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Adherence to metformin monotherapy in people with type 2 diabetes mellitus in New Zealand

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ABSTRACT

Aim: To describe adherence to metformin monotherapy in New Zealanders with type 2 diabetes mellitus (T2DM) initiating pharmacological treatment for the first time.

Methods: We created a cohort of all New Zealanders with T2DM commencing metformin monotherapy between 1 January 2006 and 30 September 2014 using national data collections and followed them until the end of 2015. We obtained data on person- and health-related characteristics at metformin initiation from these collections and calculated medication possession ratios from pharmacy dispensing data. Regression modelling was used to assess changes in adherence over time.

Results: We identified 85,066 people with T2DM who initiated metformin monotherapy. Lower adherence to metformin monotherapy was associated with time since initiating metformin, younger age and being of Māori or Pacific ethnicity. Higher adherence was associated with receiving more non-diabetic medications, a history of CVD and recent cancer registration.

Conclusions: Our findings are consistent with international literature and highlight groups of people who experience poor adherence over time. Understanding the drivers of lower adherence in Māori and Pacific peoples is a particular priority given the high prevalence of T2DM in these populations.

1. Introduction

Diabetes mellitus is a major global health issue. It is estimated that 425 million adults worldwide had diabetes mellitus in 2014, a prevalence of 8.8% [1]. In New Zealand, an estimated 6% of the general adult population in 2016 had diagnosed type 2 diabetes mellitus (T2DM) [2]. The prevalence of T2DM globally has been steadily growing over the last three

Abbreviations: CCI, Charlson Comorbidity Index; CVD, Cardiovascular Disease; DHB, District Health Board; MELAA, Middle Eastern/Latin American/African; MPR, Medication Possession Ratio; NHI, National Health Index; NZDep, New Zealand Deprivation Index; T2DM, Type 2 Diabetes Mellitus; VDR, Virtual Diabetes Register

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decades [1] and, if current trends continue, the number of adults in New Zealand with T2DM can be expected to double in the next twenty years [3]. Pacific and the indigenous Māori populations in New Zealand are particularly affected, with a three-fold and two-fold higher prevalence of T2DM compared to the non-Pacific and the non-Māori populations respectively [2]. T2DM is an important cause of cardiovascular disease (CVD), blindness, kidney failure, and lower-limb amputation, [1] and is the fifth highest cause of disability-adjusted life years (DALYs) lost in New Zealand [4].

Good glycaemic control has been demonstrated to reduce the risk of T2DM-related disease, and treatment of T2DM focuses on achieving this through lifestyle modifications and use of antidiabetic medications [5,6]. In New Zealand, metformin is the recommended first-line pharmacological treatment for T2DM [5,6].

For a medication to be effective, it needs to be taken. Adherence refers to whether a person takes a medication according to the prescribed schedule [7]. International research has found low adherence to antidiabetic medications, including metformin [8–12]. A meta-analysis of eleven antidiabetic medication adherence studies in three countries revealed substantial variation in adherence across studies, with the percentage of participants exhibiting 'good' adherence ranging from 44% to 90% (pooled percentage: 68%) [13]. This is concerning because suboptimal adherence to antidiabetic medications has been linked to poor glycaemic control [14–18] and increased risk of complications [19–21]. Good adherence is therefore important for achieving good clinical outcomes and quality of life for people with T2DM. Good adherence also makes good economic sense, with some research linking antidiabetic medication adherence (including metformin monotherapy) and improved glycaemic control to reduced healthcare costs [22–24].

We have found no published research examining adherence in metformin users in New Zealand at a national level. The extent to which metformin use is suboptimal, and to which it might drive differences in T2DM outcomes across population groups in New Zealand, is unknown and needs to be assessed. The availability of linkable national level data on metformin use and on health events in the Ministry of Health's data collections provides enormous scope for obtaining a population view of adherence among groups in New Zealand, as well as the role health and demographic factors might play. In this paper, the first from a larger study of metformin adherence, we provide an overview of the methods used and an initial examination of adherence in people with T2DM initiating metformin monotherapy for the first time utilising the opportunities provided by these national data collections. Specifically, we sought to assess changes in adherence over time and explore the associations of demographic and clinical factors at metformin monotherapy initiation with these changes in adherence.

2. Materials and methods

We employed a historical cohort new user design using routinely collected national data. We identified people with T2DM who initiated metformin monotherapy in New Zealand between 1 January 2006 and 30 September 2014, and had at least 455 days of follow-up, and assessed their adherence to metformin based on community pharmacy dispensing records.

2.1. Data sources

This study used routinely collected data from the New Zealand Ministry of Health's national data collections as its data source. Supplementary Table 1 briefly describes each of the data collections. Each of these collections includes a person's National Health Index (NHI), a unique code that is assigned to every health service user in New Zealand. An encrypted form of the NHI was used to link an individual's health records across the data collections.

We used the Virtual Diabetes Register (VDR) maintained by the Ministry of Health as the study's source population [25,26]. The VDR is an annually updated national register of all people with any form of diabetes mellitus (except gestational diabetes) identified using the national data collections, based on records of hospital admissions with diabetes mellitus, diabetes mellitus outpatient clinic visits, retinal screening, repeated HbA1c laboratory tests, and antidiabetic medication use. Evaluations suggest it has good capture of people with diagnosed diabetes mellitus [27–29]. The VDR algorithm includes checks to exclude women with gestational diabetes or polycystic ovary syndrome.

