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ARTICLE

The association of socioeconomic disadvantage and remoteness with receipt of type 2 diabetes medications in Australia: a nationwide registry study

Jedidiah I. Morton[1,2] · Jenni Ilomäki[2,3] · Dianna J. Magliano[1,2] · Jonathan E. Shaw[1,2]

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Abstract

Aims/hypothesis In recent years, several new medications for the treatment of type 2 diabetes have been released and some evidence indicates sociodemographic disparity in their utilisation. We sought to investigate sociodemographic disparities in receipt of diabetes medications across Australia.

Methods This study included 1,203,317 people with type 2 diabetes registered on the Australian National Diabetes Services Scheme (NDSS) followed from 2007 to 2015. The NDSS was linked to the Australian pharmaceutical claims database. We investigated trends in diabetes medication dispensing and variation in dispensing by sociodemographic strata.

Results Compared with individuals in the least disadvantaged areas, those in the most disadvantaged quintile were less likely to receive dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is) in the first year of availability (OR [95% CI] for most vs least disadvantaged: 0.78 [0.75, 0.82], 0.65 [0.60, 0.71] and 0.89 [0.84, 0.95], respectively). These disparities dissipated over time for DPP4is and SGLT2is but remained significant for GLP-1RAs. The OR (95% CI) of receiving DPP4is, GLP-1RAs and SGLT2is in the first year of availability for people in remote areas vs major cities was 0.46 (0.39, 0.54), 0.46 (0.35, 0.61) and 0.71 (0.59, 0.84), respectively. These disparities remained significant through to 2015.

Conclusions/interpretation People with diabetes in more disadvantaged areas are less likely to receive newer diabetes medications, although this effect decreased over time. However, there are considerable and persistent differences in receipt of newer diabetes medications between major cities and remote areas of Australia.

Keywords Australia · Diabetes · DPP4 inhibitors · GLP-1RAs · Health services research · Medications · Pharmacoepidemiology · SGLT2 inhibitors · Socioeconomic status

Dianna J. Magliano and Jonathan E. Shaw are joint senior authors.

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✉ Jedidiah I. Morton
jedidiah.morton@baker.edu.au

[1] Baker Heart and Diabetes Institute, Melbourne, VIC, Australia

[2] School of Public Health and Preventive Medicine, Monash University, Melbourne, VIC, Australia

[3] Centre for Medicine Use and Safety, Faculty of Pharmacy and Pharmaceutical Sciences, Monash University, Melbourne, VIC, Australia

Abbreviations

ARIA	Accessibility and Remoteness Index of Australia
ARS	Australian Statistical Geography Standard Remoteness Structure
DPP4i	Dipeptidyl peptidase-4 inhibitor
GLD	Glucose-lowering drug
GLP-1RA	Glucagon-like peptide-1 receptor agonist
GP	General practitioner
IRSD	Index of Relative Socioeconomic Disadvantage
NDI	Australian National Death Index
NDSS	National Diabetes Services Scheme
PBS	Australian Pharmaceutical Benefits Scheme
SGLT2i	Sodium–glucose cotransporter 2 inhibitor

Research in context

What is already known about this subject?

- There are clear sociodemographic disparities in health outcomes among people with type 2 diabetes
- Differential prescribing of medications by socioeconomic disadvantage and remoteness has been observed in Australia

What is the key question?

- How does socioeconomic disadvantage and remoteness influence the rate of uptake of new diabetes medications in Australia?

What are the new findings?

- People with diabetes in more disadvantaged areas of Australia were initially less likely to receive newer diabetes medications. For dipeptidyl peptidase-4 inhibitors (DPP4is) and sodium–glucose cotransporter 2 inhibitors (SGLT2is), but not for glucagon-like peptide-1 receptor agonists (GLP-1RAs), this effect disappeared over time
- These differences were not attributable to comorbidity, physician specialty or drug price
- There were considerable and persistent differences in receipt of newer diabetes medications between major cities and remote areas of Australia

How might this impact on clinical practice in the foreseeable future?

- Our results highlight an opportunity to improve dissemination of newer medications to those in more disadvantaged and remote areas as a means to address sociodemographic health disparities. Moreover, given Australia's size, individuals in remote areas are often many hours from healthcare and so continued receipt of older, hypoglycaemia-inducing medications is concerning

Introduction

Type 2 diabetes is one of the world's leading health problems. Effective management of blood glucose levels can prevent or delay diabetes complications, which are responsible for a considerable degree of disease burden. Glycaemic control is therefore one of the primary treatment targets for diabetes [1]. In addition to behavioural interventions, pharmacological therapies are paramount in achieving glycaemic control [2].

Current guidelines recommend commencement with metformin monotherapy if behavioural interventions are insufficient to achieve glycaemic control, and addition of second- and third-line pharmacotherapy if control remains insufficient [3]. In recent years, there have been a number of classes of glucose-lowering drugs (GLDs) developed for the treatment of type 2 diabetes, namely dipeptidyl peptidase-4 inhibitors (DPP4is), glucagon-like peptide-1 receptor agonists (GLP-1RAs) and sodium–glucose cotransporter 2 inhibitors (SGLT2is). None of these drugs directly cause hypoglycaemia or weight gain, and GLP-1RAs and SGLT2is are protective against cardiovascular and renal disease [1, 4, 5]. Because of this, these GLDs have been recommended for use in treatment guidelines for type 2 diabetes [3] and have shown high rates of uptake internationally [6–9].

In Australia, the prevalence of, and hospitalisations for, diabetes are greatest for people living in the most socioeconomically disadvantaged areas [10]. In addition, while diabetes prevalence varies only slightly by remoteness, those in remote areas have twice the diabetes-related hospitalisation rate than people living in major cities [10]. Moreover, all-cause and cardiovascular mortality rates among people with type 2 diabetes in Australia increase with remoteness [11]. Because the new GLDs are associated with a lower risk of hypoglycaemia and, for SGLT2is and GLP-1RAs, reduction in cardiovascular and renal disease, disparity in their use would be concerning and may contribute to socioeconomic disparities in outcomes.

