for starting metformin. Vertical lines represent the 95% CI. Reference values for HbA1c: normal range (≤5.9%), prediabetes range (6.0-6.4%), diabetes range (≥6.5%). Reference values for fasting blood glucose: normal range (≤6.0mmol/L), prediabetes range (6.1-6.9mmol/L), diabetes range (≥7.0 mmol/L).

Table 7.3 compares the regression coefficients (β) for the investigated associations using traditional linear regression models with ATE analyses (AIPW models) based on imputed data. Results from the traditional regression models showed that those exposed to metformin had lower mean HbA1c mmol/mol at 18-24 months (β -1.3, 95%CI -2.2;-0.3) and FBG at 6–12 months (β -0.07, 95%CI -0.17;0.02) compared to unexposed, but no difference in these parameters at other timeframes. Similar associations were observed when ATE analyses were performed, but the difference for FBG levels at 6–12 months was more evident (ATE -0.14,

95%CI -0.25;-0.04). We found similar findings in complete-case analyses (Figure F2 and Table F3, Appendix F).

Table 7.3. Comparison of the effect of metformin exposure on HbA1c and fasting blood glucose among regular adult patients with 'incident' prediabetes using traditional linear regression models or augmented inverse probability weighting (imputed data).

		Crude mean		Linear regression*		AIPW*	
	N	mmol/ mol (95% CI)	% (95% CI)	mmol/mol β. (95% CI)	% β. (95% CI)	mmol/mol ATE (95% CI)	% ATE (95% CI)
HbA1c at 6–12 months							
Unexposed	1,140	41 (40–42)	5.9 (5.8–6.0)	Ref	Ref	Ref	Ref
Exposed to metformin	232	40 (39–42)	5.8 (5.7–6.0)	0.1 (−0.5 to 0.7)	0.01 (−0.05 to 0.06)	0.0 (−0.4 to 0.7)	0.00 (−0.04 to 0.06)
HbA1c at 12–18 months							
Unexposed	1,080	42 (41–43)	6.0 (5.9–6.1)	Ref	Ref	Ref	Ref
Exposed to metformin	179	40 (38–41)	5.8 (5.6–5.9)	−0.5 (−1.3 to 0.2)	−0.05 (−0.12 to 0.02)	−0.3 (−1.2 to 0.3)	−0.03 (−0.11 to 0.03)
HbA1c at 18–24 months							
Unexposed	878	42 (40–44)	6.0 (5.8–6.2)	Ref	Ref	Ref	Ref
Exposed to metformin	145	40 (39–42)	5.8 (5.7–6.0)	−1.3 (−2.2 to −0.3)	−0.12 (−0.20 to −0.03)	−1.1 (−2.0 to 0.1)	−0.10 (−0.19 to 0.01)
FBG (mmol/L) at 6–12 months							
Unexposed	1,323	5.9 (5.8–6.1)		Ref		Ref	
Exposed to metformin	162	5.8 (5.6–6.0)		−0.07 (−0.17 to 0.02)		−0.14 (−0.25 to −0.04)	
FBG (mmol/L) at 12–18 months							
Unexposed	1,269	5.9 (5.7–6.1)		Ref		Ref	
Exposed to metformin	122	5.8 (5.6–6.1)		0.01 (−0.11 to 0.12)		0.02 (−0.08 to 0.13)	
FBG (mmol/L) at 18–24 months							
Unexposed	1,167	6.0 (5.8–6.2)		Ref		Ref	
Exposed to metformin	102	5.9 (5.6–6.1)		-0.01 (−0.21 to 0.20)		−0.07 (−0.25 to 0.12)	

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; Ref: Reference group; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

* Adjusted for practice characteristics (remoteness, practice IRSAD) and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, body mass index, smoking status, ethnicity, patients' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and total person time.

7.3.5 Discussion

This open cohort study estimated the effect of metformin on glycaemic control in patients with 'incident' prediabetes diagnosed between 2012 and 2017. First, the results demonstrated that up to 10.2% of patients with 'incident' prediabetes were prescribed metformin in general practice, despite Australian guidelines not recommending its use.[14] Second, higher baseline glycaemic levels among these patients probably influenced the GPs' decisions to start pharmacological management with metformin. Third, patients with 'incident' prediabetes managed with metformin achieved similar glycaemic control at 6–12 months than those not prescribed metformin. Fourth, some beneficial effects were seen later, with slightly better HbA1c levels at 18-24 months among those managed with metformin. Finally, all results were consistent irrespective of the methodological approach used for analysis.

Our findings are consistent with a systematic review with meta-analysis published in 2019 (N = 6,774 participants) that reported better HbA1c levels (β -0.08%, 95%CI -0.22;0.05, six trials) and better FBG values (β -0.28mmol/L, 95%CI 0.42;-0.13, 18 trials) after 1–5 years of intervention duration among patients with prediabetes managed with metformin compared to regular diet and exercise.[167] However, metformin was not better than intensive diet and exercise programs in reducing or delaying the development of diabetes among these patients.[167] Lifestyle data is not systematically recorded in MedicineInsight, hindering us from performing such comparisons. We assume patients unexposed to metformin received lifestyle recommendations from their GP according to current guidelines,[14] as they also showed better glycaemic parameters 6-12 months after prediabetes diagnosis.

From a public health perspective, intensive lifestyle interventions used in clinical trials are expensive, and the sustainable translation into real-world healthcare systems and routine clinical practice is challenging.[368] Furthermore, metformin is the ADM with the highest

adherence rate (63–74% after one year of treatment), and using that drug for diabetes prevention can be cost-effective.[27, 372, 373, 375] Despite these positive aspects, metformin adherence decreases after the first year,[382] and the beneficial effects on diabetes prevention cease after the management with metformin is stopped.[366] Still, according to our findings, patients with prediabetes started on metformin had higher glycaemic levels at baseline but average levels within the normal range between 6 and 24 months. We did not assess whether these patients used the medication or for how long (i.e. intention to treat analysis as in RCTs), thus supporting current evidence suggesting metformin could support public health strategies to prevent progression to diabetes due to its good tolerability and safety.[371]

Metformin is not currently subsidised or recommended in clinical guidelines for prediabetes management in Australia.[14] Nonetheless, the Pharmaceutical Benefits Scheme subsidised price of metformin in Australia is not much different from private prescriptions. This could explain why one in 10 patients with prediabetes was managed with metformin in our study. These figures are higher than those reported in the US (age-adjusted prevalence of metformin use in prediabetes=0.7% during 2005-2012).[370] Australian GPs are probably prescribing metformin for prediabetes management following Australian Diabetes Association suggestions that ADM could be prescribed for those with additional risk factors (e.g., BMI >35kg/m^2, age <60 years, with comorbid conditions) or high HbA1c despite lifestyle intervention. This is consistent with the evidence that metformin is more effective among patients with prediabetes and more pronounced impaired fasting glucose.[375] In our study, except for hypertension, neither age nor the presence of co-morbidities was associated with a higher frequency of metformin prescription. However, we did find that patients with 'incident' prediabetes and higher glycaemic levels were more likely to be prescribed metformin. These findings are relevant for further implementation strategies targeting patients with prediabetes at a higher risk of diabetes progression.

From a methodological perspective, our study provides evidence of the feasibility of using EHRs to assess the impact of medication management. We used different statistical techniques to handle confounding and missing data, and all analyses showed consistent results. We also found that FBG had higher variability than HbA1c, with the latter representing a more reliable parameter that reflects average blood glucose levels over the past 2–3 months.[253, 383] Additionally, measuring HbA1c is more convenient than FBG, as it does not require fasting for 8–12 hours.[22]

Some of the study's strengths include using a large sample of patients across Australian general practices, using multiple analytical strategies to improve data quality, and providing results comparable to clinical trials but at a lower cost. However, some limitations need to be recognised. First, EHRs are used to record what happens in routine clinical practice, with the completeness and validity of the extracted data varying depending on the clinician, patient healthcare-seeking behaviour and clinical information systems used. Nonetheless, the accuracy of diagnosis using MedicineInsight data compared with records stored at the practice is high, with a sensitivity of 89% and specificity of 100% for diabetes diagnosis.[248] Second, we had significant attrition of our sample size, as only 37% of eligible patients had outcome data available for analysis. Despite it did not impact our results, as the final cohort was comparable to the eligible patients according to most characteristics, including baseline HbA1c and FBG levels. This finding is concerning because patients at high risk of developing diabetes should be regularly monitored by GPs as a strategy to assess the efficacy of early interventions to avoid the progression to diabetes. A similar concern is the proportion of missing BMI data (43%) among those patients. BMI is an easy and quick measurement recommended to be assessed frequently during consultations, as it can also reflect some efficacy in treatment. To perform analyses adjusted by BMI, we employed multiple imputations for the variable, and results

obtained in sensitivity analyses were consistent and showed similarities. Finally, although we analysed a wide range of potential confounders and indicator variables, this study did not include some relevant confounders (e.g., family history, diet, exercise, healthcare insurance), which could affect exchangeability between exposed and unexposed groups. These variables are not consistently recorded in MedicineInsight, or are recorded in the progress notes, which cannot be extracted due to confidentiality issues. However, sensitivity analyses showed consistent results, strengthening the reliability of our results.

7.3.6 Conclusion

Australian GPs prescribe metformin to over one in every 10 patients with 'incident' prediabetes, particularly those with higher baseline glycaemic levels. Our study supports the use of metformin in patients with prediabetes, which may be a good intervention strategy to prevent the adverse effect of hyperglycaemia. Future longitudinal studies are needed to investigate the optimal initial dose of metformin for prediabetes treatment and diabetes prevention.

Ethics approval

The independent MedicineInsight Data Governance Committee approved the study (protocol 2016-007). The Human Research Ethics Committee of the University of Adelaide exempted this study from ethical review (No.35601) due to the use only of non-identifiable data from MedicineInsight.

Funding statement

This study received funding from The Royal Australian College of General Practitioners Foundation/Diabetes Australia Research Grant (DIA2021–06). The funding partner was not involved in any of the processes of this project.

Conflicts of interest

The authors declare no conflict of interest.

Data availability statement

Data used in this study was obtained from a third party (MedicineInsight) for this specific project and cannot be released. Information about MedicineInsight data and how they can be accessed is available on the website (https://www.nps.org.au/medicine-insight). The data extraction algorithms used in this study are available from the corresponding author upon request. DGC is the data custodian for this study.

Author contributions

MZ and DGC contributed to the conception and design of the study. MZ and S prepared the first draft of the manuscript with input from MB. MB performed the statistical analysis and helped write and edit the draft. DGC supervised this study and edited the manuscript. NS, COB, and HJ contributed to the design and writing of the manuscript. All authors contributed to the critical review of the text and provided intellectual contributions to strengthen the manuscript. All authors approved the final version for publication.

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7.4 Chapter Synopsis

This chapter provided evidence of the supporting role of metformin in the treatment of prediabetes and diabetes prevention. The findings suggest that the use of metformin for incident prediabetes with elevated baseline glycaemic parameters is a good strategy to prevent further

deterioration of glycaemic levels. These findings are expected to provide supporting evidence for further guideline recommendations.

Chapter 8. Discussion

8.1 Preface

This thesis used MedicineInsight to bring together real-world epidemiological data on diabetes and prediabetes diagnosis and management in Australian primary care settings at a national level. This chapter includes a discussion of the main findings with a comparative evaluation of the recent literature and evidence, and provides actionable practical implications.

8.2 Key Findings and Practical Implications

As noted in Section 1.5, eight hypotheses of this project were developed based on clinical needs, domain knowledge, and existing literature and guidelines. Table 8.1 summarises the key findings for each hypothesis. This section discusses the essential findings of the project and related practical implications of each finding.

Table 8.1. Summary of key findings and relevant chapters

Hypothesis		Key findings	Chapter
1	People who are at risk of diabetes are more likely to have their BG screening than those who are not at risk	Only half of those at higher risk of diabetes had their BG levels screened over 3 years, but the frequency of testing was even lower among young males at high risk of diabetes.	4
2	Patients with diagnosed diabetes, prediabetes, and undiagnosed diabetes have different sociodemographic and clinical profiles	The distribution of diabetes using MedicineInsight data resembles figures from Australian health national surveys.	4
3	Patients with diagnosed diabetes, prediabetes, and undiagnosed diabetes have different risk factors and clinical conditions	More hypertension and dyslipidaemia was found among people with prediabetes than those with diabetes.	4
4	Diabetes monitoring and control are different between patients with past and recent recorded diabetes	Only 4 out of 10 people with diabetes had their HbA1c monitored over 12 months, and just over half of them had their BG levels under control.	5
5	The prevalence of well-controlled diabetes is around 50%	Less than 20% of adults with diabetes had their HbA1c, total cholesterol, and BP well controlled.	5
6	Gender, age, and diabetes-related comorbidities influence the frequency of well-controlled diabetes	Monitoring of HbA1c, BP, and total cholesterol was not better in smokers, adults with hypertension or CVD; Patients with a history of CVD were more likely to have their diabetes well controlled, but smokers and patients with history of hypertension were not likely to have their diabetes well controlled.	5
7	Early management with metformin can help patients with newly recorded diabetes better control their BG levels, compared to those with delayed metformin management	Patients treated with metformin within 3 months of a diabetes diagnosis achieved better glycaemic parameters over 24 months than those who were started on metformin at 3–6 or 6–12 months after diagnosis.	6
8	Metformin use among patients with prediabetes is beneficial for glycaemic control	Metformin therapy for patients with prediabetes and high baseline BG levels is a good strategy to prevent further deterioration of glycaemic levels.	7

HbA1c: Haemoglobin A1c; BP: Blood pressure; BG: Blood glucose; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke).

Key finding 1: Only half of those at higher risk of diabetes had their BG levels screened over 3 years, but the frequency of testing was even lower among young males at high risk of diabetes.

We found that half of the people at increased risk of diabetes had their BG levels screened at least once over 3 years (one-third among those not at high risk of diabetes). To decrease the risk of information bias, our cross-sectional results (Paper 1) considered all forms of BG screening tests (i.e., FBG, OGTT, HbA1c, RBG, or finger-prick test). We found that HbA1c was the most frequent BG test reported by GPs for diabetes screening in Australian general practices. Since the introduction of the HbA1c screening test into the Medicare Benefits Schedule in 2014, the screening rates of HbA1c have been three times higher than OGTT, while OGTT screening rates had halved by 2019.[384] Furthermore, a study using data from the BEACH (Bettering the Evaluation and Care of Health) program found that OGTT was more common before 2014/2015, but was progressively replaced by HbA1c testing. BEACH data was a reliable Australian Primary Care data source, but was not based on EHRs, as it was implied in Paper 1. The BEACH data was obtained through a paper-based collection of information on patients reported by random samples of GPs from 1998 to 2016.[385]

Changes in BG testing may be because GPs' behaviours were greatly affected by changes of clinical screening guidelines and the national insurance scheme for hyperglycaemia-related pathology tests.[384, 385] In addition, taking into account the convenience of the patient, the GP decides in discussion with the patient which screening method they prefer to use.[385]

More frequent screening of BG levels among patients with prediabetes is strongly recommended for early detection of diabetes progression and to reduce the risk of related complications.[14, 386] However, our results found that less than half of patients with prediabetes had their BG levels screened in the last 12 months.

An additional finding was that males were less likely than females to be screened for diabetes, regardless of their risk level, which is consistent with previous research.[128, 325] This difference is probably due to women being more likely to seek healthcare services.[329, 330] Furthermore, we found a lower frequency of diabetes screening among young men (aged 18–40 years) at high risk of diabetes. However, sex disparities decreased for those aged 40–69 years, which may be due to the influence of chronic condition screening programs in this age range (e.g., 45–49 Year Old Health Check program, Guidelines for Preventive Activities in General Practice).[25, 331, 387] Health assessments for people aged 45–49 can improve diagnosis and provide support to patients in making the necessary lifestyle changes to prevent or delay the onset of chronic cconditions.[387] The gender difference we observed is also consistent with sex differences found in a recent Canadian population study (N = 1,380,697) in which adherence to diabetes screening within 3 years was lower in younger males (58.0%) than females (72.6%).[123] Therefore, our study reinforces the need for diabetes prevention activities and educational programs at the local and population levels to increase diabetes screening rates among young adults (aged 18–40 years) at high risk of diabetes, especially men at high risk of diabetes.

Practical implications of key finding 1: For researchers, HbA1c seems to be the driving biomarker for diabetes monitoring that can be used for research purposes. For health professionals, screening of BG among patients at high risk of diabetes (e.g., those with prediabetes, a history of GDM, or taking antipsychotic medications) can be substantially improved if BG screening becomes part of the systematic assessments performed by GPs during the regular clinical encounters with these patients (average five consultations per year). It would also be important to encourage more patients at higher risk of diabetes to participate in chronic disease screening programs, such as the 45–49 Year Old Health Check program, designed for patients aged 45–49 years with at least one risk factor of chronic condition (e.g., prediabetes, high BP, overweight, high cholesterol, family history of chronic disease).[387] For data collectors, it is important that users (clinicians and administrators) are engaged to maximise EHR

implementation and to promote a good data quality culture with better documentation of outcomes.

Key finding 2: The distribution of diabetes using MedicineInsight data resembles figures from Australian national health surveys.

According to national health survey data, the prevalence of diabetes among Australian adults was 5.1% in 2011–2012 (using a combination of self-reported and laboratory results), 6.2% in 2017–2018 (using self-reported data only), and 5.3% in 2020–2021 (using self-reported data only).[324, 388] Using data from MedicineInsight, we found that the prevalence of diabetes was 7.5% in 2016–2018. The lower prevalence observed in national health survey results (2011–2012, 2017–2018) may be due to the use of a community sample rather than people seeking medical care, the use of self-reported data, and the potential for misclassification of those with undiagnosed diabetes.[324] We also found that, similar to national health survey data (2011–2012), diabetes is more likely to occur in males than females.[13]

Practical implications of key finding 2: For researchers, using national EHRs to estimate the prevalence of diagnosed diabetes is reliable and cost-effective compared to conducting a national survey, even with the inclusion of pathology tests. Machine learning methods can also be used to extract and mine data from free text or images to identify diabetes cases.[42, 389] For health policymakers, how to streamline the process of these EHRs without increasing the workload of GPs. Financial incentives are a feasible approach to encourage GPs to initiate the blood tests/screenings on patients in primary care settings.[129, 390, 391]

Key finding 3: More hypertension and dyslipidaemia was found among patients with prediabetes than those with diabetes.

This finding is unexpected, as we assumed that patients with prediabetes would have a better metabolic profile than those with diabetes, due to their younger age (mean age 60.3 vs 63.5 years) and lower prevalence of obesity (63.8% vs 69.9%). It may be because of more intensive

glycaemic control among people with diabetes, which is beneficial in reducing the risk of macrovascular events.[392] Compared to patients with prediabetes, current guidelines recommend more intensive pharmacological management for patients with diabetes (especially those at high risk of CVD) to achieve better control of their metabolic parameters.[146]

A national cross-sectional study based on China National Nutrition and Health Survey involving 69,974 middle-aged and elderly (aged ≥45 years) Chinese individuals,[327] which showed that the prevalence of dyslipidaemia was higher in patients with T2D than in those with prediabetes (59.3% vs 46.8%). The main reason for this is that our results are representative of patients ≥18 years of age. Additionally, it is probable that the poorer metabolic profile observed among patients with prediabetes could be the result of various sources of error, including detection bias, survival bias, and/or underdiagnosis of patients with less severe forms of prediabetes. Furthermore, dyslipidaemia and hypertension are considered important clinical characteristics in different diabetic progression stages and different age groups.[98, 327] Therefore, our results require cautious interpretation, and more research is needed to verify them using primary data collection in longitudinal studies.

Practical implications of key finding 3: For health professionals, when patients are diagnosed with prediabetes, it is crucial to regularly monitor not only their BG but also BP and lipid levels during follow-up consultations, as without proper management they may develop diabetes and may then be at risk of similar related complications.[57, 81, 110]

Key finding 4: Only 4 out of 10 people with diabetes had their HbA1c monitored over 12 months, and just over half of them had their BG levels under control.

In general, our estimates indicate that the current diagnosis of diabetes (Paper 1) and the monitoring and control of HbA1c (Paper 2) are still consistent with the Rule of Halves. The Rule of Halves was first introduced in the 1970s by Wilber.[393] It is a classic theoretical framework in public health, which states that only half of the population with a common chronic

health condition are diagnosed, half of those diagnosed are treated, and half of those treated attain control.[23] Although it was proposed almost 50 years ago, the Rule of Halves is still a reality for chronic disease management. Our finding is also consistent with a systematic review of 123 Australian studies, which indicated that monitoring and achieving clinical targets (e.g., HbA1c, BP, or total cholesterol) for diabetes management appears to be suboptimal (40–60%) in Australia.[112] The unseen half needs more attention, as they may require more medical resources in the future due to diabetes complications (i.e., for those with undiagnosed diabetes and poorly controlled diabetes).

A 5-year retrospective cohort study (Population Level Analysis and Reporting [POLAR], 2013–2018) in Victoria found that the overall median frequency of HbA1c testing was 1.6 tests each year among patients with diabetes (aged ≥18 years, with a record of HbA1c during 2013–2018), which was less than the recommended frequency (i.e., at least two tests each year), with a moderate adherence rate of 50%.[205] Better adherence to the frequency of HbA1c testing recommended in RACGP guidelines (i.e., once every 6 months in patients with good glycaemic control, and once every 3 months among patients with poor glycaemic control) was associated with better glycaemic control and lower risk of CKD after 5 years.[205]

While we found that patients with newly recorded diabetes were less likely to have their HbA1c monitored (39.4%) than those with past recorded diabetes (45.2%), 8 out of 10 of those monitored achieved HbA1c control (vs 54.4% among those with past recorded diabetes). These patients with newly recorded diabetes were, on average, 8 years younger than those with past recorded diabetes, suggesting that their condition was in an earlier stage when complications were less common, and diabetes control was more likely to be attained with first-line medications.[35, 333] Moreover, adherence to medication is generally higher among patients with newly diagnosed diabetes (up to 65%), but tends to decrease over time, affecting diabetes control.[177] However, it is also possible that information bias, due to less frequent HbA1c

monitoring among those with newly recorded diabetes, could be an alternative explanation for these findings.

Practical implications of key finding 4: Health professionals, once patients are diagnosed with diabetes, can encourage them to participate in some intervention programs, including GP Management Plans, Team Care Agreements, and/or the National Diabetes Services Scheme, for routine management of diabetes. Moreover, GPs can actively engage their patients and use reminders to have their BG regularly checked. For patients, it is important to regularly visit GPs to monitor their BG. Since 1 November 2021, patients can access four Medicare-eligible HbA1c testing services (both laboratory-based and point-of-care) every year.[394] For health policymakers, it is important to recognise the importance of continuous surveillance and routine collection of data to monitor diabetes and potential complications. This would include encouragement of long-term monitoring of HbA1c as guidelines suggest.

Key finding 5: Less than 20% of adults with diabetes had HbA1c, total cholesterol, and BP well controlled.

Current guidelines highlight the importance of comprehensive management of cardiovascular risk factors for adults with T2D, including control of BG, BP, and lipid levels.[129, 146] However, we found that only 20% of patients with diabetes achieved clinical parameters indicating 'well controlled' diabetes (i.e., HbA1c, BP, and total cholesterol under recommended target levels). Our finding is consistent with a NHANES (National Health and Nutrition Examination Survey) study in the US (2013–2016),[395] in which 17.3% of adults with T2D without known CVD met control targets for a combination of HbA1c, BP, and LDL-C. Considering the critical role of LDL-C in CVD risk assessment among patients with diabetes,[335] we also reported the proportion of those who had their LDL-C monitored (35.7%; Appendix D). Our finding emphasises the value of monitoring and controlling these key parameters to reduce the risk of CVD among people with diabetes.