We then obtained data from the national data collections for people identified from the VDR. Supplementary Table 1 summarises the information we obtained from each of them.

2.2. Derivation of the study cohort

Fig. 1 summarises the derivation of the study cohort. All people listed in the VDR who received a metformin dispensing at least once between 1 January 2005 and 30 September 2014 were identified. The date of the first metformin dispensing was designated the cohort entry date. We then excluded people with a cohort entry date in 2005. This meant that study cohort members had not received metformin for at least a year prior to cohort entry, reducing the likelihood that they were past users of metformin. We also removed people with an initial metformin dose of more than 1000 mg per day, as new users of metformin are unlikely to start at such a high dose [6]. Because the study focussed on metformin monotherapy, we excluded people who had received a dispensing of any other antidiabetic medication prior to or within fourteen days of cohort entry. Hospitalisation and mortality data were used to identify and exclude people likely to have type 1 diabetes mellitus. We also excluded people with no data on days supplied in any of their metformin dispensings, as this information was needed to calculate metformin possession dates for assessing adherence. We then excluded people from overseas as well as people who died within 455 days of cohort entry and who permanently stopped taking metformin within 100 days of cohort entry (defined as not being in possession of metformin after the first 100 days until the end of the follow-up period according to their dispensing records). The latter two groups are described in the current paper but excluded from the study cohort used in the adherence analyses. We

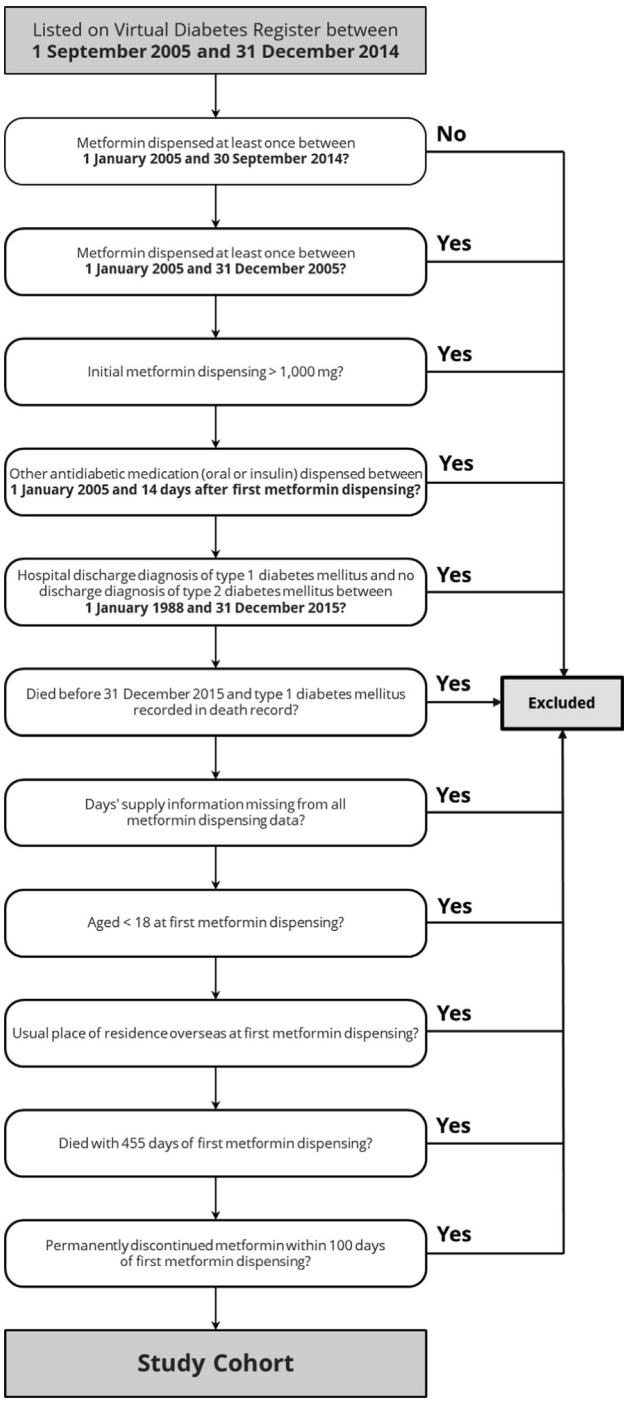

Fig. 1 – Derivation of the study cohort.

chose 455 days to provide at least a year to assess adherence and to allow us to identify if a person had discontinued in the first year of therapy (our analyses of discontinuations will be reported in future papers). We chose 100 days as it is longer than the maximum supply of metformin dispensed at a time (ninety days) and most likely represents people who stopped metformin because of side effects or clinical reasons. This group is also likely to include people who did not enter the implementation phase of medication adherence during the study period [30].

2.3. *Construction of medication record*

We created a record of metformin dispensings for each study cohort member using data from the national collections. The medication record began at the cohort entry date and stopped at whichever came first: the end of the study period (31 December 2015), date of death or the date of initiating another antidiabetic medication. To create this record, we used data from Pharms [31] on the dispensing date, days of metformin supplied and strength of metformin tablets dispensed. The days supplied were added to the dispensing date to determine the date range covered by a dispensing, with corrections made for the following situations:

- **Overlapping dispensings**, where a metformin dispensing was filled prior to the supply from the previous one being exhausted. In this situation, the dispensing date was shifted to the day after the preceding dispensing ended so that there was no overlap.
- **Simultaneous dispensings**, where a person received two dispensings for metformin at the same time for different strengths, suggesting that the actual dose per day of metformin was the sum of the different strengths. The two dispensing records were merged and, if the days supplied values were different, the longer one was used.
- **Missing days supplied value**, where the days supplied value was not recorded in Pharms. In this situation, the value from the nearest dispensing was used. If the record with the days supplied missing was equidistant from two other dispensings the mean of the two values was used.

