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TITLE PAGE

Title:

Comparative risk of new-onset diabetes following commencement of antipsychotics: A population-based study.

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Ethics Application

The University of Otago Human Ethics Committee (Health) reviewed this project as a "Minimal Risk Health Research – Audit and Audit related studies' proposal". Approval was granted (reference number HD16/061) upon satisfaction that the study described is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

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Key Words

Antipsychotics, hypnotics, diabetes, metformin, primary care, electronic prescription.

Abbreviations

T2DM = Type 2 Diabetes Mellitus

AP = Antipsychotics

FGA = First generation antipsychotics

SGA = Second generation antipsychotics

Abstract

Objective: Newer antipsychotics are increasingly prescribed off-label for non-psychotic ailments both in primary and secondary care settings, despite the purported risk of weight gain and development of type-2 diabetes mellitus. This study aims to determine any relationship between the development of clinically significant new-onset type 2 diabetes mellitus and novel antipsychotic use in New Zealand using hypnotic drugs as controls.

Design: Longitudinal population-based cohort study, using a cohort stepped-wedge cluster randomised trial design.

Setting: Routinely collected data from a complete national pharmaceutical database in New Zealand between 2005 and 2011.

Participants: Patients aged 40 to 60 years in the year 2006 who were ever dispensed antipsychotics (exposure groups – first generation antipsychotics, second generation antipsychotics, and antipsychotics with low, medium and high risk for weight gain) or hypnotics (control group) between 2006 and 2011.

Main outcome measure: First ever metformin dispensed to patients in each study group between 2006 and 2011 as proxy for development of clinically significant type-2 diabetes mellitus.

Results: Patients dispensed a second generation antipsychotic had a 1.74 times increase in risk of subsequently dispensed metformin (95% CI 1.36-2.23, P<0.01). Patients dispensed an antipsychotic with medium and high risk of weight gain also had an increased risk of commencing on metformin by 1.49 times (95% CI 1.12-1.98, P<0.01) and 2.86 times (95% CI 1.41-5.82, P<0.001) respectively. Patients dispensed hypnotics, first generation antipsychotics, and antipsychotics with low risk of weight gain did not have a statistically significant increased risk of subsequently being dispensed metformin.

Conclusions: Patients dispensed a second generation antipsychotic, and antipsychotics with medium to high risk of weight gain are at statistically significant increased risk of developing type-2 diabetes mellitus. Caution should be taken with novel antipsychotic use for patients with increased baseline risk of type-2 diabetes mellitus

ARTICLE SUMMARY

Article focus:

Measurement of the comparative risks for subsequent development of new-onset diabetes mellitus by proxy of first ever metformin dispensed for adults prescribed antipsychotics and hypnotics in New Zealand between 2006 and 2011.

Key messages:

- Patients dispensed a second generation antipsychotic have a 1.74 times (95% CI 1.36-2.23, P<0.01) increased risk of subsequently dispensed metformin for the first time.
- Patients dispensed an antipsychotic with medium risk of weight gain have an increased risk of commencing on metformin of 1.49 times (95% CI 1.12 – 1.98, P<0.01).
- Patients dispensed an antipsychotic with high risk of weight gain have 2.86 times (95% CI 1.41-5.82, P<0.001) increased risk of subsequently being dispensed metformin.
- In contrast, patients dispensed hypnotics, first generation antipsychotics, and antipsychotics with low risk of weight gain were not found to have a statistically significant increased risk of subsequently dispensed metformin.

Strengths:

- A population-based cohort study using a national electronic pharmaceutical database, representing complete population-level data for prescribing in New Zealand.
- Using the marker of first metformin dispensed as indication of development of clinically significant type-2 diabetes mellitus amongst patients prescribed antipsychotics.
- This is the first study to apply a cohort stepped-wedge design in creating an observational quasi-experimental dataset.

Limitations:

- Risk of misclassification of exposure as medications dispensed are not always taken as directed.
- Risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans.

What is already known on this topic:

- Higher doses of antipsychotics carry an increased risk of weight gain and development of type-2 diabetes mellitus in psychiatric patients.

What this study adds:

- Development of type-2 diabetes mellitus is associated with the use of second generation antipsychotics, and antipsychotics with medium to high risk of weight gain in a population setting.
- Development of type-2 diabetes mellitus is not associated with first generation antipsychotic, antipsychotics with low risk of weight gain or hypnotic agents in a population setting.

TEXT

Introduction

Higher doses of some antipsychotics (AP) increase the risk for weight gain and development of type-2 diabetes mellitus (T2DM).[1-6] This risk is widely accepted in the psychiatric community and patients on higher doses of AP, and as a result are well monitored during the course of their treatment.[4, 7, 8]

However, there is an increasing trend to prescribe AP off-label for ailments such as anxiety, insomnia, personality disorders and post-traumatic stress in primary and secondary care.[9-11] It may be perceived as less harmful, however even low doses of some AP are known to increase the risk of weight gain[1, 12, 13], which consequently may increase the risk of T2DM.[14] The risks in this population, the comparative risks of different subgroups of antipsychotics, and of standard hypnotic agents are not yet known. As obesity is now of global concern[15, 16], it is important to ascertain such risk to minimise avoidable harm from prescription medications.

Cohort studies utilising population-based electronic datasets are useful tools in analysing prescription medicine effects in the community.[17-20] This population-based cohort study investigates any associations between clinically significant new-onset T2DM, AP and hypnotic use via analyses of the national pharmaceutical dataset in New Zealand. The risk of T2DM will be measured by proxy of first dispensed metformin, indicating that clinical diagnosis is no longer amendable by lifestyle modification. The change in incidence of first dispensed metformin for patients before versus after receiving first dispensed AP (exposure group) and hypnotics (control group) will be calculated and compared to future cases who have not yet been dispensed AP and hypnotics independently.

Methods

This study utilised the national administrative electronic pharmaceutical database to evaluate the incidence of T2DM by proxy of first metformin dispensed for patients before and after they commenced on an AP. As control, the analysis was replicated in patients dispensed hypnotics, with similar exclusion criteria applied (Appendix 1). The study design was based upon a cohort stepped-wedge cluster randomised trial with a transition period (Figure 1).[21] Patients were first non-randomly allocated into cohorts according to the year they were first dispensed the exposure drug (AP or hypnotics). Outcome assessment and time between steps occur at yearly intervals, allowing for both within-subject and between-subject comparisons. This design provided a way to control for unmeasured time-invariant individual-level confounders and population-level time-variant confounders.[22]

Ethical approval

This project is approved by the University of Otago Human Ethics Committee (Health) (reference number HD16/061) upon satisfaction that this study is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994. This project is not funded externally.

Patient and Public Involvement

No identifiable patients nor public are involved.

Data source

The New Zealand government subsidises medications for all residents based on a national drug formulary. All subsidised dispensing from pharmacies in New Zealand are submitted to the New Zealand Pharmaceutical Collection (NZPC) via the State Service's General

Transaction Processing System. This data are made accessible to researchers via the New Zealand Health Information Service (NZHIS).[23] Our data were extracted via this service by Pegasus Health (Charitable) Ltd, a primary healthcare organisation in Christchurch, New Zealand. Identification and anonymity of individual patients is maintained by the encryption of their national health index (NHI) (a number unique healthcare user identifier) on data extraction and was the primary linkage key on all data extraction and analysis.

Study population and cohort construction

Dispensing data for the years 2005 to 2011 inclusive were obtained from the NZPC for individuals aged between 40 and 60 years in 2006 for the following drug classes - AP (exposure), hypnotics (exposure), metformin (outcome), and exclusion criteria drugs (patients were excluded from cohorts if they were ever dispensed drugs used to treat diabetes or drugs known to increase risk of weight gain and diabetes) (Appendix 1). The age range of patients (40 to 60 years) was selected to include individuals more commonly screened for diabetes risk in the community in New Zealand.

The four extracted datasets each contained the patients' encrypted NHI and demographics (gender and ethnicity), and dispensed medication details (name and formulation of drug, and year dispensed). Data extracts were summarised and merged by encrypted NHI and year. Individual drugs were then combined into drug classes to achieve sufficient power in the analysis. AP were grouped two ways for analysis. Firstly as first or second generation antipsychotics (FGA or SGA respectively). Secondly, by published risk of weight gain – low, medium and high-risk AP (Appendix 1). Clozapine and Olanzapine were categorised high-risk, Chlorpromazine, Quetiapine, Risperidone, and Amisulpride were categorised medium-

risk, and Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol were categorised low-risk.[6]

Binary variables were created to indicate whether an individual in a given year was ever dispensed each of the study drug classes, metformin, and/or exclusion drugs. For the purposes of the analysis, AP groups were considered the exposures of interest, hypnotics as the negative control exposure, and metformin as the outcome.

Participant selection

A sub-dataset of new patients was then prepared for constructing each of the study cohorts by selecting patients who were dispensed the exposure drug at any time between 2006 and 2011 (open cohorts). To create a cohort of "non-diabetic new-users", patients were excluded if they were dispensed the exposure drug or metformin in 2005. Patients dispensed an oral hypoglycaemic agent or injectable insulin in any calendar year before being dispensed metformin were also excluded as they were assumed to have pre-existing diabetes.

Patients in these open cohorts were followed from 2006 until 2011, or until one of the three following events occurred - the patient was dispensed metformin, the patient ceased using the exposure drug after having started it (intermittent users), or the patient started an exclusion drug.

For sensitivity analysis, closed cohorts were created by completely excluding all patients who ceased using the exposure drug after having started it, or who were recorded as having being dispensed a known diabetogenic drug between 2005 and 2011 inclusive.

Death or emigration of participants was not recorded in the dataset and was estimated to be less than 2%, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.[18]

Statistical methods and analysis

Patient and cluster characteristics were summarised using simple descriptive statistics. Crude incidence rates were initially calculated by grouping the data by exposure cohort and by year of observation, followed by counting the number of patients first dispensed metformin (numerator) and then dividing this by the total number of patients under observation (denominator). Annual incidence rates were plotted by time before and after initiating the exposure drug.

The effect of each exposure drug on incidence of metformin initiation was modelled independently using a generalised linear model (GLM), with a log link and robust 'sandwich' standard errors. Clustering of observations within an individual were accounted for using generalised estimating equations (GEE) with an 'ar1' correlation structure. Two time-dependent binary variables were used to indicate any year and the first year that an individual was dispensed the exposure medicine (labelled as 'taking exposure drug' and 'transition year' respectively). In addition, the log of 'years since first dispensed' was included to investigate acute (year 1 or 'transition year') versus chronic exposure (years 2-5). Being dispensed an exclusion drug, and year of observation were included as time-dependent confounders in the model, and gender and ethnicity as time-independent confounders. Analysis was performed using the package 'geepack' available on R.[24]

Results

Cohort characteristics:

A total of 236,826 unique patients were dispensed one of the exposure drugs during the study period. After exclusion of individuals who did not meet eligibility criteria, 171 119 patients were eligible in the open cohorts – 157 275, 5 551 and 18 942 in the groups who had prescription initiated for hypnotic, FGA, SGA, respectively (Table 1). 861 participants (15.5% of those on FGA, and 4.5% of those on SGA) were recorded as having been dispensed a both FGA and a SGA in the same year and were excluded for analysis. For patients in on all APs, 4 848, 17 955 and 2 867 met the drug inclusion criteria and were analysed in the low, medium and high-risk AP groups (for weight gain) separately from the initial analysis, but will be excluded if patients transitioned from a high to low-risk antipsychotic group during the study period.

For sensitivity analysis, a total of 39 923 patients were analysed – 32 452, 454 and 7 017 in the groups who had ever been dispensed a hypnotic, FGA, SGA, respectively (Table 1).

Table 1: Number of participants included in analysis and reasons for exclusion

	Exposure drug					
	Hypnotics	**First generation antipsychotics**	**Second generation antipsychotics**	**Low-risk antipsychotics**	**Medium-risk antipsychotics**	**High-risk antipsychotics**
Ever dispensed the exposure drug between 2005 to 2011	**217,958**	**11,903**	**33,121**	**10,218**	**30,701**	**8,393**
Dispensed exposure drug in	33,033	3,281	9,871	2,179	7,632	3,797

	Exposure drug					
	Hypnotics	**First generation antipsychotics**	**Second generation antipsychotics**	**Low-risk antipsychotics**	**Medium-risk antipsychotics**	**High-risk antipsychotics**
2005						
Dispensed exclusion drug in 2005 or 2006	34,472	4,415	6,034	4,016	6,977	3,098
Dispensed metformin in 2005	5,581	583	1,301	489	1,184	426
Dispensed insulin or oral hypoglycaemic prior to metformin	3218	419	631	362	620	136
Included in open cohort analysis	**157,275**	**5,551**	**18,942**	**4,848**	**17,955**	**2,867**
Dispensed an exclusion drug in 2005 to 2011	56,738 (36.1%)	3,938 (70.9%)	6,267 (33.1%)	3,651 (75.3%)	7,110 (39.6%)	1,699 (59.3%)
Stopped using exposure drug prior to 2011	105,561 (67.1%)	3,890 (70.1%)	8,461 (44.7%)	3,245 (66.9%)	8,853 (49.3%)	1,176 (41.0%)
Included in closed cohort analysis	**32,452**	**454**	**7,017**	**345**	**5,623**	**747**

Participant characteristics

The baseline participant characteristics of the cohorts are summarised in Table 2. There were more females dispensed a hypnotic (61.8%) than males, but sex of patients were relatively equally balanced for those dispensed all AP (regardless of type). Over three quarters of all participants were of NZ European ethnicity (79.9%) were dispensed a hypnotic and a higher proportion of those dispensed an antipsychotic were of Māori ethnicity (22.6%) compared with other ethnicities.