We also found that 54.4% of patients with previous recorded diabetes (2015–2016) met the HbA1c target, 70.5% met the systolic BP target, 94.6% met the diastolic BP target, and 43.9% met the total cholesterol target. A meta-analysis of 24 studies (n=369,251) from 20 countries evaluated the achievement of the targets for these critical parameters recommended by guidelines of the European Association for the Study of Diabetes, the American Diabetes Association, and the National Institute for Health and Care Excellence (NICE). The analysis found that 42.8% achieved HbA1c control, 29.0% BP control, 49.2% LDL-C control, 58.2% HDL-C control, and 61.9% triglyceride control.[396] Another systematic review of 123 Australian studies found that, among those who had their clinical parameters assessed, 40–60% met management goals for HbA1c, BP, or lipid levels.[112] Our findings are also consistent with data from the Australian Health Survey (2011–2012), which found that 54.7% of adults (aged ≥18 years) with known diabetes met the recommended HbA1c target (≤7.0%), 39% met the BP target (≤130/80 mmHg), and 38% met the total cholesterol target (<4.0 mmol/L).[13]

However, those two large review studies did not estimate the percentage of patients with all three parameters under control. One of the largest annual clinical audits worldwide, the National Diabetes Audit Programme in the UK, found that about 40% of patients with T2D in England had achieved control for all three clinical parameters (HbA1c ≤7.5%, BP ≤140/80 mmHg, and cholesterol <5 mmol/L) in 2018–2019.[397] Our results cannot be compared to the UK results due to the use of different cut-offs.

The global costs of diabetes and its consequences are enormous and will increase dramatically by 2030, and the global economic burden will not decrease even if countries meet international targets of diabetes control.[51] Policymakers need to take urgent action to prepare health and social protection systems to mitigate the impact of diabetes. For example, the UK provides financial incentives upfront for GPs to assess and achieve diabetes control (which requires regular reporting and monitoring of nine parameters [i.e., HbA1c, creatinine, cholesterol, BP, BMI, smoking status, urinary albumin, retinal examination, and foot examination]), while these

services are audited by the National Diabetes Audit Programme[397] to provide better monitoring and control. The Australian National Diabetes Audit provides a biennial update on diabetes practice processes and outcomes, analysing data from participating diabetes services in each Australian state and territory.[398] During 7 years follow-up, completion of annual diabetes care processes (HbA1c, creatinine, cholesterol, BP, BMI, smoking habit, urinary albumin, foot examination) <5 times, compared to 8 times, had a mortality hazard ratio of 1.32 (95%CI 1.30;1.35) among patients with T2D.[399] Therefore, more frequent data updates and more incentives like the UK's National Diabetes Audit Programme could improve the suboptimal monitoring and management of diabetes.

Practical implications of key finding 5: For researchers, the consistency of our results demonstrates that using EHRs is a cost-effective method to evaluate screening for diabetes and control of clinical parameters. For health professionals, patients' diabetes treatment plans should be regularly reviewed by a multidisciplinary team of medical doctors, diabetes educators, nurses, and specialists, based on the patient's current medications and management plan (i.e., BG, BP, and lipid levels) during regular visits or clinical recalls. For health policymakers, encouraging GPs and nurses to record more clinical and outcome data into the EHR would facilitate more accurate and useful audits and studies. Providing GPs with incentives to meet screening and clinical targets could improve the management of diabetes.

Key finding 6: Monitoring of HbA1c, BP, and total cholesterol was not better in smokers, adults with hypertension or CVD; Patients with a history of CVD were more likely to have their diabetes well controlled, but smokers and patients with history of hypertension were not likely to have their diabetes well controlled.

People with chronic health conditions (e.g., diabetes, hypertension, and CVD) attend general practice more often than those without (i.e., 'healthy' individuals).[223, 400] It is concerning that, according to our findings, patients with a history of smoking, hypertension, or CVD were poorly monitored but not as well as they should have been, as these factors increase the risk of diabetes-

related complications.[35, 401] Regarding control, patients with a history of CVD were more likely to have their diabetes well controlled, but smokers and patients with history of hypertension were not likely to have their diabetes well controlled.

Smoking is considered the most important preventable risk factor for CVD,[402] but current smoking remains prevalent among Australians with diabetes,[403] even though patients who smoke have access to a variety of subsidised smoking cessation programs. In addition, results from the Australian National Diabetes Audit cross-sectional data (2011–2017)[403] showed that current and former smokers had higher HbA1c (0.49% and 0.14% higher, respectively), lower HDL-C, and higher triglyceride levels than non-smokers. This is consistent with our findings that current smokers are not only poorly monitored, but their diabetes is also more poorly controlled their HbA1c, BP, and total cholesterol levels.

Hypertension is a common comorbidity of diabetes and another important risk factor that substantially increases the risk of CVD, stroke, CKD, and other diabetes-related complications.[100, 404] A meta-analysis of 19 RCTs found that a reduction in systolic BP by 5 mmHg reduced the risk of T2D by 11% (hazard ratio 0.89, 95%CI 0.84;0.95); therefore, reducing BP may be a strategy for preventing T2D.[101] Despite the level of evidence, we found that those with hypertension and smokers are not only not well monitored for HbA1c, BP, and total cholesterol, but also have poorer control of their parameters.

Regarding people with end-organ damage, we identified that the screening frequency for HbA1c, BP, and total cholesterol was not higher among patients with CVD, whether they had past recorded diabetes (adjusted OR=0.95, 95%CI 0.90;1.00) or newly recorded diabetes (adjusted OR=0.98, 95%CI 0.84;1.13). Even among those with CVD, only one-third achieved control of all three parameters. As reported by another MedicineInsight study among patients with CVD and T2D in 2018, the proportion of patients achieving recommended screening measurements in the past 6 months for HbA1c was 33.1% (95%CI 32.1;34.1) and for BP was

44.3% (95%CI 43.1;45.4), and for LDL-C in the last 12 months was 30% (95%CI 29.0;31.0).[92] The risk of recurrent CVD events, further complications, hospitalisations, and mortality among these patients is much higher than their peers with no history of CVD,[94, 354] therefore they should be subject to more regular monitoring and better control of their metabolic parameters.

Practical implications of key finding 6: For researchers, intervention studies are needed that promote the usage of reminders and targeted interventions to achieve better diabetes management in high-risk groups. For health professionals, encouraging the involvement of patients in diabetes annual cycle of care (Table H1, Appendix H) and annual check-ups is important and is considered the minimum level of care that should be provided.[73, 133, 405, 406] For health policymakers, incentives should be universal to all people with diabetes as in the UK, including those with hypertension or CVD, and smokers.[390, 391]

Key finding 7: Patients treated with metformin within 3 months of a diabetes diagnosis achieved better glycaemic parameters over 24 months than those who were started on metformin at 3–6 or 6–12 months after diagnosis.

We found that patients who received metformin within 3 months of diabetes diagnosis had stable and lower HbA1c levels over the 24 months of follow-up compared to those who began taking the medication more than 3 months after diagnosis. This finding is consistent with a study in Northern California that found that patients who received early treatment (within 6 months of diagnosis) were more likely to reach HbA1c targets (<7%) and a reduced risk of intensification of treatment compared to those who delayed treatment (more than 6 months).[153] Therefore, from a statistical perspective, early metformin management for patients with diabetes can be used to reach better long-term glycaemic control and diabetes management. Of note, Australia recommends that metformin should only be initiated if glycaemic control (e.g., HbA1c <7%) is not achieved after a 2-3 month trial of lifestyle modification.[151] On the other hand, the US and IDF guidelines recommend that metformin should be initiated at the time of

diagnosis of T2D (unless contraindications exist) and in combination with lifestyle modification,[50] which is consistent with the results of our study.

Achieving early and stable glycaemic control could reduce further diabetes-related complications. Elevated HbA1c levels during the first years after T2D diagnosis have also been associated with an increased risk of microvascular complications in the following 13 years.[364] Moreover, a population-based study in Denmark reported that patients with T2D who experienced a substantial initial reduction in HbA1c levels and achieved HbA1c control (<6.5%) within 6 months of initial metformin treatment had a lower risk of cardiovascular events and death.[365] In addition, achieving early control of the BG levels, thereby minimising therapeutic inertia, could result in substantial savings to society.[407]

Practical implications of key finding 7: For health professionals, when patients are diagnosed with incident diabetes, first-line medication treatment could be immediately discussed and started along with lifestyle modification to help avoid long-term diabetes complications. For health policymakers, it is worth evaluating the cost-effectiveness of following current Australian guidelines[151] on timely metformin use soon after the clinical diagnosis, compared to delayed metformin use.

Key finding 8: Metformin therapy for patients with prediabetes and high baseline BG levels is a good strategy to prevent further deterioration of glycaemic levels.

Metformin is an off-label drug for prediabetes treatment, as it has not been indicated for that purpose by the Food and Drug Administration in the US or the Therapeutic Goods Administration in Australia. This is supported by evidence from the Diabetes Prevention Program and Diabetes Prevention Program Outcomes Study published in 2022 (3,234 participants with impaired glucose tolerance with over 21 years of follow-up) that showed that neither lifestyle interventions nor metformin treatment reduced the risk of major cardiovascular events (e.g., stroke, non-fatal myocardial infarction, or cardiovascular death) compared to

placebo.[408] Nonetheless, various international guidelines and reviews suggest metformin can be used for diabetes prevention in people with prediabetes and certain other characteristics (e.g., those with BMI ≥35 kg/m^2, aged 18–60 years, or females with a history of GDM).[371, 409, 410] A recent network meta-analysis of 21,208 patients with prediabetes found that, compared to the control group, the use of acarbose, metformin, or intensive lifestyle modification was associated with reduced progression to diabetes (relative risks: acarbose = 0.37 [95%CI 0.29;0.47]; metformin = 0.39 [95%CI 0.30;0.50]; intensive lifestyle modifications = 0.61 [95%CI 0.50;0.73]).[411] Moreover, metformin and acarbose were associated with improved BG levels in that study.[411] Consistent with that meta-analysis, we found that management with metformin reduces HbA1c levels over 2 years in people with incident prediabetes, compared to their peers who did not receive that medication. We only investigated metformin mono-prescription, rather than other drugs for the treatment of prediabetes, because metformin is the leading ADM prescribed in Australia with proven long-term efficacy and safety.[81, 371, 376, 410]

Despite the evidence in favour of intensive lifestyle modifications, such interventions can be expensive and difficult to sustain in real-world healthcare systems and routine clinical practice.[368] Conversely, metformin, a commonly prescribed ADM, has a high adherence rate (63–74% after 1 year of treatment) and can be cost-effective for diabetes prevention.[27, 372, 373, 375] However, metformin adherence tends to decrease after the first year of treatment,[382] and the drug's benefits for diabetes prevention cease once it is stopped.[366] According to our findings, patients with incident prediabetes prescribed metformin had achieved better glycaemic levels at 2 years after starting that medication. Thus, our results support the idea that metformin could be a valuable tool in public health strategies aimed at preventing the progression of diabetes, due to its low cost, good tolerability, and safety.[371]

Practical implications of key finding 8: For health professionals, metformin could be suggested for prediabetes treatment among those with higher levels of BG (i.e., a recent HbA1c >6.2% or FBG >6.4 mmol/L) when more supporting evidence is available. For researchers and

health policymakers, more studies and expert consensus are urgently needed to investigate clinical effectiveness and cost-effectiveness before changing the current guideline recommendations on the usage of metformin for prediabetes.

8.3 Overall Significance of the Project

Since the Australian Government has not conducted a national health survey with pathology examinations since 2011, this thesis provides the first national evidence of the screening, diagnosis, monitoring, and treatment of prediabetes and diabetes based on EHRs with pathology results from a national primary care database (MedicineInsight).

Regarding clinical significance, the results of this thesis provide evidence for future Australian guidelines and policies on the optimal timing of first-line dosing after clinical diagnosis in patients with diabetes. Moreover, we also have provided clear evidence that the usage of metformin among patients with prediabetes can help prevent or delay progression to diabetes.

The relevance of this project for researchers lies in the use of different approaches to extract valuable information recorded in EHRs, and the application of traditional and advanced statistical modelling to analyse the data. Centralisation of EHRs could provide further opportunities for cost-effective longitudinal studies using data that will become available from ongoing data collection programs (e.g., POLAR and PATRON[10, 203-205]). Furthermore, there is a need for incentives for improving data collection by GPs, greater participation by practices, data cleaning by a central agency, possible data linkage, reasonable access costs for researchers.[20, 73, 391] The study designs and statistical analyses noted in Section 3.8 can be used for other studies based on EHR data, together with the critical steps of data extraction, dealing with confounding and potential bias, and conducting augmented inverse probability weighting (AIPW).

8.4 Strengths and Limitations

The first strength of the project was the use of a large national general practice database, and the generation of detailed algorithms to identify patients with prediabetes and diabetes based on the information routinely collected and recorded by GPs during their clinical encounters. These algorithms can be adapted and used in future studies investigating global real-world primary care data. Second, the results of our studies on initial metformin use for early diabetes treatment (Chapter 6) and the effectiveness of metformin for prediabetes treatment (Chapter 7) simulated results of RCTs by AIPW models, but at a substantially lower cost. Moreover, the results were obtained in a timely manner (i.e., no need to wait 3–5 years to complete the study), involved a national sample (i.e., similar to a multicentre study), and included results collected by health professionals (i.e., observed data rather than self-reported data).

Furthermore, the database included a range of sociodemographic and clinical data that allowed proper control for possible confounders. We also chose a double-robustness approach (AIPW)[311] to estimate the average treatment effect in Papers 3 and 4, as this technique is less likely to provide biased results. Therefore, retrospective longitudinal studies based on MedicineInsight can quickly and cost-effectively provide answers on the potential benefit of different pharmacological approaches for therapies for prediabetes or diabetes in Australia. Stakeholders and health policymakers can use the results of this project to evaluate and improve current guidelines.

Before conducting each study, potential limitations and biases were considered (Section 3.6). The limitations of each study are mentioned in each paper, but some general limitations of the project need to be addressed. First, regarding long-term complications of diabetes, this thesis did not estimate the proportions of eye or foot complications recorded because the doctor may refer patients with those complications to the optometrist or the specialist foot clinic if they are at high risk. Regarding depressed conditions in diabetes, depression or anxiety were not analysed as confounders in this thesis because these variables were not systematically included

in the database. Natural language processing can be used to extract these symptoms from EHR free-text narratives for further investigations.[44, 412] Second, a recent MedicineInsight study found that there may be disparities in test results due to the manner in which data from pathology, radiology, and other imaging providers is stored in the EHR and MedicineInsight; further investigation is needed to address this issue.[275] Third, this thesis used data for prescribed medications, but it is unknown whether these medications were taken. Data linkage to other EHRs or databases[218] has great potential to investigate more accurate information about medication use and long-term effects on BG levels. Fourth, this thesis did not link hospital data to investigate CVD events or other complications. However, the data was appropriate to investigate screening, monitoring, and management, considering that T2D is primarily managed in primary care settings.[164] And finally, the database did not allow an appropriate differentiation of patients with T1D or T2D, which is a challenge for many EHR-based studies.[22, 413]

Chapter 9. Conclusions

9.1 Preface

This final chapter summarises the original contribution to knowledge from this doctoral thesis, drawn from eight key findings from four studies. These findings may be used to develop or update more future guidelines and policies on the screening, monitoring, and management of diabetes and prediabetes in primary care settings. Further directions of the work are also highlighted.

9.2 Original Contribution to Knowledge

To our knowledge, **Paper 1 (Chapter 4)** is the first national observational study based on EHR data to explore the diagnosis and screening of diabetes in Australia using pathology results. The distribution of diabetes we found was comparable to the results of the Australian national health survey, which reinforces that primary health care EHRs are a valuable and low-cost resource for monitoring diabetes at the national level. Moreover, we found that half of the population at high risk of diabetes was not screened for diabetes over a 3-year period, while only 2 out of 3 patients with prediabetes were screened in the last 12 months.

Paper 2 (Chapter 5) investigated sociodemographic and clinical factors related to the monitoring and control of diabetes (i.e., HbA1c, BP, and total cholesterol), comparing patients with newly recorded or past recorded diabetes, which has not been previously explored in Australia. Notably, we found that half of the patients with past recorded diabetes had their HbA1c levels checked over 12 months, and consistent with existing evidence, only half of them achieved HbA1c control. Among those with newly recorded diabetes, only 4 out of 10 had their HbA1c levels monitored over 12 months, but 8 out of 10 of them reached the recommended HbA1c levels. This finding indicates that HbA1c monitoring was lower, but HbA1c control was higher among patients with newly diagnosed diabetes than with past recorded diabetes. Another striking finding was that smoking, or history of hypertension or CVD were monitored poorly,

and less than 20% of patients had achieve the recommended the three clinical parameters (i.e., HbA1c, BP, and total cholesterol). This puts them at higher risk for diabetes-related complications.

Paper 3 (Chapter 6) supported the use of metformin from the time of diagnosis, which is already recommended in the US. In Australia, lifestyle modifications are recommended as the first management strategy after diabetes diagnosis, but these modifications are challenging for patients to maintain.[414] We found that patients who received metformin within the first 3 months of diagnosis showed better HbA1c levels over 24 months of follow-up than those who started metformin after that period.

As there are no medications for prediabetes therapy approved by the Therapeutic Goods Administration in Australia, **Paper 4 (Chapter 7)** investigated the effects of metformin management on glycaemic parameters among patients with incident prediabetes. Management with metformin not only improved the glycaemic parameters of these patients in the short term, but their BG levels remained steady over 2 years. FBG levels showed a higher variation than HbA1c levels, probably because HbA1c is a better indicator of BG status (reflecting BG levels over the past 8–12 weeks).[255]

Finally, this thesis provided evidence that national primary care databases such as MedicineInsight can be used to investigate diabetes screening, monitoring, and management, as well as to provide inputs for longitudinal causal models. Using validated algorithms to extract data from free text and objective pathology results is feasible, and can complement results from large RCTs and national health surveys. Moreover, EHRs can also contribute to the use of primary health care data for research and surveillance purposes in Australia.[234]

9.3 Future Directions

Given the results of this doctoral thesis, there are several important directions and recommendations for further research.

For researchers, there is currently a lack of evidence for prevention strategies (i.e., weight management, promotion of healthy diets, and participation in physical activity) specifically for patients with prediabetes or other individuals at high risk of developing diabetes, rather than for the whole population.[12, 415, 416] Future causal studies should consider weight loss and lifestyle intervention as confounders, and investigate diabetes progression and other complications among patients with prediabetes managed with metformin. These studies are particularly relevant among patients who are not willing to participate in lifestyle intervention programs.[417] More large-scale studies linking general practice records with hospital data are also necessary, as they could support the investigation of the causal association between diabetes or prediabetes interventions and long-term outcomes.[207] It is well known that higher mortality rates in patients with diabetes are associated with a lack of routine care procedures.[399] Further research is required into whether different approaches to care might improve outcomes for patients who do not monitor their key clinical parameters or cannot complete the diabetes annual cycle of care.[399] Further avenues for future research include the use of machine learning and natural language processing[412] to automatically predict diabetes in patients attending general practice without the disease, or complications in patients diagnosed with diabetes, based on their EHR; the range of HbA1c levels that could prompt GPs prescribing metformin based on potential outcomes; the optimal dose of metformin for these patients; as well as the economic impact of prediabetes management with metformin.

For health policymakers, guideline makers, and health professionals, it remains a challenge to implement guideline recommendations. The trusting relationship between patients and their family physicians may encourage patients to participate in national prevention programs (e.g., Diabetes Prevention Program, T2D management plans) if recommended by their GPs.[390] In the UK, policymakers realise that it is only through national programs with incentives (Table I1, Appendix I) that GPs will commit to testing their patients with diabetes and helping them achieve good control of their diabetes.[180] Such a program could be adapted by the

Australian National Diabetes Audit[403] to obtain timely information on monitoring and control of diabetes.

Appendices

Appendix A. Supplementary Materials for Chapter 2

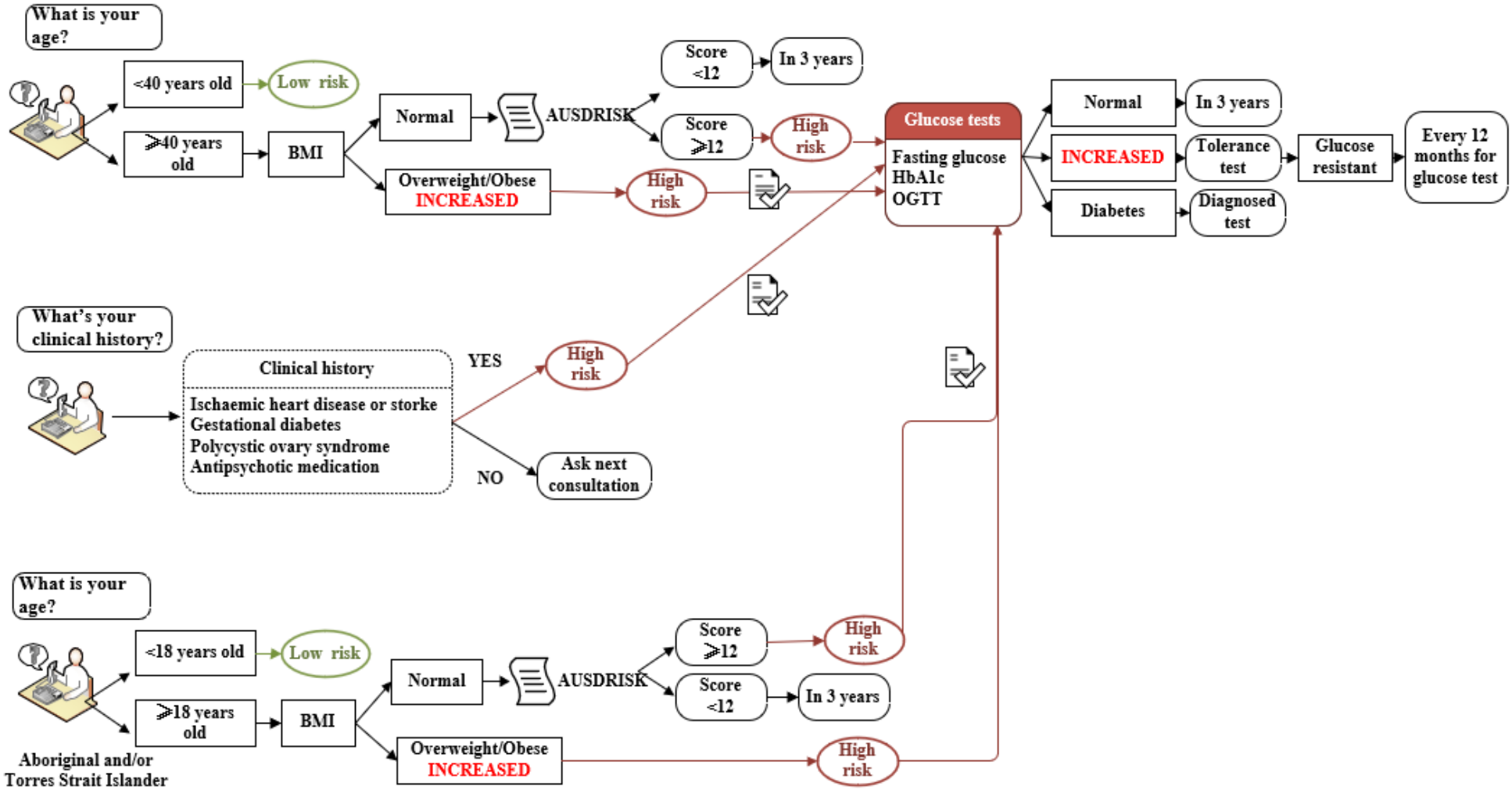
Table A1. Diagnostic criteria of prediabetes

Diagnostic criteria	Terminology	Impaired fasting glucose[a]	Impaired glucose tolerance[b]	HbA1c
American Diabetes Association[2]	Prediabetes	5.6–6.9 mmol/L (100–125 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	5.7–6.4% (39–47 mmol/mol)
World Health Organization[418]	Intermediate hyperglycaemia	6.1–6.9 mmol/L (110–125 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	Not available
International Diabetes Federation[419]	Impaired glucose tolerance[b]	6.1–6.9 mmol/L (110–125 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	Not available
Australian Diabetes Society[14]	Prediabetes	6.1–6.9 mmol/L (110–125 mg/dL)	7.8–11.0 mmol/L (140–199 mg/dL)	6.0–6.4% (42–47 mmol/mol)

HbA1c: Haemoglobin A1c

a. Impaired fasting glucose is assessed by fasting plasma glucose.

b. Impaired glucose tolerance is assessed by 2-hour plasma glucose during 75 g oral glucose tolerance test.