2.4. *Adherence measure*

We measured adherence using the medication possession ratio (MPR) [32]. Briefly, the MPR is the proportion of days during a defined time period that a person was in possession of a medication, as determined by pharmacy dispensing records. For every cohort member, an annual MPR was calculated on the anniversary of cohort entry for each year of follow-up and was truncated by the end of follow-up (that is, both the numerator and denominator were reduced if follow-up ended during the year). An MPR $\geq$ 0.80 is generally considered an indicator of good adherence in the literature [33].

2.5. *Covariates*

We obtained information on the study cohort members at cohort entry, as well as those who died within 455 days of cohort entry and those who permanently discontinued, from the data sources described in Section 2.1. Covariates extracted or derived from these data sources include: age at cohort entry, gender, self-identified ethnicity, socioeconomic deprivation, district health board (DHB) region in which the cohort member resided, first metformin dispensing dose, Charlson Comorbidity Index (CCI, calculated based on hospi-

talisations in the five years prior to cohort entry), any history of CVD prior to cohort entry, cancer registration in the year prior to cohort entry, number of hospitalisations in the year prior to cohort entry, evidence of diagnosed depression in the six months prior to cohort entry, use of non-diabetic medications in the six months prior to cohort entry, glucose laboratory test (including HbA1c, fructosamine, glucose tolerance test and serum glucose) in the six months prior to cohort entry and urinary albumin/creatinine ratio test in the six months prior to cohort entry. An explanation of each of these covariates and their operationalisation is included in Supplementary Table 2. We chose these covariates because they represented important population groups for describing metformin adherence, were identified in the literature as potentially influencing metformin adherence [34,35] or were elements of recommended practice in New Zealand when deciding whether to initiate metformin [5,6].

2.6. Statistical analyses

The primary aim of the analyses presented in this paper was to assess changes in annual MPR over time and explore associations of demographic and clinical factors at cohort entry with these changes in MPR. We created violin plots to visualise the distribution of annual MPR by year of follow-up. A linear mixed spline model was used to assess the pattern of change in annual MPR over the ten years of follow-up, with a knot at year 1. We considered potential confounding by all covariates described in Section 2.5. The model included each of those covariates and an interaction term between CCI and time (after the first year). The interaction term was included because we found a statistically significant interaction between time (after the first year) and CCI ($\chi^2 = 82.82$, $p < 0.01$) in the model selection process, suggesting change in mean annual MPR differed by comorbidity after the first year of follow-up. Other interactions with time were not included due to the high correlations between health-related variables. The estimates from the model are provided in Supplementary Table 3. We used SAS (version 9.4) for data cleaning and preparation, the R statistical environment (version 3.5.1) [36] for the descriptive analyses and violin plots and Stata/IC 15.1 for fitting the linear spline model.

2.7. Ethical approvals

We obtained ethical approval from the University of Otago Human Ethics Committee (Health) (reference number HD17/027).

3. Results

We identified 418,959 individuals in the VDR during the study period. Of these, 216,236 (52%) were dispensed metformin at least once during the study period, with 148,769 individuals (36%) identified as potential initiators of metformin (see Fig. 1). After applying the remaining inclusion and exclusion criteria listed in Fig. 1, we arrived at a study population of 90,530 individuals with T2DM who were likely to have initiated metformin monotherapy during the study period. Removal of individuals who died within 455 days or permanently discontinued within 100 days of cohort entry left a study cohort of 85,066 individuals with a total of 339,930 years of follow-up time (median: 3.6 years [IQR: 2.0–5.8 years]).

The characteristics of the study cohort at cohort entry are presented in Table 1, along with those of people who died within 455 days and those who permanently discontinued within 100 days of cohort entry. Most of the study cohort members were aged 45 years or over (median age 57) at cohort entry, reflecting the typical age distribution of T2DM onset, were of European ethnicity and lived in more socioeconomically deprived areas. The pattern of DHB residence at cohort entry in study cohort members was consistent with the relative population sizes of the DHBs, as well as the sociodemographic composition of their populations. Two thirds (67%) of cohort members had an initial metformin dose of 1000 mg per day, and had had a recent glucose test (87%), with just under half having had a recent urinary albumin/creatinine ratio test (42%). Most (89%) cohort members were dispensed at least two other non-diabetic medications in the six months prior to cohort entry, and 19% had been hospitalised at least once in the year prior to cohort entry. About a quarter (24%) of cohort members had a history of CVD.

In contrast to the study cohort members, individuals who died within 455 days of cohort entry were older (median age 74 vs 57 years), more likely to be male, more likely to be European and faired more poorly in the indicators of health status measured. Permanent discontinuers were of similar age to the study cohort (median age 59 vs 57 years) at metformin initiation, with more dying during follow-up. They were also more likely to be female and be in poorer health, and less likely to have received a urinary albumin/creatinine ratio test in the six months before cohort entry.

