The impact of sodium glucose co-transporter 2 inhibitors and glucagon-like peptide 1 receptor agonists on insulin utilisation and costs in Australia: a national retrospective observational cross-sectional study

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Summary

Background Global insulin requirements for type 2 diabetes were predicted to increase by more than 20% from 2018 to 2030. However, this did not anticipate the rapid increase in use of glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors that has occurred over recent years. The current study aims to examine changes in insulin utilisation and costs in Australia from 2003 to 2023.

Methods We conducted a large-scale observational study of national insulin utilisation and expenditure in Australia from 2003 to 2023 using the Australian Pharmaceutical Benefits Scheme. The proportion of insulin-treated people with type 2 diabetes between 2013 and 2023 was estimated using National Diabetes Services Scheme data. Joinpoint models and interrupted time series analysis were used to examine utilisation trends.

Findings Insulin utilisation (units of insulin per person with diabetes) increased by an average of 2.71% per annum (95% CI 1.97, 3.73) from 2003 to 2015, then fell by 2.70% per annum (95% CI −4.55, −1.39) from 2015 to 2023. The proportion of insulin-treated people with type 2 diabetes increased by 1.00% per annum (95% CI 0.81, 1.25) from 2013 to 2020, then fell by 0.66% per annum (95% CI −1.62, −0.04) from 2020 to 2023. A 43% reduction in inflation-adjusted insulin expenditure was observed between 2015 and 2023 due to a combination of reduced utilisation and reduction in the price of insulin glargine.

Interpretation Projected global insulin requirements and costs may be less than previously anticipated if reduced use of insulin in Australia is similarly observed in other countries.

Funding No funding was received for this study.

Keywords: Insulin utilisation; Insulin expenditure; SGLT2i; GLP-1 RA; Sodium glucose cotransporter 2 inhibitors; Glucagon-like peptide 1 receptor agonist

Introduction

In 2019 a microsimulation study predicted that global insulin requirements would increase by more than 20% between 2018 and 2030.[1] However, this study did not consider the paradigm shift in type 2 diabetes management that has taken place since the publication of landmark sodium glucose cotransporter 2 inhibitor (SGLT2i) cardiovascular outcome trials[2–4] and glucagon-like peptide 1 receptor agonist (GLP-1 RA) studies.[5,6]

The previous glucocentric approach to type 2 diabetes has given way to nuanced cardiovascular and kidney risk management strategies.[7,8]

Given the rapidly increasing use of SGLT2i and GLP-1 RAs over the past decade,[9] our study sought to explore whether insulin utilisation had been impacted, as this has implications for future global insulin requirements and costs. Changes in prescriber behaviour to implement results of major cardiovascular, heart failure and

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Research in context

Evidence before this study
Microsimulation studies have predicted that globally the insulin required to treat type 2 diabetes would increase by more than 20% from 2018 to 2030. Despite growing uptake of glucagon-like peptide- 1 receptor agonists (GLP-1 RA) and sodium-glucose cotransporter 2 inhibitors (SGLT2i) over recent years, the potential for reduced insulin utilisation has not been fully explored. We searched PubMed using the terms 'Insulin Prescribing Trends' and 'Insulin Utilization' without language restrictions for the years 2015–2024. Only one study, restricted to older adults in Northern Italy, reported insulin utilisation to 2021. The most recent general population insulin utilisation study in people with diabetes was from Hungary but did not go beyond 2020.

Added value of this study
In Australia, insulin utilisation (units of insulin per person with diabetes) increased progressively from 2003 to a peak in 2015, then declined from 2015 to 2023. The proportion of people with type 2 diabetes treated with insulin rose progressively to 2020 and then began falling. Sensitivity analysis using the general Australian population as the denominator showed similar trends. Inflation adjusted insulin expenditure fell, due to a combination of reduced utilisation and price reductions related to the introduction of a biosimilar glargine insulin.

Implications of all the available evidence
If similar reductions in insulin utilisation are replicated in other countries, projected estimates of global insulin requirements may be less than previously anticipated and have the potential to offset a proportion of the costs associated with increased use of GLP-1 RAs and SGLT2i.

kidney disease trials takes time and therapeutic inertia is well described. It was therefore important to examine insulin utilisation trends beyond 2020 in order to capture potential changes related to the evolving literature and changed clinical guidelines. As Australia has a universal medication subsidy scheme with accurate publicly available data we were able to comprehensively examine nationwide insulin utilisation trends.