BMI: Body mass index; AUSDRISK: Australian Type 2 Diabetes Risk Assessment tool; HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test.
Source: Modified from RACGP (2016) [129], with available variables in MedicineInsight.

Figure A1. Algorithm for screening people with high risk of type 2 diabetes

Table A2. Type 2 diabetes: goals for optimum management

Type 2 diabetes: Goals for optimum management

The following table lists goals for optimum management for all people with type 2 diabetes. For guidance on specific assessment intervals, advice and arrangements, refer to the relevant sections of this handbook.

Individual goals	
Encourage all people with type 2 diabetes to approach/reach these goals.	
Diet	Advise eating according to the *Australian dietary guidelines*, with attention to quantity and type of food Advise individual dietary review for people with difficulty managing weight, difficulty maintaining glucose levels in target range, CVD risk, or if otherwise concerned
BMI	Advise a goal of 5–10% weight loss for people who are overweight or obese with type 2 diabetes For people with BMI >35 kg/m² and comorbidities, or BMI >40 kg/m², consider facilitating greater weight-loss measures
Physical activity	Children and adolescents: at least 60 min/day of moderate-to-vigorous physical activity, plus muscle- and bone-strengthening activities at least three days/week Adults: 150 minutes of aerobic activity, **plus** 2–3 sessions of resistance exercise (to a total ≥60 minutes) per week
Cigarette consumption	Zero per day
Alcohol consumption	Advise ≤2 standard drinks (20 g of alcohol) per day for men and women
Blood glucose monitoring	Advise 4–7 mmol/L fasting and 5–10 mmol/L postprandial SMBG is recommended for patients with type 2 diabetes who are using insulin. Education should be provided regarding frequency and timing of insulin dose For people not on insulin, the need for and frequency of SMBG should be individualised, depending on type of glucose-lowering medications, level of glycaemic control and risk of hypoglycaemia, as an aid to self-management SMBG is recommended in pregnancy complicated by diabetes or gestational diabetes SMBG is also recommended for people with hyperglycaemia arising from intercurrent illness. It may be helpful in haemoglobinopathies or other conditions where HbA1c measurements may be unreliable

Clinical management goals	
Treatment targets for people with type 2 diabetes include the following. For a comprehensive list of assessments and screening intervals, refer to the section 'Assessment of the patient with type 2 diabetes'.	
HbA1c	Target needs individualisation according to patient circumstances Generally ≤7% (53 mmol/mol)
Lipids	Initiation of pharmacotherapy is dependent on the assessment of absolute CVD risk (refer to the Australian absolute cardiovascular disease risk calculator). This uses multiple risk factors, which is considered more accurate than the use of individual parameters Once therapy is initiated, the specified targets apply; however, these targets should be used as a guide to treatment and not as a mandatory target
Total cholesterol	<4.0 mmol/L
HDL-C	≥1.0 mmol/L
LDL-C	<2.0 mmol/L; <1.8 mmol/L if established CVD is present
Non–HDL-C	<2.5 mmol/L
Triglycerides	<2.0 mmol/L
Blood pressure	≤140/90 mmHg Lower blood pressure targets may be considered for younger people and for secondary prevention in those at high risk of stroke The target for people with diabetes and albuminuria/proteinuria remains <130/80 mmHg. As always, treatment targets should be individualised and monitored for side effects from medications used to lower blood pressure
Urine albumin excretion	UACR: • women: <3.5 mg/mmol • men: <2.5 mg/mmol Timed overnight collection: <20 µg/min; spot collection: <20 mg/L
Vaccination	Recommended immunisations: influenza, pneumococcus, diphtheria-tetanus-acellular pertussis (dTpa). Consider: hepatitis B (if travelling), herpes zoster

BMI, body mass index; CVD, cardiovascular disease; GPs, general practitioners; HbA1c, glycated haemoglobin; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SMBG, self-monitoring of blood glucose; UACR, urine albumin-to-creatinine ratio.

Source: RACGP (2020)[73]

Table A3. Annual cycle of care checklist based on the available data on MedicineInsight database

Check	How often?	Targets	Data availability
HbA1c	At least every 6–12 months	≤53 mmol/mol (7%)	YES
Blood pressure	At least every 6 months	≤130/80 to 140/90 mmHg	YES
Foot assessment	Low-risk feet: At least every year Moderate-risk feet: At least every 3–6 months High-risk feet: At least every 1–3 months	Foot health maintained	NO
Eye examination	At least every 2 years	Eye health maintained	NO
Kidney health	At least every year	Urine albumin levels in target range Kidney function test in target range	YES
Blood fats	At least every year	Total cholesterol less than 4 mmol/L LDL-C <2 mmol/L HDL-C ≥1 mmol/L Triglycerides <2 mmol/L	YES
Weight	At least every 6 months	BMI 18.5–24.9	YES
Waist circumference*	At least every 6 months	<94 cm (men) <80 cm (women)	NO
Healthy eating review	At least every year	Following a healthy eating plan	NO
Physical activity review	At least every year	At least 30 minutes of moderate physical activity, 5 or more days a week and minimise time spent sitting	NO
Medication review	At least every year	Safe use of medications	YES
Smoking	At least every year	No smoking	YES
Diabetes management	At least every year	Self-management of diabetes maintained	NO
Emotional health	As needed	Emotional health and well-being maintained	NO

HbA1c: Haemoglobin A1c; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; BMI: Body mass index.
'Data availability' means MedicineInsight database has available data excluding possible missing data. The targets listed are for adults with diabetes. Different targets apply to children and adolescents.
* BMI and waist circumference targets may not apply to non-European ethnic groups.
Source: Modified from NADD,[405] with available variables in MedicineInsight.

Australian Government
Department of Health

What is type 2 diabetes?

Type 2 diabetes is a chronic (long-term) disease marked by high levels of sugar in the blood. It occurs when the body does not produce enough insulin (a hormone released by the pancreas) or respond well enough to insulin. Type 2 diabetes is the most common form of diabetes. There are approximately 1 million people with type 2 diabetes currently. This figure is expected to increase significantly in the coming years.

People with diabetes have a higher risk of developing heart disease, stroke, high blood pressure, circulation problems, lower limb amputations, nerve damage and damage to the kidneys and eyes.

Risk factors

Many Australians, particularly those over 40, are at risk of developing type 2 diabetes through lifestyle factors such as physical inactivity and poor nutrition. Family history of diabetes and genetics also play a role in type 2 diabetes.

What can you do to lower your risk of developing type 2 diabetes?

Your lifestyle choices can prevent or, at least, delay the onset of type 2 diabetes.

You cannot change risk factors like age and your genetic background. You ***can*** do something about being overweight, your waist measurement, how active you are, eating habits, or smoking.

If there is type 2 diabetes in your family, you should be careful not to put on weight. Reducing your waist measurement reduces your risk of type 2 diabetes.

By increasing your physical activity and improving your eating habits you can lower your risk. Eat plenty of vegetables and high fibre cereal products every day and use a small amount of fats and oils. Monounsaturated oils, such as olive or canola oil, are the best choice.

You can have type 2 diabetes and not know it because there may be no obvious symptoms.

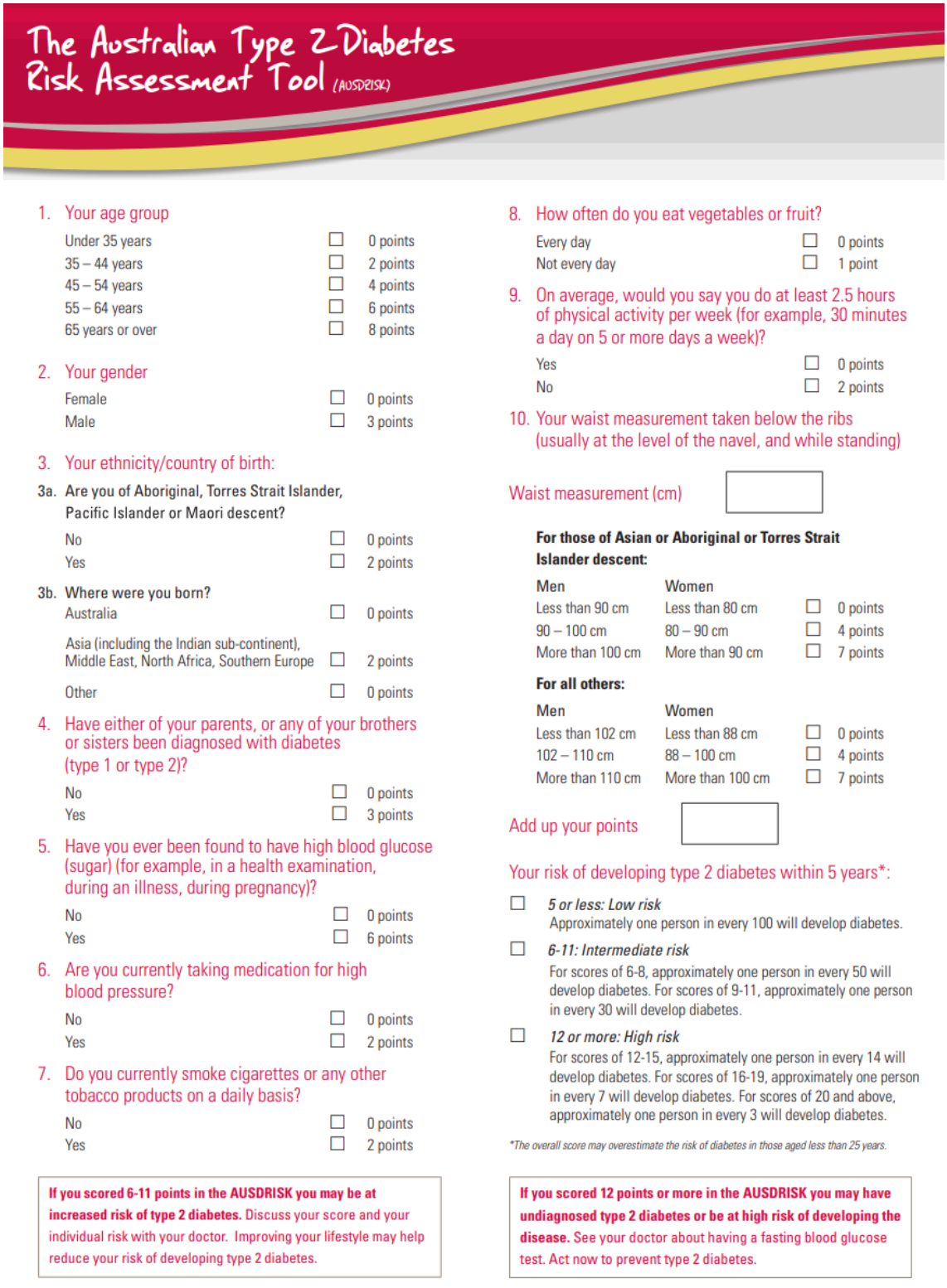
The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)

How do you score?

The Australian Type 2 Diabetes Risk Assessment Tool was developed by the Baker IDI Heart and Diabetes Institute on behalf of the Australian, State and Territory Governments as part of the COAG initiative to reduce the risk of type 2 diabetes

Current from: May 2010

6871 (10/7)



The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)

1. Your age group

Under 35 years	0 points
35 – 44 years	2 points
45 – 54 years	4 points
55 – 64 years	6 points
65 years or over	8 points

2. Your gender

Female	0 points
Male	3 points

3. Your ethnicity/country of birth:

3a. Are you of Aboriginal, Torres Strait Islander, Pacific Islander or Maori descent?

No	0 points
Yes	2 points

3b. Where were you born?

Australia	0 points
Asia (including the Indian sub-continent), Middle East, North Africa, Southern Europe	2 points
Other	0 points

4. Have either of your parents, or any of your brothers or sisters been diagnosed with diabetes (type 1 or type 2)?

No	0 points
Yes	3 points

5. Have you ever been found to have high blood glucose (sugar) (for example, in a health examination, during an illness, during pregnancy)?

No	0 points
Yes	6 points

6. Are you currently taking medication for high blood pressure?

No	0 points
Yes	2 points

7. Do you currently smoke cigarettes or any other tobacco products on a daily basis?

No	0 points
Yes	2 points

If you scored 6-11 points in the AUSDRISK you may be at increased risk of type 2 diabetes. Discuss your score and your individual risk with your doctor. Improving your lifestyle may help reduce your risk of developing type 2 diabetes.

8. How often do you eat vegetables or fruit?

Every day	0 points
Not every day	1 point

9. On average, would you say you do at least 2.5 hours of physical activity per week (for example, 30 minutes a day on 5 or more days a week)?

Yes	0 points
No	2 points

10. Your waist measurement taken below the ribs (usually at the level of the navel, and while standing)

Waist measurement (cm) ☐

For those of Asian or Aboriginal or Torres Strait Islander descent:

Men	Women	
Less than 90 cm	Less than 80 cm	0 points
90 – 100 cm	80 – 90 cm	4 points
More than 100 cm	More than 90 cm	7 points

For all others:

Men	Women	
Less than 102 cm	Less than 88 cm	0 points
102 – 110 cm	88 – 100 cm	4 points
More than 110 cm	More than 100 cm	7 points

Add up your points ☐

Your risk of developing type 2 diabetes within 5 years*:

☐ *5 or less: Low risk*
Approximately one person in every 100 will develop diabetes.

☐ *6-11: Intermediate risk*
For scores of 6-8, approximately one person in every 50 will develop diabetes. For scores of 9-11, approximately one person in every 30 will develop diabetes.

☐ *12 or more: High risk*
For scores of 12-15, approximately one person in every 14 will develop diabetes. For scores of 16-19, approximately one person in every 7 will develop diabetes. For scores of 20 and above, approximately one person in every 3 will develop diabetes.

**The overall score may overestimate the risk of diabetes in those aged less than 25 years.*

If you scored 12 points or more in the AUSDRISK you may have undiagnosed type 2 diabetes or be at high risk of developing the disease. See your doctor about having a fasting blood glucose test. Act now to prevent type 2 diabetes.

Source: Australian Government Department of Health
https://www.health.gov.au/sites/default/files/the-australian-type-2-diabetes-risk-assessment-tool-ausdrisk.pdf

Figure A2. The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK)

Table A4. List of antidiabetic medications on Pharmaceutical Benefits Scheme (Anatomical Therapeutic Chemical Classification codes A10A and A10B)

A10A – INSULINS AND ANALOGUES		
A10AB	Insulins and analogues for injection, fast-acting	- INSULIN ASPART - INSULIN GLULISINE - INSULIN LISPRO - INSULIN NEUTRAL HUMAN
A10AC	Insulins and analogues for injection, intermediate-acting	- INSULIN ISOPHANE HUMAN
A10AD	Insulins and analogues for injection, intermediate- or long-acting combined with fast-acting	- INSULIN ASPART + INSULIN ASPART PROTAMINE - INSULIN DEGLUDEC + INSULIN ASPART - INSULIN ISOPHANE HUMAN + INSULIN NEUTRAL HUMAN - INSULIN LISPRO + INSULIN LISPRO PROTAMINE
A10AE	Insulins and analogues for injection, long-acting	- INSULIN DETEMIR - INSULIN GLARGINE
A10B – BLOOD GLUCOSE LOWERING DRUGS, EXCL. INSULINS		
A10BA Biguanides		- METFORMIN
A10BB	Sulfonylureas	- GLIBENCLAMIDE - GLICLAZIDE - GLIMEPIRIDE - GLIPIZIDE
A10BD	Combinations of oral blood glucose lowering drugs	- ALOGLIPTIN + METFORMIN - DAPAGLIFLOZIN + METFORMIN - EMPAGLIFLOZIN + LINAGLIPTIN - EMPAGLIFLOZIN + METFORMIN - ERTUGLIFLOZIN + METFORMIN - ERTUGLIFLOZIN + SITAGLIPTIN - LINAGLIPTIN + METFORMIN - METFORMIN + GLIBENCLAMIDE - SAXAGLIPTIN + DAPAGLIFLOZIN - SAXAGLIPTIN + METFORMIN - SITAGLIPTIN + METFORMIN - VILDAGLIPTIN + METFORMIN
A10BF	Alpha glucosidase inhibitors	- ACARBOSE
A10BG	Thiazolidinediones	- PIOGLITAZONE
A10BH	Dipeptidyl peptidase 4 (DPP-4) inhibitors	- ALOGLIPTIN - LINAGLIPTIN - SAXAGLIPTIN - SITAGLIPTIN - VILDAGLIPTIN
A10BJ	Glucagon-like peptide-1 (GLP-1) analogues	- DULAGLUTIDE - EXENATIDE - SEMAGLUTIDE [(a)]
A10BK	Sodium-glucose co-transporter 2 (SGLT-2) inhibitors	- DAPAGLIFLOZIN - EMPAGLIFLOZIN - ERTUGLIFLOZIN

(a) SEMAGLUTIDE has been on the Pharmaceutical Benefits Scheme list since 2020.
* The category of antidiabetic medications on the Pharmaceutical Benefits Scheme website (https://www.pbs.gov.au/browse/body-system?depth=2&codes=a10#a10) was listed below in February 2021.

Appendix B. Supplementary Materials for Chapter 3

Table B1. Terms used for type 1 diabetes, type 2 diabetes/unspecified, or gestational diabetes mellitus in MedicineInsight report (2018–2019)

Condition	Terms
Type 1 diabetes	T1D relevant terms: diabetes mellitus (IDDM or juvenile-onset or type 1), IDDM, insulin-dependent diabetes mellitus, juvenile-onset diabetes
Type 2 diabetes/unspecified terms	T2D/unspecified terms: e.g., diabetes, diabetes (controlled or cortisone induced or unstable), diabetes mellitus, diabetes mellitus (NIDDM, or type ii or type 2 or type 3c), latent autoimmune diabetes of adults, NIDDM, non-insulin-dependent diabetes mellitus, pancreatogenic diabetes, t2dm, t11, tii, type two, unstable diabetes
Gestational diabetes mellitus	GDM relevant terms: gestational (diabetes or diabetes mellitus)
Cardiovascular disease	atherosclerosis, coronary heart disease (including myocardial infarction and angina), peripheral vascular disease, stroke and transient ischaemic attack
Heart failure	acute cardiac failure, biventricular heart failure, cardiac failure, CCF, chronic heart failure, congestive cardiac failure, congestive heart failure, cor pulmonale, diastolic cardiac dysfunction, diastolic heart failure, heart failure, HFmrEF, HFpEF, HFrEF, Hhgh output cardiac failure, high output heart failure, hypertensive heart failure, left heart failure, left ventricular failure, LHF (left heart failure), LVF (left ventricular failure), pulmonary oedema, RHF (right heart failure), right heart failure, right ventricular failure, RVF (right ventricular failure), systolic cardiac dysfunction, systolic heart failure, ventricular diastolic dysfunction
Stroke	cerebral (haemorrhage or infarction), cerebrovascular accident, cva, haemorrhage intracerebral, haemorrhagic (cva or stroke), intracerebral (bleed or haemorrhage or haemorrhage), ischaemic stroke, lacunar infarct, lacunar stroke, migrainous stroke, migranous stroke, stroke, thrombotic stroke, visual cortex stroke
Hypertension	antihypertensive agent prescription, (blood pressure or bp) and (labile or review or unstable), hbp, high blood pressure, ht, hypertension, hypertension (controlled or diastolic or essential or isolated systolic or labile or lifestyle management or malignant or pregnancy or primary or renal or renovascular or review or unstable), pih, pregnancy induced hypertension or severe refractory hypertension
Chronic kidney disease	anaemia - chronic renal failure, capd, catheterisation of peritoneum, chronic kidney disease or CKD (all stages), chronic renal disease (all stages), chronic renal failure, chronic renal failure – hyperparathyroidism, chronic renal insufficiency, continuous ambulatory peritoneal dialysis, CRF, dialysis, haemodialysis, hemodialysis, peritoneal catherisation for dialysis, peritoneal dialysis renal dialysis or surgery - abdomen - dialysis - catheterisation
Polycystic ovary syndrome	PCOS, polycystic (ovarian syndrome or ovary or polycystic ovary syndrome), Stein-Leventhal syndrome

Source: MedicineInsight report (2018–2019)[253]

Table B2. Study variables in six datasets from the MedicineInsight database

Variable*	Label of variable	Dataset	Type of data	Interpretations
reason	Reasons	Reason for diagnosis	string (strL)	Free-text examples: "CONTUSION" "HPV IMMUNISATION"
visit_date	Visit date	Reason for diagnosis	Numeric daily date (int)	Date (DD/MM/YYYY)
age	Age	Reason for diagnosis	numeric (int)	range: 0–109
gender	Gender			0 Male 1 Female 2 Intersex/Not stated
smoke	Smoking status	Reason for diagnosis	numeric (byte)	0 Non-smoker 1 Smoker 2 Ex-smoker 3 Not stated/not recorded . missing
irsad_q	IRSAD quintile in decrescent order	Reason for diagnosis	numeric (byte)	0 Upper quintile 1 2nd upper quintile 2 Intermediate quintile 3 2nd lower quintile 4 Lower quintile 99 Not recorded . missing
gp_remote	Geographical area of GP	Reason for diagnosis	numeric (byte)	0 Major Cities 1 Inner Regional 2 Outer Regional 3 Remote 4 Very Remote . missing
gp_irsad_q	Quintiles of IRSAD in GP area	Reason for diagnosis	numeric (byte)	0 Very High 1 High 2 Middle 3 Low 4 Very Low . missing
reason	Reason for encounter	Reason for encounter	string (strL)	Free-text examples: "DENTAL DECAY" "RUNNY NOSE"
visit_date	Visit data	Reason for encounter	numeric daily date (int)	Range: 01jan2010–31dec2018
reason	Reason for prescription	Reason for prescription	string (strL)	Free-text examples: "ANXIETY" "HELICOBACTER PYLORI INFECTION"
first_name_script	First name of prescription	Reason for prescription	string (str23)	Free-text examples: "FERINJECT" "MICONAZOLE"
first_ingred_script	First ingredient prescription	Reason for prescription	string (str23)	Free-text examples: "ESCITALOPRAM" "METFORMIN"
visit_data	Visit date	Reason for prescription	numeric daily date (long)	(01jan2016,31dec2018)