Table 2: Participant characteristics

Characteristics	Hypnotics (n = 157,275) % (n)	First generation antipsychotics (n = 5,551) % (n)	Second generation antipsychotics (n = 18,942) % (n)	Low-risk antipsychotics (n = 4,848) % (n)	Medium-risk antipsychotics (n = 17,955) % (n)	High-risk antipsychotics (n = 2,867) % (n)
Sex						
Female	61.8% (97,139)	48.2% (2,677)	52.9% (10,019)	51.0% (2471)	52.7% (9468)	48.2% (1383)
Male	38.2% (60,006)	51.7% (2,869)	47.0% (89,05)	48.9% (2371)	47.2% (8470)	51.7% (1483)
Unknown	0.1% (30)	0.1% (5)	0.1% (18)	0.1% (6)	0.1% (17)	0.0% (1)
Ethnicity						
NZ European*	79.9% (125,704)	76.0% (4217)	77.7% (14,724)	75.9% (3682)	78.1% (14020)	72.5% (2079)
Maori#	5.7% (8,936)	12.7% (703)	10.9% (2,072)	13.1% (635)	10.5% (1886)	15.7% (451)
Pacific Island~	1.0% (1,619)	2.4% (133)	1.6% (303)	2.4% (115)	1.5% (277)	2.7% (78)
Indian	1.5% (2,417)	1.1% (59)	1.2% (229)	0.9% (45)	1.2% (217)	1.4% (41)
Asian^	3.4% (5,385)	2.7% (152)	2.5% (472)	2.9% (143)	2.4% (432)	3.3% (94)
Others+	0.8% (1,285)	0.6% (34)	1.0% (181)	0.5% (23)	1.0% (184)	0.8% (24)
Unknown†	7.6% (11,929)	4.6% (253)	5.1% (961)	4.2% (205)	5.2% (939)	3.5% (100)

* NZ European/Pakeha, European not further defined and Other European.
# NZ Maori.
~ Cook Island Maori, Fijian, Niuean, Samoan, Tokelauan, Tongan, Other Pacific Island.
^ Chinese, Southeast Asian, Other Asian, Asian Not Further Defined.
+ African, Latin American/Hispanic, Middle Eastern,
† Don't Know, Not Stated, Other Ethnicity, Refused to Answer, Response Unidentifiable.

Primary analysis

After being dispensed an SGA, participants have an overall 1.74 times (95% CI 1.36 to 2.23) increased risk of starting on metformin and this risk appeared to increase the longer they remained on a SGA. Similarly, those on AP with medium or high-risk of weight gain showed increased risks of commencing metformin by 1.49 times (95% CI 1.12 to 1.98) and 2.86 times (95% CI 1.41 to 5.82) respectively. Conversely, there was little evidence of a sustained elevated risk of T2DM among subjects who were dispensed hypnotics, FGAs, or low-risk APs. All groups, except FGA and low-risk AP, showed an elevated risk of commencing on metformin in the same year they commenced the exposure drugs (year 1 or the 'transition year'). Our data also showed those who were dispensed a high-risk AP had a lower pre-exposure risk of commencing metformin compared to those dispensed other AP.

Those who initiated hypnotics during the study period had a lower pre-exposure risk of commencing metformin than those who were dispensed an AP.

The observed incidence of being dispensed metformin before and after exposure drugs are shown in Figure 2 (a and b), and effect estimates from regression models are presented in Table 3.

Table 3: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (open cohorts)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High-risk AP
Subjects (n)	157,275	5,551	18,942	4,848	17,955	2,867
Observations (n)	538,774	16,253	79,216	14,154	71,729	10,650
Baseline incidence rate (per 1000 person-years)	4.25*** (3.95, 4.57)	5.98*** (4.16, 8.61)	6.71*** (5.66, 7.95)	6.06*** (4.06, 9.04)	6.83*** (5.72, 8.16)	3.42*** (2.18, 5.35)
Incidence rate ratio	0.98	0.73	1.74***	1.11	1.49**	2.86**

for taking exposure drug						
	(0.84, 1.13)	(0.31, 1.71)	(1.36, 2.23)	(0.51, 2.40)	(1.12, 1.98)	(1.41, 5.82)
Incidence rate ratio for acute exposure	1.41***	1.71	1.44**	0.89	1.44*	2.41**
(first year of exposure)	(1.22, 1.63)	(0.68, 4.25)	(1.14, 1.83)	(0.38, 2.09)	(1.09, 1.90)	(1.37, 4.25)
Incidence rate ratio for chronic exposure	1.00	1.62	1.33*	0.92	1.29	1.31
(log years 2 to 5)	(0.84, 1.19)	(0.69, 3.81)	(1.05, 1.69)	(0.40, 2.12)	(0.96, 1.73)	(0.75, 2.29)
Sex						
Incidence rate ratio for male vs female	1.78***	1.37	1.10	1.04	1.17*	1.07
	(1.67, 1.90)	(0.99, 1.91)	(0.96, 1.27)	(0.73, 1.47)	(1.00, 1.36)	(0.76, 1.51)
Ethnicity (ref = NZ European) Incidence rate ratio for						
Māori	2.81***	2.02***	1.96***	1.74*	2.04***	1.75*
	(2.53, 3.11)	(1.34, 3.07)	(1.63, 2.36)	(1.08, 2.80)	(1.66, 2.50)	(1.14, 2.69)
Pacific	5.98***	3.70***	3.45***	4.06***	3.59***	3.35***
	(5.13, 6.98)	(1.93, 7.09)	(2.49, 4.77)	(2.04, 8.06)	(2.50, 5.15)	(1.70, 6.60)
Indian	7.29***	8.10***	3.36***	9.82***	3.56***	1.93
	(6.49, 8.19)	(4.50, 14.58)	(2.29, 4.94)	(5.52, 17.48)	(2.35, 5.39)	(0.60, 6.25)
Asian	3.17***	3.45***	2.45***	3.38***	2.68***	2.21*
	(2.82, 3.57)	(1.86, 6.40)	(1.78, 3.37)	(1.75, 6.50)	(1.91, 3.78)	(1.05, 4.64)
Other	3.58***	3.41	2.04*	N/A	2.52***	N/A
	(2.89, 4.42)	(0.88, 13.17)	(1.18, 3.53)		(1.49, 4.26)	

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. N/A = not available due to small numbers. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001

Sensitivity analysis

Repeating the analysis on closed cohorts resulted in broadly similar results, albeit with wider confidence intervals due to the reduced sample sizes (Table 4).

Table 4: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (closed cohort)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High risk AP
Subjects (n)	32,452	454	7,017	345	5,623	747
Observations (n)	176,069	2,469	39,125	1,873	31,197	4,179
Incidence rate ratio for taking exposure drug	0.98	0.75	1.89***	1.23	1.73*	2.96
	(0.77, 1.24)	(0.22, 2.56)	(1.32, 2.71)	(0.36, 4.18)	(1.12, 2.66)	(0.84, 10.36)
Incidence rate ratio for acute exposure	1.68***	2.14	1.68**	1.31	1.41	3.44**
(first year of exposure)	(1.30, 2.18)	(0.58, 7.97)	(1.20, 2.34)	(0.33, 5.28)	(0.94, 2.12)	(1.44, 8.19)
Incidence rate ratio for chronic exposure	1.16	0.96	1.26	0.83	1.11	1.6
(log years 2 to 5)	(0.90, 1.48)	(0.35, 2.64)	(0.93, 1.72)	(0.30, 2.28)	(0.75, 1.65)	(0.76, 3.36)
Sex, Incidence rate ratio for male vs female	2.10***	1.57	1.06	0.77	1.11	1.17
	(1.86, 2.37)	(0.72, 3.38)	(0.87, 1.30)	(0.35, 1.67)	(0.87, 1.42)	(0.69, 1.99)
Ethnicity (ref = NZ European)						
Incidence rate ratio for Māori	2.57***	3.54**	1.80***	1.76	2.18***	1.3
	(2.07, 3.19)	(1.55, 8.09)	(1.36, 2.39)	(0.56, 5.55)	(1.58, 3.02)	(0.60, 2.83)
Pacific	7.90***	5.35*	3.69***	6.78*	3.80***	4.07**
	(5.94, 10.51)	(1.14, 25.12)	(2.36, 5.79)	(1.37, 33.45)	(2.15, 6.71)	(1.47, 11.30)
Indian	6.43***	5.59*	3.33***	10.78***	3.82***	1.96
	(5.04, 8.20)	(1.23, 25.44)	(1.86, 5.96)	(3.91, 29.70)	(1.95, 7.46)	(0.23, 16.40)
Asian	3.24***	4.98**	2.64***	4.89**	2.63***	4.45***
	(2.62, 3.99)	(1.54, 16.13)	(1.69, 4.13)	(1.49, 16.10)	(1.51, 4.60)	(1.86, 10.63)
Other	3.56***	8.06*	2.29*	N/A	2.95**	N/A
	(2.38, 5.33)	(1.43, 45.38)	(1.09, 4.83)		(1.33, 6.57)	
Baseline incidence rate	3.00***	4.81***	5.23***	6.51***	6.70***	1.68***
(per 1000 person-years)	(2.54, 3.55)	(1.31, 17.62)	(3.86, 7.08)	(1.55, 27.29)	(4.87, 9.20)	(0.64, 4.43)

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. N/A = not available due to small numbers. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001.

Discussion

These data showed patients commenced on AP have an increased risk of developing clinically significant T2DM after having been dispensed an AP. This is the first study to utilise a population representative dataset to estimate the change in incidence of clinically significant T2DM in patients aged 40 to 60 years who were prescribed APs. Given the criticisms of clinical trial populations as being non-representative of the general population in which most prescribing occurs, these results represent important safety data from a real world population without the tightly constrained entry criteria and short study period of a trial population.

To our knowledge, this is also the first study to use apply a cohort stepped-wedge design in creating an observational and quasi-experimental dataset. Utilising this design, our study found that patients dispensed APs known to cause weight gain have a sustained elevated risk of developing clinically significant T2DM at a population level. We also found an exposure duration-response for this effect in the groups studied. The results from this study are consistent with earlier studies signalling higher risk amongst patients on AP in developing T2DM.[3, 17, 25] Although we have not looked in detail at dosages, this effect was previously been observed in patients dispensed relatively low doses of these drugs, which is important information for prescribers.[17] This new method have also successfully analysed a large dataset for associations between chronic exposure and chronic outcome whilst controlling for unmeasured confounding.

It is interesting to see a strong effect in the first year of use for both AP and hypnotics given the initial spike of first metformin dispensed compared to subsequent years. This co-prescribing bias could indicate good medical practice whereby a patient is clinically

examined and investigated appropriately for T2DM prior to prescribing an AP in this case (albeit the study age group are also commonly screened for cardiovascular risks).

The pattern of T2DM incidence following the first year of exposure may be influenced by a number of factors other than direct effects of the exposure drugs. Firstly, co-prescribing bias is likely to only last one year, with rates returning to pre-exposure levels as untreated cases of T2DM are mopped up or that borderline cases are deleted early. It could also indicate vigilance in screening as this spike only lasted one year with incidence rates remained slightly elevated above baseline thereafter.

The utility of a national electronic pharmaceutical dataset have previously been validated by others and ourselves for assessing the association between medication use and development of clinically significant diabetes.[18, 19, 26] We were also able to assess effects in this cohort longitudinally over 5 years using this approach, and as a result successfully demonstrated the utility of a proxy measure for development of clinically significant T2DM by first ever metformin dispensed.

Limitations

Our study has several limitations. The limited number of variables in the available dataset meant it was not possible to obtain information on time-dependent confounding factors linked to increased diabetes risks (e.g. changes in body mass index, initiation of other medications and family history). Hence, such potential effect modifiers are unaccounted for in this study.

Since only the dispensing dataset is available to us from the NZPC for analysis and not the prescribing dataset, there is an increased risk of misclassification of exposure as medications prescribed were not always dispensed nor were they always taken as directed. Gardner et

al. looked into the non-dispensing rate in 1992 for New Zealand. They concluded a high non-dispensing rates of medications prescribed (between 9.8% to 17.6%) and this appears to be strongly associated with a patient's eligibility for higher government funding for medications.[27] Such misclassification would reduce the effect size but not the validity of the association seen.

There is a small risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans. However, this is likely to account for only a small proportion of our study population, and there is no reason to think there is an association with the exposure of interest.

This study was unable to observe the frequency of T2DM screening in the primary care setting as the NZPC is not currently linked to the laboratory dataset on a national level. Hence, we were unable to assess the duration of mild hyperglycaemia prior to commencement of metformin, or diabetes testing rates.

Conclusion

This population-based study provides important information on the safety of antipsychotic prescribing at a population-level. This is essential information for prescribers and patients when considering the balance of harms against the potential benefit in different clinical circumstances. We observed patients receiving their first prescription of some AP are at increased risk subsequently being dispensed metformin. The effect appears to carry an exposure duration-response in the groups studied, and this is important information for prescribers and patients especially with novel AP use. These data support caution in

prescription of these agents, careful thought about the choice of agents and a reminder to limit prescription duration whenever possible.

Further Research

This study outlined a new method for assessing adverse effects after initiation of chronic medications and it will be useful to test the utility of this method with other drug combination and settings.

It would also be of interest to analyse any drug-dose response to AP use, and any cumulative effect on diabetes control following the first metformin dispensed.

Other drug classes have also been found to increase diabetes risk, including drugs used commonly to modify cardiovascular risk. Whether there is an additive risk of inducing diabetes with combinations these drugs and AP is currently unknown. This is an important area for research given the prevalence of multi-morbidity and polypharmacy.

The study demonstrated that medications make an important contribution to this disease burden, potentially contributing to substantial long-term morbidity and health services costs. As a result, these findings contribute to the importance of weighing the risk benefits of prescribing these agents, and if the prescribing decision have been made, in the choice of agents. It is important to explore the potential contribution of different combination of medications to this disease burden in studies such as this.

Development of clinically significant T2DM is still an intermediate outcome indicator. T2DM is itself a source of morbidity and mortality largely as a risk factor for other diseases, predominantly cardiovascular disease. It is unclear what other relevant morbidity and mortality outcomes these patients will subsequently have.