Methods

The population under study was every person in Australia who received at least one insulin prescription in the period 2003 to 2023 through the Australian Pharmaceutical Benefits Scheme (PBS) or Repatriation PBS (RPBS, for veterans). These schemes provide subsidised medicine for all Australian citizens and permanent residents. Private prescribing of insulin is negligible in Australia and apart from insulin dispensed for inpatients in public hospitals, all insulin utilisation in Australia is captured by the complete PBS datasets. The total number of PBS and RPBS insulin prescriptions dispensed each year in Australia from 2003 to 2023 was obtained from the Services Australia PBS Statistics public database.[10] Unique PBS codes for every insulin type were searched for each calendar year (Supplementary Table S1). To ensure data completeness, code additions or deletions (e.g. retired codes for PBS de-listed insulins) were checked using archived records.[11]

Calculation of units of insulin

The annual number of units of insulin was then calculated for the combined total of all insulin types and also separately for the main insulin types: basal (glargine and detemir only, as degludec is not available as a basal insulin in Australia), quick acting (insulin neutral bovine, insulin neutral human, insulin aspart, insulin aspart fast acting, insulin lispro, insulin glulisine), premixed (isophane human/neutral human, aspart/aspart protamine, lispro/lispro protamine, degludec/aspart) and isophane (isophane bovine, isophane human). Insulin zinc suspensions which were available from 2003 to 2005 were included in the total of all insulin, but were not presented separately. To assess the most recent trends in insulin utilisation, the proportion of use of each of the insulin types was also calculated for the 2023 calendar year.

Estimate of diabetes prevalence

The number of units of insulin dispensed each year was adjusted to account for diabetes prevalence (total of type 1, type 2 and gestational diabetes which accounts for more than 99% of diabetes in Australia[12]), using published data from the National Diabetes Services Scheme (NDSS).[12] NDSS is an Australian Government initiative that began in 1987 and aims to enhance the capacity of people with diabetes to understand and self-manage their life with diabetes and provides access to services, support and subsidised diabetes products. It is estimated that 80%–90% of people diagnosed with diabetes are registered with the NDSS.[13] NDSS data were available from 2013 to 2023 and prior to 2013 prevalence for type 1 and type 2 diabetes was estimated by extrapolation. We assumed the rate of change in prevalence of diabetes from 2013 to 2023 to be linear and fit an ordinary least squares linear regression model to the data, which showed excellent fit (r-square = 0.9465 and 0.9943 for type 1 and type 2 diabetes respectively). We then extrapolated this trend from 2003 to 2012, as we had no

evidence to suggest a different trend. Additionally, we found that fitting a logarithmic trend did not considerably improve the fit. As gestational diabetes incidence has increased significantly in Australia over the past decade, it was considered inappropriate to use extrapolation to obtain gestational diabetes prevalence for the period before 2013. The number of NDSS registrants with gestational diabetes from 2003 to 2012 was obtained separately.[14] The proportion of people with type 2 diabetes registered with NDSS who were insulin treated was able to be calculated only for the years 2013–2023 as data for earlier years were not available.[12] In a sensitivity analysis the Australian population was used as the denominator instead of people with diabetes. This method accounts for population increases over time, and allows comparison of drug utilisation to other countries.

Cost of insulin
The total cost of insulin from 2003 to 2023 was calculated using the Dispensed Price for Maximum Quantity (DPMQ) published on 1 July each year for each insulin type.[11] DPMQ includes both patient and Government contributions. In Australia, approximately two-thirds of insulin prescriptions are for concession card holders. They pay approximately a quarter of the non-concessional amount with annual limits applying to both groups. Given the relatively high cost of insulin, the Australian Government pays the major proportion of insulin costs. All costs are presented in 2023 Australian dollars after adjustment for inflation.[15]

Ethics approval was granted by Monash University Human Research Ethics Committee (Project ID: 39870).