Variable*	Label of variable	Dataset	Type of data	Interpretations
fasting_gluc	(max) fasting_gluc	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
f_gluc_result	Fasting glucose result in mmol/mol	Observation Pathology	numeric (double)	range: 2.7–39.9
random_gluc	Patient tested for random glucose	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
r_gluc_result	Random glucose result in mmol/mol	Observation Pathology	numeric (double)	range: 2.7–39.9
hba1c	Patient tested for HbA1c	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
hba1c_mmol_mol	HbA1c result in mmol/mol	Observation Pathology	numeric (float)	range: 15–130
hba1c_percent	HbA1c result in %	Observation Pathology	numeric (float)	range: 3.5–14
chol	Patient tested for cholesterol	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
chol_mmol_l	Cholesterol result in mmol/L	Observation Pathology	numeric (float)	range: 1.5–43.6
ldl	Patient tested for LDL	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
ldl_mmol_l	LDL result in mmol/L	Observation Pathology	numeric (float)	range: 0.1–17.6
hdl	Patient tested for HDL	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
hdl_mmol_l	HDL result in mmol/L	Observation Pathology	numeric (float)	range: 0.1–5
trig	Patient tested for triglycerides	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
trig_mmol_l	Triglycerides result in mmol/L	Observation Pathology	numeric (float)	range: 0.1–95.1
egfr	Patient tested for eGFR	Observation Pathology	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
egfr_ml_min	eGFR result in ml/min	Observation Pathology	numeric (float)	range: 0–198.2
observation_date	Observation date	Observation	numeric daily date (long)	01jan2010–31dec2018
bp	Patient tested for blood pressure (SYS+DIAS)	Observation	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
bp_sys	Systolic blood pressure-mean in the same date	Observation	numeric (double)	range: 60–250
bp_dias	Diastolic blood pressure-mean in the same date	Observation	numeric (double)	range: 40–140
history_diab	Personal history of diabetes	Observation	numeric (byte)	0 No 1 Yes

Variable*	Label of variable	Dataset	Type of data	Interpretations
result_date	Result date	Pathology results	numeric daily date (int)	01jan2015–31dec2018
glucose	Patient tested for Glucose	Pathology results	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
ogtt_gluc	OGTT tested	Pathology results	numeric (float)	0 No 1 Tested no valid results 2 Tested valid results
gluc_ogtt_mmol_l	OGTT glucose result in mmol/mol	Pathology results	numeric (float)	range: 2.7–35.400002
cclear	Patient tested for creatinine clearance	Pathology results	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
cclear_ml_min	Creatinine clearance result in mL/min	Pathology results	numeric (float)	range: 11.49–198
acr	Patient tests for albumin/ creatinine ratio	Pathology results	numeric (byte)	0 No 1 Tested no valid results 2 Tested valid results
acr_mg_mmol	ACR result in mg/mmol	Pathology results	numeric (float)	range: 0–1456
script_date	Date of prescription/consultation	Script items	numeric daily date (int)	01jan2010–31dec2018
medicine_active_ingredient	Medicine active ingredient	Script items	string (strL)	Free-text examples: "CELECOXIB" "FENTANYL"
medicine_name	Medicine name	Script items	string (strL)	Free-text examples: "CORDARONE" "IBILEX"
year	Year of observation/ consultation/ prescription/result	Observation DEP datasets	numeric (int)	range: (2010,2018) Date (YYYY)
como_cvd	History of CVD	DEP datasets	string (strL)	Free text
como_heart	History of heart failure			Free text
como_dys	History of dyslipidemia			Free text
como_ihd	History of ischaemic heart disease			Free text
como_hpt	History of hypertension	DEP datasets	string (strL)	Free text
como_ckd	History of CKD	DEP datasets	string (strL)	Free text

HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test; HDL: High-density lipoprotein; LDL: Low-density lipoprotein; eGFR: Estimated glomerular filtration rate; GFR: Glomerular filtration rate; ACR: Albumin-to-creatinine ratio; BG: Blood glucose; BP: blood pressure; IRSAD: Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular disease; CKD: Chronic kidney disease.
DEP datasets: 'diagnosis', 'reason for encounter', 'reason for prescription' datasets.
Description refers to a summary of MedicineInsight data tables and fields.[200]
*All datasets contain a unique patient ID (patientid) and a unique practice ID (practiceid); other patient-related information is recorded in a separate dataset, including Patient ID, Practice ID, Aboriginal status, Sex, Smoking status, Deceased, Remoteness and IRSAD of practice, Remoteness and IRSAD of patients.

Ethical exemption letter

THE UNIVERSITY of ADELAIDE

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Our reference 35601

25 January 2022

Dr Soumya
Medical Specialties

Dear Dr Soumya

PROJECT TITLE: Do patients with pre-diabetes managed with Metformin achieve a better glycaemic control? A national study using general practice data

The ethics application for the above project has been reviewed by the Secretariat, Human Research Ethics Committee and is deemed to meet the requirements of the *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018)* involving no more than negligible risk for research participants.

According to provisions within the *National Statement*, the University of Adelaide classifies research that carries only negligible risk and involves the use of existing data that contains only non-identifiable data about human beings, to be exempt from ethical review. The research conducted as part of this project meets these requirements and has been authorised as exempt from requiring ethical review.

Yours sincerely,

Miss Sarah Harman
Secretary

The University of Adelaide

Appendix C. Supplementary Materials for Chapter 4

Table C1. Definitions of recorded diabetes, recorded prediabetes, and unrecorded diabetes/prediabetes

Outcomes	Definitions
A) Recorded diabetes	(1) Have a diagnosis of 'diabetes mellitus' in two fields (either in the diagnosis, reason for encounter, or reason for prescription fields) or in two different occasions in the same field, OR; (2) They were prescribed insulin (ATC code A10A) AND/OR an oral antidiabetic medication (ATC code A10B, excepted metformin): glibenclamide, gliclazide, glimepiride, glipizide, acarbose, pioglitazone, alogliptin, linagliptin, saxagliptin, sitagliptin, vildagliptin, dulaglutide, exenatide, dapagliflozin, empagliflozin, ertugliflozin, OR; (3a) Have a diagnosis of 'diabetes mellitus' in one field (either in the diagnosis, reason for encounter, or reason for prescription fields), AND were prescribed metformin (in absence of PCOS diagnosis); (3b) Have a diagnosis of 'diabetes mellitus' in one field only (either in the diagnosis, reason for encounter, or reason for prescription fields), AND have one recorded laboratory test with raised glucose levels within the last 24 months (i.e., fasting plasma glucose ≥7.0 mmol/L; random plasma glucose ≥11.1 mmol/L; HbA1c ≥48 mmol/mol [≥6.5%]) or a OGTT ≥11.1 mmol/L.
B) Unrecorded diabetes	(1) They do not satisfy the criteria presented in 'A' for diagnosed diabetes, AND; (2) Have at least two recorded laboratory tests with raised glucose levels within 24 months (i.e., fasting plasma glucose ≥7.0 mmol/L; random plasma glucose ≥11.1 mmol/L; HbA1c ≥48 mmol/mol [≥6.5%]) or a OGTT ≥11.1 mmol/L. Note: If the patient had only one altered laboratory test compatible with diabetes, but no 'diabetes diagnosis' or a prescription for diabetes, they will be classified and reported as an 'incomplete diagnosis (insufficient data)'.
C) Recorded prediabetes	(1) They do not satisfy the criteria presented in 'A' or 'B' for diabetes, AND; (2) Have a diagnosis of 'prediabetes' in two fields (either in the diagnosis, reason for encounter, or reason for prescription fields) or in two different occasions in the same field, OR; (3a) Have a diagnosis of 'prediabetes' in one field (either in the diagnosis, reason for encounter, or reason for prescription fields), AND were prescribed metformin (in absence of PCOS diagnosis); (3b) Have a diagnosis of 'prediabetes' in one field only (either in the diagnosis, reason for encounter, or reason for prescription fields), AND have one recorded laboratory test indicating prediabetes within the last 24 months (i.e., fasting blood glucose 6.1–6.9 mmol/L and/or a OGTT between 7.8 and 11.1 mmol/L OR HbA1c between 42 and 47 mmol/mol [6.0–6.4%]).
D) Unrecorded prediabetes	(1) They do not satisfy the criteria presented in 'C' for diagnosed prediabetes, AND; (2) Have at least two laboratory results recorded within the last 24 months indicating prediabetes (i.e., fasting blood glucose 6.1–6.9 mmol/L and/or OGTT between 7.8 and 11.1 mmol/L OR HbA1c between 42 and 47 mmol/mol [6.0–6.4%]). Note: If the patient had only one altered laboratory test compatible with prediabetes and no prediabetes diagnosis, they will be classified and reported as 'incomplete diagnosis (insufficient data)'.

ATC: Anatomical Therapeutic Chemical Classification; PCOS: Polycystic ovary syndrome; HbA1c: Haemoglobin A1c; OGTT: Oral glucose tolerance test. Study period is 2016–2018.

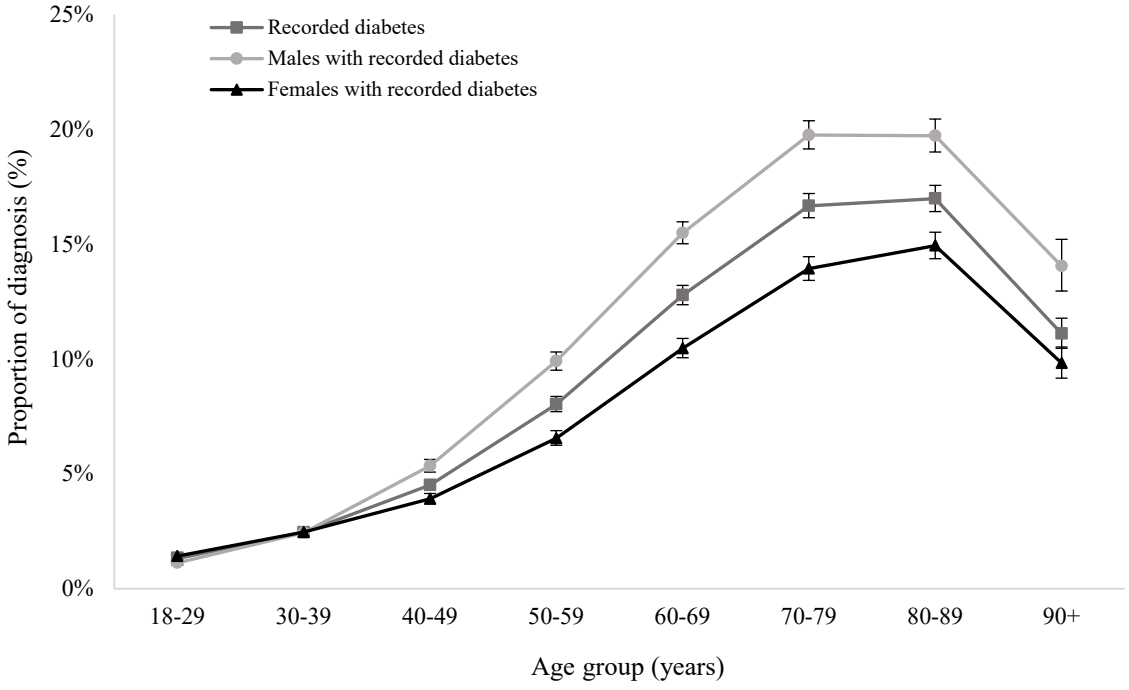
Table C2. Calculation of the Australian Type 2 Diabetes Risk (AUSDRISK) Assessment Tool score using variables available in the MedicineInsight database

Variables in MedicineInsight	Categories and points
Age	Under 35 years [0 points] 35–44 years [2 points] 45–54 years [4 points] 55–64 years [6 points] 65–109 years [8 points]
Gender	Female [0 points] Male [3 points] Not recorded [0 points]
Aboriginal/Torres Strait Islander	No [0 points] Yes [2 points] Not recorded [0 points]
High blood pressure	No record [0 points] Yes (at least one record) [6 points]
Antidiabetic medication	No record [0 points] Yes (at least one record) [2 points]
Smoking status	Non-smoker [0 points] Ex-smoker [0 points] Smoker [2 points] Not recorded [0 points]
Total points	The sum of each variable, totalling 0 to 23

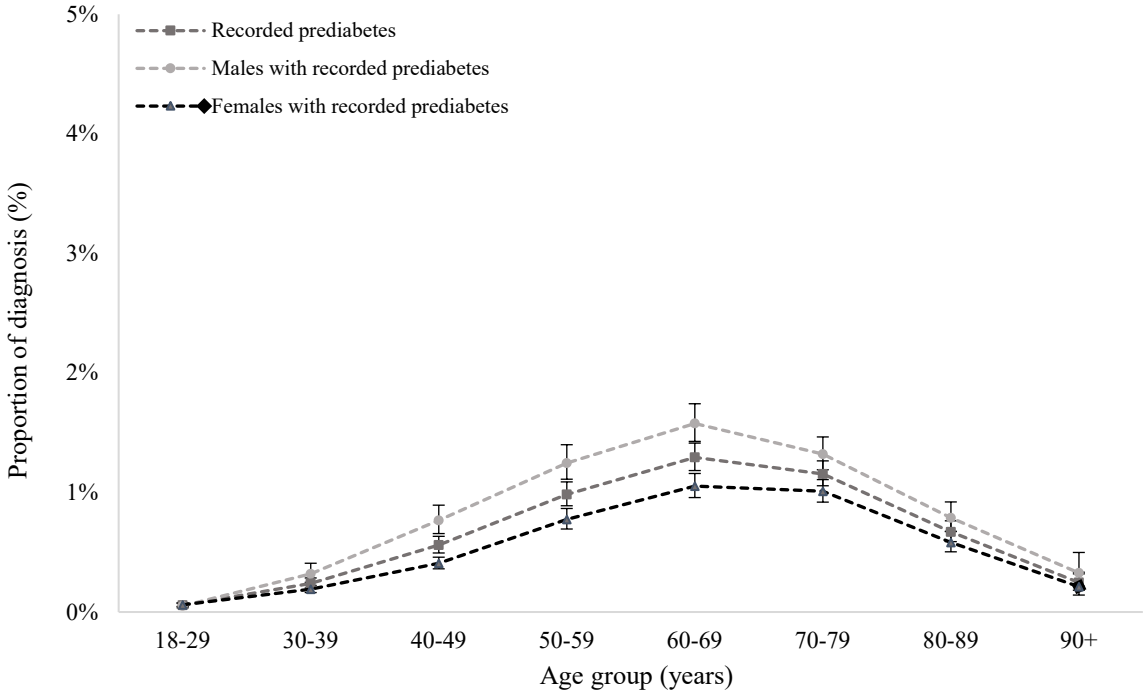
Table C3. Sociodemographic profile of the study population (regular patients aged 18+years) with 95% CI according to diabetes diagnosis status (2016–2018)

Characteristics	All regular patients, aged 18+ years		Recorded diabetes		Recorded prediabetes		Unrecorded diabetes/prediabetes	
Gender	n	%(95%CI)	n	%(95%CI)	n	%(95%CI)	n	%(95%CI)
Male	628,040	41.9 (41.4–42.3)	75,976	52.2 (51.6–52.9)	6,485	54.8 (53.1–56.5)	2,713	53.7 (52.1–55.2)
Female	893,541	58.1 (57.7–58.6)	69,762	47.8 (47.1–48.4)	5,566	45.2 (43.5–46.9)	2,398	46.3 (44.8–47.9)
Age group								
18–29	220,747	17.9 (17.2–18.7)	3,689	3.1 (2.9–3.4) [a**]	157	1.5 (1.2–1.9) [b**]	20	0.5 (0.3–0.8)
30–39	224,571	17.1 (16.4–17.8)	6,863	5.6 (5.2–6.0) [a**]	633	6.2 (5.3–7.2) [b**]	116	2.8 (2.2–3.6)
40–49	236,642	16.1 (15.7–16.4)	13,036	9.7 (9.2–10.1) [a**]	1,511	13.6 (12.4–14.7) [b**]	240	5.4 (4.7–6.3)
50–59	253,499	16.0 (15.8–16.3)	24,218	17.1 (16.7–17.6) [a**]	2,749	23.8 (22.8–24.9) [b**]	673	14.0 (13.0–15.1)
60–69	255,565	15.1 (14.6–15.5)	37,558	25.6 (25.2–26.0) [a*]	3,596	29.4 (28.3–30.6)	1,378	27.5 (26.2–28.9)
70–79	204,651	11.2 (10.6–11.7)	38,140	24.8 (24.1–25.4) [a**]	2,563	19.5 (18.1–20.9) [b**]	1,572	29.6 (28.3–31.0)
80–89	100,831	5.5 (5.2–5.8)	18,938	12.4 (11.9–12.9) [a**]	753	5.6 (5.0–6.2) [b**]	921	17.1 (15.9–18.4)
90+	20,461	1.1 (1.0–1.2)	2,476	1.7 (1.6–1.8) [a**]	58	0.4 (0.3–0.6) [b**]	144	3.0 (2.4–3.7)
Practice remoteness								
Major cities	949,538	64.5 (59.8–68.8)	85,695	60.3 (55.3–65.0)	7,611	64.5 (58.4–70.1)	2,889	57.9 (51.9–63.6)
Inner regional	377,329	23.5 (19.9–27.5)	39,506	26.2 (22.2–30.7)	2,949	23.7 (19.1–29.1)	1,437	27.2 (22.2–32.9)
Outer regional/remote	188,482	12.0 (9.6–15.1)	19,877	13.5 (10.7–16.8)	1,439	11.8 (8.8–15.7)	764	14.9 (11.6–19.0)
Practice IRSAD quintile								
Very high	380,447	25.3 (22.1–28.8)	27,275	19.1 (16.4–22.0)[a**]	2,757	23.0 (19.2–27.3)	1,170	23.1 (19.3–27.4)
High	283,925	19.4 (17.2–21.8)	24,121	17.0 (14.9–19.3)	2,282	19.3 (16.3–22.7)	859	17.3 (14.9–20.0)
Middle	351,266	22.8 (20.1–25.8)	36,259	24.6 (21.5–27.9)	2,822	23.2 (19.5–27.5)	1,195	23.1 (19.4–27.2)
Low	249,024	16.3 (14.0–18.8)	26,979	18.3 (15.8–21.1)	1,982	16.2 (13.1–20.0)	798	15.9 (13.1–19.1)
Very low	246,478	15.5 (13.0–18.3)	30,098	20.3 (17.2–23.8)	2,130	17.6 (14.1–21.8)	1,062	20.1 (16.3–24.5)

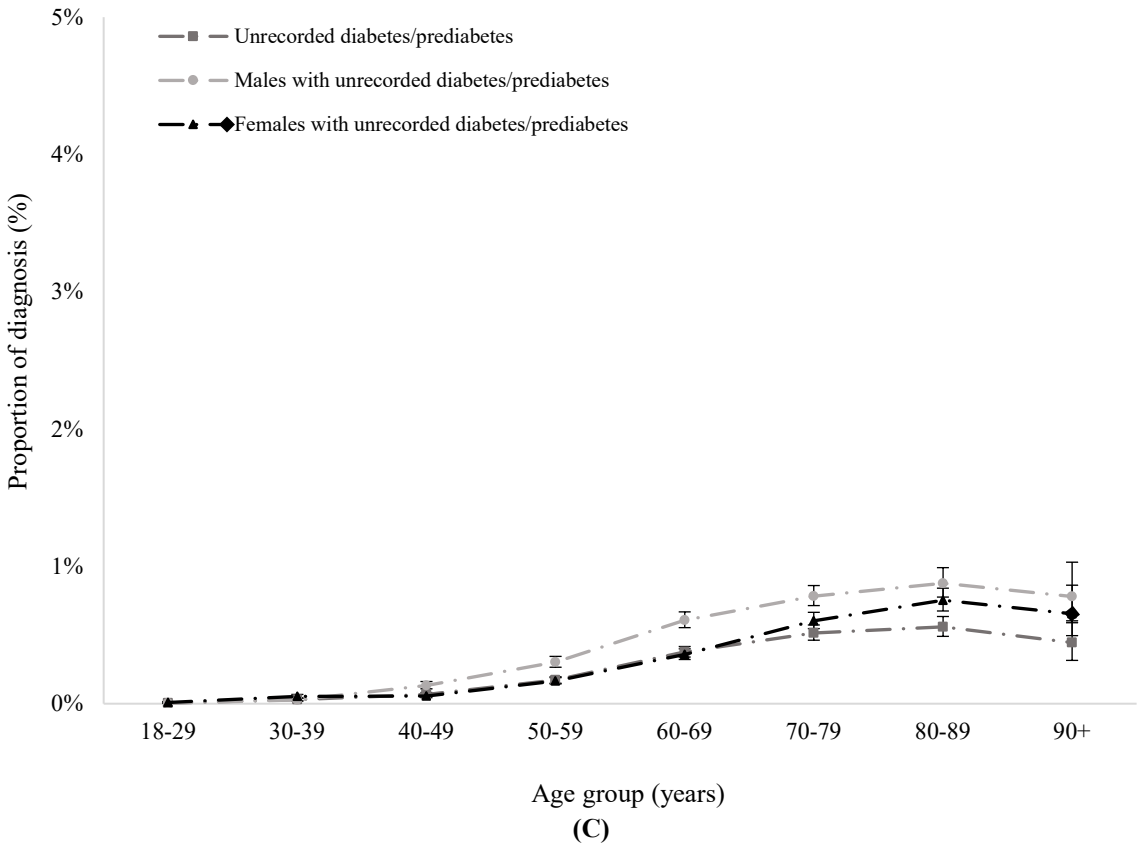
CI: Confidence interval; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.
A higher IRSAD score indicates the practice is located in a more advantaged area.
(a) P-value for the difference between people with recorded diabetes and unrecorded diabetes/prediabetes; (b) P-value for the difference between people with recorded prediabetes and unreported diabetes/prediabetes; P-value *<0.01, **<0.001; (c) Practice IRSAD quintile includes 0.8% of missing data.