In the first year of follow-up, 63% of cohort members had an MPR $\geq$ 0.80. In the second year, this had dropped to 58% and remained between 57% and 59% for the remaining years of follow-up. The unadjusted mean MPR for each year of follow-up is presented in Fig. 2. The mean MPR for the first year of follow-up was 0.80 (SD = 0.25). This underwent its most substantial drop in the second year of follow-up (0.72, SD = 0.35), with smaller reductions in mean MPR in subsequent years and progressively larger standard deviations. Of note is the highly skewed distribution of MPRs across the follow-up period; the main change in the distribution of MPRs across the follow-up period was in its increasingly bimodal shape. In the first year of follow-up, only 2% of cohort members had an MPR < 0.20. This had increased to 22% in the fifth year of follow-up and 31% by the tenth year.

Table 2 shows the unadjusted mean annual MPR in the first year of follow-up by covariates measured at cohort entry. There was a strong association between mean annual MPR and age, with mean MPR increasing from 0.59 in those under 25 years of age to 0.89 in those 75 years and older. Differences were also found by ethnicity; Māori and Pacific peoples had the lowest adherence (0.74 and 0.69 respectively, compared with 0.85 for Europeans). The unadjusted mean annual MPR in the first year of follow-up was lower in the most socioeconomically deprived quintile, while poorer health appeared to be associated with better adherence. We observed this for CCI, history of CVD, cancer registration in the year before

Table 1 – Characteristics at cohort entry of study cohort and people who were removed because of early permanent discontinuation or death. All groups are mutually exclusive.

	Study cohort (n = 85,066)	Died within 455 days (n = 1512)	Permanent discontinuers (n = 3952)
	N (%)	**N (%)**	**N (%)**
Died during follow-up			
Yes	5882 (6.9)	1512 (100.0)	421 (10.7)
Age (years)			
<25	752 (0.9)	3 (0.2)	98 (2.5)
25–34	3613 (4.2)	9 (0.6)	408 (10.3)
35–44	10,965 (12.9)	34 (2.2)	478 (12.1)
45–54	21,434 (25.2)	101 (6.7)	700 (17.7)
55–64	23,292 (27.4)	259 (17.1)	798 (20.2)
65–74	16,670 (19.6)	366 (24.2)	793 (20.1)
75 and over	8340 (9.8)	740 (48.9)	677 (17.1)
Gender			
Female	40,140 (47.2)	661 (43.7)	2256 (57.1)
Male	44,926 (52.8)	851 (56.3)	1696 (42.9)
Ethnicity (total count)*			
Māori	13,596 (16.0)	222 (14.7)	610 (15.4)
Pacific	11,365 (13.4)	94 (6.2)	445 (11.3)
European	46,896 (55.1)	1111 (73.5)	2306 (58.4)
Asian (Non-Indian)	6,072 (7.1)	48 (3.2)	323 (8.2)
Indian	6416 (7.5)	18 (1.2)	228 (5.8)
MELAA†	1051 (1.2)	7 (0.5)	64 (1.6)
Other	199 (0.2)	0 (0.0)	11 (0.3)
Unknown	3065 (3.6)	47 (3.1)	124 (3.1)
Ethnicity (prioritised)*			
Māori	13,596 (16.0)	222 (14.7)	610 (15.4)
Pacific	11,135 (13.1)	92 (6.1)	436 (11.0)
European	44,578 (52.4)	1083 (71.6)	2189 (55.4)
Asian (non-Indian)	5969 (7.0)	47 (3.1)	323 (8.2)
Indian	5536 (6.5)	14 (0.9)	200 (5.1)
Other	1187 (1.4)	7 (0.5)	70 (1.8)
Unknown	3065 (3.6)	47 (3.1)	124 (3.1)
Socioeconomic deprivation (NZDep13)			
Quintile 1	10,308 (12.1)	192 (12.7)	446 (11.3)
Quintile 2	12,002 (14.1)	190 (12.6)	505 (12.8)
Quintile 3	15,054 (17.7)	291 (19.2)	748 (18.9)
Quintile 4	19,427 (22.8)	397 (26.3)	956 (24.2)
Quintile 5	28,271 (33.2)	442 (29.2)	1297 (32.8)
Unknown	4 (0.0)	0 (0.0)	0 (0.0)
DHB			
Auckland	9453 (11.1)	93 (6.2)	363 (9.2)
Bay of Plenty	3665 (4.3)	91 (6.0)	188 (4.8)
Canterbury	7634 (9.0)	165 (10.9)	309 (7.8)
Capital and Coast	4505 (5.3)	86 (5.7)	254 (6.4)
Counties Manukau	14,700 (17.3)	154 (10.2)	562 (14.2)
Hawkes Bay	3403 (4.0)	72 (4.8)	147 (3.7)
Hutt	2811 (3.3)	44 (2.9)	114 (2.9)
Lakes	1880 (2.2)	44 (2.9)	102 (2.6)
MidCentral	3466 (4.1)	67 (4.4)	211 (5.3)
Nelson Marlborough	1864 (2.2)	54 (3.6)	87 (2.2)
Northland	3440 (4.0)	88 (5.8)	204 (5.2)
South Canterbury	1066 (1.3)	27 (1.8)	54 (1.4)
Southern	4939 (5.8)	115 (7.6)	257 (6.5)
Tairawhiti	999 (1.2)	26 (1.7)	47 (1.2)
Taranaki	2049 (2.4)	44 (2.9)	103 (2.6)
Waikato	6355 (7.5)	125 (8.3)	397 (10.0)
Wairarapa	857 (1.0)	20 (1.3)	44 (1.1)
Waitemata	10,103 (11.9)	151 (10.0)	419 (10.6)
West Coast	472 (0.6)	9 (0.6)	23 (0.6)
Whanganui	1396 (1.6)	37 (2.4)	67 (1.7)
Unknown	9 (0.0)	0 (0.0)	0 (0.0)