Statistical analysis
Average annual percent changes in the units of insulin dispensed from 2003 to 2023 were calculated using the Joinpoint Regression Program, Version 5.0.2–May 2023; Statistical Methodology and Applications Branch, Surveillance Research Program, NCI.[16] As basal insulins were first PBS listed in 2006, the annual percent changes for them were calculated from 2008, as the first two years of use commenced from a very low base. Joinpoint regression calculates average annual percent changes and also determines if there are any breakpoints in trends of utilisation over time. Joinpoint analysis assumed homoscedasticity (constant variance). Data were log transformed to minimise variance in the series. Weighted Bayesian information criterion was applied and empirical quantiles were used for confidence intervals. Interrupted time series analysis models with an autoregressive term of 1 and robust standard errors were used in a sensitivity analysis to quantify the change in slopes of insulin utilisation before and after 2015, the year identified as a breakpoint by Joinpoint analysis (2013 for Isophane insulin). For a descriptive display of the trend data, we used restricted cubic splines (with 6 knots) to provide a smoothed trend data.

Data analysis was performed in Stata SE V18.0 (Stata Corp, College Station, TX, USA) and level of significance was set at 5%.

Role of funding source
No funding was obtained for this study.

Results
Utilisation
There were 138.2 billion units of insulin dispensed in Australia from 2003 to 2023 (an average of 450,750 defined daily doses per day).[17] The estimated number of people with diabetes, annual total units of insulin per person with diabetes, units of the different insulin types per person with diabetes and annual insulin costs in Australia from 2003 to 2023 is shown in Table 1. Insulin utilisation per capita of the Australian population is shown in Supplementary Table S2. The total number of units of insulin per person with diabetes increased by an average of 2.71% per annum (95% CI 1.97, 3.73) from 2003 to 2015, then fell by 2.70% per annum (95% CI −4.55, −1.39) from 2015 to 2023 (Table 2, Fig. 1). In 2023, total insulin utilisation per person with diabetes was 23.8% lower than that of 2015. In 2023, 34.9% of insulin utilisation was for basal insulin (32.2% glargine, 2.7% detemir), 34.6% quick acting insulin, 27.9% premixed insulin and 2.7% isophane (Supplementary Fig. S1).

Basal insulin utilisation increased by 7.65% per annum (95% CI 2.39, 19.06) from 2008 to 2015, then fell by 4.06% per annum from 2015 (95% CI −15.52, −0.69) (Table 2, Supplementary Fig. S2). Quick acting insulin utilisation increased by 3.51% per annum (95% CI 2.77, 4.52) from 2003 to 2015 then fell by 1.51% per annum (95% CI −3.42, −0.22) from 2015 (Table 2, Supplementary Fig. S2). There was no change before or after 2015 in the average percent change in use of premixed insulin which fell at an average annual rate of 1.94% (95% CI −2.54, −1.35) across the whole period of 2003–2023 (Table 2, Supplementary Fig. S2). Isophane insulin utilisation reduced in an exponential manner over the study period (Supplementary Fig. S2) with four different rates identified by Joinpoint analysis: −4.28% per annum in the period 2003 to 2006, −27.05% per annum from 2006 to 2009 (after the introduction of basal insulins), −15.30% per annum from 2009 to 2013 and −6.02% per annum from 2013 to 2023.

Significant differences between the slopes of insulin utilisation before and after 2015 (Table 3) were demonstrated for total insulin (Fig. 2), basal insulin and quick acting insulin, but not premixed insulin. Isophane insulin demonstrated an exponential decline from 2003.

Sensitivity analyses using the general Australian population as the denominator showed qualitatively similar findings, with the statistical significance of differences between slopes of insulin utilisation before and

Year	Estimated number of people with diabetes[a]	Total Units per person with diabetes	Units of zinc suspension per person with diabetes	Units of Isophane per person with diabetes	Units of basal per person with diabetes	Units of quick acting per person with diabetes	Units of premixed per person with diabetes	Annual Cost (2023 AUD, millions)
2003	715,117	5085	153	1373		1447	2112	170.2
2004	751,452	5158	131	1366		1462	2199	179.4
2005	788,657	5149	60	1368		1472	2249	185.4
2006	825,235	5186		1256	222	1482	2227	194.3
2007	862,271	5547		855	1013	1590	2089	240.1
2008	899,879	5545		617	1372	1644	1911	258.7
2009	935,884	5969		510	1746	1793	1920	294.0
2010	973,816	5972		408	1893	1793	1878	305.5
2011	1,011,920	5947		335	2004	1799	1809	313.0
2012	1,049,927	6622		307	2341	2017	1957	360.3
2013	1,088,973	5834		236	2146	1791	1661	326.4
2014	1,150,032	7042		252	2613	2173	2004	409.8
2015	1,186,039	7408		235	2842	2291	2041	421.9
2016	1,231,982	6402		192	2520	2014	1676	359.2
2017	1,265,787	6215		184	2498	1980	1553	353.2
2018	1,299,239	6176		181	2523	1966	1507	266.8
2019	1,331,198	6171		162	2436	1969	1603	281.9
2020	1,395,026	6123		152	2343	1979	1650	275.0
2021	1,415,542	5652		156	2073	1876	1548	260.7
2022	1,475,442	5550		132	2004	1897	1518	267.7
2023	1,451,881	5648		149	1963	1965	1570	241.6