Differential prescribing of medications by remoteness and socioeconomic disadvantage has been observed in Australia [12–14]. However, disparities in use of the new GLDs in Australia, or how disparities change over time, have not been investigated. Moreover, studies to date have not investigated medication utilisation in populations with prevalent disease, instead relying on area-level estimates of prevalence with which to compare disparate medication utilisation. Therefore, we linked the National Diabetes Services Scheme (NDSS; an Australian diabetes registry) to the Australian Pharmaceutical Benefits Scheme (PBS) and examined the

associations of socioeconomic disadvantage and remoteness with dispensing of newer medications among people with type 2 diabetes.

Methods

Data sources The Australian government established the NDSS in 1987, and it is estimated to include 80–90% of people with diagnosed diabetes in Australia [15]. We included members with type 2 diabetes registered on the NDSS as of 1 January 2007 and all new registrants from this date until 31 December 2015 as our study population. Diabetes type was assigned as previously described [16]. NDSS registrants were linked to the PBS and Australian National Death Index (NDI). The NDI contains records of all registered deaths in Australia since 1980; date of death was derived from the NDI. The PBS is an Australian government programme that subsidises the cost of medicines and collects data on all prescriptions filled in Australian pharmacies under the scheme. Dates of prescription and dispensing, concession status, prescriber specialty, PBS item codes and Anatomical Therapeutic Chemical (ATC) codes were derived from the PBS data. The PBS provides a larger benefit for subsidised medicines to individuals who qualify for a concession; these prescriptions enter the PBS database with a concession code. Concessions are available to individuals holding pensioner, veteran and healthcare cards. Therefore, these individuals are likely to be older and have more comorbidities than the general population. Prior to July 2012, the PBS did not collect data for medications that had a cost that was under the co-payment price; all newer GLDs were above the co-payment price, while some older GLDs (such as metformin) were under the co-payment price. However, for concession beneficiaries, the cost of a medication was higher than the co-payment if purchased via the PBS and therefore would have been included in the data prior to July 2012. Therefore, we established a subset of our population who purchased ≥80% of their prescription medications under a concession code, for those analyses that examined use of all GLDs prior to 2012. Because Aboriginal and Torres Strait Islander Australians are able to access PBS-listed medications through the Remote Area Aboriginal Health Services Program, and therefore may not have prescription medications listed on the PBS, we restricted our analysis to non-Indigenous Australians. This study used data from 1 January 2002 up to and including 31 December 2015. Linkage was performed by the Australian Institute of Health and Welfare as previously reported [17].

This study was approved by the Alfred Hospital Ethics Committee (project no. 15/15) and the Australian Institute of Health and Welfare Ethics Committee (EO 2015/1/148).

Measures of socioeconomic status Registrants were assigned a Socio-Economic Index for Areas: Index of Relative Socioeconomic Disadvantage (IRSD) and Australian Statistical Geography Standard Remoteness Structure (ARS) class based on their last known postcode. Registrants for whom a postcode was missing were excluded from all analyses ($n = 5010$ [0.4%]). The IRSD was developed by the Australian Bureau of Statistics and ranks areas in Australia according to relative socioeconomic disadvantage based on information about income, education, employment, occupation, housing and other indicators from the census [18]. In this study, registrants were stratified by quintiles of IRSD score (a higher IRSD score indicates a lower proportion of disadvantaged people in an area). The ARS divides Australia into five classes of remoteness based on relative access to services within an area, which is measured by the Accessibility and Remoteness Index of Australia (ARIA) [19]. The five classes are 'major city', 'inner regional', 'outer regional', 'remote' and 'very remote'. However, because of low numbers of individuals in the 'very remote' category, these individuals were included in the 'remote' category for this study.

Data analysis To determine whether sociodemographic characteristics influenced the receipt of new GLDs, the proportion of people dispensed a DPP4i, GLP-1RA and SGLT2i each year since each drug class was initially made available on the PBS was calculated and stratified by IRSD and ARIA. This was calculated as the number of people dispensed ≥1 prescription for the new GLD that year, divided by the number of people with type 2 diabetes registered on the NDSS before the end of that year who survived the full year. The first DPP4i to be listed on the PBS was sitagliptin on 1 August 2008, the first GLP-1RA (exenatide) was listed on 1 August 2010 and the SGLT2is dapagliflozin and canagliflozin were both listed on the PBS on 1 December 2013. We conducted logistic regression to determine whether differences in these proportions were statistically significant. In the regression model, the outcome was receipt of each new GLD per year (1 for the specific GLD, 0 for no prescription of that GLD).

Because we could only examine all GLD use prior to 2012 in the concession subset of our population, we conducted the remaining analyses just on this subset. To examine trends in GLD use among people with type 2 diabetes in Australia, we estimated the proportion of people dispensed each GLD each calendar year. Fixed-dose combination therapies were counted as a dispensing of each GLD in the combination. Additionally, we estimated the trends in use of each GLD as an add-on; an individual was considered to have added on a GLD if they received a second GLD while maintaining use of the first GLD, or if they received a third GLD while maintaining use of the first two. A detailed description of these definitions can be found in the electronic supplementary material (ESM) Methods. Receipt of add-on GLDs was calculated as

the number of people who received each GLD as the add-on, divided by the total number of add-on events that year. We also estimated the trends in the proportion of people receiving no GLDs, one GLD, two GLDs and three or more GLDs. Statistical significance of the annual trends was evaluated with logistic regression.

In order to account for differences in number of GLDs and propensity to add-on GLDs across sociodemographic strata, we performed logistic regression for adding on each GLD among only those who received an add-on GLD each year (1 for the GLD, 0 for add-on of another GLD).

All regression analyses were adjusted for age, sex and duration of diabetes. To test for interactions between IRSD and ARIA, we repeated the regression including an interaction term. We also stratified analyses by whether the add-on GLD was prescribed as a second- or third-line GLD. When restricted to the concession population, analyses were further adjusted for a comorbidity index, as comorbidity and polypharmacy may influence the likelihood of receiving a prescription for newer medications [20]. The RxRisk comorbidity index assigns a weighted comorbidity score based on all medications received in the preceding year [21]; because all people in the current study had type 2 diabetes, no weights were assigned for diabetes.