Our research found a general increased risk of all patients developing T2DM over the study period, as indication by cumulative proportion of participants being dispensed metformin over the study period. This mirrors with both national and global concern about increasing development of T2DM, possibility in relation to increasing obesity rate.[15, 16]

Contributorship Statement

Dr. Olivia Currie:
The research fellow who collated all data, performed initial analysis and is the main author of this article in drafting and revision of the article critically for important intellectual content.

Dr. Jonathan Williman:
The biostatistician who made substantial contribution tostudy design, analysis and interpretation of data.

Prof. Dr. Derelie Mangin:
Supervisor on the project who provided substantial contribution to conception and study design and gave final approval of the article prior to submission for publication.

Bianca McKinnon Gee:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers

Paul Bridgford:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers.

Conflict of Interest Statement

None

Funding

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Data Sharing Statement

Technical appendix, statistical code, and dataset available from one of the

corresponding author at jonathan.williman@otago.ac.nz.

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Figure legends

Figure 1: Study Design

Subjects were grouped into cohorts according to the year they were first dispensed the exposure drug. In 2005 (orange), no patients were dispensed any of the outcome, exposure or exclusion drugs. Patients were then observed from 2006 to 2011, where they moved from being unexposed (green), to exposed (blue). The first year of exposure (light blue) indicates the transition year. By 2011 all patients had been dispensed the exposure medication. The proportion of patients commencing on metformin was observed each year.

Figure 2: Observed incidence of first metformin dispensed by exposure drug, and first year of exposure.

Figure 2a: First and second-generation antipsychotics when compared to hypnotics.

Figure 2b: Low, medium and high-risk antipsychotics for weight gain when compared to hypnotics.

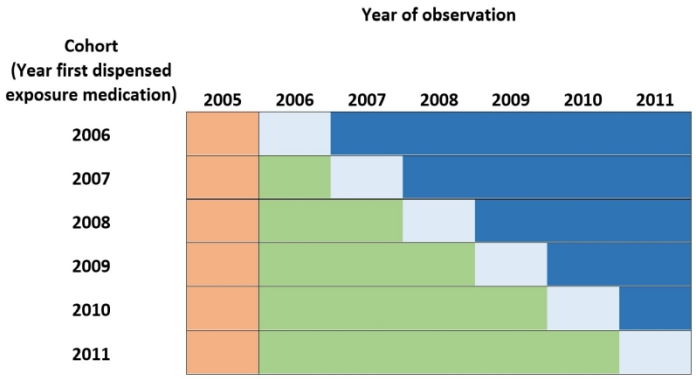

Figure 1 study design

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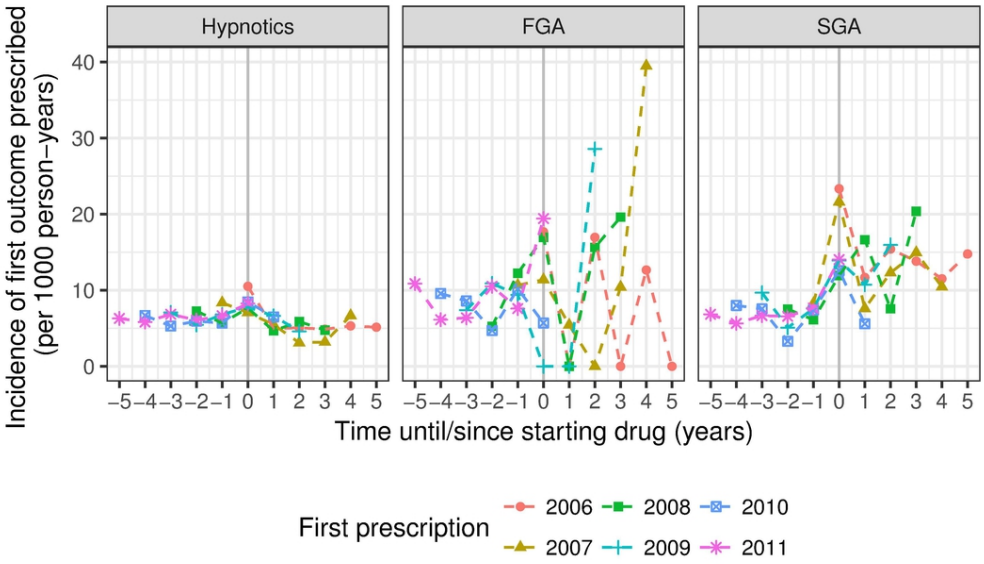

Figure 2a outcome

89x53mm (300 x 300 DPI)

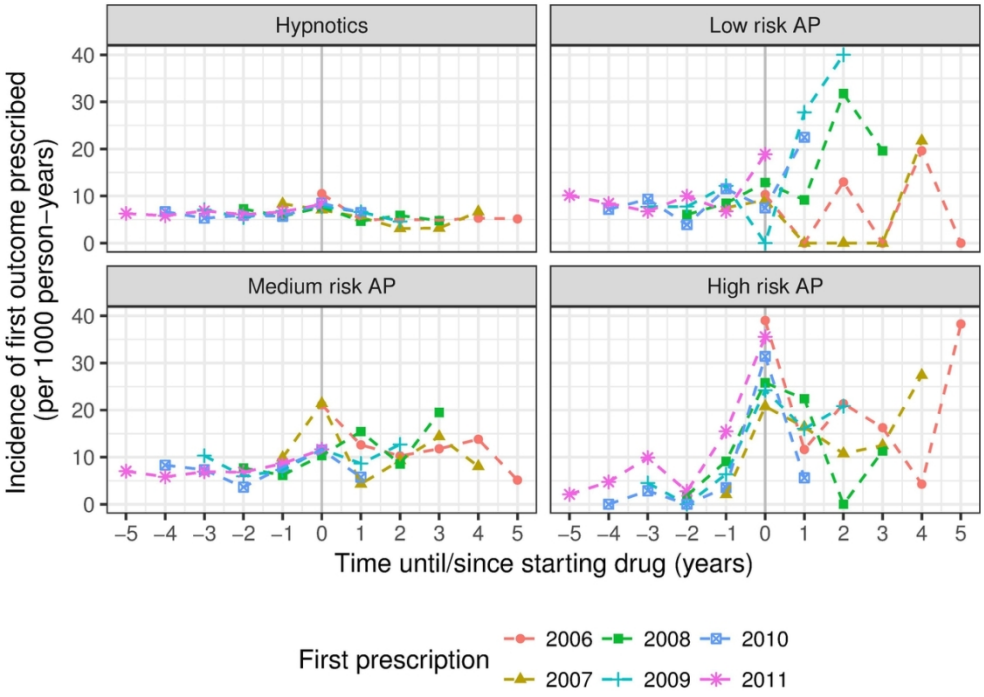

Figure 2b outcome

110x80mm (300 x 300 DPI)

Appendices

Appendix 1: Lists of drugs by exposure class, outcome and exclusion indicators.

INCLUSION CRITERIA	
Exposure drug class	**Drug names (all doses)**
Hypnotics	Nitrazepam, Lormetazepam, Temazepam, Triazolam, Zopiclone
First generation (typical) antipsychotics	Chlorpromazine hydrochloride, Haloperidol, Pericyazine, Trifluoperazine hydrochloride, Zuclopenthixol hydrochloride
Second generation (atypical) antipsychotics	Amisulpride, Aripriprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone
Antipsychotics with low-risk of weight gain	Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol
Antipsychotics with medium-risk of weight gain	Chlorpromazine, Quetiapine, Risperidone, and Amisulpride
Antipsychotics with high-risk of weight gain	Clozapine, Olanzapine
Outcome drug class	**Drug names (all doses)**
Metformin	Metformin hydrochloride
Exclusion drug class	**Drug names (all doses)**
Oral hypoglycaemics	Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone,
Injectable insulin	Insulin neutral, insulin isophane, insulin isophane with insulin neural, insulin lispro with insulin lispro protamine, insulin glargine, insulin aspart, insulin glulisine, insulin lispro
Exclusion	spironolactone, cyproterone acetate with ethinyloestrodiol, cyproterone acetate, dexamethasone, fludrocortisone acetate, hydrocortisone, methylprednisone, prednisone sodium phosphate, prednisone

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	CHECK	Section/ Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y	Maindoc.docx Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Maindoc.docx Page 4-5
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	Maindoc.docx Page 8
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Maindoc.docx Page 8
Methods				
Study design	4	Present key elements of study design early in the paper	Y	Maindoc.docx Page 9
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y	Maindoc.docx Page 10
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y	Maindoc.docx Page 10-12
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Y	Maindoc.docx Page 10-12
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y	Maindoc.docx Page 10-12
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*	Maindoc.docx Page 9
Bias	9	Describe any efforts to address potential sources of bias	Y	Maindoc.docx Page 9
Study size	10	Explain how the study size was arrived at	Y	Maindoc.docx Page 13
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Maindoc.docx Page 10-11
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y	Maindoc.docx Page 12
		(*b*) Describe any methods used to examine subgroups and interactions	Y	Maindoc.docx Page 12
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A	
		(*e*) Describe any sensitivity analyses	Y	Maindoc.docx Page 17
Results				

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y	Maindoc.docx Page 8-9
		(b) Give reasons for non-participation at each stage	Y	Maindoc.docx Page 7 (included in analysis)
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y	Maindoc.docx Page 13
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Y	Maindoc.docx Page 13-17
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y	Maindoc.docx Page 13-17
		(*b*) Report category boundaries when continuous variables were categorized	Y	Maindoc.docx Page 13-17
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Y	Maindoc.docx Page 13-17
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y	Maindoc.docx Page 17
Discussion				
Key results	18	Summarise key results with reference to study objectives	Y	Maindoc.docx Page 19-20
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y	Maindoc.docx Page 20
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Maindoc.docx Page 21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y	Maindoc.docx Page 21
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y	Maindoc.docx Page 2

*Give information separately for exposed and unexposed groups.

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

BMJ Open

Comparative risk of new-onset diabetes following commencement of antipsychotics: A population-based clustered multiple baseline time-series design.

Journal:	*BMJ Open*
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Date Submitted by the Author:	17-Jul-2018
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, antipsychotics, metformin, hypnotics, PRIMARY CARE, electronic prescription

TITLE PAGE

Title:

Comparative risk of new-onset diabetes following commencement of antipsychotics: A population-based clustered multiple baseline time-series design.

Authors:

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Prior Presentations

None

Prior Publication

None

Word count

Abstract 247 **Text** 2977

Number of Tables 4

Number of figures 2

Ethics Application

The University of Otago Human Ethics Committee (Health) reviewed this project as a "Minimal Risk Health Research – Audit and Audit related studies' proposal". Approval was granted (reference number HD16/061) upon satisfaction that the study described is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Acknowledgements

We thank the Canterbury Chair of General Practice Trust (Inc.) for the sponsoring the role of the General Practice Research Registrar for this project, and Pegasus Health (Charitable) Ltd for supplying the data.

Key Words

Antipsychotics, hypnotics, diabetes, metformin, primary care, electronic prescription.

Abbreviations

T2DM = Type 2 Diabetes Mellitus

AP = Antipsychotics

FGA = First generation antipsychotics

SGA = Second generation antipsychotics

ABSTRACT

Objective: Newer antipsychotics are increasingly prescribed off-label for non-psychotic ailments both in primary and secondary care settings, despite the purported risk of weight gain and development of type-2 diabetes mellitus. This study aims to determine any relationship between the development of clinically significant new-onset type 2 diabetes mellitus and novel antipsychotic use in New Zealand using hypnotic drugs as controls.

Design: A population-based clustered multiple baseline time-series design.

Setting: Routinely collected data from a complete national pharmaceutical database in New Zealand between 2005 and 2011.

Participants: Patients aged 40 to 60 years in the year 2006 who were ever dispensed antipsychotics (exposure groups – first generation antipsychotics, second generation antipsychotics, and antipsychotics with low, medium and high risk for weight gain) or hypnotics (control group) between 2006 and 2011.

Main outcome measure: First ever metformin dispensed to patients in each study group between 2006 and 2011 as proxy for development of clinically significant type-2 diabetes mellitus, no longer amendable by lifestyle modifications.

Results: Patients dispensed a second-generation antipsychotic had 1.49 times increased risk (95% CI 1.10-2.03, p=0.011) of being subsequently commencing metformin. Patients dispensed an antipsychotic with high-risk of weight gain also had a 2.41 times increased risk of commencing on metformin (95% CI 1.42-4.09, p=0.001).

Conclusions: Patients dispensed a second-generation antipsychotic, and antipsychotics with high-risk of weight gain appear to be at increased risk of developing type-2 diabetes mellitus. Caution should be taken with novel antipsychotic use for patients with increased baseline risk of type-2 diabetes mellitus.

ARTICLE SUMMARY

Article focus:

Measurement of the comparative risks for subsequent development of new-onset diabetes mellitus by proxy of first ever metformin dispensed for adults prescribed antipsychotics and hypnotics in New Zealand between 2006 and 2011.

Key messages:

- Patients dispensed a second-generation antipsychotic have 1.49 times (95% CI 1.10-2.03, p=0.011) increased risk of subsequently dispensed metformin for the first time.
- Patients dispensed an antipsychotic with high-risk of weight gain have 2.41 times (95% CI 1.42-4.09, P=0.001) increased risk of subsequently being dispensed metformin.
- Patients dispensed hypnotics, first generation antipsychotics, and antipsychotics with low and medium-risk of weight gain were not found to have a statistically significant increased risk of subsequently dispensed metformin.

Strengths:

- A population-based cohort study using a national electronic pharmaceutical database, representing complete population-level data for prescribing in New Zealand.
- Using the marker of first metformin dispensed as indication of development of clinically significant type-2 diabetes mellitus amongst patients prescribed antipsychotics.
- This is the first pharmacoepidemiological study to apply robust quasi-experimental study design to control for time-invariant confounding.

Limitations:

- Risk of misclassification of exposure as medications dispensed are not always taken as directed as participant's level of drug adherence were not accounted for.
- Risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans.

What is already known on this topic:

- Higher doses of antipsychotics carry an increased risk of weight gain and development of type-2 diabetes mellitus in psychiatric patients.

