Received: 19 January 2023 | Accepted: 27 June 2023

DOI: 10.1111/dme.15170

DIABETIC Medicine

RESEARCH: TREATMENT

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

Mingyue Zheng[1] | **Soumya**[1] | **Mumtaz Begum**[1] | **Carla De Oliveira Bernardo**[1] | **Nigel Stocks**[1] | **Habiba Jahan**[1] | **David Gonzalez-Chica**[1,2]

[1]Discipline of General Practice, Adelaide Medical School, The University of Adelaide, Adelaide, South Australia, Australia

[2]Adelaide Rural Clinical School, The University of Adelaide, Adelaide, South Australia, Australia

Correspondence
Mumtaz Begum and David Gonzalez-Chica, Discipline of General Practice, Adelaide Medical School, The University of Adelaide, 115 Grenfell Street, Level-8, Adelaide, SA 5000, Australia.
Email: mumtaz.begum@adelaide.edu.au and david.gonzalez@adelaide.edu.au

Funding information
The Royal Australian College of General Practitioners Foundation/ Diabetes Australia Research Grant (DIA2021-06)

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.

KEYWORDS
drug prescriptions, electronic health records, epidemiologic methods, general practice, hypoglycaemic agents, population health, pre-diabetic state

1 | INTRODUCTION

Prediabetes is a condition characterised by elevated blood glucose levels (i.e. fasting blood glucose [FBG] 6.1–6.9 mmol/L, haemoglobin A1c [HbA1c] 6.0%–6.4% and/or oral glucose tolerance tests [OGTT] 7.8–11.0 mmol/L).[1] Similar to diabetes mellitus, prediabetes also increases the risk of complications such as diabetes retinopathy, chronic kidney disease and cardiovascular disease.[1,2] It is estimated that prediabetes affects about 16.4% (3.3 million) of Australian adults,[1] with up to 75% potentially progressing to diabetes over their lifetime.[3] Managing prediabetes through lifestyle modifications is crucial to prevent its progression to diabetes and avoid relevant complications.[1,4] However, long-term adherence to lifestyle modifications is challenging.[5–7] 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.[1,4,8]

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.[1,5,9] 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.[6,10–14] 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 3234 adults with prediabetes. Compared to placebo, metformin and lifestyle intervention substantially reduced progression to diabetes by 31% and 58%, respectively.[6] The Diabetes Prevention Program Outcomes Study ($N = 2276$) 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.[14] 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.[5,15–17]

People with prediabetes are already being prescribed metformin (off-label prescribing) in many countries, including Australia, the United States and the United Kingdom (UK).[9–11] However, in Australia the use of ADM for prediabetes management is not yet recommended in current guidelines.[1,8] 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.

What's new?

- In Australia, general practitioners prescribed metformin to over one in 10 adults with incident prediabetes. Despite having higher baseline haemoglobin A1c (HbA1c) levels, participants 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.
- Metformin therapy for incident prediabetes with high baseline glycaemic levels could help prevent further deterioration of glycaemic parameters.

In Australia, adults with prediabetes visit their general practitioners (GP) on average five times per year,[18] with data on the prescriptions they received and laboratory results systematically recorded and stored electronically.[19] 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.[20,21] Confounding in these studies (i.e. longitudinal observational data) was handled by creating a pseudo population that considers every participant 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.[21] Therefore, by using a large Australian general practice database (MedicineInsight), we aimed to investigate whether participants with recent prediabetes diagnosis who received metformin achieved

better glycaemic levels (HbA1c and FBG) within the first 2 years than their peers, not on metformin.