(*continued on next page*)

Table 1 – (*continued*)

	Study cohort (n = 85,066)	Died within 455 days (n = 1512)	Permanent discontinuers (n = 3952)
	N (%)	**N (%)**	**N (%)**
Initial metformin dose (mg)			
<500	1186 (1.4)	45 (3.0)	62 (1.6)
500	25,480 (30.0)	525 (34.7)	1328 (33.6)
501–849	317 (0.4)	11 (0.7)	15 (0.4)
850	842 (1.0)	16 (1.1)	45 (1.1)
851–999	12 (0.0)	915 (60.5)	2502 (63.3)
1000	57,229 (67.3)	0 (0.0)	0 (0.0)
Charlson comorbidity index			
0	73,315 (86.2)	670 (44.3)	3233 (81.8)
1	8125 (9.6)	328 (21.7)	450 (11.4)
2	2662 (3.1)	271 (17.9)	180 (4.6)
3 or more	964 (1.1)	243 (16.1)	89 (2.3)
History of CVD			
Yes	20,508 (24.1)	900 (59.5)	1085 (27.5)
Cancer registration in past year			
Yes	505 (0.6)	126 (8.3)	36 (0.9)
Number of hospitalisations in past year			
0	68,662 (80.7)	730 (48.3)	2924 (74.0)
1	10,797 (12.7)	306 (20.2)	635 (16.1)
2–4	5054 (5.9)	357 (23.6)	330 (8.4)
5–9	480 (0.6)	99 (6.5)	48 (1.2)
10 or more	73 (0.1)	20 (1.3)	15 (0.4)
Depression in past six months			
Yes	7259 (8.5)	177 (11.7)	314 (7.9)
Number of other medications used in past six months			
0–1	9207 (10.8)	51 (3.4)	481 (12.2)
2–3	17,443 (20.5)	118 (7.8)	783 (19.8)
4–5	18,443 (21.7)	156 (10.3)	773 (19.6)
6–7	14,482 (17.0)	182 (12.0)	595 (15.1)
8–9	10,074 (11.8)	206 (13.6)	463 (11.7)
10–19	14,466 (17.0)	652 (43.1)	787 (19.9)
20 or more	951 (1.1)	147 (9.7)	70 (1.8)
Glucose test in past six months‡			
Yes	73,939 (86.9)	1248 (82.5)	3311 (83.8)
Urinary albumin/creatinine ratio test in past six months			
Yes	35,434 (41.7)	462 (30.6)	1366 (34.6)

* In New Zealand, people can record up to six ethnicities. For total response, a person is counted in each of the ethnic groups they reported. For prioritised ethnicity, a person's ethnicity is allocated to a single ethnic group using a prioritisation algorithm [50]. MELAA was included in Other for the prioritised figures if not included in one of the other groups. Middle Eastern/Latin American/African.

‡ Includes HbA1c, fructosamine, glucose tolerance and serum glucose tests.

cohort entry and number of hospitalisations in year before cohort entry. The number of non-diabetic medications dispensed in the six months prior to cohort entry was strongly associated with mean annual MPR, with adherence also slightly higher in people who had had a glucose test in the six months prior to cohort entry.

Table 3 shows, other than for CCI, the average difference in annual mean MPR over time between the levels of each variable as obtained from the linear mixed spline model. On average, the mean annual MPR decreased by 0.09 (95% CI −0.09 to −0.08) from the year 1 annual MPR to the year 2 annual MPR. From year 2, the changes in mean MPR differed by CCI (Supplementary Table 3), with progressively larger reductions in mean annual MPR with increasing CCI. After adjusting for all the person- and health-related factors measured at cohort entry and the interaction between CCI and time, over years 1 – 10 the mean annual MPR was lower for those aged under 25 years and higher for those aged 45 years and over. Differences by ethnicity were also persisted, with the annual MPR for Māori and for Pacific peoples lower than for Europeans. There was very little socioeconomic differential; the difference in annual MPR over years 1 – 10 between Quintiles 1 and 5 was −0.01 (95% CI −0.02 to 0.00). There was also no difference in the annual MPR between those with a CCI score of 3 or more vs CCI of 0 at cohort entry. The annual MPR over years 1 to 10 was higher for people who had a history of CVD or a cancer registration in the year before cohort entry. It was also higher for those dispensed greater numbers of non-diabetic medications in the 6 months before cohort entry but was lower for those with a greater number of hospitalisations. Both a glucose test and a urinary albumin/creatinine ratio test in the 6 months before cohort entry were associated with a higher mean annual MPR over years 1 to 10.