What this study adds:

- Development of type-2 diabetes mellitus is also associated with the use of second generation antipsychotics, and antipsychotics with high-risk of weight gain in a general population setting, regardless of drug doses.
- Development of type-2 diabetes mellitus is not associated with first generation antipsychotic, antipsychotics with low or medium-risk of weight gain or hypnotic agents in a population setting, regardless of drug doses.

TEXT

Introduction

Higher doses of some antipsychotics (AP) increase the risk for weight gain and development of type-2 diabetes mellitus (T2DM).[1-6] This risk is widely accepted in the psychiatric community and patients on higher doses of AP are well monitored during the course of their treatment as a result.[4, 7, 8]

However, there is an increasing trend to prescribe AP off-label for ailments such as anxiety, insomnia, personality disorders and post-traumatic stress in primary and secondary care.[9-11] It may be perceived as less harmful, however even low doses of some AP are known to increase the risk of weight gain[1, 12, 13], which consequently may increase the risk of T2DM.[14] The comparative risks of different subgroups of antipsychotics are not yet known. As obesity is now of global concern[15, 16], it is important to ascertain such risk to minimise avoidable harm from prescription medications.

Cohort studies utilising population-based electronic datasets are useful tools in analysing prescription medicine effects in the community.[17-20] This population-based cohort study investigates any associations between clinically significant new-onset T2DM with AP use via analyses of the national pharmaceutical dataset in New Zealand. The risk of T2DM will be measured by proxy of first dispensed metformin, indicating that clinical diagnosis is no longer amendable by lifestyle modification. The change in incidence of first dispensed metformin for patients before versus after receiving first dispensed AP (exposure group) and is calculated and compared to future cases who have not yet been dispensed AP. Independent analysis is repeated with hypnotics as control group, as they are also commonly prescribed for off-label use.

Methods

This study utilised the national administrative electronic pharmaceutical database to evaluate the incidence of T2DM by proxy of first metformin dispensed for patients before and after they commenced on an AP. As a further control, the analysis was replicated in patients dispensed hypnotics, with similar exclusion criteria applied (Appendix 1). The study used a multiple baseline time series design[21] comprising of interrupted time-series (ITS), a pre- post- quasi-experimental approach where subjects are observed multiple times before and after the introduction of exposure drugs. Similar to other within-subject or self-controlled designs ITS helps control for time-invariant confounders[22], allow for estimation of pre-exposure trends, and immediate (level change) and delayed (slope change) effects following commencement of exposure drugs.[23] The multiple baseline time series provides additional control for population level time-variant effects by staggering the timing of the study cohort across subjects or clusters of subjects.[24] Where the ordering of the exposure is randomised, the design is also known as a cohort stepped-wedge cluster randomised trial, and may include a transition period immediately after the introduction of the exposure drug (Figure 1).[25] For the current study, patients were non-randomly allocated into clusters according to the year they were first dispensed the exposure drug (AP or hypnotics). Outcome assessment and time between steps occurred at yearly intervals, allowing for both within-subject and between-subject comparisons.

Ethical approval

This project is approved by the University of Otago Human Ethics Committee (Health) (reference number HD16/061) upon satisfaction that this study is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994. This project is not funded externally.

Patient and Public Involvement

No identifiable patients nor public are involved.

Data source

The New Zealand government subsidises medications for all residents based on a national drug formulary. All subsidised dispensing from pharmacies in New Zealand are submitted to the New Zealand Pharmaceutical Collection (NZPC) via the State Service's General Transaction Processing System. This data are made accessible to researchers via the New Zealand Health Information Service (NZHIS).[26] Our data were extracted via this service by Pegasus Health (Charitable) Ltd, a primary healthcare organisation in Christchurch, New Zealand. Identification and anonymity of individual patients is maintained by the encryption of their national health index (NHI) (a number unique healthcare user identifier) on data extraction and was the primary linkage key on all data extraction and analysis.

Study population and cohort construction

Dispensing data for the years 2005 to 2011 inclusive were obtained from the NZPC for individuals aged between 40 and 60 years in 2006 for the following drug classes - AP (exposure), hypnotics (exposure), metformin (outcome), and exclusion criteria drugs (patients were excluded from cohorts if they were ever dispensed drugs used to treat diabetes or drugs known to increase risk of weight gain and diabetes) (Appendix 1). The age range of patients (40 to 60 years) was selected to include individuals more commonly screened for diabetes risk in the community in New Zealand.

The four extracted datasets each contained the patients' encrypted NHI and demographics (gender and ethnicity), and dispensed medication details (name and formulation of drug, and year dispensed). Data extracts were summarised and merged by encrypted NHI and year. Individual drugs were then combined into drug classes to achieve sufficient power in the analysis. AP were grouped two ways for analysis. Firstly as first or second generation antipsychotics (FGA or SGA respectively). Secondly, by published risk of weight gain – low, medium and high-risk AP (Appendix 1). Clozapine and Olanzapine were categorised high-risk. Chlorpromazine, Quetiapine, and Risperidone were categorised medium-risk. Amisulpride, Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol were categorised low-risk.[6, 27]

Binary variables were created to indicate whether an individual in a given year was ever dispensed each of the study drug classes, metformin, and/or exclusion drugs. For the purposes of the analysis, AP groups were considered the exposures of interest, hypnotics as the negative control exposure, and metformin as the outcome.

Participant selection

A sub-dataset of new patients was then prepared for constructing each of the study cohorts by selecting patients who were dispensed the exposure drug at any time between 2006 and 2011 (open cohorts). To create a cohort of "non-diabetic new-users", patients were excluded if they were dispensed the exposure drug or any treatment for diabetes in 2005. Patients dispensed an oral or injectable hypoglycaemic agent in any calendar year before being dispensed metformin were also excluded as they were assumed to have pre-existing diabetes.

Patients in these open cohorts were followed from 2006 until 2011, or until one of the three following events occurred - the patient was dispensed metformin, the patient ceased using the exposure drug after having started it (intermittent users), or the patient started an exclusion drug or an antipsychotic with higher risk of weight gain.

For sensitivity analysis, closed cohorts were created by completely excluding all patients who ceased using the exposure drug after having started it, or who were recorded as having being dispensed a known diabetogenic drug between 2005 and 2011 inclusive.

Death or emigration of participants was not recorded in the dataset and was estimated to be less than 2%, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.[18]

Statistical methods and analysis

Patient and cluster characteristics were summarised using simple descriptive statistics. Crude incidence rates were initially calculated by grouping the data by exposure cohort and by year of observation, followed by counting the number of patients first dispensed metformin (numerator) and then dividing this by the total number of patients under observation (denominator). Annual incidence rates were plotted by time before and after initiating the exposure drug.

The effect of each exposure drug on incidence of metformin initiation was modelled using independently using a generalised linear model, with a log link and robust 'sandwich' standard errors. Clustering of observations within an individual were accounted for using generalised estimating equations with an 'ar1' correlation structure. Two time-dependent binary variables were used to indicate when subjects were exposed versus non-exposed, and the year that an individual was first dispensed the exposure medicine (labelled as

'exposed and 'transition year' respectively). In addition, 'time exposed' was included to investigate cumulative effects of exposure. Year of observation was included as a time-dependent confounder in the model, and gender and ethnicity as time-independent confounders. Analysis was performed using the package 'geepack' available on R.[28]

Results

Cohort characteristics:

A total of 262 982 unique patients were dispensed one of the exposure drugs during the study period. After exclusion of individuals who did not meet eligibility criteria, 181 768 patients were eligible in the open cohorts – 157 275, 5 551 and 18 942 in the groups who had prescription initiated for hypnotic, FGA, SGA, respectively (Table 1). 861 participants (15.5% of those on FGA, and 4.5% of those on SGA) were recorded as having been dispensed a both FGA and a SGA in the same year and were excluded for analysis. For patients on APs, 4 977, 18 288 and 3 996 met the drug inclusion criteria and were analysed in the low, medium and high-risk AP groups (for weight gain) separately from the initial analysis but were excluded if patients transitioned from a low to high-risk antipsychotic group during the study period.

For sensitivity analysis, a total of 39 923 patients were analysed – 32 452, 454 and 7 017 in the groups who had ever been dispensed a hypnotic, FGA, SGA, respectively (Table 1).

Table 1: Number of participants included in analysis and reasons for exclusion

	Exposure drug					
	Hypnotics	**First generation antipsychotics**	**Second generation antipsychotics**	**Low-risk antipsychotics**	**Medium-risk antipsychotics**	**High-risk antipsychotics**
Ever dispensed the exposure drug between 2005 to 2011	**217,958**	**11,903**	**33,121**	**10,510**	**30,566**	**8,393**
Dispensed exposure drug in 2005	33,033	3,281	9,871	2,179	7,632	3,797
Dispensed exclusion drug in 2005 or 2006	34,472	4,415	6,034	4,177	6,236	984
Dispensed metformin in 2005	5,581	583	1,301	505	1,173	426
Dispensed insulin or oral hypoglycaemic prior to metformin	3218	419	631	365	616	136
Included in open cohort analysis	**157,275**	**5,551**	**18,942**	**4,977**	**18,288**	**3,996**
Dispensed an exclusion drug in 2005 to 2011	56,738 (36.1%)	3,938 (70.9%)	6,267 (33.1%)	3,748 (75.3%)	6,755 (36.9%)	921 (23.0%)
Stopped using exposure drug prior to 2011	105,561 (67.1%)	3,890 (70.1%)	8,461 (44.7%)	3,280 (65.9%)	9,054 (49.5%)	1,618 (40.5%)
Included in closed cohort analysis	**32,452**	**454**	**7,017**	**363**	**5,919**	**1,816**

Participant characteristics

The baseline participant characteristics of the cohorts are summarised in Table 2. There were more females dispensed a hypnotic (61.8%) than males, but sex of patients were relatively equally balanced for those dispensed all AP (regardless of type). Over three quarters of all participants were of NZ European ethnicity (79.9%) were dispensed a hypnotic and a higher proportion of those dispensed an antipsychotic were of Māori ethnicity (12.4%) compared with other ethnicities.

Table 2: Participant characteristics

Characteristics	Hypnotics (n = 157,275) % (n)	First generation antipsychotics (n = 5,551) % (n)	Second generation antipsychotics (n = 18,942) % (n)	Low-risk antipsychotics (n = 4,977) % (n)	Medium-risk antipsychotics (n = 18,288) % (n)	High-risk antipsychotics (n = 3,996) % (n)
Sex						
Female	61.8% (97,139)	48.2% (2,677)	52.9% (10,019)	51.0% (2,536)	52.8% (9,662)	49.9% (1,996)
Male	38.2% (60,006)	51.7% (2,869)	47.0% (89,05)	48.9% (2,435)	47.1% (8,609)	50.0% (1,997)
Unknown	0.1% (30)	0.1% (5)	0.1% (18)	0.1% (6)	0.1% (17)	0.1% (3)
Ethnicity						
NZ European*	79.9% (125,704)	76.0% (4217)	77.7% (14,724)	75.9% (3776)	78.1% (14,286)	73.0% (2,917)
Maori#	5.7% (8,936)	12.7% (703)	10.9% (2,072)	13.0% (647)	10.5% (1,923)	16.0% (641)
Pacific Island~	1.0% (1,619)	2.4% (133)	1.6% (303)	2.4% (118)	1.6% (285)	2.7% (107)
Indian	1.5% (2,417)	1.1% (59)	1.2% (229)	1.0% (48)	1.2% (217)	1.3% (52)
Asian^	3.4% (5,385)	2.7% (152)	2.5% (472)	3.0% (149)	2.4% (437)	3.0% (121)
Others+	0.8% (1,285)	0.6% (34)	1.0% (181)	0.5% (27)	1.0% (186)	0.8% (30)
Unknown†	7.6% (11,929)	4.6% (253)	5.1% (961)	4.3% (212)	5.2% (954)	3.2% (128)

* NZ European/Pakeha, European not further defined and Other European.
# NZ Maori.
~ Cook Island Maori, Fijian, Niuean, Samoan, Tokelauan, Tongan, Other Pacific Island.
^ Chinese, Southeast Asian, Other Asian, Asian Not Further Defined.
+ African, Latin American/Hispanic, Middle Eastern,
† Don't Know, Not Stated, Other Ethnicity, Refused to Answer, Response Unidentifiable.

Primary analysis

After being dispensed an SGA, participants have an overall 1.49 times (95% CI 1.10-2.03) increased risk of starting on metformin and there was weak evidence that this risk increased the longer they remained on SGA. Similarly, those on AP with medium or high-risk of weight gain showed increased risks of commencing metformin by 1.37 times (95% CI 0.96-1.95) and 2.41 times (95% CI 1.42-4.09) respectively. Conversely, there was little evidence of a sustained elevated risk of T2DM among subjects who were dispensed hypnotics, FGAs, or low-risk APs. All groups, except FGA and low-risk AP, showed an elevated risk of commencing on metformin in the same year they commenced the exposure drugs (year 1 or the 'transition year'). Our data also suggested that those who were dispensed a high-risk AP had a lower pre-exposure risk of commencing metformin compared to those dispensed other AP.

Those who initiated hypnotics during the study period had a lower pre-exposure risk of commencing metformin than those who were dispensed an AP.

The observed incidence of being dispensed metformin before and after exposure drugs are shown in Figure 2, and effect estimates from regression models are presented in Table 3.