[a]Number of people with diabetes (type 1, type 2 and gestational diabetes) sourced from National Diabetes Services Scheme, with extrapolation for the period 2003–2012 from published 2013–2023 data.

Table 1: Estimated number of people with diabetes, total units of insulin, units of the different insulin types and annual insulin costs in Australia 2003–2023.

after 2015 (2013 for Isophane) persisting (Supplementary Figs. S4 and S5 and Tables S3 and S4).

Insulin treated type 2 diabetes
From 2013 to 2020, there was an average increase of 1.00% (95% CI 0.81, 1.25) per annum in the proportion of NDSS registrants with type 2 diabetes who were insulin treated. From 2020 there was a fall of 0.66% per annum (95% CI −1.62, −0.04). The difference between the slopes before and after 2020 was statistically significant (p = 0.018).

Insulin expenditure
The weighted mean dispensed prices for maximum quantities of five common insulin types (expressed in 2023 Australian dollars) are shown in the Supplementary Material (Supplementary Fig. S6 and Table S5) and the cost per unit of insulin for common insulin types in 2023 is shown in Supplementary Table S6. There was a downward trend in prices for all insulin types over the study period from 2003 until 2017. In 2018 there was a rise in the weighted mean price of premixed insulin due to the listing of insulin degludec/insulin aspart and a 38% reduction in the price of insulin glargine due to the listing of a biosimilar.

Annual insulin expenditure (2023 Australian dollars) increased from $170.2 million in 2003 to a peak of $421.9 million in 2015 (Supplementary Fig. S7). There was a 43% reduction in insulin expenditure between

	Total Insulin	Basal units	Quick Acting	Premixed	Isophane[a]
Average Annual Percent Change in units of Insulin 2003–2015 (95% CI)	2.71% (1.97, 3.73)	7.65% (2.39, 19.06)	3.51% (2.77, 4.52)	−1.94% (−2.54, −1.35)	−15.30% (−18.40, +2.20)
Average Annual Percent Change in units of Insulin 2015–2023 (95% CI)	−2.70% (−4.55, −1.39)	−4.06% (−15.52, −0.69)	−1.51% (−3.42, −0.22)	−1.94% (−2.54, −1.35)	−6.02% (−17.37, +2.20)

Annual percent changes in basal (glargine and detemir) insulin from 2008 as the first two years after Pharmaceutical Benefits Subsidy listing in 2006 started from a low base with high annual changes. [a]Isophane insulin 2009–2013 and 2013–2023.

Table 2: Annual percent changes (mean, (95% CI)) in insulin utilisation (units of insulin per person with diabetes) in Australia before and after 2015.
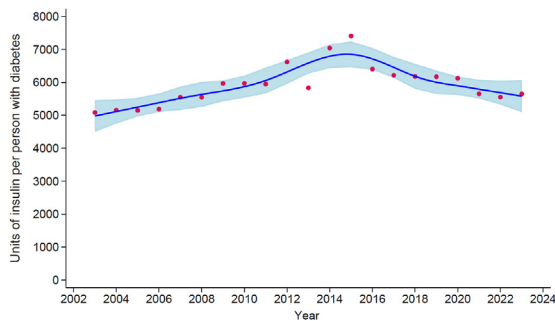
Fig. 1: Total units of insulin per person with diabetes dispensed in Australia 2003–2023. To obtain defined daily doses divide units by 40.[17] Solid line represents smoothed means, shaded area 95% confidence intervals.