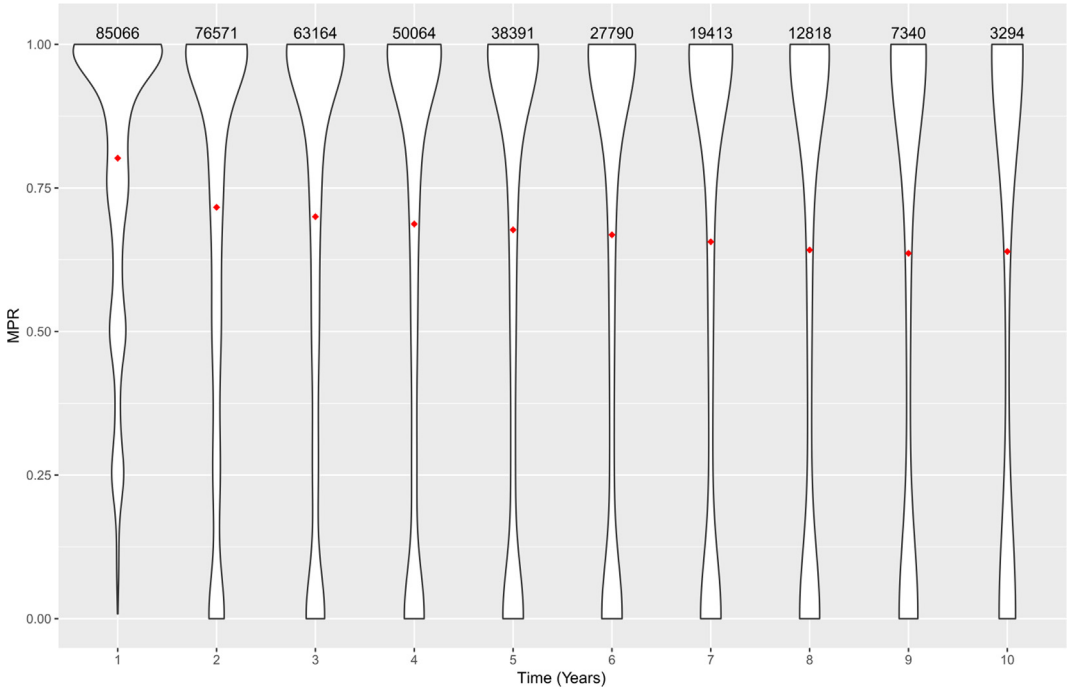

Fig. 2 – Distribution of MPR by year since metformin initiation, with number of people still in the cohort in each year. The red square indicates the unadjusted mean MPR for that year of follow-up. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

4. Discussion

This is the first study of adherence to metformin monotherapy at a national level in New Zealand. Adherence appeared high in the first year of follow-up, with a mean MPR of 0.80. However, using the commonly applied threshold for good adherence of MPR $\geq$ 0.80 revealed that only 63% of the study cohort had achieved that criterion, which is consistent with the international literature. Repeating these analyses without excluding people who permanently discontinued in the first 100 days after cohort entry did not materially alter the findings, with the mean MPR for the first year following cohort entry dropping to 0.78 and 61% of cohort members achieving an MPR of 0.80 or higher. Interestingly, the percentage of cohort members achieving good adherence remained quite stable across the follow-up years. The main change we observed was with the proportion of cohort members with an MPR < 0.20, where the proportion grew from 2% to nearly a quarter of the cohort within five years of follow-up and then to nearly a third after a decade. There is clear evidence that antidiabetic adherence is associated with glycaemic control, particularly in the early stages of T2DM progression [14–18], so the dramatic rise of very poor adherence within five years of initiation is concerning and speaks to the importance of identifying people at risk of poor adherence early in their treatment. At the other end of the adherence spectrum, 70% of those cohort members with an MPR $\geq$ 0.80 in the first year of follow-up, and who contributed ten years of follow-up time, had an MPR $\geq$ 0.80 in the tenth year of follow-up. Of the latter group, 94% had a mean MPR $\geq$ 0.80 over the ten-year follow-up period. This suggests that there may be a core group of people who are good adherers over long periods of time.

The finding that adherence was better in older cohort members is consistent with other studies of antidiabetic medication adherence [8,34,37–39]. Kirkman et al. [38] has suggested that perceived good health is a factor behind the poorer adherence observed in younger age groups. Our findings are broadly consistent with this hypothesis; after adjustment for other factors, indicators of poorer health status did appear to be associated with better adherence and persistence. That adherence was lowest in younger age groups is a concern as evidence mounts that the age of onset for T2DM in New Zealand is decreasing [40].

We observed lower metformin adherence in Māori and Pacific peoples. This finding is consistent with previous work on ethnic inequities in T2DM management in New Zealand, with Māori more likely to have sub-optimal glycaemic control and poor access to retinal screening, for example [41]. Work using the national routine data collections also suggests that Māori and Pacific peoples receive fewer prescriptions for oral hypoglycaemics, both for starting these medications and continuing once initiated [42]. This might partially be driven by socioeconomic factors posing a barrier to health care access, with Māori and Pacific peoples more likely to report not accessing primary care services or filling a prescription in the past twelve months because of cost [2,43]. However, these ethnic differences in self-reported cost barriers to filling a prescription persist, though not as strongly, even after adjusting for socioeconomic deprivation, suggesting other factors may also be playing an important role [43]. A recent report has noted

Table 2 – Unadjusted mean annual MPR during the first year after cohort entry by person- and health-related factors at cohort entry.