2 | METHODS

2.1 | Study design and data source

In this observational retrospective cohort study, we used deidentified EHRs of adult participants from general practices included in the Australian primary care database MedicineInsight, with data recorded between 2011 and 2018. In 2018, MedicineInsight comprised more than 2700 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.[19]

2.2 | Study population

We used EHRs from practices with consistent data provision over time (i.e. established at least 2 years before the end of the analysis period, gap lower than 6 weeks in data provided during the last 2 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]).[19] A total of 383 practices were included. Additionally, we only included 'regular' participants (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 2 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 participants). 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). Participants 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 6.1–6.9 mmol/L; HbA1c 42–46 mmol/mol [6.0%–6.4%]; or OGTT 7.8–11.0 mmol/L)[1] was reported up to 4 weeks before or up to 2 weeks after the recorded diagnosis. We included only participants 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 participant commenced with the first recorded diagnosis of prediabetes (T0) and ended at the earliest of (1) 24 months after diagnosis, (2) on the 30 December 2018 or (3) the appointment before diabetes diagnosis. The final investigated cohort sample consisted of 4770 regular adult participants 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 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,[12,18,22] or (3) had a diagnosis of diabetes within 90 days of being diagnosed with prediabetes. The methodology used to identify participants with diabetes has been previously described.[18]

2.3 | Exposure

Information on whether or not a participant 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),[23] 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 participants were prescribed metformin after the first prescription, as that is a similar approach to the intention to treat analysis in RCTs.

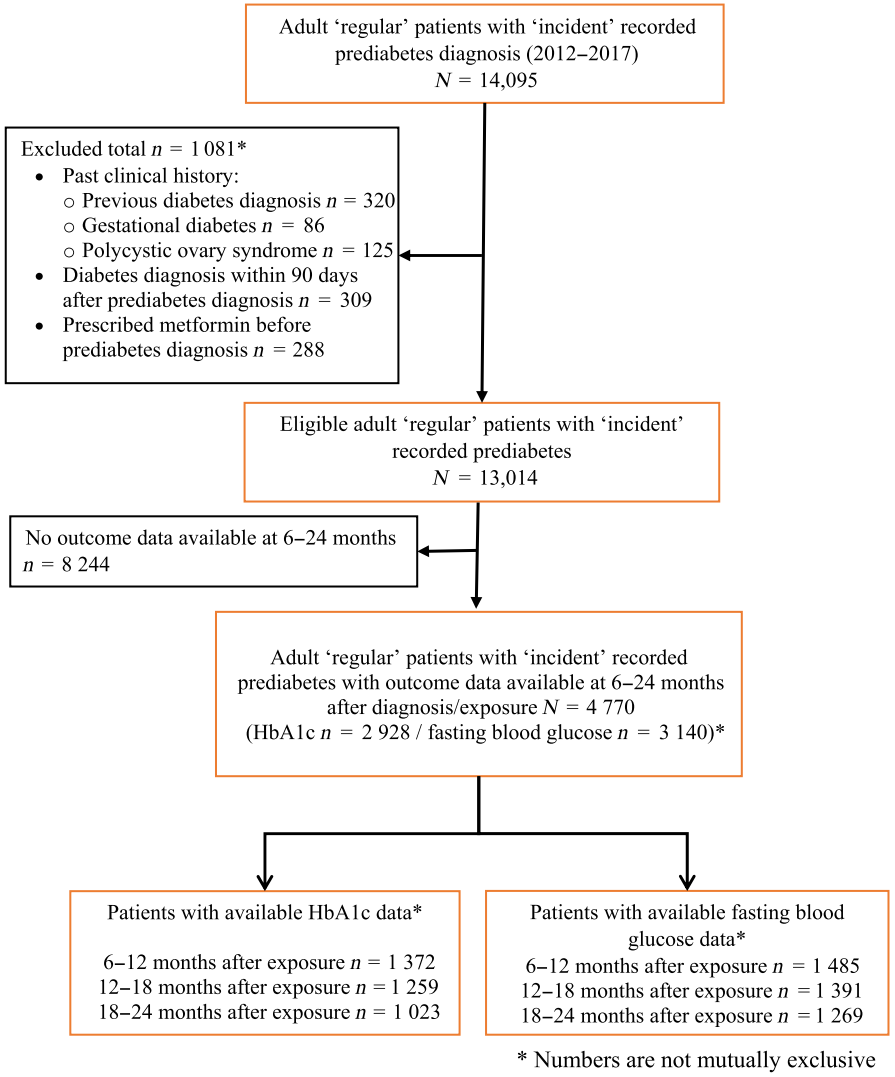


FIGURE 1 Flow chart of the study sample.