Recorded diabetes
Males with recorded diabetes
Females with recorded diabetes
25%
20%
15%
10%
5%
0%
Proportion of diagnosis (%)
18-29
30-39
40-49
50-59
60-69
70-79
80-89
90+
Age group (years)

(A)

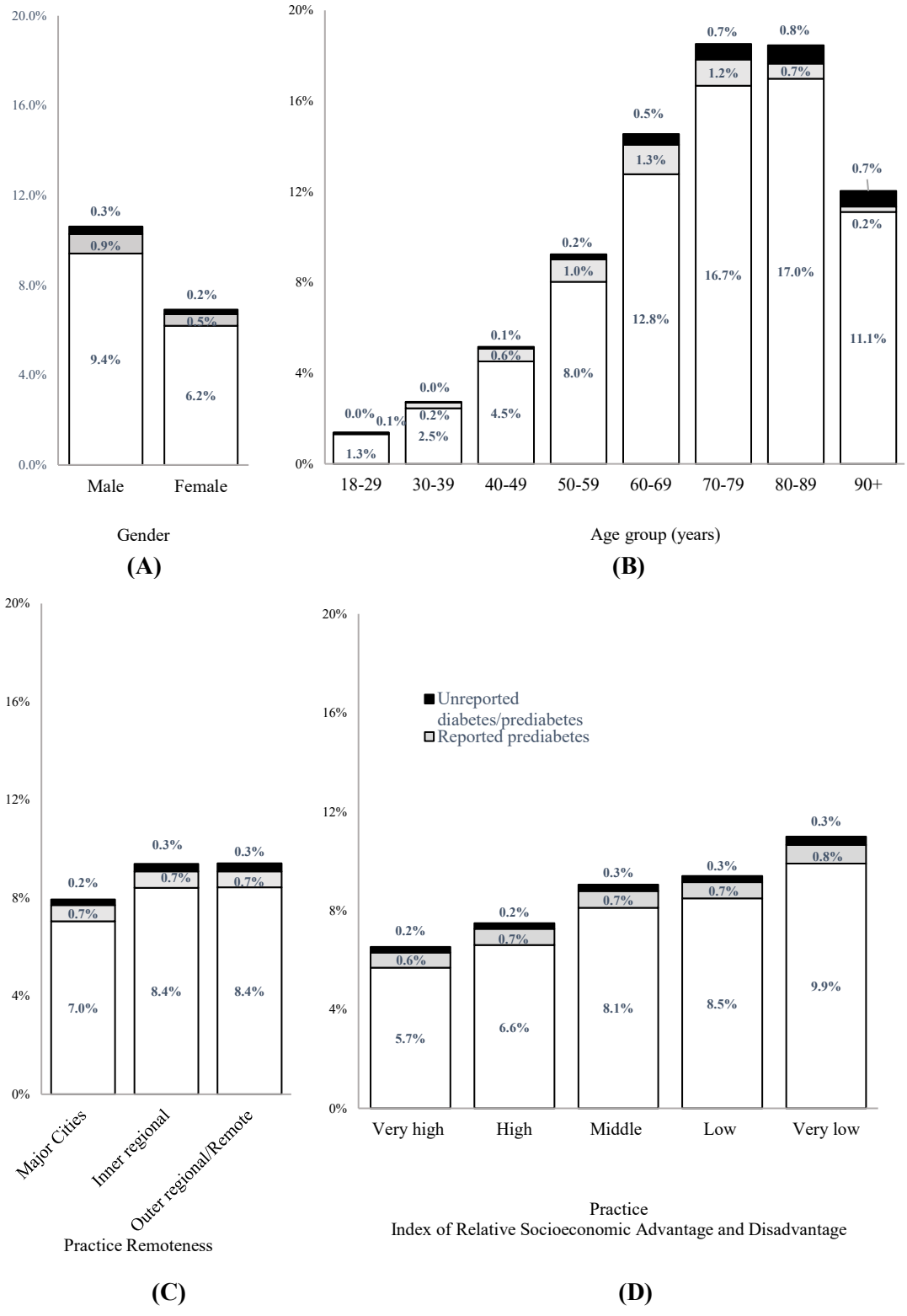

Recorded prediabetes
Males with recorded prediabetes
Females with recorded prediabetes
5%
4%
3%
2%
1%
0%
Proportion of diagnosis (%)
18-29
30-39
40-49
50-59
60-69
70-79
80-89
90+
Age group (years)

（B）



(C)

Figure C1. Prevalence of recorded diabetes (A), recorded prediabetes (B), and unrecorded diabetes/prediabetes (C) among all adults aged 18+years, by age group and gender, Australia, 2016–2018



IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

Figure C2. Proportion of recorded diabetes, recorded prediabetes, and unrecorded diabetes/prediabetes among regular patients aged 18+ years, by gender (A), age (B), practice remoteness (C), and practice IRSAD (D), Australia, 2016–2018

Appendix D. Supplementary Materials for Chapter 5

Table D1. Proportion† of patients with different blood glucose parameters monitored in 2018 among those with past (2015–2016) or newly recorded diabetes (2017)

Clinical parameters monitored	Patients monitored among those with past recorded diabetes (n=101,875) % (95%CI)	Patients monitored among those with newly recorded diabetes (n=9,236) % (95% CI)
Number of different blood glucose tests monitored§		
0	39.8 (37.5–42.0)	45.5 (43.2–47.9)
1	23.8 (22.4–25.2)	21.7 (20.3–23.1)
2	27.5 (25.7–29.2)	25.2 (23.5–27.0)
3	9.0 (7.9–10.1)	7.5 (6.4–8.6)

95%CI: 95% Confidence interval

† Results adjusted for differences between these two groups in terms of practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, or depressive symptoms using logistic regression models.

§ Considering either HbA1c, fasting blood glucose and/or random blood glucose.

Table D2. Adjusted odds ratio† of patients who had all three parameters (HbA1c, blood pressure, and total cholesterol) monitored, among those with past (2015–2016) or newly recorded diabetes (2017), according to sociodemographic and clinical characteristics

All three parameters monitored	Patients monitored among those with past recorded diabetes (n=101,875) Odds ratio (95%CI)	Patients monitored among those with newly recorded diabetes (n=9,236) Odds ratio (95%CI)
Practice characteristics		
Geographical area of GP		
Major cities	Ref	Ref
Inner regional	1.04 (0.79–1.37)	1.11 (0.86–1.44)
Outer regional/remote/very remote	1.64 (1.22–2.19)	1.64 (1.22–2.20)
GP IRSAD		
More disadvantaged	Ref	Ref
Middle	0.96 (0.72–1.28)	0.81 (0.62–1.05)
More advantaged	0.90 (0.70–1.17)	0.95 (0.74–1.22)
Patient's characteristics		
Gender		
Female	Ref	Ref
Male	1.08 (1.04–1.12)	1.26 (1.13–1.40)
Age group (years)		
18–39	Ref	Ref
40–64	2.72 (2.50–2.97)	3.15 (2.60–3.82)
65+	3.05 (2.76–3.38)	3.87 (3.15–4.76)
Smoking status		
Non-smoker or ex-smoker	Ref	Ref
Smoker	0.91 (0.86–0.96)	0.97 (0.82–1.12)
History of hypertension		
No	Ref	Ref
Yes	1.11 (1.04–1.18)	1.17 (1.04–1.30)
History of CVD		
No	Ref	Ref
Yes	0.97 (0.92–1.02)	0.98 (0.84–1.13)
History of dyslipidaemia		
No	Ref	Ref
Yes	1.26 (1.18–1.35)	1.23 (1.09–1.39)
History of CKD		
No	Ref	Ref
Yes	0.91 (0.81–1.02)	0.84 (0.62–1.14)
History of liver disease		
No	Ref	Ref
Yes	1.02 (0.85–1.22)	0.93 (0.53–1.63)
History of depressive syndrome		
No	Ref	Ref
Yes	0.89 (0.84–0.94)	0.91 (0.81–1.03)

GP: General practice; Ref: Reference group; 95%CI: 95% Confidence interval; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular disease (including heart failure, ischemic heart disease, and stroke); CKD: Chronic kidney disease.

† Adjusted odds ratio of patients who had all three parameters (HbA1c, blood pressure, and total cholesterol) monitored based on logistic regression models that considered differences among patients with past or newly

recorded diabetes adjusted for practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, or depressive symptoms.

Table D3. Adjusted proportion† of the combination of clinical parameters controlled in 2018 among patients with past (2015-2016) or newly recorded diabetes (2017) and available results for all three parameters (HbA1c, blood pressure, and LDL-C)

	Past recorded diabetes (n= 34,476)		Newly recorded diabetes (n= 2,521)		
	n	**% (95%CI)**	**N**	**% (95%CI)**	Adjusted† odds ratio (95%CI)
None controlled	2,784	8.1 (7.6–8.6)	117	4.6 (3.8–5.4)	0.33 (0.27–0.40)
Only HbA1c controlled	3,223	9.3 (8.9–9.8)	428	16.9 (15.3–18.6)	1.05 (0.92–1.20)
Only BP controlled	5,373	15.6 (15.0–16.2)	231	9.2 (8.0–10.3)	0.34 (0.29–0.39)
Only LDL-C controlled	2,224	6.5 (6.1–6.8)	50	2.0 (1.5–2.5)	0.18 (0.13–0.23)
HbA1c and BP controlled	6,867	19.9 (19.2–20.6)	871	34.5 (32.5–36.6)	base outcome
HbA1c and LDL-C controlled	2,518	7.3 (6.9–7.7)	173	6.9 (5.7–8.0)	0.54 (0.44–0.65)
BP and LDL-C controlled	5,144	14.9 (14.4–15.4)	131	5.2 (4.2–6.2)	0.20 (0.16–0.24)
All controlled	6,343	18.4 (17.7–19.1)	520	20.6 (18.9–22.4)	0.64 (0.56–0.72)

95%CI: 95% Confidence interval; HbA1c: Haemoglobin A1c; BP: Blood pressure; LDL-C: Low-density lipoprotein cholesterol; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular disease (including heart failure, ischemic heart disease, and stroke); CKD: Chronic kidney disease.

† Adjusted proportion of the most frequent combination of clinical parameters controlled in 2018 based on multinomial logistic regression models adjusted for practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, or depressive symptoms.

Table D4. Adjusted odds ratio† of distribution of patients with all three clinical parameters controlled (HbA1c, blood pressure, and total cholesterol) according to sociodemographic and clinical characteristics among those with past (2015-2016) or newly recorded diabetes (2017)

Variables	'All-controlled' among past recorded diabetes (n=40,008) Odds ratio (95%CI)	'All-controlled' among newly recorded diabetes (n=2,912) Odds ratio (95%CI)
Practice characteristics		
Geographical area of GP		
Major Cities	Ref	Ref
Inner regional	1.05 (0.93–1.20)	1.12 (0.86–1.45)
Outer/Remote/Very Remote	0.93 (0.80–1.10)	0.94 (0.70–1.27)
GP IRSAD		
More disadvantaged	Ref	Ref
Middle	1.00 (0.87–1.14)	1.08 (0.82–1.41)
More advantaged	0.99 (0.80–1.09)	0.81 (0.63–1.06)
Patient's characteristics		
Gender		
Female	Ref	Ref
Male	1.50 (1.41–1.58)	1.77 (1.44–2.16)
Age group (years)		
18–39	Ref	Ref
40–64	1.78 (1.38–2.30)	1.25 (0.76–2.05)
65+	3.31 (2.58–4.25)	2.09 (1.26–3.49)
Smoking status		
Non-smoker or ex-smoker	Ref	Ref
Smoker	0.91 (0.83–1.00)	1.10 (0.83–1.44)
History of hypertension		
No	Ref	Ref
Yes	0.89 (0.84–0.95)	0.98 (0.81–1.19)
History of CVD		
No	Ref	Ref
Yes	1.38 (1.28–1.47)	2.42 (1.81–3.22)
History of dyslipidaemia		
No	Ref	Ref
Yes	1.07 (0.99–1.15)	1.16 (0.93–1.43)
History of CKD		
No	Ref	Ref
Yes	0.97 (0.85–1.11)	0.86 (0.42–1.77)
History of liver disease		
No	Ref	Ref
Yes	1.29 (0.92–1.80)	3.30 (1.33–8.19)
History of depressive syndrome		
No	Ref	Ref
Yes	0.91 (0.84–1.00)	0.87 (0.67–1.11)

GP: General practitioner; Ref: Reference group; 95%CI: 95% Confidence interval; HbA1c: Hemoglobin A1c; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular disease (including heart failure, ischemic heart disease, and stroke); CKD: Chronic kidney disease.

† 'All-controlled' are those patients with HbA1c≤7.0%, BP≤140/90mmHg, and total cholesterol <4.0mmol/L. Adjusted odds ratio of patients who had each clinical parameter controlled based on logistic regression models adjusted for practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, or depressive symptoms.

Table D5. Adjusted odds ratio† of distribution of patients with all three clinical parameters controlled (HbA1c, blood pressure, and LDL-C) according to sociodemographic and clinical characteristics among those with past (2015-2016) or newly recorded diabetes (2017)

Variables	'All-controlled' among past recorded diabetes (n=34,475) Odds ratio (95%CI)	'All-controlled' among newly recorded diabetes (n=2,521) Odds ratio (95%CI)
Practice characteristics		
Geographical area of GP		
Major cities	Ref	Ref
Inner regional	1.11 (0.98–1.26)	1.14 (0.88–1.50)
Outer/remote/very remote	1.05 (0.90–1.21)	1.07 (0.77–1.49)
GP IRSAD		
More disadvantaged	Ref	Ref
Middle	1.02 (0.89–1.17)	0.80 (0.58–1.12)
More advantaged	1.03 (0.92–1.16)	0.94 (0.70–1.27)
Patient's characteristics		
Gender		
Female	Ref	Ref
Male	1.18 (1.11–1.25)	1.23 (1.00–1.51)
Age group (years)		
18-39	Ref	Ref
40-64	2.29 (1.67–3.14)	2.18 (1.13–4.19)
65+	4.38 (3.20–5.98)	3.80 (1.97–7.35)
Smoking status		
Non-smoker or ex-smoker	Ref	Ref
Smoker	0.94 (0.84–1.04)	1.15 (0.84–1.56)
History of hypertension		
No	Ref	Ref
Yes	0.89 (0.84–0.95)	0.97 (0.80–1.17)
History of CVD		
No	Ref	Ref
Yes	1.33 (1.22–1.43)	2.09 (1.54–2.83)
History of dyslipidaemia		
No	Ref	Ref
Yes	1.10 (1.01–1.19)	1.40 (1.11–1.76)
History of CKD		
No	Ref	Ref
Yes	1.05 (0.91–1.20)	1.19 (0.62–2.30)
History of liver disease		
No	Ref	Ref
Yes	1.14 (0.78–1.68)	3.37 (1.08–10.57)
History of depressive syndrome		
No	Ref	Ref
Yes	0.94 (0.87–1.03)	0.87 (0.67–1.13)

HbA1c: Haemoglobin A1c; LDL-C: Low-density lipoprotein cholesterol; GP: General practitioner; Ref: Reference group; 95%CI: 95% Confidence interval; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; CVD: Cardiovascular disease (including heart failure, ischemic heart disease, and stroke); CKD: Chronic kidney disease.

† 'All-controlled' are those patients with HbA1c≤7.0%, BP≤140/90mmHg, and total cholesterol <4.0mmol/L. Adjusted odds ratio of patients who had each clinical parameter controlled based on logistic regression models adjusted for practice characteristics (remoteness, IRSAD quintiles), patient sociodemographics (gender, age), and clinical characteristics (smoking status, history of hypertension, CVD, CKD, dyslipidaemia, liver disease, or depressive symptoms.

Appendix E. Supplementary Materials for Chapter 6

Table E1. Comparison of characteristics in the eligible patients and study sample with newly recorded diabetes (crude results)

	Patients with newly recorded diabetes† (N=25,897) n (%)	Patients with newly recorded diabetes with glycaemic outcome‡ (N=18,856) n (%)
Proportion of study cohort		
No treatment within 12 months	13,700 (52.9)	9,632 (51.1)
Early treatment (<3 months)	9,710 (37.5)	7,321 (38.8)
Timely treatment (3–6months)	962 (3.7)	733 (3.9)
Delayed treatment (6–12months)	1,525 (5.9)	1,170 (6.2)
Practice characteristics		
Geographical area of GP		
Major cities	14,117 (54.5)	9,938 (52.7)
Inner regional	7,903 (30.5)	5,703 (30.2)
Outer regional/remote/very remote	3,877 (15.0)	3,215 (17.1)
IRSAD quintiles		
More disadvantaged (lower two quintiles)	10,427 (40.3)	7,926 (42.0)
Middle	6,418 (24.8)	4,472 (23.7)
More advantaged (upper two quintiles)	8,954 (3.6)	6,395 (33.9)
Patient demographic characteristics		
Gender: Male	13,548 (52.3)	9,896 (52.5)
Age, mean ± SD	64.0 ± 11.4	64.4 ± 11.4
Patient IRSAD		
More disadvantaged (lower two quintiles)	10,691 (41.3)	8078 (42.8)
Middle	6,469 (25.0)	4570 (24.2)
More advantaged (upper two quintiles)	8,554 (33.0)	6076 (32.2)
Aboriginal and/or Torres Strait Islander, n (%) Yes	605 (2.3)	458 (2.4)
Smoking status, n (%) Yes	2,830 (10.9)	2,016 (10.7)
Crude baseline BMI (kg/m^2), mean (SD)	32.8 (6.9)	32.8 (6.9)
Patient clinical characteristics		
Baseline HbA1c (%), mean (SD)	7.0 (1.5)	7.0 (1.5)
Baseline FBG (mmol/L), mean (SD)	7.7 (2.7)	7.8 (2.7)
History of hypertension, n (%) Yes	3,880 (15.0)	2,794 (14.8)
History of dyslipidaemia, n (%) Yes	1,092 (4.2)	804 (4.3)
History of CVD, n (%) Yes	658 (2.5)	483 (2.6)
History of CKD, n (%) Yes	65 (0.3)	40 (0.2)
Antipsychotics, n (%) Yes	962 (3.7)	720 (3.8)

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; QR: Interquartile range; SD: Standard deviation; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease; BMI: Body mass index.

† Eligible patients: regular patients (40+ years) with newly recorded diabetes diagnosis, N=25,897.

‡ Study sample: regular patients (40+ years) with newly recorded diabetes who had at least one HbA1c or FBG measure at 3–24 months after diagnosis/exposure, N=18,856.

Table E2. Baseline characteristics of the eligible patients with newly recorded diabetes (N=25,897) (imputed data)

	No treatment within 12 months n=13,700 %	Early treatment (<3 months) n=9,710 %	Timely treatment (3–6 months) n=962 %	Delayed treatment (6–12 months) n=1,525 %
Practice characteristics				
Geographical area of GP				
Major cities	56.8	51.8	52.9	52.7
Inner regional	30.8	29.3	33.3	33.6
Outer regional/remote/very remote	12.4	18.9	13.8	13.7
GP IRSAD				
More disadvantaged (lower two quintiles)	36.9	45.2	39.7	39.3
Middle	25.0	23.9	26.7	27.3
More advantaged (upper two quintiles)	37.8	30.4	33.2	32.9
Patient demographic characteristics				
Gender: Male	50.8	54.8	49.9	51.9
Age, mean ± SE	65.7 ± 0.1	62.0 ± 0.1	62.5 ± 0.4	62.2 ± 0.3
Patient IRSAD				
More disadvantaged (lower two quintiles)	38.3	45.6	41.2	40.4
Middle	24.9	24.6	25.9	27.3
More advantaged (upper two quintiles)	36.2	28.9	32.3	31.7
Aboriginal and/or Torres Strait Islander (% Yes)	1.9	2.9	3.1	2.5
Smoking status (% Yes)	9.0	13.3	12.5	11.9
Patient clinical characteristics				
Baseline BMI (kg/m^2), mean ± SE	31.9 ± 0.07	33.8 ± 0.08	33.4 ± 0.26	33.4 ± 0.22
Baseline HbA1c (%), mean ± SE	6.4 ± 0.01	7.6 ± 0.03	7.1 ± 0.07	6.8 ± 0.05
Baseline FBG (mmol/L), mean ± SE	6.8 ± 0.03	8.8 ± 0.06	7.9 ± 0.21	7.4 ± 0.10
History of hypertension (% Yes)	14.2	16.1	12.3	16.1
History of dyslipidaemia (% Yes)	3.8	4.8	3.3	4.6
History of CVD (% Yes)	2.4	2.6	2.9	2.8
History of CKD (% Yes)	0.4	0.1	0.2	0.1
Antipsychotics (% Yes)	3.0	4.5	4.5	4.6

CI: Confidence interval; HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; SD: Standard deviation; SE: Standard error; BMI: Body mass index; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease.

Table E3. Baseline characteristics of the regular patients (aged 40+ years) with newly recorded diabetes and with baseline glycaemic measure and follow-up HbA1c data at each time point (N=13,427)* (imputed data)

	No treatment with metformin within 12 months (unexposed) (%)				Early treatment (metformin script at <3 months) (%)				Timely treatment (metformin script at 3–6 months) (%)				Delayed treatment (metformin script at 6–12 months) (%)			
Follow-up months with HbA1c outcome	3–6 n= 2,450	6–12 n= 4,234	12–18 n= 2,578	18–24 n= 4,839	3–6 n= 2,757	6–12 n= 3,970	12–18 n= 2,325	18–24 n= 4,022	3–6 n= 360	6–12 n= 398	12–18 n= 241	18–24 n= 411	3–6 n= 222	6–12 n= 682	12–18 n= 397	18–24 n= 634
Practice characteristics																
Geographical area of GP																
Major cities	53.3	54.7	53.2	54.8	45.6	46.5	45.2	46.4	49.4	49.7	48.5	48.4	51.8	49.9	46.1	49.5
Inner regional	32.3	29.3	30.2	29.2	30.3	29.9	31.7	29.7	31.7	31.7	32.0	31.9	28.8	31.7	36.0	33.3
Outer regional/remote/very remote	14.4	16.0	16.6	16.0	24.1	23.6	23.0	23.9	18.9	18.6	19.5	19.7	19.4	18.5	17.9	17.2
GP IRSAD																
More disadvantaged	38.0	37.4	36.9	38.0	46.9	47.0	46.9	47.7	45.0	41.2	42.7	43.8	41.9	41.2	37.5	40.0
Middle	25.7	25.9	28.2	26.0	23.8	23.6	23.3	23.5	24.4	25.6	25.3	24.3	25.7	25.2	28.2	28.2
More advantaged	35.8	36.5	34.8	35.8	28.9	29.1	29.4	28.4	30.3	32.2	31.1	31.4	32.4	33.3	34.3	31.7
Patient demographic characteristics																
Gender: Male	51.5	51.2	50.3	52.6	53.9	55.1	56.1	54.9	54.4	50.5	51.9	52.8	52.3	52.3	51.1	54.6
Age, mean ± SE	66.3 ±0.2	66.5 ±0.2	66.4 ±0.2	66.0 ±0.2	62.3 ±0.2	62.3 ±0.2	62.5 ±0.2	62.1 ±0.2	62.1 ±0.6	63.0 ±0.6	61.9 ±0.7	62.4 ±0.6	63.6 ±0.7	62.1 ±0.4	62.2 ±0.6	62.3 ±0.4
Patient IRSAD																
More disadvantaged	38.5	39.0	38.1	39.0	46.3	47.1	46.8	47.5	45.6	44.7	47.7	45.3	40.5	41.9	38.5	40.7
Middle	25.9	26.0	28.1	26.6	24.7	24.0	24.9	24.6	25.3	25.1	22.4	25.1	25.2	25.0	27.5	29.2
More advantaged	35.1	34.6	33.5	34.0	28.0	28.0	27.1	27.0	28.6	29.6	29.5	29.2	33.8	32.2	33.2	29.7
Aboriginal and/or Torres Strait Islander (% Yes)	1.7	1.5	1.7	1.6	2.6	3.0	2.9	3.0	3.6	3.5	5.0	2.4	1.4	2.6	2.0	2.4
Smoking status (% Yes)	7.7	7.8	7.6	7.9	13.4	12.6	13.0	13.3	11.7	11.1	12.0	11.7	7.2	11.4	11.3	11.7
Patient clinical characteristics																
Baseline BMI (kg/m^2), mean ± SE	31.8 ±0.1	31.8 ±0.1	32.0 ±0.1	32.0 ±0.1	33.5 ±0.2	33.8 ±0.1	33.8 ±0.2	33.8 ±0.1	33.3 ±0.4	33.3 ±0.4	33.5 ±0.5	33.2 ±0.4	33.2 ±0.5	33.6 ±0.3	33.4 ±0.4	33.7 ±0.3
Baseline HbA1c (%), mean ± SE	6.4 ±0.0	6.4 ±0.0	6.4 ±0.0	6.4 ±0.1	7.8 ±0.0	7.7 ±0.0	7.6 ±0.1	7.7 ±0.0	7.2 ±0.1	7.1 ±0.1	7.1 ±0.1	7.0 ±0.1	6.8 ±0.1	6.9 ±0.1	6.8 ±0.1	6.7 ±0.1

	No treatment with metformin within 12 months (unexposed) (%)				Early treatment (metformin script at <3 months) (%)				Timely treatment (metformin script at 3–6 months) (%)				Delayed treatment (metformin script at 6–12 months) (%)			
Baseline FBG (mmol/L), mean ± SE	7.1 ±0.0	7.0 ±0.0	6.9 ±0.0	6.9 ±0.0	9.0 ±0.1	8.8 ±0.1	8.8 ±0.1	8.8 ±0.1	7.9 ±0.2	7.8 ±0.2	7.5 ±0.2	7.8 ±0.2	7.5 ±0.2	7.5 ±0.1	7.5 ±0.1	7.3 ±0.1
History of hypertension (% Yes)	15.1	14.1	13.7	14.1	14.4	15.4	14.9	14.9	13.6	13.6	12.0	11.4	15.8	15.4	15.1	14.4
History of dyslipidaemia (% Yes)	4.4	4.7	3.9	4.1	4.9	5.5	4.5	4.9	3.6	3.5	4.6	2.7	3.6	4.3	4.5	3.8
History of CVD (% Yes)	2.5	2.5	2.4	2.5	2.4	2.8	2.9	2.6	2.8	2.8	2.9	2.2	3.6	2.6	2.0	2.4
History of CKD (% Yes)	0.3	0.2	0.3	0.3	0.0	0.1	0.1	0.1	0.3	0.5	0.4	0.2	N/O	N/O	N/O	N/O
Antipsychotics (% Yes)	3.0	2.9	2.6	2.7	4.9	4.8	4.8	4.7	3.9	4.3	5.4	4.4	4.1	5.7	5.3	4.7

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; SE: Standard error; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease; BMI: Body mass index; N/O: No observations.