In order to investigate potential contributions to sociodemographic disparities in GLD use, we conducted a number of sensitivity analyses. As controls, we investigated whether receipt of metformin, sulfonylureas, thiazolidinediones and insulin varied by IRSD, ARIA, age, duration of diabetes and sex. We compared the proportion of people on ≥2 GLDs (multiple therapy) in a given year by IRSD, ARIA, age, duration of diabetes and sex using logistic regression, as well as the proportion who received an add-on GLD each year. Because physician specialty has been shown to influence medication prescribing [20], we investigated whether specialists were more likely to prescribe the add-on GLD than general practitioners (GPs) by IRSD and ARIA, and whether the GLDs prescribed as add-on agents differed between specialists and GPs. We then repeated the logistic regression among those who received add-on GLDs, stratifying by GP or specialist prescription of the add-on drug. Prescriber specialty was available for 99.9% of GLD prescriptions.

Analyses were performed in the Stata statistical software, version 15 (College Station, TX, USA).

Results

Population characteristics This study included 1,203,317 people with type 2 diabetes (54% male). The median age at diagnosis of diabetes was 58.3 (IQR 49.1–67.3) years and the median age at end of follow-up was 68.9 (IQR 59.1–78.3) years (Table 1).

Trends in GLD use Figure 1a shows the proportion of people with type 2 diabetes dispensed each GLD, each year from 2007 to 2015, among the concession population. The proportion of people dispensed metformin and insulin increased during the study period, while use of sulfonylureas and thiazolidinediones decreased ($p < 0.001$ for all). By 2012, DPP4is had replaced sulfonylureas as the most common add-on GLD, while the proportion of people adding on insulin remained relatively stable (Fig. 1b). Choice of add-on GLD differed considerably between specialists and GPs (ESM Fig. 1).

Over time, the proportion of the concession population receiving no GLDs decreased from 28.3% in 2007 to 22.3% in 2015 ($p < 0.001$), while the proportion receiving two GLDs increased from 28.5% to 30.2% and the proportion receiving three or more GLDs increased from 9.6% to 13.8% ($p < 0.001$ for both). The proportion of people receiving one GLD remained relatively constant at ~34% ($p = 0.283$ for trend).

Socioeconomic disadvantage and GLD dispensing Socioeconomic disparities were small for receipt of SGLT2is (Fig. 2 and Table 2). After adjusting for age, sex and duration of diabetes, those living in more disadvantaged areas were significantly less likely to receive a DPP4i during the first 2 years following their listing on the PBS (OR [95% CI]: 0.78 [0.75, 0.82] and 0.83 [0.80, 0.86] in the most vs least disadvantaged areas for the first and second years, respectively). In subsequent years, individuals in more disadvantaged areas were more likely to receive DPP4is. Individuals living in more disadvantaged areas were significantly less likely to receive a GLP-1RA across the entire study period (Table 2).

Among the concession population, those in more disadvantaged areas were more likely to be on multiple GLDs and receive add-on GLDs (data not shown). To account for differences in number of GLDs and propensity to add-on GLDs, we investigated dispensing of the new GLDs as add-ons among only those who received an add-on GLD each year (Table 3). Disparities in receipt of newer GLDs as add-ons by socioeconomic disadvantage were similar to the differences in the whole population described above, except that individuals in more disadvantaged areas were not more likely to receive add-on DPP4is in later years.

These results were similar in the concession subset of the population, after further adjustment for comorbidity (ESM Table 1). Overall, those in more disadvantaged areas were more likely to receive metformin, sulfonylureas, thiazolidinediones and insulin throughout the study than those in less disadvantaged areas. However, there were no consistent associations between socioeconomic disadvantage and receipt of metformin, sulfonylureas or insulin as add-on GLDs; those living in more disadvantaged areas were more likely to receive thiazolidinediones as the add-on GLD (ESM Table 2).

Table 1 Population characteristics, by socioeconomic disadvantage (IRSD) and remoteness (ARIA)

Characteristic	IRSD					ARIA				Total
	5 (least disadvantaged)	4	3	2	1 (most disadvantaged)	Major city	Inner regional	Outer regional	Remote	
Number of people	212,871 (17.7)	227,930 (18.9)	250,497 (20.8)	252,595 (21.0)	259,424 (21.6)	813,327 (67.6)	254,820 (21.2)	117,775 (9.8)	17,395 (1.4)	1,203,317 (100.0)
Number with concession	108,098 (50.8)	131,886 (57.9)	156,409 (62.4)	170,859 (67.6)	186,938 (72.1)	492,919 (60.6)	174,537 (68.5)	77,680 (66.0)	9054 (52.0)	754,190 (62.7)
Number of men	119,582 (56.2)	125,556 (55.1)	135,345 (54.0)	136,663 (54.1)	137,629 (53.1)	439,739 (54.1)	139,826 (54.9)	65,345 (55.5)	9865 (56.7)	654,775 (54.4)
Age at diagnosis of diabetes	58.7 (49.4–67.8)	58.3 (49.0–67.3)	58.2 (48.9–67.2)	58.6 (49.4–67.5)	58.0 (48.7–66.9)	58.1 (48.6–67.2)	59.3 (50.4–67.9)	58.6 (49.6–67.2)	55.4 (46.4–64.3)	58.3 (49.1–67.3)
Age at end of follow-up	69.2 (59.6–78.9)	68.7 (58.8–78.2)	68.8 (58.9–78.2)	69.3 (59.7–78.5)	68.6 (58.8–77.7)	68.6 (58.6–78.3)	69.8 (60.8–78.7)	69.1 (59.8–77.9)	65.9 (56.4–74.9)	68.9 (59.1–78.3)
Number dispensed a DPP4i	49,073 (23.1)	53,570 (23.5)	59,636 (23.8)	59,911 (23.7)	63,095 (24.3)	194,646 (23.9)	60,319 (23.7)	27,049 (23.0)	3271 (18.8)	285,285 (23.7)
Proportion prescribed initial DPP4i by specialist (%)	20.8	13.9	11.9	10.8	10.6	15.8	8.3	6.7	7.1	13.3
Number dispensed a GLP-1RA	8433 (4.0)	8936 (3.9)	9571 (3.8)	9449 (3.7)	9126 (3.5)	30,667 (3.8)	9833 (3.9)	4471 (3.8)	544 (3.1)	45,515 (3.8)
Proportion prescribed initial GLP-1RA by specialist (%)	63.5	53.0	45.8	42.4	40.7	55.5	37.1	29.1	35.2	48.7
Number dispensed an SGLT2i	8643 (4.1)	9839 (4.3)	10,506 (4.2)	11,132 (4.4)	10,768 (4.2)	34,677 (4.3)	10,810 (4.2)	4996 (4.2)	405 (2.3)	50,888 (4.2)
Proportion prescribed initial SGLT2i by specialist (%)	42.0	32.3	25.9	26.3	26.3	34.4	21.9	17.7	21.3	30.0