2.4 | 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 participant was diagnosed with diabetes.

2.5 | Confounders

Confounders were identified a priori based on background knowledge[1,16,18] and their relationships assessed using a directed acyclic graph (Figure S1). These confounders included practice level and participant 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.[19,24] Higher IRSAD scores indicate that people are in more advantaged areas.

Participants' characteristics included age (continuous variable), gender (men and women), 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 participants 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 2 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.[19]

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.

2.6 | 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).[21] 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 participants with 'incident' prediabetes managed with metformin compared to those not prescribed that medication. AIPW is a doubly robust method that can produce consistent estimates if either the 'treatment' or 'outcome' model is correctly specified.[21] To obtain reliable estimates of the ATE of metformin management on glycaemic parameters in participants with incident prediabetes, we used linear regression and AIPW models, incorporating key assumptions (i.e. exchangeability, positivity, no interference, consistency).[21,25,26] Regarding exchangeability, we included a wide range of potential confounders and indicator variables (e.g. socio-economic 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 unavailable in Medicineinsight. Therefore, we performed different sensitivity analyses to minimise the potential impact of unmeasured confounders. Second, to ensure that all participants had a non-zero probability of receiving metformin management (i.e. positivity),[25] we explored for extremely large or small weights (0.7%), which were discarded before weighting. Third, our analyses achieved minimal interference by considering the clustering of participants within practices (i.e. intragroup correlation). Fourth, we assumed consistency[26] 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.[27] Based on current literature regarding the use of multiple imputation, we included the outcome in the imputation model to avoid biased estimates.[28,29] Apart from all confounders mentioned in Table 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.[30] Rubin's rules[31] 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), and all models considered the clustering of participants 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.

3 | RESULTS

Of the 13,014 eligible regular adult participants with 'incident' recorded prediabetes between 2012 and 2017 (51.7% men, mean age 63.9 ± 12.7 years), 4770 (51.9% men, mean age 65.9 years) had data available about at least one of the investigated outcomes at one of the assessed time points (Figure 1; Table 1). The final analysed cohort had sociodemographic and clinical characteristics similar to the original eligible sample, except for a higher proportion of participants attending practices located in outer regional/remote/very remote areas. Moreover, no systematic

TABLE 1 Characteristics of the eligible sample and the final cohort included in our study. Participants with 'incident' recorded diabetes between 2012 and 2017.

	Eligible sample[a] $N = 13,014$ initial data (%)	Final cohort[b] $N = 4770$ 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
Participants' demographic characteristics		
Gender: male	51.7	51.9
Age, mean ± SD	63.9 ± 12.7	65.9 (SE = 0.2)
Participants' 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
Participants' 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%

Abbreviations: FBG, fasting blood glucose; GP, general practitioner; HbA1c, haemoglobin A1c; IRSAD, Index of Relative Socio-Economic Advantage and Disadvantage; SD, standard deviation; SE, standard error.

[a]Eligible sample (regular adult participants with 'incident' recorded prediabetes).

[b]Final cohort (regular adult participants with 'incident' recorded prediabetes, with outcome data available at 6–24 months after diagnosis/exposure).

differences were observed when those with available outcome data at 6–12, 12–18 or 18–24 months were considered (Table S1). Overall, 10.2% of the analysed cohort was managed with metformin.

Table 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). Participants with 'incident' prediabetes who were prescribed metformin were more likely to be women, live in more socio-economically 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 S2).

HbA1c (Figure 2a) and FBG levels (Figure 2b) at baseline were higher among participants with 'incident' prediabetes who were prescribed metformin than their peers (imputed adjusted data). Participants who received metformin experienced considerable attenuation in their HbA1c and FBG levels at 6–12 months after exposure