	Unadjusted mean annual MPR over year 1
Age (years)	
<25	0.59
25–34	0.63
35–44	0.71
45–54	0.77
55–64	0.83
65–74	0.87
75 and over	0.89
Gender	
Female	0.80
Male	0.80
Ethnicity (prioritised)*	
Māori	0.74
Pacific	0.69
European	0.85
Asian (Non-Indian)	0.80
Indian	0.76
Other	0.79
Socioeconomic deprivation (NZDep13)	
Quintile 1	0.83
Quintile 2	0.82
Quintile 3	0.82
Quintile 4	0.81
Quintile 5	0.76
DHB	
Auckland	0.77
Bay of Plenty	0.82
Canterbury	0.83
Capital and Coast	0.81
Counties Manukau	0.76
Hawkes Bay	0.82
Hutt	0.81
Lakes	0.81
MidCentral	0.83
Nelson Marlborough	0.83
Northland	0.80
South Canterbury	0.86
Southern	0.85
Tairawhiti	0.77
Taranaki	0.84
Waikato	0.81
Wairarapa	0.84
Waitemata	0.80
West Coast	0.84
Whanganui	0.80
Charlson comorbidity index	
0	0.79
1	0.84
2	0.87
3 or more	0.87
History of CVD	
No	0.78
Yes	0.86
Cancer registration in past year	
No	0.80
Yes	0.85
Number of hospitalisations in past year	
0	0.80
1	0.80
2–4	0.82
5–9	0.82
10 or more	0.85

(*continued on next page*)

Table 2 – (continued)

	Unadjusted mean annual MPR over year 1
Depression in past six months	
No	0.80
Yes	0.84
Number of non-diabetic medications used in past six months	
0–1	0.71
2–3	0.75
4–5	0.80
6–7	0.82
8–9	0.85
10–19	0.86
20 or more	0.89
Glucose test in past six months[†]	
No	0.75
Yes	0.81
Urinary albumin/creatinine ratio test in past six months	
No	0.80
Yes	0.81

[*] For prioritised ethnicity, a person's ethnicity is allocated to a single ethnic group using a prioritisation algorithm [50].
[†] Includes HbA1c, fructosamine, glucose tolerance and serum glucose tests.

Table 3 – Comparison of mean annual MPR over years 1 to 10 by person- and health-related factors at cohort entry.

	Adjusted difference in mean annual MPR over years 1 to 10[*] (95% CI)
Age (years)	
<25	−0.15 (−0.18 to −0.13)
25–34	−0.09 (−0.10 to −0.07)
35–44	Reference
45–54	0.07 (0.06 to 0.07)
55–64	0.11 (0.11 to 0.12)
65–74	0.12 (0.12 to 0.13)
75 and over	0.09 (0.08 to 0.10)
Gender	
Female	Reference
Male	0.01 (0.01 to 0.02)
Ethnicity (prioritised)[†]	
Māori	−0.08 (−0.08 to −0.07)
Pacific	−0.09 (−0.10 to −0.08)
European	Reference
Asian (Non-Indian)	0.00 (−0.01 to 0.00)
Indian	−0.02 (−0.03 to −0.01)
Other	−0.03 (−0.05 to −0.02)
Socioeconomic deprivation (NZDep13)	
Quintile 1	Reference
Quintile 2	0.00 (0.00 to 0.01)
Quintile 3	0.00 (−0.01 to 0.01)
Quintile 4	0.00 (−0.01 to 0.01)
Quintile 5	−0.01 (−0.02 to 0.00)
DHB	
Auckland	Reference
Bay of Plenty	0.03 (0.02 to 0.05)
Canterbury	0.03 (0.02 to 0.04)
Capital and Coast	0.03 (0.02 to 0.04)
Counties Manukau	0.01 (0.00 to 0.01)
Hawkes Bay	0.03 (0.02 to 0.04)

(*continued on next page*)

Table 3 – (*continued*)

	Adjusted difference in mean annual MPR over years 1 to 10* (95% CI)
Hutt	0.04 (0.03 to 0.05)
Lakes	0.03 (0.01 to 0.04)
MidCentral	0.02 (0.01 to 0.03)
Nelson Marlborough	0.03 (0.02 to 0.05)
Northland	0.01 (0.00 to 0.02)
South Canterbury	0.05 (0.04 to 0.07)
Southern	0.04 (0.03 to 0.05)
Tairawhiti	0.00 (−0.02 to 0.02)
Taranaki	0.04 (0.02 to 0.05)
Waikato	0.02 (0.01 to 0.03)
Wairarapa	0.03 (0.01 to 0.05)
Waitemata	0.02 (0.01 to 0.02)
West Coast	0.02 (−0.01 to 0.05)
Whanganui	0.02 (0.01 to 0.04)
Charlson comorbidity index‡	
0	Reference
1	0.01 (0.00 to 0.02)
2	0.02 (0.00 to 0.03)
3 or more	0.00 (−0.01 to 0.02)
History of CVD	
No	Reference
Yes	0.03 (0.02 to 0.03)
Cancer registration in past year	
No	Reference
Yes	0.02 (0.00 to 0.05)
Number of hospitalisations in past year	
0	Reference
1	−0.02 (−0.03 to −0.02)
2–4	−0.02 (−0.03 to −0.01)
5–9	−0.07 (−0.09 to −0.04)
10 or more	−0.03 (−0.10 to 0.03)
Depression in past six months	
No	Reference
Yes	0.02 (0.00 to 0.05)
Number of non-diabetic medications used in past six months	
0–1	Reference
2–3	0.04 (0.03 to 0.05)
4–5	0.07 (0.06 to 0.08)
6–7	0.09 (0.08 to 0.10)
8–9	0.10 (0.09 to 0.11)
10–19	0.10 (0.10 to 0.11)
20 or more	0.10 (0.08 to 0.12)
Glucose test in past six months¶	
No	Reference
Yes	0.04 (0.04 to 0.05)
Urinary albumin/creatinine ratio test in past six months	
No	Reference
Yes	0.02 (0.02 to 0.03)