Table 3: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (open cohorts)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High-risk AP
Subjects (n)	157,275	5,551	18,942	4,977	18,288	3,996
Baseline incidence rate per 1000 person-years, (95% CI)	3.24*** (3.05, 3.44)	4.78*** (3.46, 6.59)	4.87*** (4.24, 5.60)	5.19*** (3.78, 7.12)	4.96*** (4.29, 5.73)	4.61*** (3.38, 6.30)
Incident rate ratios (95% CI)						
Exposure vs non-exposed (level change)	0.90 (0.72, 1.12)	0.47 (0.12, 1.77)	1.49* (1.10, 2.03)	0.76 (0.20, 2.82)	1.37 (0.96, 1.95)	2.41** (1.42, 4.09)
Time exposed (years, slope change)	1.05 (0.95, 1.15)	1.32 (0.87, 2.00)	1.11 (0.99, 1.24)	1.29 (0.85, 1.96)	1.04 (0.91, 1.20)	1.11 (0.94, 1.32)
Transition year (year of first exposure)	1.57*** (1.25, 1.96)	3.34 (0.85, 13.07)	1.67** (1.22, 2.29)	2.24 (0.57, 8.76)	1.51* (1.05, 2.18)	1.95** (1.19, 3.18)
Sex						
Male vs female	1.81*** (1.69, 1.93)	1.31 (0.93, 1.83)	1.11 (0.96, 1.29)	1.02 (0.71, 1.46)	1.17 (1.00, 1.36)	1.06 (0.82, 1.37)
Ethnicity (ref = NZ European)						
Māori	2.80*** (2.52, 3.12)	1.98** (1.28, 3.08)	1.98*** (1.64, 2.41)	1.65 (0.99, 2.74)	1.99*** (1.61, 2.46)	1.58** (1.15, 2.17)
Pacific	6.09*** (5.19, 7.13)	3.95*** (2.06, 7.60)	3.42*** (2.43, 4.81)	3.96*** (1.92, 8.15)	3.77*** (2.63, 5.42)	2.47** (1.38, 4.40)
Indian	7.47*** (6.63, 8.41)	8.79*** (4.88, 15.82)	3.47*** (2.33, 5.18)	10.62*** (6.03, 18.71)	4.07*** (2.71, 6.10)	1.89 (0.78, 4.61)
Other (Asian and Others)	3.24*** (2.91, 3.62)	3.66*** (2.06, 6.51)	2.43*** (1.83, 3.23)	3.29*** (1.75, 6.18)	2.74*** (2.03, 3.68)	1.97* (1.16, 3.34)

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001.

Sensitivity analysis

Repeating the analysis on closed cohorts resulted in broadly similar results, albeit with wider confidence intervals due to the reduced sample sizes (Table 4).

Table 4: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (closed cohort)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High-risk AP
Subjects (n)	32,452	454	7,017	363	5,919	1,816
Baseline incidence rate per 1000 person-years, (95% CI)	2.80*** (2.51, 3.13)	4.44*** (1.83, 10.81)	4.18*** (3.38, 5.17)	7.53*** (3.42, 16.57)	4.43*** (3.53, 5.56)	4.25*** (2.82, 6.40)
Incident rate ratios (95% CI)						
Exposure vs non-exposed (level change)	0.97 (0.73, 1.30)	1.14 (0.28, 4.61)	1.80** (1.22, 2.66)	1.74 (0.41, 7.34)	1.70* (1.09, 2.65)	2.14* (1.14, 4.04)
Time exposed (years, slope change)	1.07 (0.96, 1.19)	0.94 (0.59, 1.49)	1.10 (0.97, 1.25)	0.92 (0.57, 1.48)	0.99 (0.84, 1.16)	1.15 (0.96, 1.38)
Transition year (year of first exposure)	1.68*** (1.23, 2.29)	1.88 (0.43, 8.25)	1.75** (1.18, 2.60)	1.41 (0.32, 6.32)	1.36 (0.86, 2.17)	2.34** (1.30, 4.21)
Sex						
Male vs female	2.10*** (1.86, 2.37)	1.57 (0.74, 3.35)	1.06 (0.86, 1.30)	0.73 (0.35, 1.55)	1.15 (0.91, 1.45)	1.16 (0.85, 1.60)
Ethnicity (ref = NZ European)						
Māori	2.58*** (2.08, 3.20)	3.55** (1.56, 8.08)	1.80*** (1.36, 2.39)	1.72 (0.56, 5.29)	2.18*** (1.60, 2.98)	1.75** (1.18, 2.60)
Pacific	7.92*** (5.96, 10.53)	5.76* (1.28, 25.94)	3.70*** (2.36, 5.80)	7.21* (1.53, 34.00)	3.86*** (2.24, 6.67)	2.91** (1.36, 6.21)
Indian	6.44*** (5.05, 8.21)	6.07* (1.38, 26.62)	3.33*** (1.86, 5.95)	10.05*** (4.10, 24.66)	4.52*** (2.46, 8.29)	2.59 (0.94, 7.18)
Other (Asian and Others)	3.31*** (2.73, 4.00)	5.53** (1.93, 15.87)	2.54*** (1.72, 3.76)	3.28 (0.97, 11.10)	3.00*** (1.94, 4.65)	3.05*** (1.72, 5.41)

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001.

Discussion

These data showed patients have an increased risk of developing clinically significant T2DM after having been dispensed either an SGA or a high-risk AP. This is the first study to utilise a general population representative dataset to estimate the change in incidence of clinically significant T2DM in patients aged 40 to 60 years who were prescribed APs. These results represent important safety data from a real-world population where most prescribing occurs without the tightly constrained entry criteria and short study period of a clinical trial population, or limitation to the psychiatric population.

To our knowledge, this is also the first study to apply multiple baseline time-series design to analyse national pharmaceutical data. This design has been considered by some to be a 'viable alternative to the RCT' and the case for causation can be compelling if the following criteria are meet: 1) baseline pre-exposure rates are stable within and across subjects/clusters, 2) the introduction of the exposure of interest results in a detectable and meaningful change that is consistently replicated across each of the subjects/clusters, and 3) the direction and magnitude of the change is exposure specific and is consistent with prior theory and research.[21, 24] Further, unlike many other case-only used in pharmacoepidemiology, the multiple baseline design can be used to detect associations between long-lived exposures and chronic outcomes.[22]

Utilising this design, our study found that patients in the general population dispensed SGA and high-risk APs have a sustained elevated risk of developing clinically significant T2DM at a population level.[3, 17, 29] Although we have not looked in detail at dosages, this effect was previously observed in patients dispensed relatively low doses of these drugs.[17] This is important information for prescribers especially in prescribing SGA and high-risk APs for non-serious psychiatric conditions.

It is interesting to see a strong effect in the first year of use for both AP and hypnotics given the initial spike of first metformin dispensed compared to subsequent years. This co-prescribing bias could indicate good medical practice whereby a patient is clinically examined and investigated appropriately for T2DM prior to prescribing an AP in this case (albeit the study age group are also commonly screened for cardiovascular risks).

The pattern of T2DM incidence following the first year of exposure may be influenced by several factors other than direct effects of the exposure drugs. Firstly, co-prescribing bias is likely to only last one year, with rates returning to pre-exposure levels or lower as untreated cases of T2DM are mopped up or that borderline cases are deleted early. It could also indicate vigilance in screening as this spike only lasted one year with incidence rates remained slightly elevated above baseline thereafter.

The utility of a national electronic pharmaceutical dataset have previously been validated by others and ourselves for assessing the association between medication use and development of clinically significant diabetes.[18, 19, 30] We were also able to assess effects in this cohort longitudinally over 5 years using this approach, and as a result successfully demonstrated the utility of a proxy measure for development of clinically significant T2DM by first ever metformin dispensed.

Limitations

Our study has several limitations. The limited number of variables in the available dataset meant it was not possible to obtain information on time-dependent confounding factors linked to increased diabetes risks (e.g. changes in body mass index, initiation of other medications and family history). Hence, such potential effect modifiers are unaccounted for in this study.

Since only the dispensing dataset is available from the NZPC for analysis and not the prescribing dataset, there is an increased risk of misclassification of outcome as medications prescribed were not always dispensed nor were they always taken as directed. Gardner et al. looked into the non-dispensing rate in 1992 for New Zealand. They concluded a high non-dispensing rates of medications prescribed (between 9.8% to 17.6%) and this appears to be strongly associated with a patient's eligibility for higher government funding for medications.[31] Such misclassification would reduce the effect size but not the validity of the association seen.

There is a very small risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans. However, this is likely to account for only a small proportion of our study population, and there is no reason to think there is an association with the exposure of interest.

This study was unable to observe the frequency of T2DM screening in the primary care setting as the NZPC is not currently linked to the laboratory dataset on a national level. Hence, we were unable to assess the duration of mild hyperglycaemia prior to commencement of metformin, or diabetes testing rates.

Conclusion

This population-based study provides important information on the safety of antipsychotic prescribing at a population-level. We observed patients receiving their first prescription of SGA and high-risk AP are at increased risk subsequently being dispensed metformin. The effect may carry an exposure duration-response in the groups studied, and this is important information for prescribers and patients especially with novel AP use. These data support caution in prescription of these agents, especially when prescribed off-label, careful thought about the choice of agents and a reminder to limit prescription duration whenever possible. This is essential information for prescribers and patients when considering the balance of harms against the potential benefit in different clinical circumstances.

The study demonstrated that medications make an important contribution to this disease burden, potentially contributing to substantial long-term morbidity and health services costs. As a result, these findings contribute to the importance of weighing the risk benefits of prescribing these agents, and if the prescribing decision have been made, in the choice of agents. It is important to explore the potential contribution of different combination of medications to this disease burden in studies such as this.

Further Research

This study outlined an alternative method for assessing adverse effects after initiation of chronic medications and it will be useful to test the utility of this method with other drug combination and settings.

It would also be of interest to analyse any drug-dose response to AP use, and any cumulative effect on diabetes control following the first metformin dispensed.

Other drug classes have also been found to increase diabetes risk, including drugs used commonly to modify cardiovascular risk. Whether there is an additive risk of inducing diabetes with combinations these drugs and AP is currently unknown. This is an important area for research given the prevalence of multi-morbidity and polypharmacy.

Development of clinically significant T2DM is still an intermediate outcome indicator. T2DM is itself a source of morbidity and mortality largely as a risk factor for other diseases, predominantly cardiovascular disease. It is unclear what other relevant morbidity and mortality outcomes these patients will subsequently have.

Our research found a general increased risk of all patients developing T2DM over the study period, as indication by cumulative proportion of participants being dispensed metformin over the study period. This mirrors with both national and global concern about increasing development of T2DM, possibility in relation to increasing obesity rate.[15, 16]

Contributorship Statement

Dr. Olivia Currie:
The research fellow who collated all data, performed initial analysis and is the main author of this article in drafting and revision of the article critically for important intellectual content, and gave final approval of the article prior to submission for publication.

Dr. Jonathan Williman:
The biostatistician who made substantial contribution to study design, analysis and interpretation of data, revising the article critically for important intellectual content, and gave final approval of the article prior to submission for publication.

Prof. Dr. Derelie Mangin:
Supervisor on the project who provided substantial contribution to conception and study design and gave final approval of the article prior to submission for publication.

Bianca McKinnon Gee:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers

Paul Bridgford:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers.

Conflict of Interest Statement

None

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Data Sharing Statement

Technical appendix, statistical code, and dataset available from one of the corresponding author at jonathan.williman@otago.ac.nz.

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Figure legends

Figure 1: Study Design

Subjects were grouped into clusters according to the year they were first dispensed the exposure drug. In 2005 (orange), no patients were dispensed any of the outcome, exposure or exclusion drugs. Patients were then observed from 2006 to 2011, where they moved from being unexposed (green), to exposed (blue). The year of first exposure (light blue) indicates the transition year. By 2011 all patients had been dispensed the exposure medication. The proportion of patients commencing on metformin was observed each year.

Figure 2: Incidence of first metformin dispensed by exposure drug (cohort) and year of first exposure (cluster).

Points (error bars) represent observed incidence rates (95% 'Wilson' binomial CI). Dotted vertical lines represent year of first exposure (transition year), points to the left of the line represent unexposed subjects, points to the right of the line represent exposed subjects. Lines (shading) represent incidence rates predicted by generalised linear regression models.

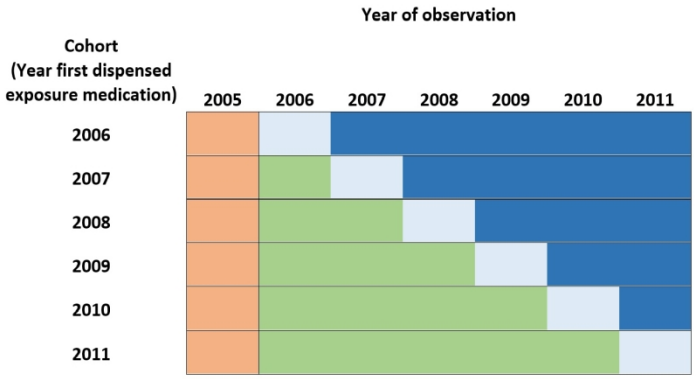

Figure 1: Study Design

513x336mm (96 x 96 DPI)

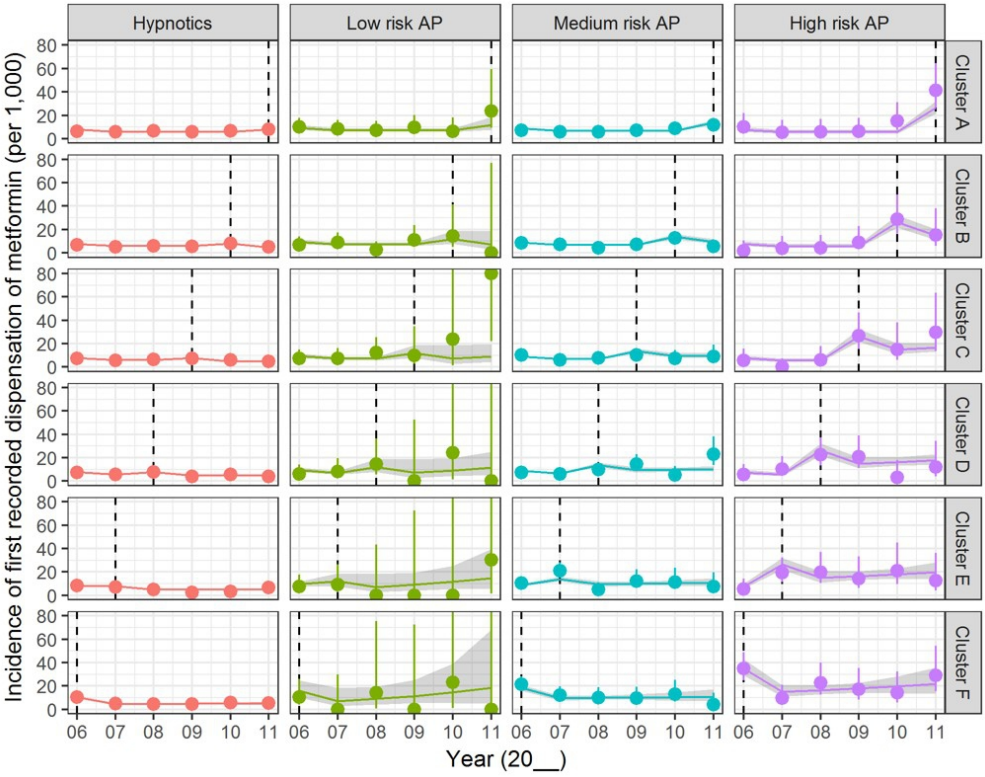

Figure 2: Incidence of first metformin dispensed by exposure drug (cohort) and year of first exposure (cluster).