Data are presented as *n* (%) or median (25th–75th percentile), unless otherwise indicated

People in more disadvantaged areas were significantly less likely to have add-on GLDs prescribed by a specialist (data not shown). However, the association between socioeconomic disadvantage and receipt of DPP4is and SGLT2is was broadly consistent for prescriptions from both GPs and specialists (ESM Tables 3, 4). There was evidence that the socioeconomic disadvantage gradient was only present for GLP-1RA prescriptions from specialists in the initial years; however, this should be interpreted with caution, as there were few GLP-1RA prescriptions from GPs initially (ESM Fig. 1).

Remoteness and GLD dispensing Receipt of DPP4is and SGLT2is was similar for those in major cities and regional areas (Fig. 2 and Table 2). Individuals in regional areas were initially less likely to receive a GLP-1RA than those in major cities, but GLP-1RAs became more common in regional areas than major cities over time. Those in remote areas were significantly less likely to receive any new GLD, although the magnitude of the difference became smaller over time for DPP4is and GLP-1RAs (OR [95% CI]: 0.46 [0.39, 0.54] and 0.71 [0.67, 0.74] for receipt of a DPP4i in remote areas vs major cities in the first and seventh year since DPP4i release, respectively; and for GLP-1RA in the first and fifth years: 0.46 [0.35, 0.61] and 0.77 [0.68, 0.86], respectively).

The likelihood of a person being on multiple GLDs and receiving an add-on GLD decreased with increasing remoteness (data not shown). When considering only add-on GLDs, the disparity between outer regional, remote and major city DPP4i receipt was mildly attenuated relative to the whole of population analysis (from ORs of 0.95, 0.83 and 0.46 in the first year of DPP4i availability in the whole population [Table 2] to 1.09, 0.88 and 0.53 in their use as add-on GLDs among the concession population [Table 3] for inner regional, outer regional and remote areas vs major cities, respectively). Similarly, the relationship between GLP-1RA use as an add-on and remoteness was attenuated; those in remote areas were significantly less likely to receive GLP-1RAs as an add-on GLD in their first year only. SGLT2i use as an add-on was more common among those in regional areas (OR [95% CI]: 1.20 [1.09, 1.33] and 1.26 [1.10, 1.44] in their first year for inner and outer regional areas vs major cities, respectively) but less common in remote areas than major

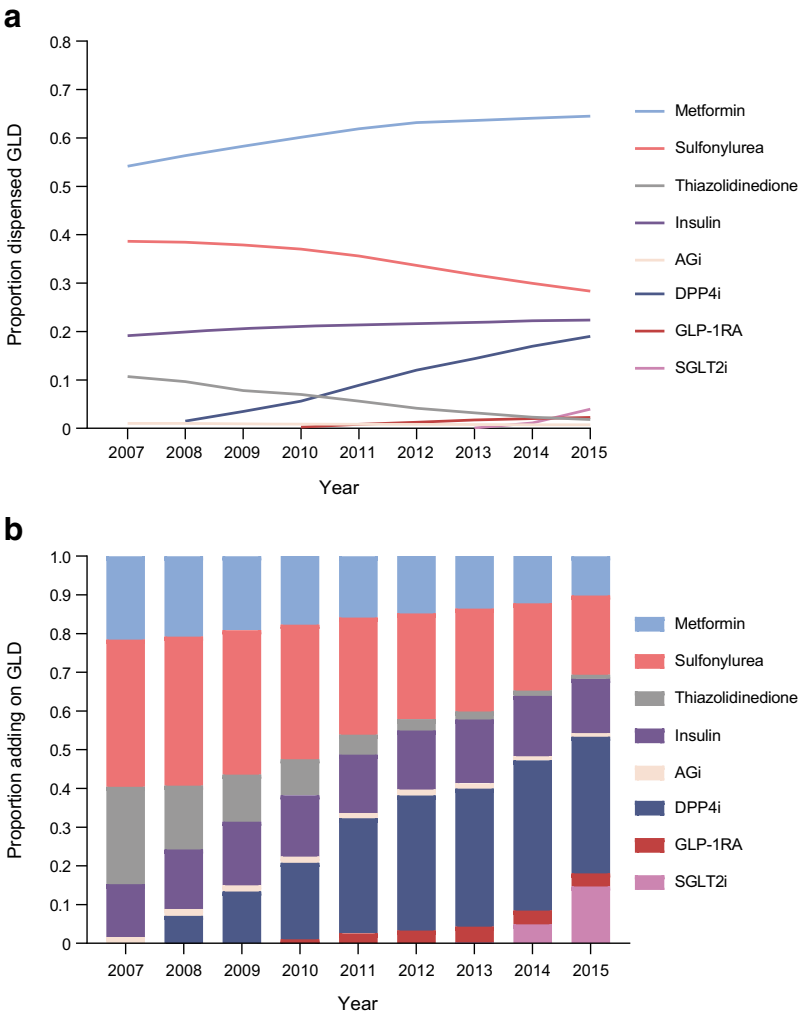

Fig. 1 (**a**) Proportion of people dispensed a prescription for each GLD by calendar year ($p < 0.001$ for all trends). Concession population only. (**b**) Proportional use of each GLD as an add-on GLD each year ($p < 0.001$ for all trends, except insulin [$p = 0.376$]). Concession population only. AGi, α-glucosidase inhibitor