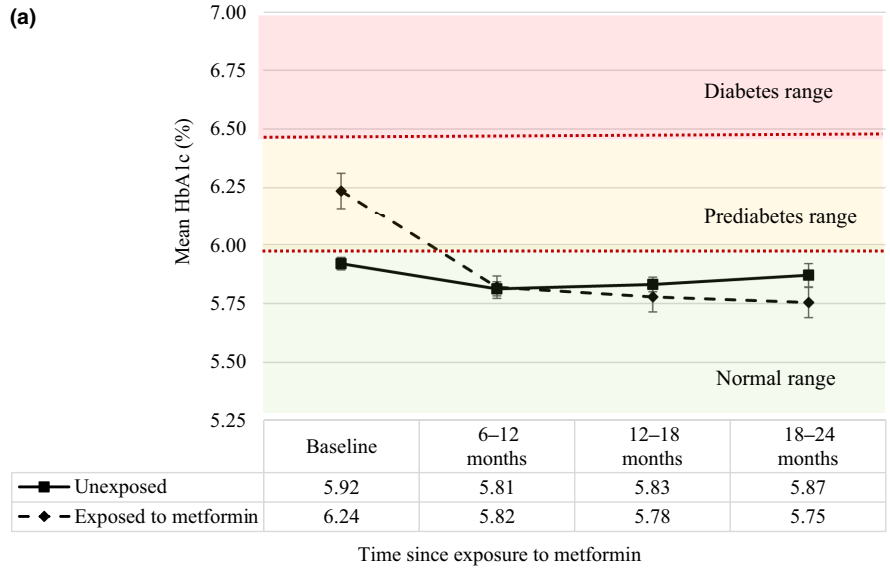
TABLE 2 Baseline characteristics of the regular adult participants (18+) with 'incident' recorded prediabetes included for analysis according to exposure and outcome variables (imputed data, unadjusted results).

	HbA1c as an outcome $N = 2928$		FBG as an outcome $N = 3140$	
	Unexposed $n = 2526$ (%)	**Exposed to metformin** $n = 402$ (%)	**Unexposed** $n = 2860$ (%)	**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
Participants' 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)
Participants' 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
Participants' 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

Abbreviations: FBG, fasting blood glucose; GP, general practitioner; HbA1c, haemoglobin A1c; IRSAD, Index of Relative Socio-Economic Advantage and Disadvantage; SE, standard error.

to metformin, following a similar curve of no difference (FBG) or slightly lower glycaemic levels (HbA1c) within 24 months than participants not managed with metformin.

Table 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 S2; Table S3).



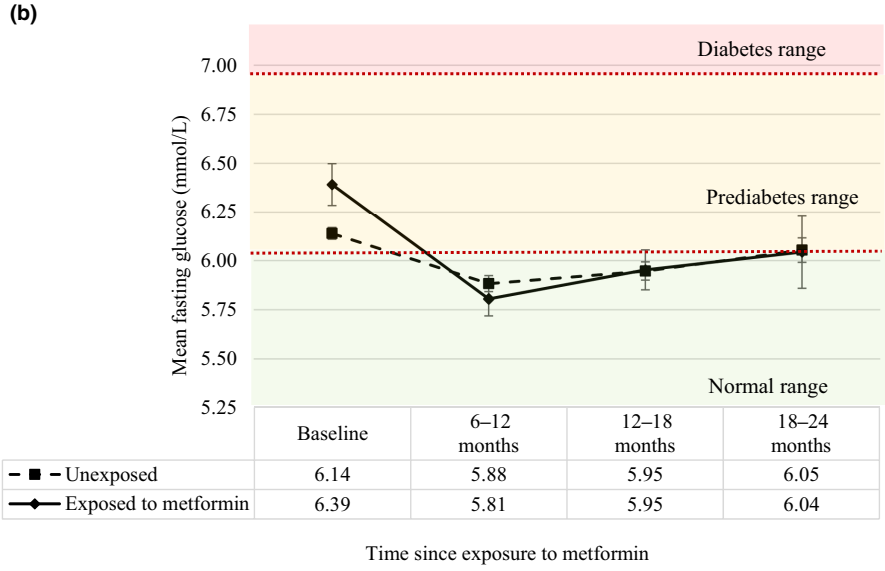


FIGURE 2 Predicted adjusted mean of HbA1c (a) or fasting blood glucose (b) at baseline, 6–12, 12–18 and 18–24 months after diagnosis/exposure (imputed data). Results based on linear regression models adjusted for practice characteristics (remoteness, and practice Index of Relative Socio-economic Advantage and Disadvantage [IRSAD]) and participant characteristics (baseline glycaemic levels, age, gender, smoking status, ethnicity, participants' 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 (≤6.0 mmol/L), prediabetes range (6.1–6.9 mmol/L), diabetes range (≥7.0 mmol/L).