171x135mm (150 x 150 DPI)

Appendices

Appendix 1: Lists of drugs by exposure class, outcome and exclusion indicators.

INCLUSION CRITERIA	
Exposure drug class	**Drug names (all doses)**
Hypnotics	Nitrazepam, Lormetazepam, Temazepam, Triazolam, Zopiclone
First generation (typical) antipsychotics	Chlorpromazine hydrochloride, Haloperidol, Pericyazine, Trifluoperazine hydrochloride, Zuclopenthixol hydrochloride
Second generation (atypical) antipsychotics	Amisulpride, Aripriprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone
Antipsychotics with low-risk of weight gain	Amisulpride, Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol
Antipsychotics with medium-risk of weight gain	Chlorpromazine, Quetiapine, and Risperidone
Antipsychotics with high-risk of weight gain	Clozapine, Olanzapine
Outcome drug class	**Drug names (all doses)**
Metformin	Metformin hydrochloride
Exclusion drug class	**Drug names (all doses)**
Oral hypoglycaemics	Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone,
Injectable insulin	Insulin neutral, insulin isophane, insulin isophane with insulin neural, insulin lispro with insulin lispro protamine, insulin glargine, insulin aspart, insulin glulisine, insulin lispro
Exclusion	spironolactone, cyproterone acetate with ethinyloestrodiol, cyproterone acetate, dexamethasone, fludrocortisone acetate, hydrocortisone, methylprednisone, prednisone sodium phosphate, prednisone

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	CHECK	Section/ Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y	Maindoc.docx Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Maindoc.docx Page 4
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	Maindoc.docx Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Maindoc.docx Page 7
Methods				
Study design	4	Present key elements of study design early in the paper	Y	Maindoc.docx Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y	Maindoc.docx Page 9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y	Maindoc.docx Page 9-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Y	Maindoc.docx Page 9-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y	Maindoc.docx Page 9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*	Maindoc.docx Page 9
Bias	9	Describe any efforts to address potential sources of bias	Y	Maindoc.docx Page 9
Study size	10	Explain how the study size was arrived at	Y	Maindoc.docx Page 12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Maindoc.docx Page 9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y	Maindoc.docx Page 11-12
		(*b*) Describe any methods used to examine subgroups and interactions	Y	Maindoc.docx Page 11-12
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A	
		(*e*) Describe any sensitivity analyses	Y	Maindoc.docx Page 18
Results				

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y	Maindoc.docx Page 10-11
		(b) Give reasons for non-participation at each stage	Y	Maindoc.docx Page 10 (included in analysis)
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y	Maindoc.docx Page 13
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Y	Maindoc.docx Page 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y	Maindoc.docx Page 15-19
		(*b*) Report category boundaries when continuous variables were categorized	Y	Maindoc.docx Page 15-19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Y	Maindoc.docx Page 15-19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y	Maindoc.docx Page 18
Discussion				
Key results	18	Summarise key results with reference to study objectives	Y	Maindoc.docx Page 20-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y	Maindoc.docx Page 20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Maindoc.docx Page 20-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y	Maindoc.docx Page 21
Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y	Maindoc.docx Page 2

*Give information separately for exposed and unexposed groups.

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

BMJ Open

Comparative risk of new-onset diabetes following commencement of antipsychotics in New Zealand: A population-based clustered multiple baseline time-series design.

Journal:	*BMJ Open*
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Primary Subject Heading:	General practice / Family practice
Secondary Subject Heading:	Pharmacology and therapeutics, Mental health, Medical management, Diabetes and endocrinology
Keywords:	General diabetes < DIABETES & ENDOCRINOLOGY, antipsychotics, metformin, hypnotics, PRIMARY CARE, electronic prescription

TITLE PAGE

Title:

Comparative risk of new-onset diabetes following commencement of antipsychotics in New Zealand: A population-based clustered multiple baseline time-series design.

Authors:

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Prior Presentations

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Prior Publication

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Number of Tables 4

Number of figures 2

Ethics Application

The University of Otago Human Ethics Committee (Health) reviewed this project as a "Minimal Risk Health Research – Audit and Audit related studies' proposal". Approval was granted (reference number HD16/061) upon satisfaction that the study described is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994.

Transparency declaration

The lead author* affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

*The manuscript's guarantor.

Acknowledgements

We thank the Canterbury Chair of General Practice Trust (Inc.) for the sponsoring the role of the General Practice Research Registrar for this project, and Pegasus Health (Charitable) Ltd for supplying the data.

Key Words

Antipsychotics, hypnotics, diabetes, metformin, primary care, electronic prescription.

Abbreviations

T2DM = Type 2 Diabetes Mellitus

AP = Antipsychotics

FGA = First generation antipsychotics

SGA = Second generation antipsychotics

ABSTRACT

Objective: Newer antipsychotics are increasingly prescribed off-label for non-psychotic ailments both in primary and secondary care settings, despite the purported risk of weight gain and development of type-2 diabetes mellitus. This study aims to determine any relationship between the development of clinically significant new-onset type 2 diabetes mellitus and novel antipsychotic use in New Zealand using hypnotic drugs as controls.

Design: A population-based clustered multiple baseline time-series design.

Setting: Routinely collected data from a complete national pharmaceutical database in New Zealand between 2005 and 2011.

Participants: Patients aged 40 to 60 years in the year 2006 who were ever dispensed antipsychotics (exposure groups – first generation antipsychotics, second generation antipsychotics, and antipsychotics with low, medium and high risk for weight gain) or hypnotics (control group) between 2006 and 2011.

Main outcome measure: First ever metformin dispensed to patients in each study group between 2006 and 2011 as proxy for development of clinically significant type-2 diabetes mellitus, no longer amendable by lifestyle modifications.

Results: Patients dispensed a second-generation antipsychotic had 1.49 times increased risk (95% CI 1.10-2.03, p=0.011) of being subsequently commencing metformin. Patients dispensed an antipsychotic with high-risk of weight gain also had a 2.41 times increased risk of commencing on metformin (95% CI 1.42-4.09, p=0.001).

Conclusions: Patients dispensed a second-generation antipsychotic, and antipsychotics with high-risk of weight gain appear to be at increased risk of being secondarily dispensed metformin.

Caution should be taken with novel antipsychotic use for patients with increased baseline risk of type-2 diabetes mellitus.

ARTICLE SUMMARY

Strengths:

- A population-based cohort study using a national electronic pharmaceutical database, representing complete population-level data for prescribing in New Zealand.
- Using the marker of first metformin dispensed as indication of development of clinically significant type-2 diabetes mellitus amongst patients prescribed antipsychotics.
- This is the first pharmacoepidemiological study to apply robust quasi-experimental study design to control for time-invariant confounding.

Limitations:

- Risk of misclassification of exposure as medications dispensed are not always taken as directed as participant's level of drug adherence were not accounted for.
- Risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans.

TEXT

Introduction

Higher doses of some antipsychotics (AP) increase the risk for weight gain and development of type-2 diabetes mellitus (T2DM).[1-6] This risk is widely accepted in the psychiatric community and patients on higher doses of AP are well monitored during the course of their treatment as a result.[4, 7, 8]

However, there is an increasing trend to prescribe AP off-label for ailments such as anxiety, insomnia, personality disorders and post-traumatic stress in primary and secondary care.[9-11] It may be perceived as less harmful, however even low doses of some AP are known to increase the risk of weight gain[1, 12, 13], which consequently may increase the risk of T2DM.[14] The comparative risks of different subgroups of antipsychotics are not yet known. As obesity is now of global concern[15, 16], it is important to ascertain such risk to minimise avoidable harm from prescription medications.

Cohort studies utilising population-based electronic datasets are useful tools in analysing prescription medicine effects in the community.[17-20] This population-based cohort study investigates any associations between clinically significant new-onset T2DM with AP use via analyses of the national pharmaceutical dataset in New Zealand. The risk of T2DM will be measured by proxy of first dispensed metformin, indicating that clinical diagnosis is no longer amendable by lifestyle modification. The change in incidence of first dispensed metformin for patients before versus after receiving first dispensed AP (exposure group) and is calculated and compared to future cases who have not yet been dispensed AP. Independent analysis is

repeated with hypnotics as control group, as they are also commonly prescribed for off-label use.

Methods

This study utilised the national administrative electronic pharmaceutical database to evaluate the incidence of T2DM by proxy of first metformin dispensed for patients before and after they commenced on an AP. As a further control, the analysis was replicated in patients dispensed hypnotics, with similar exclusion criteria applied (Appendix 1). The study used a multiple baseline time series design[21] comprising of interrupted time-series (ITS), a pre- post- quasi-experimental approach where subjects are observed multiple times before and after the introduction of exposure drugs. Similar to other within-subject or self-controlled designs ITS helps control for time-invariant confounders[22], allow for estimation of pre-exposure trends, and immediate (level change) and delayed (slope change) effects following commencement of exposure drugs.[23] The multiple baseline time series provides additional control for population level time-variant effects by staggering the timing of the study cohort across subjects or clusters of subjects.[24] Where the ordering of the exposure is randomised, the design is also known as a cohort stepped-wedge cluster randomised trial, and may include a transition period immediately after the introduction of the exposure drug (Figure 1).[25] For the current study, patients were non-randomly allocated into clusters according to the year they were first dispensed the exposure drug (AP or hypnotics). Outcome assessment and time between steps occurred at yearly intervals, allowing for both within-subject and between-subject comparisons.

Ethical approval

This project is approved by the University of Otago Human Ethics Committee (Health) (reference number HD16/061) upon satisfaction that this study is consistent with Rule 11(2)(c) of the Health Information Privacy Code 1994. This project is not funded externally.

Patient and Public Involvement

No identifiable patients nor public are involved.

Data source

The New Zealand government subsidises medications for all residents based on a national drug formulary. All subsidised dispensing from pharmacies in New Zealand are submitted to the New Zealand Pharmaceutical Collection (NZPC) via the State Service's General Transaction Processing System. This data are made accessible to researchers via the New Zealand Health Information Service (NZHIS).[26] Our data were extracted via this service by Pegasus Health (Charitable) Ltd, a primary healthcare organisation in Christchurch, New Zealand. Identification and anonymity of individual patients is maintained by the encryption of their national health index (NHI) (a number unique healthcare user identifier) on data extraction and was the primary linkage key on all data extraction and analysis.

Study population and cohort construction

Dispensing data for the years 2005 to 2011 inclusive were obtained from the NZPC for individuals aged between 40 and 60 years in 2006 for the following drug classes - AP (exposure), hypnotics (exposure), metformin (outcome), and exclusion criteria drugs (patients were excluded from cohorts if they were ever dispensed drugs used to treat diabetes or drugs known

to increase risk of weight gain and diabetes) (Appendix 1). The age range of patients (40 to 60 years) was selected to include individuals more commonly screened for diabetes risk in the community in New Zealand.

The four extracted datasets each contained the patients' encrypted NHI and demographics (gender and ethnicity), and dispensed medication details (name and formulation of drug, and year dispensed). Data extracts were summarised and merged by encrypted NHI and year. Individual drugs were then combined into drug classes to achieve sufficient power in the analysis. AP were grouped two ways for analysis. Firstly, as first or second-generation antipsychotics (FGA or SGA respectively). Secondly, by published risk of weight gain – low, medium and high-risk AP (Appendix 1). Clozapine and Olanzapine were categorised high-risk. Chlorpromazine, Quetiapine, and Risperidone were categorised medium-risk. Amisulpride, Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol were categorised low-risk.[6, 27]

Binary variables were created to indicate whether an individual in a given year was ever dispensed each of the study drug classes, metformin, and/or exclusion drugs. For the purposes of the analysis, AP groups were considered the exposures of interest, hypnotics as the negative control exposure, and metformin as the outcome.

Participant selection

A sub-dataset of new patients was then prepared for constructing each of the study cohorts by selecting patients who were dispensed the exposure drug at any time between 2006 and 2011 (open cohorts). To create a cohort of "non-diabetic new-users", patients were excluded if they were dispensed the exposure drug or any treatment for diabetes in 2005. Patients dispensed an

oral or injectable hypoglycaemic agent in any calendar year before being dispensed metformin were also excluded as they were assumed to have pre-existing diabetes.

Patients in these open cohorts were followed from 2006 until 2011, or until one of the three following events occurred - the patient was dispensed metformin, the patient ceased using the exposure drug after having started it (intermittent users), or the patient started an exclusion drug or an antipsychotic with higher risk of weight gain.

For sensitivity analysis, closed cohorts were created by completely excluding all patients who ceased using the exposure drug after having started it, or who were recorded as having been dispensed a known diabetogenic drug between 2005 and 2011 inclusive.