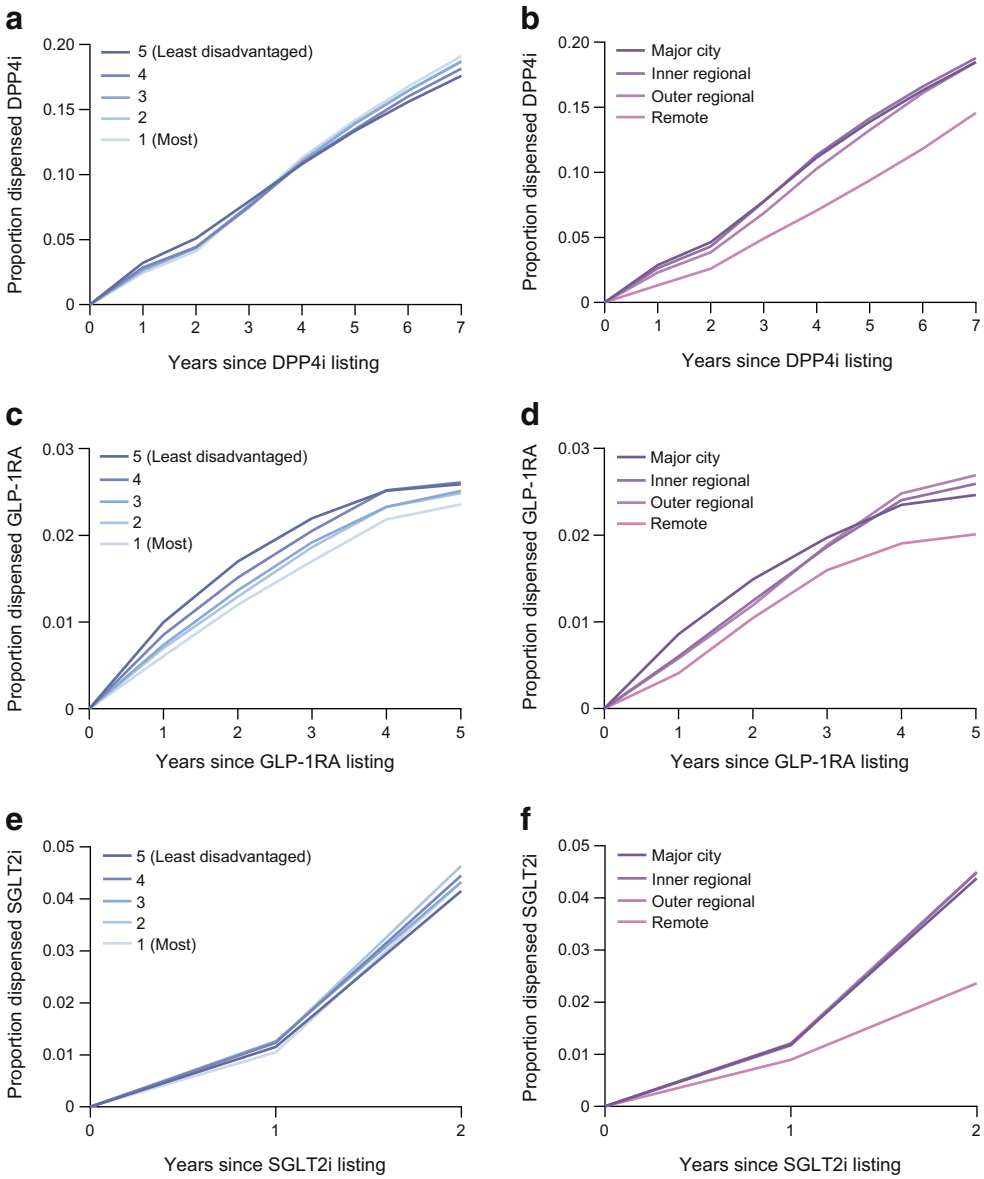

Fig. 2 Proportion of people dispensed a prescription for new GLDs each year since their respective listing on the PBS, by quintiles of the IRSD (**a**, **c**, **e**) and the ARIA (**b**, **d**, **f**)

cities (OR 0.60 [95% CI 0.38, 0.97]) for remote areas vs major cities in the first year; Table 3).

Those in increasingly remote areas were less likely to receive metformin, sulfonylureas and thiazolidinediones (ESM Table 1). Insulin became a more common add-on GLD as remoteness increased, and sulfonylureas were a more common add-on for those in remote areas (ESM Table 2).

As expected, people in more remote areas were significantly less likely to have add-on GLDs prescribed by a specialist (data not shown). The overall associations between remoteness and receipt of new GLDs were consistent when the new GLDs were added on by GPs (ESM Table 3). However, the disparity between remote areas and major cities in receipt of new GLDs was no longer statistically significant when prescribed by specialists (ESM Table 4), although there was substantial uncertainty in this analysis, as very few add-on GLDs were prescribed by specialists to individuals in remote areas. Adjustment for prescriber specialty did not materially affect the association of remoteness with receiving a DPP4i or SGLT2i as the add-on GLD, but the associations for GLP-1RA dispensing were slightly attenuated (data not shown).

Age, duration of diabetes, sex and GLD dispensing There was a significant association between age and receipt of DPP4is as the add-on GLD in the first year since the medications' release, but the effect of age was comparatively mild thereafter (ESM Table 5), presumably because older individuals were already more likely to be on DPP4is (ESM Table 6). The odds of receiving a GLP-1RA decreased substantially with increasing age for those over 60 years old; a similar phenomenon occurred with SGLT2is for individuals aged over 70 years. In general, older individuals were more likely to receive

Table 2 ORs and 95% CIs for receipt of new GLDs each year since their respective listing on the PBS, by socioeconomic disadvantage (IRSD) and remoteness (ARIA)