* Numbers are not mutually exclusive.

Table E4. Baseline characteristics of the regular patients (aged 40+ years) with newly recorded diabetes and with baseline glycaemic measure and follow-up fasting blood glucose data at each time point (N=6,318)* (imputed data)

	No treatment with metformin within 12 months (unexposed) (%)				Early treatment (metformin script at <3 months) (%)				Timely treatment (metformin script at 3–6 months) (%)				Delayed treatment (metformin script at 6–12 months) (%)			
Follow-up months with HbA1c outcome	3–6 n= 917	6–12 n= 1,813	12–18 n= 1,032	18–24 n= 2,076	3–6 n= 848	6–12 n= 1,439	12–18 n= 884	18–24 n= 1,607	3–6 n= 162	6–12 n= 152	12–18 n= 94	18–24 n= 161	3–6 n= 107	6–12 n= 288	12–18 n= 138	18–24 n= 242
Practice characteristics																
Geographical area of GP																
Major cities	44.4	44.0	44.2	48.0	44.0	45.1	43.7	44.4	43.8	54.6	55.3	47.2	50.5	44.1	43.5	46.7
Inner regional	38.6	37.8	39.3	36.2	36.2	34.3	36.2	34.3	37.0	32.2	29.8	34.2	36.4	38.2	37.7	35.5
Outer regional/remote/very remote	16.9	18.1	16.5	15.8	19.8	20.6	20.1	21.2	19.1	13.2	14.9	18.6	13.1	17.7	18.8	17.8
GP IRSAD																
More disadvantaged	40.6	43.1	42.2	43.1	45.2	46.8	45.7	45.5	46.9	40.8	41.5	46.6	40.2	36.5	31.1	35.4
Middle	25.5	25.2	26.5	24.0	26.8	25.2	24.5	26.4	27.8	26.3	22.3	28.0	30.8	32.6	37.0	33.1
More advantaged	33.2	31.4	31.0	32.5	27.9	27.6	29.4	27.4	24.1	32.9	36.2	24.8	29.0	30.2	31.9	31.4
Patient demographic characteristics																
Gender: Male	49.6	49.6	50.6	52.7	56.5	53.8	51.4	54.6	50.6	50.7	53.2	54.0	54.2	50.7	52.9	52.5
Age, mean ± SE	66.2 ±0.4	66.1 ±0.3	67.0 ±0.3	66.2 ±0.2	62.2 ±0.4	62.5 ±0.3	62.7 ±0.4	62.2 ±0.3	62.2 ±0.9	62.2 ±0.9	62.0 ±1.2	62.9 ±0.9	62.6 ±1.0	62.9 ±0.7	63.0 ±0.9	63.0 ±0.7
Patient IRSAD																
More disadvantaged	41.7	44.3	42.0	42.6	44.2	46.8	46.6	46.0	46.3	41.4	43.6	47.8	42.1	37.1	32.6	35.5
Middle	26.2	25.4	26.7	25.1	28.3	26.5	26.6	28.5	27.8	27.0	23.4	30.4	28.0	32.0	34.8	34.3
More advantaged	31.6	29.9	31.2	31.7	26.5	26.0	26.2	24.8	24.7	30.9	33.0	21.7	29.0	29.9	31.9	29.3
Aboriginal and/or Torres Strait Islander (% Yes)	1.6	1.5	1.7	1.7	2.7	1.7	2.5	3.0	3.1	5.3	3.2	2.5	4.7	3.1	1.4	2.1
Smoking status (% Yes)	7.7	8.0	7.7	8.3	13.4	11.7	11.3	13.4	12.3	11.2	12.8	9.9	6.5	9.0	10.1	9.5
Patient clinical characteristics																
Baseline BMI (kg/m^2), mean ± SE	31.8 ±0.2	32.0 ±0.2	31.9 ±0.2	31.8 ±0.2	33.7 ±0.3	33.9 ±0.2	34.2 ±0.3	34.0 ±0.2	33.5 ±0.7	33.0 ±0.7	33.5 ±0.8	33.0 ±0.7	33.3 ±0.8	33.4 ±0.4	33.5 ±0.7	33.3 ±0.5
Baseline HbA1c (%), mean ± SE	6.3 ±0.0	6.3 ±0.0	6.3 ±0.0	6.3 ±0.0	7.5 ±01	7.5 ±0.1	7.4 ±0.1	7.6 ±0.1	7.0 ±0.2	6.9 ±0.1	6.9 ±0.2	6.9 ±0.1	6.7 ±0.1	6.7 ±0.1	6.6 ±0.1	6.8 ±0.1
Baseline FBG (mmol/L), mean ± SE	6.9 ±0.1	6.8 ±0.0	6.8 ±0.0	6.8 ±0.0	8.8 ±0.1	8.8 ±0.1	8.5 ±0.1	8.9 ±0.1	7.6 ±0.2	7.7 ±0.2	7.2 ±0.2	7.5 ±0.2	7.3 ±0.2	7.4 ±0.1	7.5 ±0.2	7.4 ±0.1

	No treatment with metformin within 12 months (unexposed) (%)				Early treatment (metformin script at <3 months) (%)				Timely treatment (metformin script at 3–6 months) (%)				Delayed treatment (metformin script at 6–12 months) (%)			
History of hypertension (% Yes)	15.4	14.9	14.0	13.5	12.7	15.1	13.9	14.9	11.7	11.2	9.6	8.7	16.8	15.3	11.6	11.6
History of dyslipidaemia (% Yes)	4.9	4.9	4.3	4.3	6.1	6.0	5.2	4.6	3.1	4.6	5.3	5.6	5.6	4.9	5.1	2.9
History of CVD (% Yes)	2.5	2.5	2.4	2.3	1.8	2.7	2.6	2.2	3.1	2.0	3.2	3.1	4.7	2.4	2.2	3.3
History of CKD (% Yes)	N/O	0.3	N/O	0.1	N/O	0.1	0.1	0.1	0.6	N/O	N/O	0.6	N/O	N/O	N/O	N/O
Antipsychotics (% Yes)	4.1	3.3	3.3	3.1	4.8	5.8	4.6	5.2	3.7	3.9	6.4	4.3	5.6	5.6	5.8	4.5

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; SE: Standard error; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease; BMI: Body mass index; N/O: No observations.

* Numbers are not mutually exclusive.

Table E5. Baseline characteristics of the regular patients (aged 40+) with newly recorded diabetes and with baseline glycaemic measure (eligible patients, N=12,185)* (complete-case data)

	No treatment with metformin within 12 months (unexposed), n=6,320 n (%)	Early treatment (metformin script at <3 months), n=4,960 n (%)	Timely treatment (metformin script at 3–6 months), n=349 n (%)	Delayed treatment (metformin script at 6–12 months), n=556 n (%)
Practice characteristics				
Geographical area of GP				
Major cities	3,417 (54.1)	2,429 (49.0)	186 (53.3)	289 (52.0)
Inner regional	1,902 (30.1)	1,483 (29.9)	115 (33.0)	180 (32.4)
Outer regional/remote/very remote	1,001 (15.8)	1,048 (21.1)	48 (13.8)	87 (15.6)
GP IRSAD				
More disadvantaged (lower two quintiles)	2,402 (38.0)	2,305 (46.5)	155 (44.4)	236 (42.4)
Middle	1,566 (24.8)	1,148 (23.1)	92 (26.4)	136 (24.5)
More advantaged (upper two quintiles)	2,336 (37.0)	1,490 (30.0)	101 (28.9)	183 (32.9)
Patient demographic characteristics				
Gender: Male	3,302 (52.2)	2,700 (54.4)	171 (49.0)	273 (49.1)
Age, mean ± SD	66.6 ± 11.6	61.6 ± 11.2	63.4 ± 11.8	62.6 ± 105
Patient IRSAD				
More disadvantaged (lower two quintiles)	2,509 (39.7)	2,329 (47.0)	162 (46.4)	240 (43.2)
Middle	1,602 (25.3)	1,189 (24.0)	88 (25.2)	138 (24.8)
More advantaged (upper two quintiles)	2,172 (34.4)	1,400 (28.2)	95 (27.2)	174 (31.3)
Aboriginal and/or Torres Strait Islander, n (%) Yes	132 (2.1)	176 (3.5)	16 (4.6)	19 (3.4)
Smoking status, n (%) Yes	543 (8.6)	674 (13.6)	46 (13.2)	68 (12.2)
Patient clinical characteristics				
Baseline BMI (kg/m^2), mean (SD)	31.6 (6.4)	34.1 (7.2)	33.0 (7.0)	33.7 (7.1)
Baseline HbA1c (%), mean (SD)	6.3 (0.8)	7.6 (1.8)	7.1 (1.3)	6.8 (0.9)
Baseline FBG (mmol/L), mean (SD)	6.8 (1.6)	8.8 (3.4)	7.8 (2.1)	7.4 (1.7)
History of hypertension, n (%) Yes	935 (14.8)	800 (16.1)	40 (11.5)	85 (15.3)
History of dyslipidaemia, n (%) Yes	256 (4.1)	271 (5.5)	15 (4.3)	27 (4.9)
History of CVD, n (%) Yes	160 (2.5)	140 (2.8)	11 (3.2)	15 (2.7)
History of CKD, n (%) Yes	23 (0.4)	2 (<1.0)	0 (0.0)	1 (0.2)
Antipsychotics, n (%) Yes	202 (3.2)	233 (4.7)	16 (4.6)	29 (5.2)

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantag; SD: Standard deviation; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease; BMI: Body mass index.

Table E6. Baseline characteristics of the regular patients (aged 40+) with newly recorded diabetes and with baseline glycaemic measure and follow-up data (final cohort, N=10,868)* (complete-case data)

	No treatment with metformin within 12 months (unexposed), n=5,599 n (%)	Early treatment (metformin script <3 months), n=4,424 n (%)	Timely treatment (metformin script at 3–6 months), n=326 n (%)	Delayed treatment (metformin script at 6–12 months), n=519 n (%)
Practice characteristics				
Geographical area of GP				
Major cities	3,031 (54.1)	2,135 (48.3)	175 (53.7)	268 (51.6)
Inner regional	1,650 (29.5)	1,322 (29.9)	104 (31.9)	166 (32.0)
Outer regional/remote/very remote	918 (16.4)	9,67 (21.9)	47 (14.4)	85 (16.4)
GP IRSAD				
More disadvantaged (lower two quintiles)	2,136 (38.1)	2,090 (47.2)	145 (44.5)	224 (43.2)
Middle	1,392 (24.9)	1,007 (22.8)	86 (26.4)	125 (24.1)
More advantaged (upper two quintiles)	2,056 (36.7)	1,311 (29.6)	95 (29.1)	169 (32.6)
Patient demographic characteristics				
Gender: Male	2,939 (52.5)	2,405 (54.4)	158 (48.5)	254 (48.9)
Age, mean ± SD	66.4 ± 11.2	61.8 ± 11.2	63.7 ± 11.8	62.4 ± 10.4
Patient IRSAD				
More disadvantaged (lower two quintiles)	2,227 (39.8)	2,096 (47.4)	153 (46.9)	226 (43.5)
Middle	1,427 (25.5)	1,052 (23.8)	80 (24.5)	127 (24.5)
More advantaged (upper two quintiles)	1,916 (34.2)	1,237 (28.0)	90 (27.6)	162 (31.2)
Aboriginal and/or Torres Strait Islander, n (%) Yes	110 (2.0)	157 (3.5)	16 (4.9)	19 (3.7)
Smoking status, n (%) Yes	452 (8.1)	596 (13.5)	42 (12.9)	67 (12.9)
Patient clinical characteristics				
Baseline BMI (kg/m^2), mean (SD)	31.6 (6.3)	34.1 (7.2)	33.2 (7.1)	33.8 (7.1)
Baseline HbA1c (%), mean (SD)	6.3 (0.8)	7.6 (1.8)	7.1 (1.3)	6.8 (0.9)
Baseline FBG (mmol/L), mean (SD)	6.8 (1.4)	8.7 (3.4)	7.9 (2.1)	7.4 (1.7)
History of hypertension, n (%) Yes	829 (14.8)	708 (16.0)	37 (11.3)	79 (15.2)
History of dyslipidaemia, n (%) Yes	238 (4.3)	241 (5.4)	15 (4.6)	26 (5.0)
History of CVD, n (%) Yes	144 (2.6)	122 (2.8)	11 (3.4)	14 (2.7)
History of CKD, n (%) Yes	17 (0.3)	2 (<1.0)	0 (0.0)	No observations
Antipsychotics, n (%) Yes	183 (3.3)	213 (4.8)	15 (4.6)	26 (5.0)

HbA1c: Haemoglobin A1c; FBG: Fasting blood glucose; GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; SD: Standard deviation; CVD: Cardiovascular disease (including heart failure, ischaemic heart disease, and stroke); CKD: Chronic kidney disease; BMI: Body mass index.

Table E7. Average treatment effect of early or delayed metformin commencement on HbA1c levels among regular patients (aged 40+ years) with newly recorded diabetes (N=10,868) (complete-case analysis)

		Crude results	Linear regression*	ATE using AIPW*
	N	Crude (SD)	β (95%CI)	ATE (95%CI)
HbA1c (%) at 3–6 months	**n=3,748**			
No treatment within 12 months	1,686	6.1 (0.6)	**Ref**	**Ref**
Early treatment (<3 months)	1,730	6.5 (0.9)	0.20 (0.15 to 0.26)	0.21 (0.16 to 0.27)
Timely treatment (3–6 months)	180	7.2 (1.2)	0.91 (0.74 to 1.09)	0.91 (0.74 to 1.08)
Delayed treatment (6–12 months)	152	6.7 (0.8)	0.52 (0.40 to 0.63)	0.58 (0.46 to 0.71)
HbA1c (%) at 6–12 months	**n=5,606**			
No treatment within 12 months	2,796	6.2 (0.6)	**Ref**	**Ref**
Early treatment (<3 months)	2,301	6.4 (0.9)	0.08 (0.03 to 0.13)	0.09 (0.04 to 0.14)
Timely treatment (3–6 months)	156	6.6 (0.8)	0.36 (0.24 to 0.48)	0.33 (0.24 to 0.43)
Delayed treatment (6–12 months)	353	7.1 (1.2)	0.96 (0.78 to 1.14)	0.91 (0.77 to 1.05)
HbA1c (%) at 12–18 months	**n=3,272**			
No treatment within 12 months	1,690	6.2 (0.8)	**Ref**	**Ref**
Early treatment (<3 months)	1,297	6.4 (0.9)	0.05 (–0.02 to 0.11)	0.02 (–0.05 to 0.09)
Timely treatment (3–6 months)	94	6.5 (0.8)	0.18 (0.04 to 0.31)	0.15 (0.04 to 0.26)
Delayed treatment (6–12 months)	191	6.7 (0.9)	0.43 (0.30 to 0.55)	0.37 (0.23 to 0.50)
HbA1c (%) at 18–24 months	**n=5,461**			
No treatment within 12 months	2,994	6.2 (0.7)	**Ref**	**Ref**
Early treatment (<3 months)	2,052	6.4 (0.9)	0.03 (–0.02 to 0.08)	0.05 (–0.01 to 0.10)
Timely treatment (3–6 months)	145	6.6 (0.9)	0.24 (0.11 to 0.38)	0.24 (0.11 to 0.37)
Delayed treatment (6–12 months)	270	6.6 (0.8)	0.31 (0.21 to 0.40)	0.29 (0.20 to 0.39)

HbA1c: Haemoglobin A1c; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; SD: Standard deviation; CI: Confidence interval; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

*Adjusted for practice characteristics (remoteness, practice IRSAD), and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.

Table E8. Average treatment effect of early or delayed metformin commencement on fasting blood glucose levels among regular patients (aged 40+ years) with newly recorded diabetes (N=10,868) (complete-case analysis)

		Crude results	Linear regression*	ATE using AIPW*
	N	Crude (SD)	β (95%CI)	ATE (95%CI)
FBG (mmol/L) at 3–6 months	**n=1,037**			
No treatment within 12 months	607	6.5 (1.2)	**Ref**	**Ref**
Early treatment (<3 months)	563	6.9 (2.0)	0.16 (–0.02 to 0.36)	0.21 (0.00 to 0.41)
Timely treatment (3–6 months)	77	8.3 (2.6)	1.60 (1.06 to 2.14)	1.19 (0.74 to 1.63)
Delayed treatment (6–12 months)	60	7.5 (1.8)	1.02 (0.54 to 1.50)	1.11 (0.35 to 1.86)
FBG (mmol/L) at 6–12 months	**n=2,217**			
No treatment within 12 months	1,162	6.5 (1.2)	**Ref**	**Ref**
Early treatment (<3 months)	847	6.8 (1.6)	0.02 (–0.11 to 0.15)	0.11 (–0.13 to 0.15)
Timely treatment (3–6 months)	67	7.1 (1.4)	0.40 (0.10 to 0.71)	0.29 (0.05 to 0.54)
Delayed treatment (6–12 months)	141	8.2 (2.3)	1.65 (1.23 to 2.10)	1.56 (1.09 to 2.04)
FBG (mmol/L) at 12–18 months	**n=1,330**			
No treatment within 12 months	691	6.6 (1.5)	**Ref**	**Ref**
Early treatment (<3 months)	530	6.9 (1.8)	–0.05 (–0.23 to 0.13)	–0.33 (–0.63 to –0.03)
Timely treatment (3–6 months)	41	6.9 (1.4)	0.00 (–0.40 to 0.41)	–0.47 (–1.00 to –0.05)
Delayed treatment (6–12 months)	68	7.2 (1.9)	0.55 (0.11 to 0.99)	0.43 (–0.32 to 1.18)
FBG (mmol/L) at 18–24 months	**n=2,317**			
No treatment within 12 months	1,287	6.7 (1.8)	**Ref**	**Ref**
Early treatment (<3 months)	867	7.0 (1.9)	–0.06 (–0.23 to 0.11)	–0.04 (–0.22 to 0.14)
Timely treatment (3–6 months)	58	7.3 (1.6)	0.33 (–0.05 to 0.71)	0.22 (–0.12 to 0.57)
Delayed treatment (6–12 months)	105	7.1 (1.9)	0.24 (–0.10 to 0.58)	0.28 (–0.17 to 0.72)

FBG: Fasting blood glucose; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; SD: Standard deviation; CI: Confidence interval; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; HbA1c: Haemoglobin A1c.

*Adjusted for practice characteristics (remoteness, practice IRSAD), and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.

Table E9. Average treatment effect of early or delayed metformin commencement on HbA1c levels among regular patients (aged 40+ years) with newly recorded diabetes, with other ADM prescriptions during follow-up points (N=13,427) (imputed data)

		Crude results	Linear regression	ATE using AIPW*
	N	Crude (SE)	β (95%CI)	ATE (95%CI)
HbA1c (%) at 3–6 months	**n= 5,789**			
No treatment within 12 months	2,450	6.2 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	2,757	6.6 (0.0)	0.28 (0.23 to 0.34)	0.21 (0.16 to 0.27)
Timely treatment (3–6 months)	360	7.4 (0.1)	1.14 (0.96 to 1.30)	0.91 (0.74 to 1.10)
Delayed treatment (6–12 months)	222	6.8 (0.1)	0.55 (0.43 to 0.67)	0.58 (0.46 to 0.70)
HbA1c (%) at 6–12 months	**n= 9,284**			
No treatment within 12 months	4,234	6.2 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	3,970	6.5 (0.0)	0.19 (0.14 to 0.24)	0.09 (0.04 to 0.14)
Timely treatment (3–6 months)	398	6.7 (0.1)	0.43 (0.32 to 0.54)	0.33 (0.24 to 0.43)
Delayed treatment (6–12 months)	682	7.3 (0.1)	1.02 (0.88 to 1.15)	0.91 (0.77 to 1.05)
HbA1c (%) at 12–18 months	**n= 5,541**			
No treatment within 12 months	2,578	6.3 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	2,325	6.6 (0.0)	0.14 (0.08 to 0.21)	0.02 (−0.05 to 0.09)
Timely treatment (3–6 months)	241	6.6 (0.1)	0.22 (0.09 to 0.35)	0.15 (0.04 to 0.26)
Delayed treatment (6–12 months)	397	6.7 (0.1)	0.36 (0.24 to 0.48)	0.37 (0.23 to 0.540)
HbA1c (%) at 18–24 months	**n= 9,906**			
No treatment within 12 months	4,839	6.4 (0.0)	**Ref**	**Ref**
Early treatment (<3 months)	4,022	6.7 (0.0)	0.17 (0.11 to 0.22)	0.04 (−0.05 to 0.10)
Timely treatment (3–6 months)	411	6.7 (0.1)	0.27 (0.17 to 0.38)	0.24 (0.11 to 0.37)
Delayed treatment (6–12 months)	634	6.7 (0.0)	0.31 (0.21 to 0.40)	0.29 (0.20 to 0.39)

HbA1c: Haemoglobin A1c; ADM: Antidiabetic medication; SE: Standard error; CI: Confidence interval; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage.