4 | DISCUSSION

This open cohort study estimated the effect of metformin on glycaemic control in participants with 'incident' prediabetes diagnosed between 2012 and 2017. First, the results demonstrated that up to 10.2% of participants with 'incident' prediabetes were prescribed metformin in general practice, despite Australian guidelines not recommending its use.[1] Second, higher baseline glycaemic levels among these participants probably influenced the GPs' decisions to start pharmacological management with metformin. Third, participants 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 ($N = 6774$ participants) that reported better HbA1c levels (β −0.08%, 95% CI −0.22; 0.05, six trials) and better FBG values (β −0.28 mmol/L, 95% CI 0.42; −0.13, 18 trials) after 1–5 years of intervention duration among participants with prediabetes managed with metformin compared to regular diet and exercise.[32] However, metformin was not better than intensive diet and exercise programs in reducing or delaying the development of diabetes among these participants.[32] Lifestyle data is not systematically recorded in MedicineInsight, hindering us from performing such comparisons. We assume participants unexposed to metformin received lifestyle recommendations from their GP according to current guidelines,[1] as they also showed

TABLE 3 Comparison of the effect of metformin exposure on HbA1c and fasting blood glucose among regular adult participants with 'incident' prediabetes using traditional linear regression models or augmented inverse probability weighting (imputed data).

		Crude mean		Linear regression[a]		AIPW[a]	
		mmol/mol	%	mmol/mol	%	mmol/mol	%
	N	(95% CI)	(95% CI)	*β*. (95% CI)	*β*. (95% CI)	ATE (95% CI)	ATE (95% CI)
HbA1c at 6–12 months							
Unexposed	1140	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	1080	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	1323	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	1269	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	1167	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)	

Abbreviations: AIPW, augmented inverse probability weighting; ATE, average treatment effect; FBG, fasting blood glucose; HbA1c, haemoglobin A1c; IRSAD, Index of Relative Socio-economic Advantage and Disadvantage; Ref, reference group.

[a]Adjusted for practice characteristics (remoteness, practice IRSAD) and participant 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, participants' IRSAD, heart failure, dyslipidaemia, ischaemic heart disease, hypertension, prescription of antipsychotic medication and total person time.

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.[7] Furthermore, metformin is the ADM with the highest adherence rate (63%–74% after 1 year of treatment), and using that drug for diabetes prevention can be cost-effective.[12–14,16] Despite these positive aspects, metformin adherence decreases after the first year,[33] and the beneficial effects on diabetes prevention cease after the management with metformin is stopped.[5] Still, according to our findings, participants with prediabetes who were 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 participants 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.[11]

Metformin is not currently subsidised or recommended in clinical guidelines for prediabetes management in Australia.[1] 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 participants 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).[10] 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 >35 kg/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 participants with prediabetes and more pronounced impaired fasting glucose.[16] 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 participants with 'incident' prediabetes and higher glycaemic levels were more likely to be prescribed metformin. These findings are relevant for further implementation strategies targeting participants 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.[34,35] Additionally, measuring HbA1c is more convenient than FBG, as it does not require fasting for 8–12 h.[35]

Some of the study's strengths include using a large sample of participants 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, participant 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.[24] Second, we had significant attrition of our sample size, as only 37% of eligible participants had outcome data available for analysis. Despite it did not impact our results, as the final cohort was comparable to the eligible participants according to most characteristics, including baseline HbA1c and FBG levels. This finding is concerning because participants 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 participants. 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 the 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.

5 | CONCLUSIONS

Australian GPs prescribe metformin to over one in every 10 participants with 'incident' prediabetes, particularly those with higher baseline glycaemic levels. Our study supports the use of metformin in participants 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.