GLD	Years since GLD listing on PBS						
	1	2	3	4	5	6	7
DPP4i							
IRSD[a]							
5	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
4	0.90 (0.86, 0.94)	0.87 (0.84, 0.90)	0.95 (0.92, 0.98)	1.01 (0.99, 1.04)	1.02 (1.00, 1.04)	1.04 (1.02, 1.05)	1.04 (1.03, 1.06)
3	0.85 (0.82, 0.89)	0.87 (0.84, 0.90)	0.97 (0.95, 1.00)	1.03 (1.01, 1.06)	1.06 (1.04, 1.08)	1.08 (1.06, 1.10)	1.09 (1.07, 1.11)
2	0.85 (0.81, 0.89)	0.89 (0.86, 0.92)	0.96 (0.93, 0.99)	1.05 (1.03, 1.08)	1.07 (1.05, 1.09)	1.08 (1.06, 1.10)	1.09 (1.08, 1.11)
1	0.78 (0.75, 0.82)	0.83 (0.80, 0.86)	0.98 (0.96, 1.01)	1.08 (1.05, 1.10)	1.09 (1.07, 1.12)	1.11 (1.09, 1.13)	1.12 (1.10, 1.14)
p_{trend}	<0.001	<0.001	0.520	<0.001	<0.001	<0.001	<0.001
ARIA							
Major city	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Inner regional	0.95 (0.92, 0.99)	0.96 (0.93, 0.98)	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)	1.00 (0.98, 1.01)	0.99 (0.98, 1.01)	0.99 (0.98, 1.00)
Outer regional	0.83 (0.79, 0.88)	0.85 (0.82, 0.88)	0.87 (0.84, 0.89)	0.88 (0.86, 0.91)	0.91 (0.89, 0.93)	0.95 (0.93, 0.97)	0.96 (0.94, 0.98)
Remote	0.46 (0.39, 0.54)	0.55 (0.49, 0.61)	0.59 (0.54, 0.64)	0.57 (0.53, 0.61)	0.60 (0.57, 0.64)	0.65 (0.61, 0.68)	0.71 (0.67, 0.74)
p_{trend}	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
GLP-1RA							
IRSD[a]							
5	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
4	0.88 (0.81, 0.95)	0.90 (0.85, 0.95)	0.92 (0.88, 0.97)	0.98 (0.94, 1.03)	0.99 (0.95, 1.03)		
3	0.78 (0.73, 0.85)	0.81 (0.77, 0.86)	0.86 (0.82, 0.90)	0.89 (0.85, 0.93)	0.93 (0.89, 0.97)		
2	0.78 (0.72, 0.84)	0.79 (0.74, 0.84)	0.83 (0.79, 0.88)	0.89 (0.85, 0.93)	0.91 (0.87, 0.95)		
1	0.65 (0.60, 0.71)	0.71 (0.67, 0.76)	0.75 (0.71, 0.79)	0.82 (0.78, 0.85)	0.85 (0.81, 0.88)		
p_{trend}	<0.001	<0.001	<0.001	<0.001	<0.001		
ARIA							
Major city	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
Inner regional	0.79 (0.74, 0.85)	0.93 (0.89, 0.97)	1.04 (1.00, 1.08)	1.11 (1.07, 1.15)	1.13 (1.09–1.17)		
Outer regional	0.75 (0.68, 0.82)	0.87 (0.82, 0.93)	1.03 (0.98, 1.09)	1.12 (1.07, 1.17)	1.15 (1.10, 1.20)		
Remote	0.46 (0.35, 0.61)	0.67 (0.57, 0.80)	0.77 (0.67, 0.89)	0.77 (0.68, 0.87)	0.77 (0.68, 0.86)		
p_{trend}	<0.001	<0.001	0.817	<0.001	<0.001		
SGLT2i							
IRSD[a]							
5	1 (ref)	1 (ref)					
4	1.06 (1.00, 1.13)	1.07 (1.03, 1.10)					
3	1.09 (1.02, 1.15)	1.04 (1.00, 1.07)					
2	1.06 (1.00, 1.13)	1.12 (1.08, 1.16)					
1	0.89 (0.84, 0.95)	1.03 (0.99, 1.06)					
p_{trend}	<0.001	0.030					
ARIA							
Major city	1 (ref)	1 (ref)					
Inner regional	1.01 (0.96, 1.06)	1.05 (1.02, 1.07)					
Outer regional	1.03 (0.97, 1.10)	1.02 (0.98, 1.05)					
Remote	0.71 (0.59, 0.84)	0.48 (0.43, 0.54)					
p_{trend}	0.356	<0.001					

Adjusted for age, sex, duration of diabetes, and IRSD or ARIA; ORs by age, duration of diabetes and sex can be found in ESM Table 6

[a] For IRSD: 5, least disadvantaged; 1, most disadvantaged

p_{trend}, p value for trend; Ref, reference

Table 3 ORs and 95% CIs for adding on new GLDs, among people who added on a GLD, each year since their respective listing on the PBS, by socioeconomic disadvantage (IRSD) and remoteness (ARIA)