* Change in mean MPR adjusted by all other covariates listed in the table and the interaction between CCI and time.
† For prioritised ethnicity, a person's ethnicity is allocated to a single ethnic group using a prioritisation algorithm [50].
‡ The difference refers to the difference in mean annual MPR calculated over year 1. The differences in annual MPR by comorbidity changed during follow-up as reported in the model presented in Supplementary Table 3.
¶ Includes HbA1c, fructosamine, glucose tolerance and serum glucose tests.

that the primary health care sector has not been properly funded to achieve Māori health equity and that Māori have not had adequate input into the design and delivery of primary health care services to Māori [44]. Other researchers have described how cost barriers for Māori may encompass not just monetary barriers, but also an assessment of whether the effort to access health services outweighs the potential benefits, and indirect costs such as transport, childcare and time taken off work [45]. Such findings are not unique to metformin; other research has found lower levels of adherence in Māori and Pacific peoples for many other classes of medicines, some of which is also likely to be driven by access issues [42,46]. Given the high prevalence of T2DM in Māori and Pacific populations in particular, our

findings are deeply concerning and point to the need for more work to identify the reasons behind them.

This study has some key strengths. The study population is derived from the VDR, which evaluations suggest has good capture of the diagnosed diabetes mellitus population and algorithms to exclude people with gestational diabetes or polycystic ovary syndrome [25,27,28]. Coupled with our exclusion criteria for removing people with type 1 diabetes mellitus, we are confident that the people included in this study were dispensed metformin for T2DM. Another strength of this study is that it is likely to include nearly all of the dispensings of metformin to people in the study cohort. In New Zealand, the cost of most commonly used medicines dispensed by community pharmacies is subsidised by the state, and community pharmacies submit claims for part of the cost of each dispensing. The details of these dispensings are recorded in Pharms. Pharms therefore generally has excellent capture of dispensings of subsidised medicines by community pharmacies. Metformin was a subsidised medicine during the entire study period, and so is likely to be very well recorded in Pharms. The only metformin dispensings which will not have been included are those dispensed during hospitalisations or those which might have occurred during extended overseas stays. Dispensings in either of these situations are impossible to detect in the national data collections at present. However, the number of overseas dispensings is likely to be extremely small and the impact of hospital stays is likely to be negligible as 95% of hospitalisations among cohort members during the study period were for 14 days or fewer and only 1.5% for longer than 30 days.

An unavoidable limitation of electronic health records-based research on medication adherence is that we can never truly know whether the medication dispensed was actually taken by the person to whom it was dispensed. While possession is not equal to consumption, there is good evidence to suggest that the MPR calculated from dispensing data exhibits good specificity for non-consumption of medicines [7], and that it is associated with clinical outcomes across a range of conditions including T2DM [33,47].

Another limitation was the lack of certain clinical data. Important covariates, such as body mass index, smoking status and blood pressure were not available or reliably recorded in the national data collections. While we were able to determine whether certain laboratory tests had occurred, the results of these tests were not recorded in the national data collections. Though HbA1c level may be an important influence on adherence behaviour, we were not able to assess this using the data sources available.

Perhaps one of the most important limitations is the use of the MPR itself. While reasonably unambiguous at its upper and lower quintiles, it can be difficult to interpret what it means between those values. As an example of this point, an MPR of 0.50 may represent a person who possessed metformin for the first half of a year and then stopped, a person who was completely non-adherent for the first half of the year but then became perfectly adherent in the second half, or a person who adopted a 'month on, month off' approach. Each of these scenarios are likely to lead to different clinical outcomes and require a different approach to improving adherence. As the violin plot in Fig. 2 shows, an important proportion of the cohort fell between the upper and lower quintiles. At a population level, the MPR can provide a useful metric for comparing groups and potential benchmarking, but its usefulness as a tool for understanding the process of adherence and its relationship to clinical outcomes at an individual level to ultimately inform clinical practice is limited. More nuanced approaches to characterising the temporal patterning of adherence need to be used. Researchers are applying sophisticated statistical techniques, such trajectory modelling [19,48] and multistate models [37,49], in their attempts to better characterise the temporal patterning of adherence.

In this study of people with T2DM in New Zealand who were likely to have initiated metformin monotherapy for the first time, we identified lower adherence to metformin monotherapy to be associated with time since starting metformin, younger age, and being of Māori or Pacific ethnicity, while higher adherence was associated with receiving more non-diabetic medications in the six months prior to starting metformin, a history of CVD and recent cancer registration. This is the first study to identify these associations at a national level in New Zealand. The associations with Māori and Pacific ethnic groups are particularly concerning given the higher prevalence of T2DM in these groups and, in conjunction with the existing evidence about poor experiences of interactions with clinicians and difficulties with accessing health services, point to the need for improvement across all levels of the health system to better respond to the needs of these groups. Further work based on this study cohort will extend these initial analyses by incorporating persistence and patterns of use to give a more nuanced picture of adherence in the New Zealand population.

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Declaration of Competing Interest

None

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2019.107902.

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