AUTHOR CONTRIBUTIONS

Mingyue Zheng and David Gonzalez-Chica contributed to the conception and design of the study. Mingyue Zheng and Soumya prepared the first draft of the manuscript with input from Mumtaz Begum. Mumtaz Begum performed the statistical analysis and helped write and edit the draft. David Gonzalez-Chica supervised this study and edited the manuscript. Nigel Stocks, Carla De Oliveira Bernardo and Habiba Jahan 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.

ACKNOWLEDGEMENTS

We thank NPS MedicineWise for providing the MedicineInsight data for this study. In addition, we are grateful to all general practices and general practitioners that participate in MedicineInsight, and the participants who allow the use of their deidentified information. Open access publishing facilitated by The University of Adelaide, as part of the Wiley - The University of Adelaide agreement via the Council of Australian University Librarians.

FUNDING INFORMATION

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.

CONFLICT OF INTEREST STATEMENT

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.

ETHICS STATEMENT

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.

DISCLOSURE SUMMARY

The authors have nothing to disclose.

ORCID

Mingyue Zheng https://orcid.org/0000-0002-7946-8911
Mumtaz Begum https://orcid.org/0000-0001-6302-3697

REFERENCES

1. Bell K, Shaw JE, Maple-Brown L, et al. A position statement on screening and management of prediabetes in adults in primary care in Australia. *Diabetes Res Clin Pract*. 2020;164:1872-8227.
2. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. *Diabetes Care*. 2021;44(Suppl 1):S15-S33. doi:10.2337/dc21-S002.
3. Ligthart S, van Herpt TTW, Leening MJG, et al. Lifetime risk of developing impaired glucose metabolism and eventual progression from prediabetes to type 2 diabetes: a prospective cohort study. *Lancet Diabetes Endocrinol*. 2016;4(1):44-51.
4. American Diabetes Association. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2020. *Diabetes Care*. 2020;43:1935-5548.
5. Haw JS, Galaviz KI, Straus AN, et al. Long-term sustainability of diabetes prevention approaches: a systematic review and meta-analysis of randomized clinical trials. *JAMA Intern Med*. 2017;177(12):1808-1817.
6. Knowler WC, Barrett-Connor E, Fowler SE, et al. Diabetes prevention program research G. reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002;346(6):393-403.
7. Dunkley AJ, Bodicoat DH, Greaves CJ, et al. Diabetes prevention in the real world: effectiveness of pragmatic lifestyle interventions for the prevention of type 2 diabetes and of the impact of adherence to guideline recommendations: a systematic review and meta-analysis. *Diabetes Care*. 2014;37(4):922-933.
8. The Royal Australian College of General Practitioners. *General Practice Management of Type 2 Diabetes: 2016–18*. RACGP; 2016.
9. Sheng Z, Cao JY, Pang YC, et al. Effects of lifestyle modification and anti-diabetic medicine on prediabetes progress: a systematic review and meta-analysis. *Front Endocrinol*. 2019;10:455.
10. Tseng E, Yeh HC, Maruthur NM. Metformin use in prediabetes among U.S. adults, 2005-2012. *Diabetes Care*. 2017;40(7):887-893.
11. Hostalek U, Gwilt M, Hildemann S. Therapeutic use of metformin in prediabetes and diabetes prevention. *Drugs*. 2015;75(10):1071-1094.
12. Moin T, Schmittdiel JA, Flory JH, et al. Review of metformin use for type 2 diabetes prevention. *Am J Prev Med*. 2018;55(4):565-574.
13. Zhou X, Siegel KR, Ng BP, et al. Cost-effectiveness of diabetes prevention interventions targeting high-risk individuals and whole populations: a systematic review. *Diabetes Care*. 2020;43(7):1593-1616.
14. Diabetes Prevention Program Research Group. Long-term effects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the diabetes prevention program outcomes study. *Lancet Diabetes Endocrinol*. 2015;3(11):866-875.
15. Uusitupa M, Khan TA, Viguiliouk E, et al. Prevention of type 2 diabetes by lifestyle changes: a systematic review and meta-analysis. *Nutrients*. 2019;11(11):2611.
16. Aroda VR, Knowler WC, Crandall JP, et al. Metformin for diabetes prevention: insights gained from the diabetes prevention program/diabetes prevention program outcomes study. *Diabetologia*. 2017;60(9):1601-1611.
17. Warrilow A, Somerset S, Pumpa K, Fleet R. Metformin use in prediabetes: is earlier intervention better? *Acta Diabetol*. 2020;57(11):1359-1366.
18. Zheng M, Bernardo CO, Stocks N, Gonzalez-Chica D. Diabetes mellitus diagnosis and screening in Australian general practice: a National Study. *J Diabetes Res*. 2022;2022:1566408.
19. Busingye D, Gianacas C, Pollack A, et al. Data resource profile: MedicineInsight, an Australian national primary health care database. *Int J Epidemiol*. 2019;48(6):1741-1741h.
20. Chang KCM, Lee JT, Vamos EP, et al. Impact of the National Health Service Health Check on cardiovascular disease risk: a difference-in-differences matching analysis. *Can Med Assoc J*. 2016;188(10):E228-E238.
21. Funk MJ, Westreich D, Wiesen C, Stürmer T, Brookhart MA, Davidian M. Doubly robust estimation of causal effects. *Am J Epidemiol*. 2011;173(7):761-767.
22. Abdalla MA, Shah N, Deshmukh H, et al. Impact of metformin on the clinical and metabolic parameters of women with polycystic ovary syndrome: a systematic review and meta-analysis of randomised controlled trials. *Ther Adv Endocrinol Metab*. 2022;13. doi:10.1177/20420188221127142
23. Levesque LE, Hanley JA, Kezouh A, Suissa S. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ*. 2010;340:b5087.