Death or emigration of participants was not recorded in the dataset and was estimated to be less than 2%, assuming death and emigration rate were similar to the overall New Zealand population within similar age groups during the study period.[18]

Statistical methods and analysis

Patient and cluster characteristics were summarised using simple descriptive statistics. Crude incidence rates were initially calculated by grouping the data by exposure cohort and by year of observation, followed by counting the number of patients first dispensed metformin (numerator) and then dividing this by the total number of patients under observation (denominator). Annual incidence rates were plotted by time before and after initiating the exposure drug.

The effect of each exposure drug on incidence of metformin initiation was modelled using independently using a generalised linear model, with a log link and robust 'sandwich' standard errors. Clustering of observations within an individual were accounted for using generalised

estimating equations with an 'ar1' correlation structure. Two time-dependent binary variables were used to indicate when subjects were exposed versus non-exposed, and the year that an individual was first dispensed the exposure medicine (labelled as 'exposed and 'transition year' respectively). In addition, 'time exposed' was included to investigate cumulative effects of exposure. Year of observation was included as a time-dependent confounder in the model, and gender and ethnicity as time-independent confounders. Analysis was performed using the package 'geepack' available on R.[28]

Results

Cohort characteristics:

A total of 262 982 unique patients were dispensed one of the exposure drugs during the study period. After exclusion of individuals who did not meet eligibility criteria, 181 768 patients were eligible in the open cohorts – 157 275, 5 551 and 18 942 in the groups who had prescription initiated for hypnotic, FGA, SGA, respectively (Table 1). 861 participants (15.5% of those on FGA, and 4.5% of those on SGA) were recorded as having been dispensed a both FGA and a SGA in the same year and were excluded for analysis. For patients on APs, 4 977, 18 288 and 3 996 met the drug inclusion criteria and were analysed in the low, medium and high-risk AP groups (for weight gain) separately from the initial analysis but were excluded if patients transitioned from a low to high-risk antipsychotic group during the study period.

For sensitivity analysis, a total of 39 923 patients were analysed – 32 452, 454 and 7 017 in the groups who had ever been dispensed a hypnotic, FGA, SGA, respectively (Table 1).

Table 1: Number of participants included in analysis and reasons for exclusion

	Exposure drug					
	Hypnotics	**First generation antipsychotics**	**Second generation antipsychotics**	**Low-risk antipsychotics**	**Medium-risk antipsychotics**	**High-risk antipsychotics**
Ever dispensed the exposure drug between 2005 to 2011	**217,958**	**11,903**	**33,121**	**10,510**	**30,566**	**8,393**
Dispensed exposure drug in 2005	33,033	3,281	9,871	2,179	7,632	3,797
Dispensed exclusion drug in 2005 or 2006	34,472	4,415	6,034	4,177	6,236	984
Dispensed metformin in 2005	5,581	583	1,301	505	1,173	426
Dispensed insulin or oral hypoglycaemic prior to metformin	3218	419	631	365	616	136
Included in open cohort analysis	**157,275**	**5,551**	**18,942**	**4,977**	**18,288**	**3,996**
Dispensed an exclusion drug in 2005 to 2011	56,738 (36.1%)	3,938 (70.9%)	6,267 (33.1%)	3,748 (75.3%)	6,755 (36.9%)	921 (23.0%)
Stopped using exposure drug prior to 2011	105,561 (67.1%)	3,890 (70.1%)	8,461 (44.7%)	3,280 (65.9%)	9,054 (49.5%)	1,618 (40.5%)
Included in closed cohort analysis	**32,452**	**454**	**7,017**	**363**	**5,919**	**1,816**

Participant characteristics

The baseline participant characteristics of the cohorts are summarised in Table 2. There were more females dispensed a hypnotic (61.8%) than males, but sex of patients were relatively equally balanced for those dispensed all AP (regardless of type). Over three quarters of all participants were of NZ European ethnicity (79.9%) were dispensed a hypnotic and a higher proportion of those dispensed an antipsychotic were of Māori ethnicity (12.4%) compared with other ethnicities.

Table 2: Participant characteristics

Characteristics	Hypnotics (n = 157,275) % (n)	First generation antipsychotics (n = 5,551) % (n)	Second generation antipsychotics (n = 18,942) % (n)	Low-risk antipsychotics (n = 4,977) % (n)	Medium-risk antipsychotics (n = 18,288) % (n)	High-risk antipsychotics (n = 3,996) % (n)
Sex						
Female	61.8% (97,139)	48.2% (2,677)	52.9% (10,019)	51.0% (2,536)	52.8% (9,662)	49.9% (1,996)
Male	38.2% (60,006)	51.7% (2,869)	47.0% (89,05)	48.9% (2,435)	47.1% (8,609)	50.0% (1,997)
Unknown	0.1% (30)	0.1% (5)	0.1% (18)	0.1% (6)	0.1% (17)	0.1% (3)
Ethnicity						
NZ European*	79.9% (125,704)	76.0% (4217)	77.7% (14,724)	75.9% (3776)	78.1% (14,286)	73.0% (2,917)
Maori#	5.7% (8,936)	12.7% (703)	10.9% (2,072)	13.0% (647)	10.5% (1,923)	16.0% (641)
Pacific Island~	1.0% (1,619)	2.4% (133)	1.6% (303)	2.4% (118)	1.6% (285)	2.7% (107)
Indian	1.5% (2,417)	1.1% (59)	1.2% (229)	1.0% (48)	1.2% (217)	1.3% (52)
Asian^	3.4% (5,385)	2.7% (152)	2.5% (472)	3.0% (149)	2.4% (437)	3.0% (121)
Others+	0.8% (1,285)	0.6% (34)	1.0% (181)	0.5% (27)	1.0% (186)	0.8% (30)
Unknown†	7.6% (11,929)	4.6% (253)	5.1% (961)	4.3% (212)	5.2% (954)	3.2% (128)

* NZ European/Pakeha, European not further defined and Other European.
# NZ Maori.
~ Cook Island Maori, Fijian, Niuean, Samoan, Tokelauan, Tongan, Other Pacific Island.
^ Chinese, Southeast Asian, Other Asian, Asian Not Further Defined.
+ African, Latin American/Hispanic, Middle Eastern,
† Don't Know, Not Stated, Other Ethnicity, Refused to Answer, Response Unidentifiable.

Primary analysis

After being dispensed an SGA, participants have an overall 1.49 times (95% CI 1.10-2.03) increased risk of starting on metformin and there was weak evidence that this risk increased the longer they remained on SGA. Similarly, those on AP with medium or high-risk of weight gain showed increased risks of commencing metformin by 1.37 times (95% CI 0.96-1.95) and 2.41 times (95% CI 1.42-4.09) respectively. Conversely, there was little evidence of a sustained elevated risk of being dispensed metformin among subjects who were dispensed hypnotics, FGAs, or low-risk APs. All groups, except FGA and low-risk AP, showed an elevated risk of commencing on metformin in the same year they commenced the exposure drugs (year 1 or the 'transition year'). Our data also suggested that those who were dispensed a high-risk AP had a lower pre-exposure risk of commencing metformin compared to those dispensed other AP.

Those who initiated hypnotics during the study period had a lower pre-exposure risk of commencing metformin than those who were dispensed an AP.

The observed incidence of being dispensed metformin before and after exposure drugs are shown in Figure 2, and effect estimates from regression models are presented in Table 3.

Table 3: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (open cohorts)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High-risk AP
Subjects (n)	157,275	5,551	18,942	4,977	18,288	3,996
Baseline incidence rate per 1000 person-years, (95% CI)	3.24*** (3.05, 3.44)	4.78*** (3.46, 6.59)	4.87*** (4.24, 5.60)	5.19*** (3.78, 7.12)	4.96*** (4.29, 5.73)	4.61*** (3.38, 6.30)
Incident rate ratios (95% CI)						
Exposure vs non-exposed (level change)	0.90 (0.72, 1.12)	0.47 (0.12, 1.77)	1.49* (1.10, 2.03)	0.76 (0.20, 2.82)	1.37 (0.96, 1.95)	2.41** (1.42, 4.09)
Time exposed (years, slope change)	1.05 (0.95, 1.15)	1.32 (0.87, 2.00)	1.11 (0.99, 1.24)	1.29 (0.85, 1.96)	1.08 (0.91, 1.20)	1.11 (0.94, 1.32)
Transition year (year of first exposure)	1.57*** (1.25, 1.96)	3.34 (0.85, 13.07)	1.67** (1.22, 2.29)	2.24 (0.57, 8.76)	1.54* (1.05, 2.18)	1.95** (1.19, 3.18)
Sex						
Male vs female	1.81*** (1.69, 1.93)	1.31 (0.93, 1.83)	1.11 (0.96, 1.29)	1.02 (0.71, 1.46)	1.19* (1.00, 1.36)	1.06 (0.82, 1.37)
Ethnicity (ref = NZ European)						
Māori	2.80*** (2.52, 3.12)	1.98** (1.28, 3.08)	1.98*** (1.64, 2.41)	1.65 (0.99, 2.74)	1.99*** (1.61, 2.46)	1.58** (1.15, 2.17)
Pacific	6.09*** (5.19, 7.13)	3.95*** (2.06, 7.60)	3.42*** (2.43, 4.81)	3.96*** (1.92, 8.15)	3.77*** (2.63, 5.42)	2.47** (1.38, 4.40)
Indian	7.47*** (6.63, 8.41)	8.79*** (4.88, 15.82)	3.47*** (2.33, 5.18)	10.62*** (6.03, 18.71)	4.07*** (2.71, 6.10)	1.89 (0.78, 4.61)
Other (Asian and Others)	3.24*** (2.91, 3.62)	3.66*** (2.06, 6.51)	2.43*** (1.83, 3.23)	3.29*** (1.75, 6.18)	2.74*** (2.03, 3.68)	1.97* (1.16, 3.34)

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001.

Sensitivity analysis

Repeating the analysis on closed cohorts resulted in broadly similar results, albeit with wider confidence intervals due to the reduced sample sizes (Table 4).

Table 4: Risk of commencing on metformin according to exposure to hypnotics or antipsychotics (closed cohort)

	Hypnotics	FGA	SGA	Low-risk AP	Medium-risk AP	High-risk AP
Subjects (n)	32,452	454	7,017	363	5,929	1,816
Baseline incidence rate per 1000 person-years, (95% CI)	2.80*** (2.51, 3.13)	4.44*** (1.83, 10.81)	4.18*** (3.38, 5.17)	7.53*** (3.42, 16.57)	4.43*** (3.53, 5.56)	4.25*** (2.82, 6.40)
Incident rate ratios (95% CI)						
Exposure vs non-exposed (level change)	0.97 (0.73, 1.30)	1.14 (0.28, 4.61)	1.80** (1.22, 2.66)	1.74 (0.41, 7.34)	1.78* (1.09, 2.65)	2.14* (1.14, 4.04)
Time exposed (years, slope change)	1.07 (0.96, 1.19)	0.94 (0.59, 1.49)	1.10 (0.97, 1.25)	0.92 (0.57, 1.48)	0.99 (0.84, 1.16)	1.15 (0.96, 1.38)
Transition year (year of first exposure)	1.68*** (1.23, 2.29)	1.88 (0.43, 8.25)	1.75** (1.18, 2.60)	1.41 (0.32, 6.32)	1.36 (0.86, 2.17)	2.34** (1.30, 4.21)
Sex						
Male vs female	2.10*** (1.86, 2.37)	1.57 (0.74, 3.35)	1.06 (0.86, 1.30)	0.73 (0.35, 1.55)	1.15 (0.91, 1.45)	1.16 (0.85, 1.60)
Ethnicity (ref = NZ European)						
Māori	2.58*** (2.08, 3.20)	3.55** (1.56, 8.08)	1.80*** (1.36, 2.39)	1.72 (0.56, 5.29)	2.19*** (1.60, 2.98)	1.75** (1.18, 2.60)
Pacific	7.92*** (5.96, 10.53)	5.76* (1.28, 25.94)	3.70*** (2.36, 5.80)	7.21* (1.53, 34.00)	3.86*** (2.24, 6.67)	2.91** (1.36, 6.21)
Indian	6.44*** (5.05, 8.21)	6.07* (1.38, 26.62)	3.33*** (1.86, 5.95)	10.05*** (4.10, 24.66)	4.52*** (2.46, 8.29)	2.59 (0.94, 7.18)
Other (Asian and Others)	3.31*** (2.73, 4.00)	5.53** (1.93, 15.87)	2.54*** (1.72, 3.76)	3.28 (0.97, 11.10)	3.08*** (1.94, 4.65)	3.05*** (1.72, 5.41)

Results presented are incidence rate ratios (95% confidence intervals), unless otherwise indicated. The baseline incidence rate represents the rate for European females prior to commencing on exposure drug. Models also adjusted for year of observation. Asterisk denote level of statistical significance; * = p<0.05; ** = p<0.01; *** = p<0.001.

Discussion

These data showed patients have an increased risk of developing clinically significant T2DM, by proxy of a patient being dispensed metformin, after having been dispensed either an SGA or a high-risk AP. This is the first study to utilise a general population representative dataset to estimate the change in incidence of clinically significant T2DM in patients aged 40 to 60 years who were prescribed APs. These results represent important safety data from a real-world population where most prescribing occurs without the tightly constrained entry criteria and short study period of a clinical trial population, or limitation to the psychiatric population.

To our knowledge, this is also the first study to apply multiple baseline time-series design to analyse national pharmaceutical data. This design has been considered by some to be a 'viable alternative to the RCT' and the case for causation can be compelling if the following criteria are meet: 1) baseline pre-exposure rates are stable within and across subjects/clusters, 2) the introduction of the exposure of interest results in a detectable and meaningful change that is consistently replicated across each of the subjects/clusters, and 3) the direction and magnitude of the change is exposure specific and is consistent with prior theory and research.[21, 24] Further, unlike many other case-only used in pharmacoepidemiology, the multiple baseline design can be used to detect associations between long-lived exposures and chronic outcomes.[22]

Utilising this design, our study found that patients in the general population dispensed SGA and high-risk APs have a sustained elevated risk of developing clinically significant T2DM at a population level, by proxy of being dispensed metformin following initiation of study medications.[3, 17, 29] Although we have not looked in detail at dosages, this effect was previously observed in patients dispensed relatively low doses of these drugs.[17] This is important

information for prescribers especially in prescribing SGA and high-risk APs for non-serious psychiatric conditions.