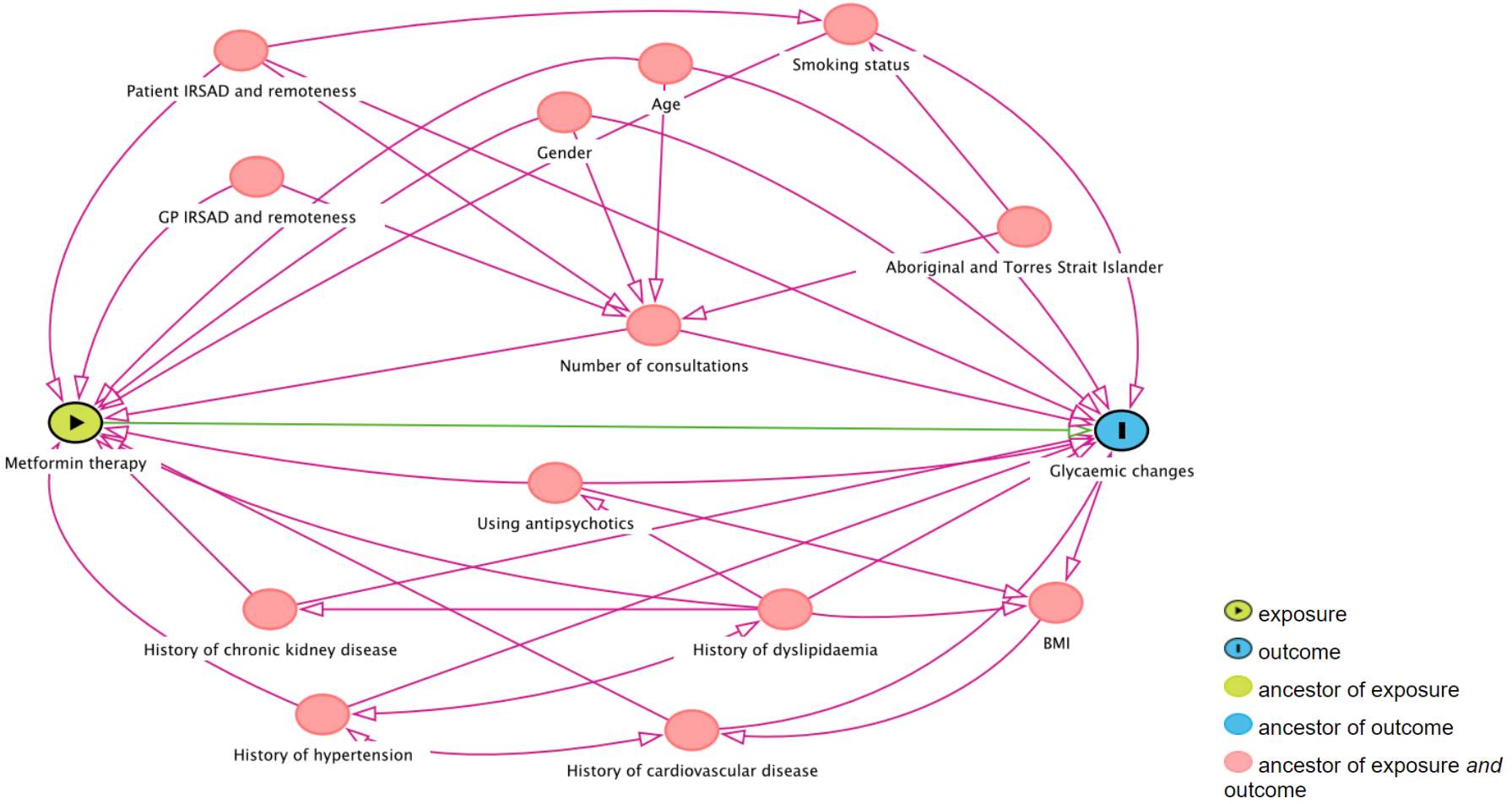
* Adjusted for practice characteristics (remoteness, practice IRSAD), and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, and previous history of heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.

Table E10. Average treatment effect of early or delayed metformin commencement on fasting blood glucose levels among regular patients (aged 40+ years) with newly recorded diabetes, with other ADM prescriptions during follow-up points (N=6,318) (imputed data)

		Crude results	Linear regression	ATE using AIPW*
	N	Crude (SE)	β (95%CI)	ATE (95%CI)
FBG (mmol/L) at 3–6 months	**n=2,034**			
No treatment within 12 months	917	6.5 (0.0)	**Ref**	Ref
Early treatment (<3 months)	848	7.1 (0.1)	0.30 (0.08 to 0.52)	0.21 (0.00 to 0.41)
Timely treatment (3–6 months)	162	8.7 (0.2)	1.93 (1.45 to 2.41)	1.12 (0.74 to 1.64)
Delayed treatment (6–12 months)	107	7.5 (0.2)	0.88 (0.52 to 1.23)	1.11 (0.35 to 1.86)
FBG (mmol/L) at 6–12 months	**n=3,692**			
No treatment within 12 months	1,813	6.6 (0.0)	**Ref**	Ref
Early treatment (<3 months)	1,439	7.2 (0.1)	0.24 (0.08 to 0.41)	0.01 (–0.13 to 0.15)
Timely treatment (3–6 months)	152	7.2 (0.1)	0.43 (0.10 to 0.75)	0.29 (0.05 to 0.54)
Delayed treatment (6–12 months)	275	8.4 (0.2)	1.65 (1.32 to 1.97)	1.56 (1.10 to 2.04)
FBG (mmol/L) at 12–18 months	**n=2,148**			
No treatment within 12 months	1,032	6.7 (0.1)	**Ref**	Ref
Early treatment (<3 months)	884	7.2 (0.1)	0.08 (–0.14 to 0.30)	–0.33 (–0.63 to –0.03)
Timely treatment (3–6 months)	94	7.1 (0.2)	0.11 (–0.32 to 0.54)	–0.47 (–1.00 to 0.05)
Delayed treatment (6–12 months)	138	7.1 (0.2)	0.21 (–0.14 to 0.57)	0.43 (–0.32 to 1.18)
FBG (mmol/L) at 18–24 months	**n=4,086**			
No treatment within 12 months	2,076	6.8 (0.0)	**Ref**	Ref
Early treatment (<3 months)	1,607	7.5 (0.1)	0.34 (0.15 to 0.53)	–0.04 (–0.22 to 0.14)
Timely treatment (3–6 months)	161	7.4 (0.2)	0.43 (0.05 to 0.82)	0.22 (–0.12 to 0.56)
Delayed treatment (6–12 months)	242	7.2 (0.1)	0.25 (–0.04 to 0.55)	0.28 (–0.17 to 0.72)

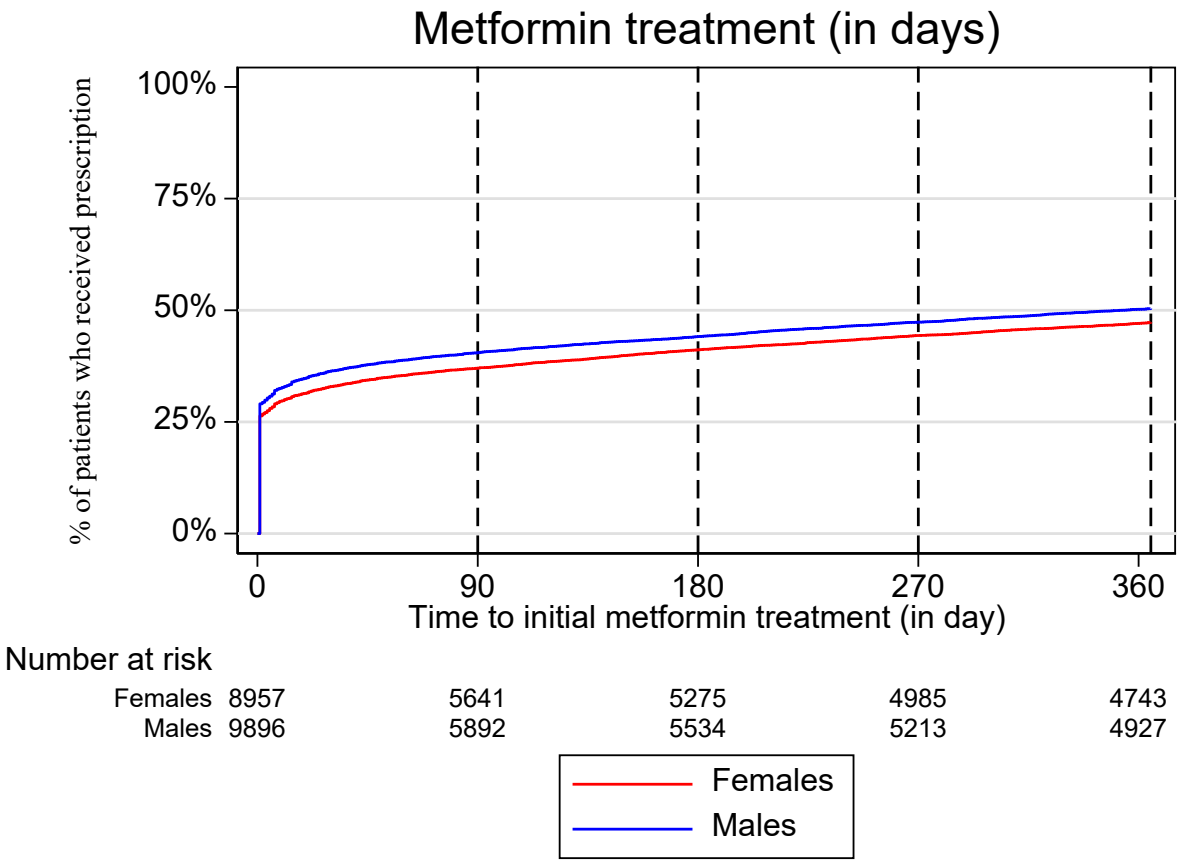
ADM: Antidiabetic medication; FBG: Fasting blood glucose; SE: Standard error; CI: Confidence interval; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; Ref: Reference group; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; HbA1c: Haemoglobin A1c.

* Adjusted for practice characteristics (remoteness, practice IRSAD), and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, body mass index, and previous history of heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, and average number of consultations during the study period.



GP: General practice; IRSAD: Index of Relative Socio-economic Advantage and Disadvantage; BMI: Body mass index.

Figure E1. Directed acyclic graph showing the confounding structure between initial metformin monotherapy and glycaemic changes



The Kaplan–Meier failure function curve shows the time of metformin prescription during the first 12 months after diagnosis. The starting point was the date of the first diagnosis of diabetes. The endpoint was the date of initial metformin therapy within 12 months, or no treatment until 31 December 2017. Approximately 51.1% of the patients were not treated with metformin within 12 months after diagnosis. A total of 38.8% of patients received a timely prescription for metformin in the first 3 months.

Figure E2. Time to initial metformin treatment (in days, up to 365 days) – Kaplan–Meier failure function curve

Appendix F. Supplementary Materials for Chapter 7

Table F1. Characteristics of the eligible sample and the final cohort and those who with outcome measures included in our study, patients with 'incident' recorded diabetes between 2012 and 2017.

	Eligible sample† N=13,014 Initial data	Final Cohort‡ N=4,770 Imputed data	Final Cohort ‡ Patients with available HbA1c data after exposure*			Final Cohort ‡ Patients with available FBG data after exposure*		
			6-12 months n=1,372	12-18 months n=1,259	18-24 months n=1,023	6-12 months n=1,485	12-18 months n=1,391	18-24 months n=1,269
Practice characteristics	%	%	%	%	%	%	%	%
Geographical area of GP								
Major Cities	60.1	53.0	59.0	58.0	59.6	49.0	48.3	50.0
Inner Regional	25.5	27.2	24.2	24.9	20.9	31.2	31.0	29.1
Outer regional /Remote/Very Remote	14.4	19.8	16.8	17.2	19.5	19.9	20.7	20.9
GP IRSAD								
More advantaged	40.4	40.1	43.2	41.9	44.4	38.1	35.2	38.3
Middle	21.4	22.0	18.4	20.1	17.9	24.0	26.9	25.9
More disadvantaged	38.3	38.0	38.4	38.0	37.7	37.9	38.0	35.8
Patients' demographic characteristics								
Gender: Male	51.7	51.9	50.1	51.2	49.8	53.1	54.0	54.1
Aboriginal and/or Torres Strait Islander (% Yes)	1.6	1.6	1.6	1.8	2.0	1.6	1.4	1.1
Age, mean ± SD	63.9±12.7	65.9	66.0	66.2	66.2	66.8	66.6	66.8
Patients' IRSAD								
More advantaged	38.8	38.1	41.3	41.0	40.8	36.5	34.2	35.4
Middle	22.4	23.9	21.5	22.8	21.4	25.7	28.2	27.2
More disadvantaged	38.8	38.0	37.2	36.1	37.8	37.8	37.7	37.5
Patients' clinical characteristics								
Smoking status (% Yes)	10.0	8.8	10.1	8.9	7.6	8.1	7.0	7.0

Heart failure (% Yes)	1.2	1.3	1.7	2.2	1.4	1.0	1.5	0.7
Stroke (% Yes)	2.5	2.9	2.9	2.5	3.2	3.2	2.9	3.3
Dyslipidaemia (% Yes)	36.8	37.4	40.1	38.3	37.1	38.7	35.5	37.2
Ischaemic heart disease (% Yes)	6.8	7.7	8.7	9.3	6.7	6.8	8.8	7.3
Hypertension (% Yes)	43.8	46.4	49.1	48.5	47.7	47.4	45.6	47.8
Antipsychotic scripts (% Yes)	2.7	2.5	3.1	3.3	3.1	3.1	2.1	2.4
Baseline Hba1c (mmol/mol): Mean ± SD	43± 7.7	41 (0.1)	41 (0.2)	41 (0.1)	41 (0.2)	41 (0.2)	41 (0.2)	41 (0.2)
(%): Mean ± SD	6.1 ± 0.7	5.9 (0.01)	5.9 (0.02)	5.9 (0.01)	5.9 (0.02)	5.9 (0.02)	5.9 (0.02)	5.9 (0.02)
Baseline FBG (mmol/L): Mean ± SD	6.2 ± 0.8	6.1 (0.01)	6.2 (0.03)	6.2 (0.02)	6.1 (0.03)	6.1 (0.01)	6.1 (0.01)	6.1 (0.02)
Exposed to metformin (%)	12.4	10.2	16.9	14.2	14.2	10.9	8.8	8.0

FBG: Fasting blood glucose; GP: General practitioner; IRSAD: Index of Relative Socio-Economic Advantage and Disadvantage; SE: Standard error.
† Eligible sample (regular adult patients with 'incident' recorded prediabetes).
‡ Final cohort (regular adult patients with 'incident' recorded prediabetes, with outcome data available at 6-24 months after diagnosis/exposure) (complete-case analysis).
*Numbers are not mutually exclusive.

Table F2. Baseline characteristics of the regular adult patients (18+) with 'incident' recorded prediabetes, with measured outcomes HbA1c or fasting blood glucose (original data before imputation, with missing data shown for each variable).

	Measured HbA1c		Measured FBG	
	Unexposed	Exposed to Metformin	Unexposed	Exposed to Metformin
	N=2526	N=402	N=2860	N=280
	N (%)	N (%)	N (%)	N (%)
Practice characteristics				
Geographical area of GP	1501 (59.4%)	208 (51.7%)	1363 (47.7%)	156 (55.7%)
Major Cities	592 (23.4%)	118 (29.4%)	852 (29.8%)	91 (32.5%)
Inner Regional	433 (17.1%)	76 (18.9%)	645 (22.6%)	33 (11.8%)
GP IRSAD				
More advantaged	1112 (44.0%)	138 (34.3%)	1070 (37.4%)	92 (32.9%)
Middle	466 (18.4%)	75 (18.7%)	733 (25.6%)	71 (25.4%)
More disadvantaged	938 (37.1%)	187 (46.5%)	1045 (36.5%)	114 (40.7%)
Missing data	10 (0.4%)	2 (0.5%)	12 (0.4%)	3 (1.1%)
Patients' characteristics				
Gender: Male	1309 (51.8%)	175 (43.5%)	1537 (53.7%)	122 (43.6%)
Age, mean (SD)	65.7 (11.9)	64.6 (11.1)	66.6 (11.7)	64.0 (11.5)
Ethnicity				
Neither Aboriginal nor Torres Strait Islander	2008 (79.5%)	337 (83.8%)	2312 (80.8%)	233 (83.2%)
Aboriginal and/or Torres Strait Islander	38 (1.5%)	12 (3.0%)	37 (1.3%)	7 (2.5%)
Not stated	480 (19.0%)	53 (13.2%)	511 (17.9%)	40 (14.3%)
Patients' IRSAD				
More advantaged	1053 (41.7%)	136 (33.8%)	1029 (36.0%)	92 (32.9%)
Middle	543 (21.5%)	84 (20.9%)	750 (26.2%)	75 (26.8%)
More disadvantaged	913 (36.1%)	181 (45.0%)	1066 (37.3%)	112 (40.0%)
Missing date	17 (0.7%)	1 (0.2%)	15 (0.5%)	1 (0.4%)
Smoking status				
Non smoker	1316 (52.1%)	217 (54.0%)	1452 (50.8%)	141 (50.4%)
Smoker	228 (9.0%)	39 (9.7%)	227 (7.9%)	23 (8.2%)
Ex smoker	897 (35.5%)	133 (33.1%)	1103 (38.6%)	109 (38.9%)
Not stated/not recorded	85 (3.4%)	13 (3.2%)	78 (2.7%)	7 (2.5%)
Patients' clinical variables				
Baseline HbA1c				
mmol/mol, mean (SD)	41 (4.4)	42 (4.4)	41 (4.4)	41 (4.4)
%, mean (SD)	5.9 (0.4)	6.0 (0.4)	5.9 (0.4)	5.9 (0.4)

Baseline FBG, mean (SD)	6.2 (0.7)	6.3 (0.7)	6.1 (0.6)	6.2 (0.7)
Heart failure				
No	2487 (98.5%)	396 (98.5%)	2830 (99.0%)	279 (99.6%)
Yes	39 (1.5%)	6 (1.5%)	30 (1.0%)	1 (0.4%)
Stroke				
No	2456 (97.2%)	390 (97.0%)	2775 (97.0%)	271 (96.8%)
Yes	70 (2.8%)	12 (3.0%)	85 (3.0%)	9 (3.2%)
Dyslipidaemia				
No	1538 (60.9%)	260 (64.7%)	1797 (62.8%)	187 (66.8%)
Yes	988 (39.1%)	142 (35.3%)	1063 (37.2%)	93 (33.2%)
Ischaemic heart disease				
No	2325 (92.0%)	366 (91.0%)	2657 (92.9%)	261 (93.2%)
Yes	201 (8.0%)	36 (9.0%)	203 (7.1%)	19 (6.8%)
Hypertension				
No	1333 (52.8%)	192 (47.8%)	1568 (54.8%)	143 (51.1%)
Yes	1193 (47.2%)	210 (52.2%)	1292 (45.2%)	137 (48.9%)
Antipsychotic scripts				
No	2457 (97.3%)	386 (96.0%)	2791 (97.6%)	271 (96.8%)
Yes	69 (2.7%)	16 (4.0%)	69 (2.4%)	9 (3.2%)
BMI, mean (SD)	31.5 (7.2)	32.9 (9.9)	30.9 (6.9)	34.0 (8.2)

FBG: Fasting blood glucose; GP: General practitioner; IRSAD: Index of Relative Socio-Economic Advantage and Disadvantage; SD: Standard deviation.

Table F3. Comparison of the effect of metformin exposure on HbA1c and fasting blood glucose among regular adult patients with 'incident' prediabetes using traditional linear regression models or augmented inverse probability weighting (complete-case analysis)

		Crude results	Adjusted Results Linear regression*	AIPW models*	AIPW models additionally adjusted for BMI*
	N	Crude mean (SE)	Coef. (95% CI)	ATE (95% CI)	ATE (95% CI)
HbA1c at 6–12 months					
Unexposed	941	5.8 (0.4)		Ref	Ref
Exposed to metformin	193	5.9 (0.4)	0.00 (-0.1 to 0.1)	-0.02 (-0.1 to 0.0)	-0.01 (-0.1 to 0.1)
HbA1c (%) at 12–18 months					
Unexposed	884	5.8 (0.5)		Ref	Ref
Exposed to metformin	146	5.8 (0.4)	-0.05(-0.1 to 0.0)	-0.03 (-0.1 to 0.0)	-0.07 (-0.2 to 0.0)
HbA1c (%) at 18–24 months					
Unexposed	688	5.9 (0.6)		Ref	Ref
Exposed to metformin	120	5.8 (0.4)	-0.12(-0.2 to 0.0)	-0.12 (-0.2 to 0.0)	-0.04 (-0.1 to 0.1)
FBG (mmol/L) at 6–12 months					
Unexposed	1,210	5.9 (0.7)		Ref	Ref
Exposed to metformin	143	5.9 (0.7)	-0.07(-0.2 to 0.0)	-0.10 (-0.2 to 0.0)	-0.13 (-0.2 to 0.0)
FBG (mmol/L) at 12–18 months					
Unexposed	1147	5.9 (0.8)		Ref	Ref
Exposed to metformin	111	6.0 (0.7)	0.00(-0.1 to 0.1)	0.03 (-0.1 to 0.1)	0.02 (-0.2 to 0.2)
FBG (mmol/L) at 18–24 months					
Unexposed	1,047	6.0 (1.0)		Ref	Ref
Exposed to metformin	93	6.1 (0.8)	-0.09 (-0.3 to 0.1)	-0.07 (-0.3 to 0.1)	-0.01 (-0.3 to 0.3)

SE: Standard error; FBG: Fasting blood glucose; AIPW: Augmented inverse probability weighting; ATE: Average treatment effect; Ref: reference group
*Adjusted for practice characteristics; remoteness, GP IRSAD (The Index of Relative Socio-economic Advantage and Disadvantage); and patient characteristics, including baseline glycaemic measures combined as a categorical variable (HbA1c, baseline fasting glucose, random glucose, and oral glucose tolerance test), age, gender, smoking status, ethnicity, patients' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication and total person time.