24. Havard A, Manski-Nankervis JA, Thistlethwaite J, et al. Validity of algorithms for identifying five chronic conditions in MedicineInsight, an Australian national general practice database. *BMC Health Serv Res*. 2021;21(1):551.
25. Igelström E, Craig P, Lewsey J, Lynch J, Pearce A, Katikireddi SV. Causal inference and effect estimation using observational data. *J Epidemiol Community Health*. 2022;76(11):960-966.
26. Shiba K, Kawahara T. Using propensity scores for causal inference: pitfalls and tips. *J Epidemiol*. 2021;31(8):457-463.
27. Sterne JA, White IR, Carlin JB, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ*. 2009;338:b2393.
28. Moons KG, Donders RA, Stijnen T, Harrell FE Jr. Using the outcome for imputation of missing predictor values was preferred. *J Clin Epidemiol*. 2006;59(10):1092-1101.
29. Leyrat C, Seaman SR, White IR, et al. Propensity score analysis with partially observed covariates: how should multiple imputation be used? *Stat Methods Med Res*. 2019;28(1):3-19.
30. Begum M, Chittleborough C, Pilkington R, et al. Educational outcomes among children with type 1 diabetes: whole-of-population linked-data study. *Pediatr Diabetes*. 2020;21(7):1353-1361.
31. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Vol 81. John Wiley & Sons; 2004.
32. Madsen KS, Chi Y, Metzendorf MI, Richter B, Hemmingsen B. Metformin for prevention or delay of type 2 diabetes mellitus and its associated complications in persons at increased risk for the development of type 2 diabetes mellitus. *Cochrane Database Syst Rev*. 2019;12:CD008558.
33. Lee DSU, Lee H. Adherence and persistence rates of major antidiabetic medications: a review. *Diabetol Metab Syndr*. 2022;14(1):12.
34. Little RR, Rohlfing C, Sacks DB. The National Glycohemoglobin Standardization Program: over 20 years of improving hemoglobin A1c measurement. *Clin Chem*. 2019;65(7):839-848.
35. NPS MedicineWise. *MedicineInsight Report: HbA1c Testing in MedicineInsight Patients Newly Diagnosed, or with a History of Diabetes in 2018–2019*. NPS MedicineWise; 2020.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: Zheng M, Soumya, Begum M, et al. Do patients with prediabetes managed with metformin achieve better glycaemic control? A national study using primary care medical records. *Diabet Med*. 2023;40:e15170. doi:10.1111/dme.15170