	Coefficient before 2015	Coefficient after 2015	Coefficient difference	Coefficient difference 95% confidence intervals	p-value
Total units of insulin	153.5	−180.7	−344.2	−435.1, −233.3	<0.001
Basal Insulin	258.1	−104.8	−362.9	−478.0, −247.8	<0.001
Quick Acting Insulin	60.3	−31.4	−91.7	−126.1, −57.4	<0.001
Isophane insulin (before and after 2013)	−131.9	−6.9	125.1	92.9, 157.2	<0.001
Premixed insulin	−36.9	−37.4	−0.5	−60.6, +59.6	0.986

The coefficient differences were obtained by subtracting the coefficients of the annual units of insulin after 2015 from the coefficients before 2015, (2013 for isophane). p-value refers to the statistical significance of the changes in slope.

Table 3: Interrupted Time Series Analysis of changes in slope of annual numbers of units of insulin per person with diabetes before and after 2015 (2013 for Isophane).

2015 and 2023, with a 16% reduction ($68.6 million) in the period 2015 to 2017, before the 2018 premixed insulin price increase and insulin glargine price reduction. Expenditure fell from $353.2 million in 2017 to $241.6 million in 2023, due to a combination of reduced utilisation and insulin price changes.

Discussion

Using national data, insulin utilisation increased progressively between 2003 and 2015 and thereafter declined. The change after 2015 was observed for insulin overall, basal insulin and quick acting insulin but not for premixed insulin or isophane insulin which both continued long term declines. Expenditure reductions paralleled utilisation falls after 2015, with interpretation of further expenditure reductions after 2018 complicated by price reductions for insulin glargine and price increases for premixed insulin.

To our knowledge, this is the first time that total national insulin utilisation has been shown to fall following the widespread adoption of SGLT2i and GLP-1 RAs for the treatment of type 2 diabetes. In Northern Italy in an older population, GLP-1 RA utilisation increased from 0.4% to 10.2% and SGLT2i from 0.6% to 11.1% between 2010 and 2021.[18] The national changes for GLP-1 RA were similar in Australia (1.7% to 11%, despite global shortages), but SGLT2i changes were more pronounced (from 0% in 2013 to 21.9% in 2023).[9] SGLT2i were first PBS listed in 2014 in Australia. The insulin utilisation changes began in 2016, the year after publication of the landmark empagliflozin cardiovascular outcome study.[2] It is noteworthy how rapidly the reduction in insulin utilisation occurred, before the publication of updated guidelines recommending SGLT2i for people with cardiovascular disease in 2018.[19] Insulin availability was not disrupted during the COVID-19 pandemic, despite extensive local lockdowns, with the Government supporting online medical consultations and electronic prescribing. Our findings are consistent with an analysis of insulin utilisation in EMPA REG OUTCOME study participants, where empagliflozin treatment was associated with 60% lower rates of insulin initiation, and in those already taking insulin, the proportion achieving sustained greater than 20% insulin dose reductions without subsequent increases in HbA1c compared with placebo increased (9.2% vs. 4.9%).[20] Further reductions coincided with the PBS listing of semaglutide in 2020. The insulin changes were predominantly due to reduced utilisation of basal and quick acting insulins. The gradient of the long-term decline in premixed insulin utilisation from 2003 did not change after 2015. Isophane insulin utilisation was low compared to the other insulin types and did not demonstrate any significant change after 2015.

Some of the reduction in insulin use may have been related to technology changes for type 1 diabetes, as continuous subcutaneous insulin infusion (CSII) pump therapy use increased from approximately 10% in 2012 to 21% in 2020.[21,22] This would be expected to lead to a reduction in basal insulin utilisation and also insulin
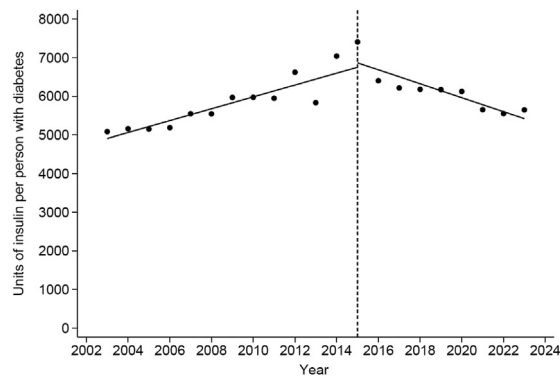

Fig. 2: Interrupted time series analysis of utilisation of total units of insulin per person with diabetes in Australia before and after 2015.

overall because of more efficient absorption of insulin related to the technology.[23] However, the absolute increase of 11% of people with type 1 diabetes using CSII between 2010 and 2020 would only account for approximately 3% of overall insulin utilisation as only 29% of insulin use in Australia is for people with type 1 diabetes.[12] There is no reason to expect that non-CSII users with type 1 diabetes would have a reduction in insulin utilisation, as adjuvant therapy with GLP-1 RAs and SGLT2i even in specialised diabetes centres is only 2.1% in Australia.[24]