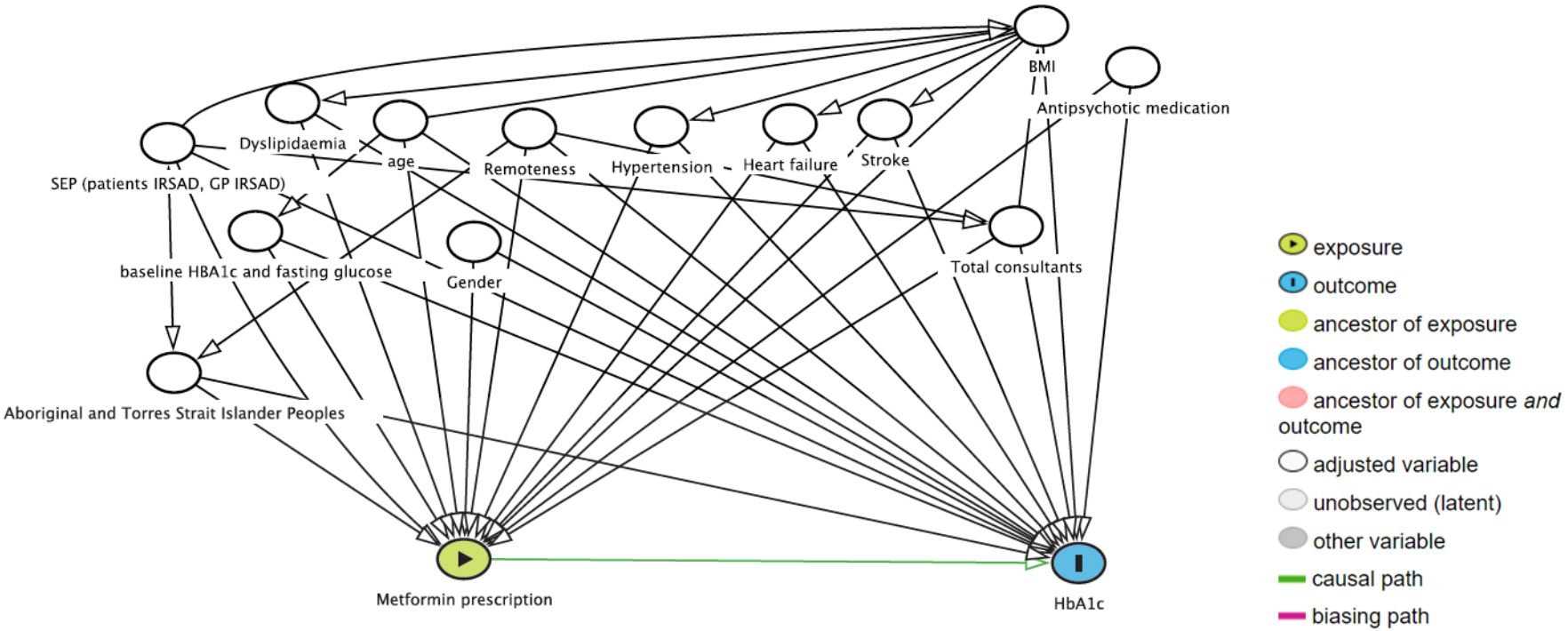
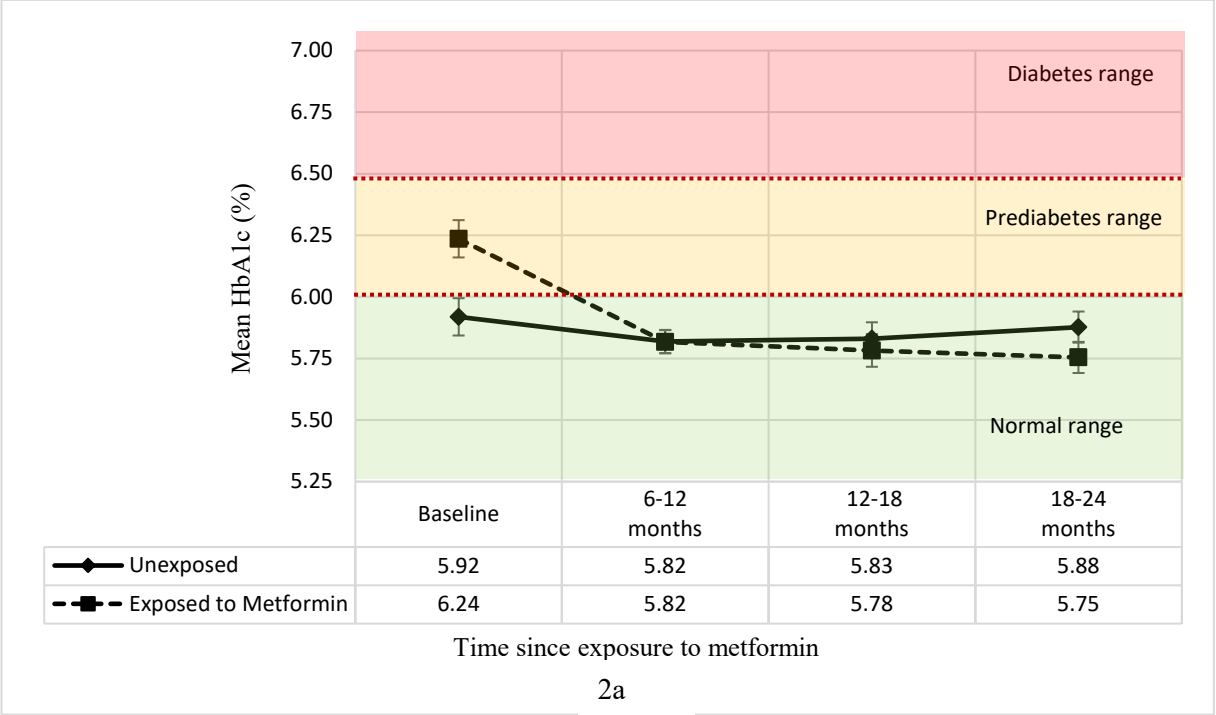
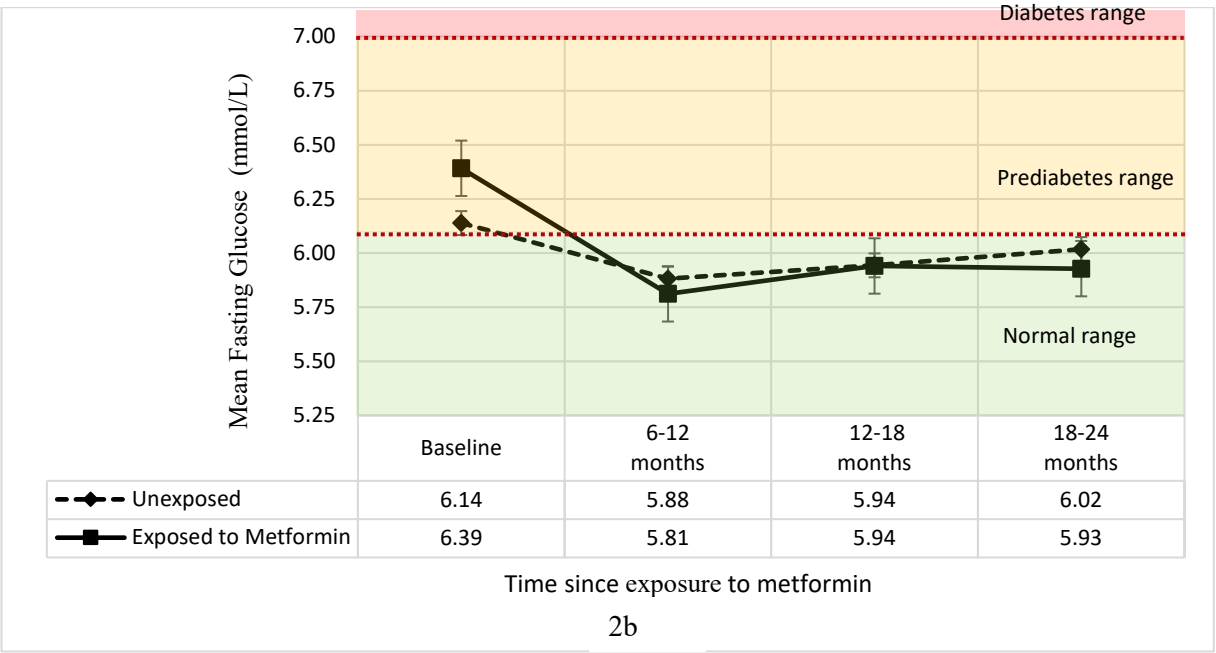


Figure F1. Directed acyclic graph showing the confounding structure



2a



2b

Figure F2. adjusted mean HbA1c (2a) or fasting blood glucose (2b) at baseline, 6-12, 12-18, and 18-24 months after diagnosis/exposure (complete-case analysis).

Results based on linear regression models adjusted for practice characteristics (remoteness, and practice IRSAD) and patient characteristics (baseline glycaemic levels, age, gender, smoking status, ethnicity, patients' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication, number of consultations, and wait time for starting metformin. Vertical lines represent the 95% CI. Reference values for HbA1c: normal range (≤5.9%), prediabetes range (6.0-6.4%), diabetes range (≥6.5%). Reference values for fasting blood glucose: normal range (≤6.0mmol/L), prediabetes range (6.1-6.9mmol/L), diabetes range (≥7.0 mmol/L).

Appendix G. Abstracts of Published Manuscripts

Paper 1

Hindawi
Journal of Diabetes Research
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Research Article

Diabetes Mellitus Diagnosis and Screening in Australian General Practice: A National Study

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Aims. To investigate the epidemiology of diabetes diagnosis and screening in Australian general practice. *Methods.* Cross-sectional study using electronic health records of 1,522,622 patients aged 18+ years attending 544 Australian general practices (MedicineInsight database). The prevalence of diagnosed diabetes and diabetes screening was explored using all recorded diagnoses, laboratory results, and prescriptions between 2016 and 2018. Their relationship with patient sociodemographic and clinical characteristics was also investigated. *Results.* Overall, 7.5% (95% CI 7.3, 7.8) of adults had diabetes diagnosis, 0.7% (95% CI 0.6, 0.7) prediabetes, and 0.3% (95% CI 0.3, 0.3) unrecorded diabetes/prediabetes (elevated glucose levels without a recorded diagnosis). Patients with unrecorded diabetes/prediabetes had clinical characteristics similar to those with recorded diabetes, except for a lower prevalence of overweight/obesity (55.5% and 69.9%, respectively). Dyslipidaemia was 1.8 times higher (36.2% vs. 19.7%), and hypertension was 15% more likely (38.6% vs. 33.8%) among patients with prediabetes than with diabetes. Diabetes screening (last three years) among people at high risk of diabetes was 55.2% (95% CI 52.7, 57.7), with lower rates among young or elderly males. *Conclusions.* Unrecorded diabetes/prediabetes is infrequent in Australian general practice, but prediabetes diagnosis was also lower than expected. Diabetes screening among high-risk individuals can be improved, especially in men, to enhance earlier diabetes diagnosis and management.

1. Introduction

Diabetes mellitus is a major global health problem and one of the fastest-growing chronic conditions [1]. In Australia, the age-standardised ratio of self-reported diabetes has increased from 3.3% in 2001 to 4.4% in 2017-2018 [2]. However, diabetes is not always medically diagnosed. Globally, it is estimated that one in two people living with diabetes is unaware of their condition [3]. Several nationwide studies have investigated the actual magnitude of undiagnosed diabetes, either using electronic health records (EHRs) [4] or through laboratory tests used as part of national surveys [5–7]. The prevalence of unreported diabetes in the United States (US) was estimated at 0.9% in 1988-1994 and 1.2% in 2011-2014 [5], while a French national study found a prevalence of 1.7% in 2014-2016 [7].

Moreover, prediabetes (a condition where the glycaemic parameters are above normal but below the threshold for diabetes [8]) increases the burden of diabetes, with a conversion rate to diabetes of 5%-10% per year [9]. Globally, the estimated prevalence of prediabetes was 7.5% in 2019 (~374 million people) and is projected to reach 8.6% (~548 million people) by 2045 [3]. In Australia, prediabetes affects 3.1% of adults [10]. Undiagnosed prediabetes is an additional concern, as these

Paper 2

Open access Original research

BMJ Open

Diabetes mellitus monitoring and control among adults in Australian general practice: a national retrospective cohort study

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ABSTRACT

Objectives This study investigated whether the monitoring and control of clinical parameters are better among patients with newly compared with past recorded diabetes diagnosis.

Design Retrospective cohort study.

Setting MedicineInsight, a national general practice database in Australia.

Participants 101 875 'regular' adults aged 18+ years with past recorded (2015–2016) and 9236 with newly recorded (2017) diabetes diagnosis.

Main outcome measures Two different groups of outcomes were assessed in 2018. The first group of outcomes was the proportion of patients with clinical parameters (ie, glycated haemoglobin A1c (HbA1c), blood pressure (BP), total cholesterol, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol, triglycerides, estimated glomerular filtration rate and albumin-to-creatinine ratio) monitored at least once in 2018. The second group of outcomes were those related to diabetes control in 2018 (HbA1c ≤7.0%, (BP) ≤140/90 mm Hg, total cholesterol <4.0 mmol/L and LDL-C <2.0 mmol/L). Adjusted ORs (OR_{adj}) and adjusted probabilities (%) were obtained based on logistic regression models adjusted for practice variables and patients' socio-demographic and clinical characteristics.

Results The study included 111 111 patients (51.7% men; mean age 65.3±15.0 years) with recorded diabetes diagnosis (11.0% of all 1 007 714 adults in the database). HbA1c was monitored in 39.2% (95% CI 36.9% to 41.6%) of patients with newly recorded and 45.2% (95% CI 42.6% to 47.8%) with past recorded diabetes (OR_{adj} 0.78, 95% CI 0.73 to 0.82). HbA1c control was achieved by 78.4% (95% CI 76.7% to 80.0%) and 54.4% (95% CI 53.4% to 55.4%) of monitored patients with newly or past recorded diabetes, respectively (OR_{adj} 3.11, 95% CI 2.82 to 3.39). Less than 20% of patients with newly or past recorded diabetes had their HbA1c, BP and total cholesterol levels controlled (OR_{adj} 1.08, 95% CI 0.97 to 1.21).

Conclusions The monitoring of clinical parameters was lower among patients with newly than past recorded diabetes. However, diabetes control was similarly low in both groups, with only one in five monitored patients achieving control of all clinical parameters.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This retrospective cohort used a large sample of patients attending primary healthcare services across all Australian states and territories.
⇒ A wide range of socio-demographic and clinical variables related to diabetes monitoring and control were included for adjustment.
⇒ Lifestyle variables were not included for adjustment, as they are not consistently recorded in the electronic medical records.
⇒ Patients may have had their diabetes parameters monitored somewhere else (eg, different practices or by specialists).

INTRODUCTION

Diabetes mellitus is a lifelong disease that requires regular monitoring and control to reduce the risk of diabetes-related complications.[1–5] Microvascular and macrovascular complications of uncontrolled diabetes (eg, hypertension, dyslipidaemia, chronic kidney disease (CKD), cardiovascular disease (CVD)) increase the health burden worldwide.[6] Blood glucose control is the most critical clinical goal of diabetes management, but other clinical variables also require regular monitoring.[5] The Royal Australian College of General Practitioners (RACGP) guidelines recommend patients with diabetes should have their glycated haemoglobin A1c (HbA1c), blood pressure (BP) and lipid levels evaluated annually to improve management and control of these clinical parameters.[7] Treatment options may vary depending on individual characteristics (eg, age, gender, presence of comorbidities)[7 8] and the stage of diabetes progression (ie, recent or past diagnosis, presence of diabetes complications).[9]

Maintaining optimal levels of diabetes control with a combination of drug monotherapy and lifestyle changes is often possible for several years, after which a combination

Paper 4

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DIABETIC Medicine

RESEARCH ARTICLE

Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records

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Abstract

Aims: To estimate the effectiveness of metformin on glycaemic parameters among participants with incident prediabetes attending Australian general practices.

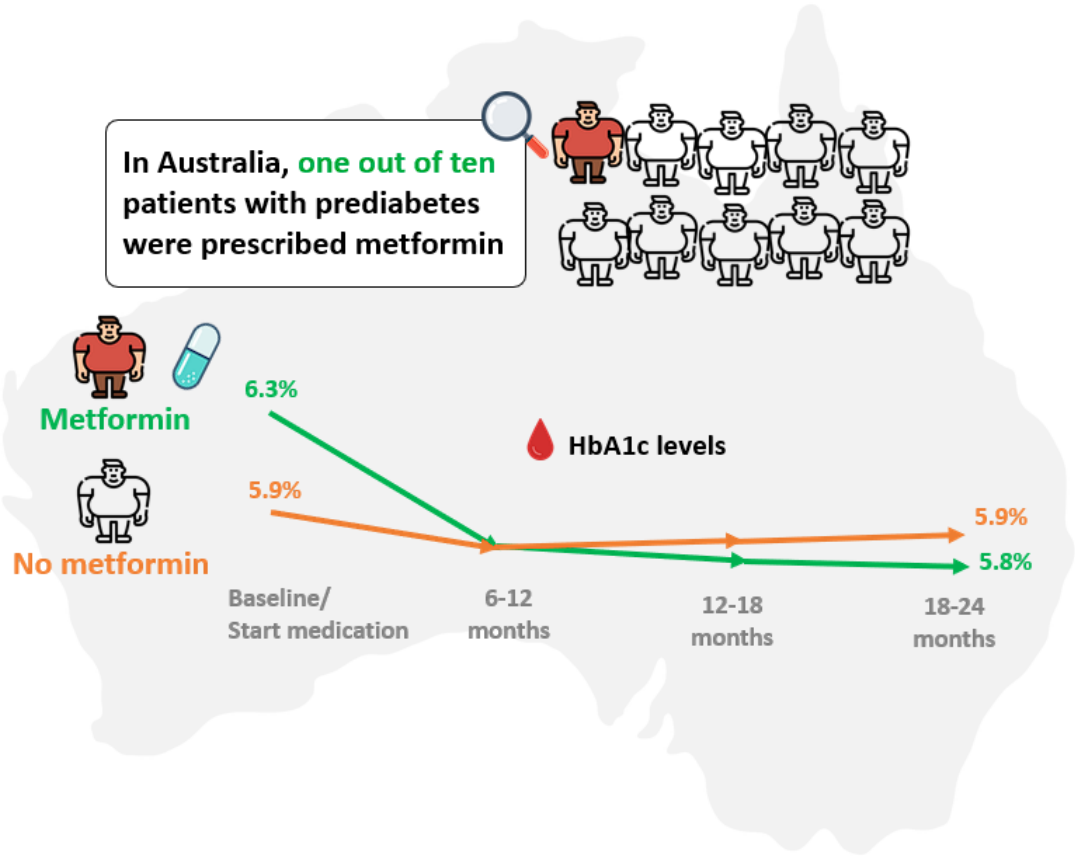
Methods: This retrospective cohort study used electronic health records of regular participants (3+ visits in two consecutive years) attending 383 Australian general practices (MedicineInsight). Participants with 'incident' prediabetes (newly recorded diagnosis between 2012 and 2017) and their glycaemic parameters (haemoglobin A1c [HbA1c] or fasting blood glucose [FBG]) at 6-, 12-, and 18–24 months post diagnosis (unexposed) or post-management with metformin (treatment) were identified from the database. We estimated the average treatment effect (ATE) of metformin management on glycaemic parameters using both linear regression and augmented inverse probability weighting.

Results: Of the 4770 investigated participants with 'incident' prediabetes, 10.2% were managed with metformin. Participants on metformin had higher HbA1c levels at the baseline than those unexposed (mean 45 mmol/mol [6.2%] and 41 mmol/mol [5.9%], respectively), but no differences were observed at 6–12 months (mmol/mol ATE 0.0, 95% CI −0.4; 0.7) or 12–18 months (ATE −0.3, 95% CI −1.2; 0.3). However, participants on metformin had lower mean HbA1c mmol/mol at 18–24 months (ATE −1.1, 95% CI −2.0; 0.1) than those unexposed. Consistent results were observed for FBG (ATE at 6–12 months −0.14 [95% CI −0.25; −0.04], 12–18 months 0.02 [95% CI −0.08; 0.13] and 18–24 months −0.07 [95% CI −0.25; 0.12]).

Conclusion: The higher HbA1c and FBG baseline levels among participants with 'incident' prediabetes managed with metformin improved after 6–12 months of starting pharmacological management, and the effect persisted for up to 24 months. Management with metformin could prevent further deterioration of glycaemic levels.

Mingyue Zheng and Soumya should be considered joint first author.

Graphical Abstract of Paper 4



Appendix H. Supplementary Materials for Chapter 8

Table H1. Medicare Benefits Schedule item number 2517 – Minimum requirements of care to complete an annual diabetes cycle of care for patients with established diabetes mellitus

Minimum requirements	Frequency
Weight and height plus body mass index (BMI)	At least twice every cycle of care
Blood pressure index	At least twice every cycle of care
Feet examination	At least twice every cycle of care
Measure total cholesterol, triglycerides and high-density lipoprotein-cholesterol (HDL-C)	At least once every year
Glycated haemoglobin (HbA1c)	At least once every year
Microalbuminuria	At least once every year
Estimated glomerular filtration rate (eGFR)	At least once every year
Self-care education, diet, physical activity, smoking evaluation	At least once every year
Medication review	At least once every year
Ensure that a comprehensive eye examination is carried out at least once every two years	At least once a year if complications are detected
NB: A new item on the Medicare Benefits Schedule (MBS) for retinal photography with a non-mydriatic retinal camera will be available for general practice use from November 2016. The listing is expected to benefit Aboriginal and Torres Strait Islander peoples and communities in rural and remote locations, where there is limited access to optometric and ophthalmic services to diagnose diabetic retinopathy	

Source: RACGP (2020)[73]

Appendix I. Supplementary Materials for Chapter 9

Table I1. Forms of incentive schemes offered for practices participating in National Diabetes Prevention Programme (by responding site) in England

Site	Per referral letter sent (fee-for-service)	Per actual patient referred (pay-for-performance)	Per patient population (capitation)	Other	Amount
ProviderA					
Local site 1	Y	N	N	N	£1.50 per referral letter sent
Local site 2	Y	N	N	N	Amount not Stated
Local site 3	N	N	N	N	No incentives offered
Local site 4	N	Y	N	N	CCG two pay point referral contract with GP Federations (400-700 = £6,000; 700+ =£12,000)
Local site 5	Y	N	N	N	£0.70 per referral letter sent
Local site 6	Y	N	N	N	£1.50 per referral letter sent
Local site 7	N	N	Y	N	No incentives offered by most CCGs. One CCG per patient population amount not stated
Local site 8	N	N	N	Y	Part of local long-term care contract
Provider B					
Local site 9	N	Y	Y	N	£0.20 per patient population Yr1. 41 practices offered £1.00 per patient contact Yr2
Local site 10	Y	N	N	N	£1.50 per referral letter sent
Local site 11	N	N	N	Y	Part of local primary care contract
Local site 12	N	N	Y	N	Funding from NHS England split between practices.
Local site 13	N	N	N	Y	Part of local Quality Outcomes for Health
Local site 14	N	Y	Y	N	£2.05 per patient population in one area (including case finding). Others gave block payments but amounts not stated
Local site 15	Y	N	N	N	£2.91 per referral letter sent (one CCG)
Provider C					
Local site 16	N	N	N	N	No incentives offered
Local site 17	N	Y	N	N	£4.00 per actual referral
Local site 18	N	N	Y	N	£0.10 per patient population
Local site 19	Y	N	N	N	£1 per referral letter sent
Local site 20	Y	N	N	N	Incentives Yr1 but dropped. Declined to provide financial details
Local site 21	N	Y	N	N	£9 per actual referral (approx. as CCGs differ)
Local site 22	Y	N	Y	N	£1.50 per referral letter sent Yr1. £0.05 per patient population Yr2
Local site 23	N	N	N	N	No incentives offered
Local site 24	Y	Y	N	N	Declined to provide financial details
Local site 25	Y	N	N	N	Amount not Stated
Provider D					
Local site 26	N	Y	N	N	£10 per actual referral Yr1. £2 per actual referral Yr2
Local site 27	Y	N	N	N	£1.50 per referral letter sent
Local site 28	N	Y	N	Y	£250 one off practice payment then £45 for actual uptake (one CCG) £13.52 per actual referral (one CCG)
Local site29	Y	N	N	N	£4 per referral letter sent and phone follow up
Local site 30	N	Y	Y	N	£5.95 per patient (one CCG). £0.07 per patient population (one CCG)

Source: Stokes (2019)[180]

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