GLD	Years since GLD listing on PBS						
	1	2	3	4	5	6	7
DPP4i							
IRSD[a]							
5	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
4	0.81 (0.74, 0.88)	0.90 (0.83, 0.98)	0.98 (0.91, 1.05)	1.05 (0.99, 1.13)	0.95 (0.89, 1.02)	1.02 (0.95, 1.09)	0.97 (0.91, 1.03)
3	0.75 (0.68, 0.81)	0.92 (0.84, 1.00)	1.04 (0.97, 1.11)	1.09 (1.02, 1.16)	1.02 (0.95, 1.08)	1.03 (0.96, 1.09)	1.00 (0.94, 1.07)
2	0.76 (0.69, 0.83)	0.95 (0.87, 1.03)	0.98 (0.91, 1.05)	1.07 (1.00, 1.14)	1.02 (0.96, 1.09)	1.01 (0.95, 1.08)	1.00 (0.94, 1.06)
1	0.67 (0.62, 0.73)	0.81 (0.75, 0.88)	1.04 (0.97, 1.11)	1.06 (1.00, 1.13)	0.99 (0.93, 1.05)	1.03 (0.96, 1.09)	1.00 (0.94, 1.06)
p_{trend}	<0.001	<0.001	0.321	0.172	0.598	0.507	0.609
ARIA							
Major city	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)
Inner regional	1.09 (1.02, 1.16)	1.04 (0.98, 1.11)	1.16 (1.10, 1.21)	1.11 (1.06, 1.16)	1.15 (1.10, 1.20)	1.08 (1.03, 1.13)	1.06 (1.01, 1.11)
Outer regional	0.88 (0.80, 0.98)	0.88 (0.81, 0.96)	0.95 (0.88, 1.01)	0.98 (0.92, 1.05)	1.05 (0.98, 1.12)	1.02 (0.96, 1.09)	1.05 (0.99, 1.12)
Remote	0.53 (0.38, 0.75)	0.62 (0.47, 0.81)	0.56 (0.45, 0.69)	0.57 (0.47, 0.69)	0.70 (0.59, 0.84)	0.67 (0.57, 0.80)	0.90 (0.77, 1.06)
p_{trend}	0.028	0.005	0.365	0.375	0.070	0.979	0.090
GLP-1RA							
IRSD[a]							
5	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
4	0.77 (0.64, 0.93)	0.88 (0.74, 1.04)	0.96 (0.81, 1.13)	0.99 (0.84, 1.17)	1.02 (0.85, 1.22)		
3	0.69 (0.57, 0.83)	0.75 (0.63, 0.89)	0.81 (0.69, 0.96)	0.90 (0.77, 1.06)	0.90 (0.76, 1.08)		
2	0.66 (0.54, 0.79)	0.65 (0.55, 0.77)	0.72 (0.61, 0.85)	0.95 (0.81, 1.11)	0.90 (0.75, 1.07)		
1	0.57 (0.48, 0.69)	0.62 (0.53, 0.73)	0.73 (0.62, 0.86)	0.75 (0.64, 0.88)	0.81 (0.68, 0.96)		
p_{trend}	<0.001	<0.001	<0.001	<0.001	0.002		
ARIA							
Major city	1 (ref)	1 (ref)	1 (ref)	1 (ref)	1 (ref)		
Inner regional	0.83 (0.72, 0.97)	1.10 (0.97, 1.24)	1.27 (1.13, 1.41)	1.28 (1.15, 1.42)	1.24 (1.11, 1.39)		
Outer regional	0.88 (0.71, 1.08)	0.97 (0.82, 1.16)	1.26 (1.08, 1.46)	1.30 (1.13, 1.49)	1.15 (0.98, 1.34)		
Remote	0.30 (0.12, 0.72)	0.84 (0.51, 1.40)	1.16 (0.77, 1.75)	0.92 (0.61, 1.39)	0.99 (0.64, 1.53)		
p_{trend}	0.003	0.914	<0.001	<0.001	0.011		
SGLT2i							
IRSD[a]							
5	1 (ref)	1 (ref)					
4	1.03 (0.89, 1.20)	1.04 (0.95, 1.14)					
3	1.03 (0.89, 1.19)	0.97 (0.89, 1.06)					
2	0.90 (0.78, 1.04)	1.07 (0.98, 1.17)					
1	0.75 (0.65, 0.87)	0.91 (0.84, 1.00)					
p_{trend}	<0.001	0.028					
ARIA							
Major city	1 (ref)	1 (ref)					
Inner regional	1.20 (1.09, 1.33)	1.16 (1.10, 1.23)					
Outer regional	1.26 (1.10, 1.44)	1.05 (0.97, 1.14)					
Remote	0.60 (0.38, 0.97)	0.38 (0.28, 0.53)					
p_{trend}	0.004	0.654					

Adjusted for age, sex, duration of diabetes, IRSD or ARIA and weighted RxRisk score. ORs by age, duration of diabetes and sex for concession population only can be found in ESM Table 5

[a] For IRSD: 5, least disadvantaged; 1, most disadvantaged

p_{trend}, p value for trend; Ref, reference

metformin and less likely to receive insulin (data not shown). Sulfonylurea use showed a strong association with increasing age, which decreased over time.

The odds of being on multiple therapies increased with increasing duration of diabetes, whereas add-ons were most common before 15 years of diabetes duration (data not shown). In the first year of DPP4i availability, those with a longer duration of diabetes were more likely to receive DPP4is as the add-on GLD, whereas in the following years those with longer durations of diabetes were increasingly less likely to receive a DPP4i (ESM Table 5). Conversely, the odds of receiving a GLP-1RA and SGLT2i were much higher for those with a longer duration of diabetes. Predictably, insulin use became substantially more likely with increasing duration of diabetes (data not shown).

Women were ~13% less likely to be on multiple therapies than men in 2007 and this increased to 27% by 2015; women were consistently ~12–15% less likely to receive an add-on GLD than men (data not shown). Women were initially more likely than men to receive DPP4is and GLP-1RAs as an add-on but there was no such association for SGLT2is (ESM Table 5), metformin or insulin (data not shown).

Interactions There was no evidence of strong interactions between socioeconomic disadvantage and remoteness (data not shown). However, stratification by second- vs third-line add-on revealed that the associations between socioeconomic disadvantage and remoteness with DPP4i receipt were attenuated when DPP4is were received as third-line drugs (data not shown). DPP4is were preferentially used as third-line GLDs in more disadvantaged areas in later years, and there was no significant difference in DPP4i receipt as third-line drugs when comparing remote areas with major cities (data not shown).

Discussion

Main findings In this study, we found that the use of new GLDs increased over time but the rate of uptake depended on sociodemographic factors. Utilisation of DPP4is and SGLT2is was initially lower among individuals living in more disadvantaged areas but disparities resolved within 2 years, whereas utilisation of GLP-1RAs remained lower in more disadvantaged areas throughout the entire study, even after accounting for socioeconomic differences in rates of intensification of therapy. Remoteness also affected new GLD use. After accounting for differences in overall GLD prescription patterns, it appeared that individuals living in regional areas were more likely to receive the new GLDs than those in major cities. Individuals in remote areas and major cities had comparable receipt of GLP-1RAs as an add-on, yet those in remote areas were considerably less likely to receive DPP4is and SGLT2is.