It is interesting to see a strong effect in the first year of use for both AP and hypnotics given the initial spike of first metformin dispensed compared to subsequent years. This co-prescribing bias could indicate good medical practice whereby a patient is clinically examined and investigated appropriately for T2DM prior to prescribing an AP in this case (albeit the study age group are also commonly screened for cardiovascular risks).

The pattern of T2DM incidence following the first year of exposure may be influenced by several factors other than direct effects of the exposure drugs. Firstly, co-prescribing bias is likely to only last one year, with rates returning to pre-exposure levels or lower as untreated cases of T2DM are mopped up or that borderline cases are deleted early. It could also indicate vigilance in screening as this spike only lasted one year with incidence rates remained slightly elevated above baseline thereafter.

The utility of a national electronic pharmaceutical dataset have previously been validated by others and ourselves for assessing the association between medication use and development of clinically significant diabetes.[18, 19, 30] We were also able to assess effects in this cohort longitudinally over 5 years using this approach, and as a result successfully demonstrated the utility of a proxy measure for development of clinically significant T2DM by first ever metformin dispensed.

Limitations

Our study has several limitations. The limited number of variables in the available dataset meant it was not possible to obtain information on time-dependent confounding factors linked to increased diabetes risks (e.g. changes in body mass index, initiation of other medications and family history). Hence, such potential effect modifiers are unaccounted for in this study.

Since only the dispensing dataset is available from the NZPC for analysis and not the prescribing dataset, there is an increased risk of misclassification of outcome as medications prescribed were not always dispensed nor were they always taken as directed. Gardner et al. investigated the non-dispensing rate in 1992 for New Zealand. They concluded a high non-dispensing rates of medications prescribed (between 9.8% to 17.6%) and this appears to be strongly associated with a patient's eligibility for higher government funding for medications.[31] Such misclassification would reduce the effect size but not the validity of the association seen.

There is a very small risk of misclassification of outcome as metformin is also dispensed for management of other medical conditions such as polycystic ovary syndrome and extreme insulin resistance with acanthosis nigricans. For antipsychotic users, it may have also been prescribed off-label for prevention of weight gain or weight reduction. However, this is likely to account for only a small proportion of our study population, and there is no reason to think there is an association with the exposure of interest.

This study was unable to observe the frequency of T2DM screening in the primary care setting as the NZPC is not currently linked to the laboratory dataset on a national level. Hence, we were unable to assess the duration of mild hyperglycaemia prior to commencement of metformin, or diabetes testing rates.

Conclusion

This population-based study provides important information on the safety of antipsychotic prescribing at a population-level. We observed patients receiving their first prescription of SGA and high-risk AP are at increased risk subsequently being dispensed metformin. The effect may carry an exposure duration-response in the groups studied, and this is important information for prescribers and patients especially with novel AP use. These data support caution in prescription of these agents, especially when prescribed off-label, careful thought about the choice of agents and a reminder to limit prescription duration whenever possible. This is essential information for prescribers and patients when considering the balance of harms against the potential benefit in different clinical circumstances.

The study demonstrated that medications make an important contribution to this disease burden, potentially contributing to substantial long-term morbidity and health services costs. As a result, these findings contribute to the importance of weighing the risk benefits of prescribing these agents, and if the prescribing decision have been made, in the choice of agents. It is important to explore the potential contribution of different combination of medications to this disease burden in studies such as this.

Further Research

This study outlined an alternative method for assessing adverse effects after initiation of chronic medications and it will be useful to test the utility of this method with other drug combination and settings.

It would also be of interest to analyse any drug-dose response to AP use, and any cumulative effect on diabetes control following the first metformin dispensed.

Other drug classes have also been found to increase diabetes risk, including drugs used commonly to modify cardiovascular risk. Whether there is an additive risk of inducing diabetes with combinations these drugs and AP is currently unknown. This is an important area for research given the prevalence of multi-morbidity and polypharmacy.

Development of clinically significant T2DM is still an intermediate outcome indicator. T2DM is itself a source of morbidity and mortality largely as a risk factor for other diseases, predominantly cardiovascular disease. It is unclear what other relevant morbidity and mortality outcomes these patients will subsequently have.

Our research found a general increased risk of all patients developing T2DM over the study period, as indication by cumulative proportion of participants being dispensed metformin over the study period. This mirrors with both national and global concern about increasing development of T2DM, possibility in relation to increasing obesity rate.[15, 16]

Contributorship Statement

Dr. Olivia Currie:
The research fellow who collated all data, performed initial analysis and is the main author of this article in drafting and revision of the article critically for important intellectual content, and gave final approval of the article prior to submission for publication.

Dr. Jonathan Williman:
The biostatistician who made substantial contribution to study design, analysis and interpretation of data, revising the article critically for important intellectual content, and gave final approval of the article prior to submission for publication.

Prof. Dr. Derelie Mangin:
Supervisor on the project who provided substantial contribution to conception and study design and gave final approval of the article prior to submission for publication.

Bianca McKinnon Gee:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers

Paul Bridgford:
A Pegasus Health (Charitable) Ltd. collaborator on data acquisition from the New Zealand Health Information Service (NZHIS), where de-identified pharmaceutical dispensing data is made available to researchers.

Conflict of Interest Statement

None

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Data Sharing Statement

Technical appendix, statistical code, and dataset available from one of the corresponding author at jonathan.williman@otago.ac.nz.

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Figure legends

Figure 1: Study Design

Subjects were grouped into clusters according to the year they were first dispensed the exposure drug. In 2005 (orange), no patients were dispensed any of the outcome, exposure or exclusion drugs. Patients were then observed from 2006 to 2011, where they moved from being unexposed (green), to exposed (blue). The year of first exposure (light blue) indicates the transition year. By 2011 all patients had been dispensed the exposure medication. The proportion of patients commencing on metformin was observed each year.

Figure 2: Incidence of first metformin dispensed by exposure drug (cohort) and year of first exposure (cluster).

Points (error bars) represent observed incidence rates (95% 'Wilson' binomial CI). Dotted vertical lines represent year of first exposure (transition year), points to the left of the line represent unexposed subjects, points to the right of the line represent exposed subjects. Lines (shading) represent incidence rates predicted by generalised linear regression models.

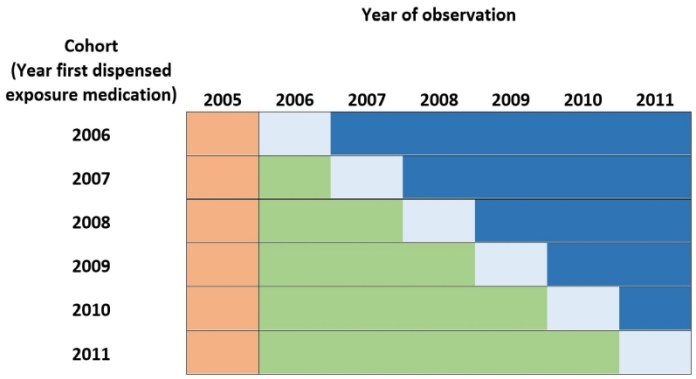

Figure 1: Study Design

164x107mm (300 x 300 DPI)

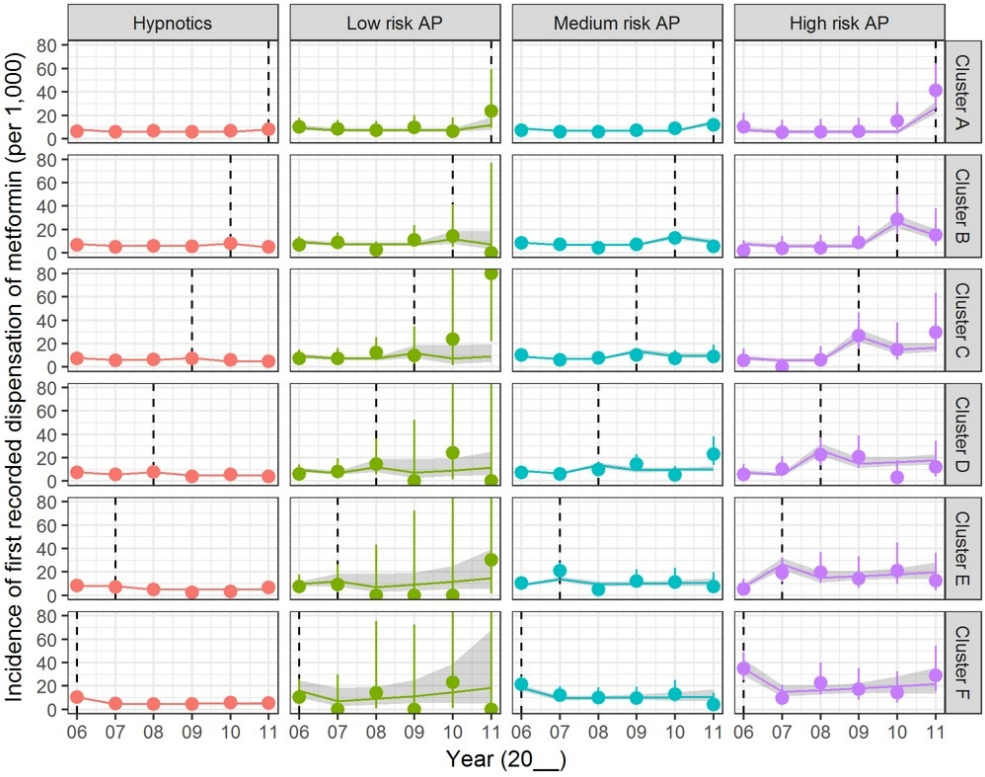

Figure 2: Incidence of first metformin dispensed by exposure drug (cohort) and year of first exposure (cluster).

85x67mm (300 x 300 DPI)

Appendices

Appendix 1: Lists of drugs by exposure class, outcome and exclusion indicators.

INCLUSION CRITERIA	
Exposure drug class	**Drug names (all doses)**
Hypnotics	Nitrazepam, Lormetazepam, Temazepam, Triazolam, Zopiclone
First generation (typical) antipsychotics	Chlorpromazine hydrochloride, Haloperidol, Pericyazine, Trifluoperazine hydrochloride, Zuclopenthixol hydrochloride
Second generation (atypical) antipsychotics	Amisulpride, Aripriprazole, Clozapine, Olanzapine, Quetiapine, Risperidone, Ziprasidone
Antipsychotics with low-risk of weight gain	Amisulpride, Aripiprazole, Haloperidol, Ziprasidone, Pericyazine, Trifluoperazine, and Zuclopenthixol
Antipsychotics with medium-risk of weight gain	Chlorpromazine, Quetiapine, and Risperidone
Antipsychotics with high-risk of weight gain	Clozapine, Olanzapine
Outcome drug class	**Drug names (all doses)**
Metformin	Metformin hydrochloride
Exclusion drug class	**Drug names (all doses)**
Oral hypoglycaemics	Acarbose, Glibenclamide, Gliclazide, Glipizide, Pioglitazone,
Injectable insulin	Insulin neutral, insulin isophane, insulin isophane with insulin neural, insulin lispro with insulin lispro protamine, insulin glargine, insulin aspart, insulin glulisine, insulin lispro
Exclusion	spironolactone, cyproterone acetate with ethinyloestrodiol, cyproterone acetate, dexamethasone, fludrocortisone acetate, hydrocortisone, methylprednisone, prednisone sodium phosphate, prednisone

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation	CHECK	Section/ Page number
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	Y	Maindoc.docx Page 1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	Y	Maindoc.docx Page 4
Introduction				
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	Y	Maindoc.docx Page 7
Objectives	3	State specific objectives, including any prespecified hypotheses	Y	Maindoc.docx Page 7
Methods				
Study design	4	Present key elements of study design early in the paper	Y	Maindoc.docx Page 8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Y	Maindoc.docx Page 9
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	Y	Maindoc.docx Page 9-11
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	Y	Maindoc.docx Page 9-11
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	Y	Maindoc.docx Page 9-11
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*Y*	Maindoc.docx Page 9
Bias	9	Describe any efforts to address potential sources of bias	Y	Maindoc.docx Page 9
Study size	10	Explain how the study size was arrived at	Y	Maindoc.docx Page 12
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	Y	Maindoc.docx Page 9-10
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	Y	Maindoc.docx Page 11-12
		(*b*) Describe any methods used to examine subgroups and interactions	Y	Maindoc.docx Page 11-12
		(*c*) Explain how missing data were addressed	N/A	
		(*d*) If applicable, explain how loss to follow-up was addressed	N/A	

		(*e*) Describe any sensitivity analyses	Y	Maindoc.docx Page 18
Results				
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	Y	Maindoc.docx Page 10-11
		(b) Give reasons for non-participation at each stage	Y	Maindoc.docx Page 10 (included in analysis)
		(c) Consider use of a flow diagram	N/A	
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Y	Maindoc.docx Page 13
		(b) Indicate number of participants with missing data for each variable of interest	N/A	
		(c) Summarise follow-up time (eg, average and total amount)	N/A	
Outcome data	15*	Report numbers of outcome events or summary measures over time	Y	Maindoc.docx Page 12
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Y	Maindoc.docx Page 15-19
		(*b*) Report category boundaries when continuous variables were categorized	Y	Maindoc.docx Page 15-19
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Y	Maindoc.docx Page 15-19
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Y	Maindoc.docx Page 18
Discussion				
Key results	18	Summarise key results with reference to study objectives	Y	Maindoc.docx Page 20-21
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Y	Maindoc.docx Page 20-21
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	Y	Maindoc.docx Page 20-21
Generalisability	21	Discuss the generalisability (external validity) of the study results	Y	Maindoc.docx Page 21

Other information				
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Y	Maindoc.docx Page 2

*Give information separately for exposed and unexposed groups.

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