Recent insulin utilisation studies have shown inconsistent findings. A Japanese study reported insulin utilisation declines across all age groups from 2012 to 2019 and a study of the Hungarian population reported a slight reduction in insulin use between 2015 and 2020.[25,26] Consistent with our findings, a recent study of Scottish patients with type 2 diabetes demonstrated small declines between 2010 and 2020 in incident insulin utilisation as initial monotherapy or as first add-on therapy to metformin or sulphonylurea,[25] but we observed larger declines in overall insulin utilisation and only after 2015.[27] However a study of older adults with diabetes from Northern Italy showed a slight increase from 2010 to 2021 as did a Romanian study over the seven-year period to 2019.[18,28] An Australian study showed a 58% per capita increase in insulin utilisation between 2003 and 2019, but did not break down utilisation for specific time periods (e.g. 2015–2019).[29] A study from Denmark showed a more than doubling of insulin utilisation per capita over a 22-year period to 2017[30] whilst an Austrian study reported stable insulin utilisation between 2012 and 2018.[31] The differences in insulin utilisation in these studies may reflect ethnic differences, differences in the local availability of glucose lowering drug classes, variations in patterns of SGLT2i and GLP-1 RAs use and the different time periods examined. Additionally, many insulin utilisation studies are incomplete as they comprise only a proportion of those with diabetes in the country (e.g. over 65 years of age, or with particular insurance coverage) and have not examined a complete national dataset as reported in our study.

The changes in insulin utilisation observed from analysis of the Australian national prescribing data is supported by the National Diabetes Services Scheme data showing the proportion of people with type 2 diabetes treated with insulin stopped increasing after 2020 and then began falling. Taken together the findings from our study suggest that people with diabetes are now being treated with less insulin and in addition, fewer people with type 2 diabetes are commencing insulin.

Expenditure on insulin started to decline after 2015. The period between 2015 and 2017 was not affected by significant insulin price changes. In that period insulin expenditure reduced by 16% due to reduced utilisation.

From 2018 interpretation of expenditure reductions is more complex, given the substantial reduction in insulin glargine costs and the rising costs of premixed insulin. It is reasonable to assume however that a proportion of the reduced expenditure was related to reduced insulin utilisation.

Our findings have important implications for health budgets as reduced insulin utilisation is associated with cost savings which may at least partially offset the increases in costs especially of GLP-1 RAs.[32] Additional cost savings may be realised relating to less severe hypoglycaemia, reduced frequency of glucose self-monitoring, reduced healthcare provider time teaching insulin administration and time savings for people with diabetes (fewer taking insulin and less frequent glucose testing). Reduced weight gain and possible longer term cardiovascular and renal benefits may also occur. Given the widespread dissemination of the results of the SGLT2i and GLP-1 RA cardiovascular outcome trials and the EASD/ADA consensus guidelines prioritising these drugs for certain groups of people with diabetes, it is likely that our findings in relation to reduced insulin utilisation are generalisable to other countries where these glucose lowering drugs are available.

Strengths
As the PBS provides universal coverage, this has enabled a comprehensive assessment of insulin utilisation over a 21-year period in Australia. Expenditure is reflective of the full costs of insulin as it includes both Government and patient contributions and the transparent reporting of prices of the different insulin types aids in the interpretation of expenditure changes.

Limitations
The study design precludes causal inference, and the associations between the trends in insulin utilisation and the use of SGLT2i and GLP-1 RA are only hypothesis-generating. The PBS only provides grouped data and it is therefore not possible to explore potential differences related to age, sex, urban/rural location or socio-economic status. The dataset does not provide age and sex breakdown of insulin utilisation, so age and sex standardisation were unable to be presented. It is also not possible to discern how much insulin was used for people with type 1, type 2 or gestational diabetes, or less common diabetes types (e.g. type 3c diabetes).

Conclusion
Since 2015 significant reductions in insulin utilisation and expenditure in Australia have occurred. The timing correlates with the first reports of cardiovascular benefits of SGLT2i and further subsequent reductions correlate with the introduction of semaglutide. If these changes are replicated in other countries, projections relating to global insulin requirements and costs will need to be revised.

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