Similar disparities have been observed in the use of cholinesterase inhibitors in Australia [14]; yet statins generally show a pattern of use concomitant with area-level CVD risk by sociodemographic disadvantage many years after their release [13]. Together, these results suggest that the disparities in receipt of newer medications are not specific to GLDs and suggest the existence of an effect of disadvantage in limiting receipt of newer medications in Australia that wanes over time.

People in remote areas also seem to have reduced initial access to newer medications, but the presence, magnitude and duration appear to be more dependent on the medication in question. Cholinesterase inhibitors and statins both exhibit lower use as remoteness increases [12, 14] whereas use of cyclooxygenase-2 (COX-2) inhibitors was not found to be different between comparable remote and urban areas [22], although the prevalence of the conditions under treatment was not available in these studies.

The effects of age and duration of diabetes on GLD receipt were mostly expected: sulfonylureas and DPP4is appeared to be added on early in the time course of diabetes, whereas GLP-1RAs, SGLT2is, insulin and, surprisingly, metformin were favoured as add-ons as duration of diabetes increased. We also found that women were more likely than men to receive DPP4is and GLP-1RAs but not SGLT2is.

Potential contributors to disparities in access to newer medications Depending on the medication subsidy policies of a country, affordability of newer medications can be a driver of the earlier adoption of new medications by higher-income patients [20]. In Australia, the cost of newer medications can be higher than older medications for people without concession status. For example, a pack of metformin costs ~$10–20, while DPP4is, GLP-1RAs and SGLT2is all cost the maximum co-payment of $41 per pack. It is therefore reasonable to hypothesise that affordability could limit access to newer medications. However, the disparities by socioeconomic disadvantage we observed were consistent in the concession population, for whom medication prices are substantially reduced. Furthermore, these disparities decreased over time, despite co-payments remaining unchanged, suggesting affordability is not the primary factor driving our observations. This is consistent with findings of a similar study undertaken in patients receiving an add-on to metformin in primary care in the UK, where the National Health Service covers all medication costs for people with type 2 diabetes, which found that those in more disadvantaged areas were less likely to receive an SGLT2i than a sulfonylurea as the add-on GLD [23].

Another conceivable contributor may be differential access to specialists [24], who were more likely to prescribe the new GLDs, as reported in previous studies [25–27]. It should be noted that a proportion of this is likely due to referral bias, as those who visit specialists are likely to have elevated HbA_{1c} and more complex disease [28] and, therefore, may require more intensive care. However, the association between disadvantage and receipt of new GLDs was present for both GPs and specialists as the

prescriber of the add-on GLD. Furthermore, while the significant differences in receipt of newer GLDs between individuals in remote areas and major cities were no longer apparent for individuals who received add-ons from a specialist, the level of uncertainty in this analysis was high due to a paucity of add-on GLD prescriptions by specialists in remote areas, precluding robust conclusions about the contribution of specialist access to new GLD availability in remote areas. Nevertheless, adjustment for prescriber specialty suggested that access to specialists may have played a role in lower initial use of GLP-1RAs, but not DPP4is or SGLT2is, in remote areas.

The fact that the association of disadvantage with receipt of new GLDs was not completely explained by prescriber specialty, price or adjustment for comorbidity, suggests the presence of other unmeasured contributors to the effect of sociodemographic factors on receipt of new medications.

Strengths and limitations This large, nationwide population-based study allows a near-whole population examination of medication receipt in type 2 diabetes. Through using a registry, we were able to effectively control for differences in diabetes prevalence across sociodemographic strata. Additionally, DPP4i receipt eventually became more common in more disadvantaged areas in the overall analysis, but not when restricted to receipt as an add-on. This highlights the importance of accounting for not only disease prevalence, but also how overall treatment patterns vary when analysing new drug uptake. Finally, we were able to adjust for a comorbidity index, concession status and specialist prescriptions, and could therefore account for potentially important drivers of disparities in access to newer medications.

However, there are a number of important limitations of this study that should be considered. Because this study used national administrative data, we do not have data on important clinical covariates, such as HbA_{1c}, and therefore cannot comment on the appropriate use of medications. Nevertheless, we attempted to control for this by looking at GLD receipt among those who added on a GLD, assuming this decision was made because glycaemic control was unsatisfactory. Additionally, we did not have access to individual level information about socioeconomic disadvantage, instead relying on area-level measures. Finally, it is important to note that these disparities do not necessarily imply inequitable care, as contraindications and patient preference may be important contributors; moreover, during the period under study, the benefits of SGLT2is and GLP-1RAs on cardiovascular and renal complications had not yet been established [1]. Nevertheless, what is clear from our analysis is that care for diabetes differs by socioeconomic disadvantage and remoteness.

Implications Insulin and sulfonylureas, both of which carry a greater risk of hypoglycaemia than newer GLDs [29, 30], were more common in remote areas than major cities. Disparate utilisation of the best available medications in remote areas, which may be in part due to disparate access to healthcare [31–33], may contribute to the worse mortality and health outcomes in these areas [10]. Therefore, efficient dissemination of newer medications may be an appropriate intervention to address health disparity for people in remote and disadvantaged areas of Australia.

Conclusions The receipt of newer medications is initially lower among those with type 2 diabetes in more disadvantaged areas of Australia but the disparities decreased over time. This phenomenon does not appear to be driven by differential access to specialists or affordability of newer medications. Access to newer medications in remote areas compared with major cities of Australia appears far more variable and may be an important point of intervention to address disparities in diabetes outcomes for individuals in remote areas of Australia.

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Data availability The datasets analysed during the current study are not publicly available due to privacy concerns.

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Authors' relationships and activities JI has consulted for AstraZeneca Australia. JES has received honoraria from Astra Zeneca, Sanofi, Novo Nordisk, MSD, Eli Lilly, Abbott, Mylan and Boehringer Ingelheim. All other authors declare that there are no relationships or activities that might bias, or be perceived to bias, their work.

Contribution statement JIM contributed to the design of the study and interpretation of data, performed the statistical analysis and literature search, and wrote and revised the manuscript. JI contributed to the design of the study, interpretation of data and revision of the manuscript. DJM and JES are principal investigators and made contributions to the design of the study, acquisition and interpretation of the data, and revision of the manuscript. All authors have read and approved the final version of this manuscript. JIM is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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