BMJ Open

Trends in national pharmaceutical expenditure on diabetes in Ireland 2011–2015: a repeated cross-sectional study

Kate N O Neill ![ORCID],[1] Kathleen E Bennett ![ORCID],[2] Sheena M Mc Hugh,[1] Anthony P Fitzgerald,[1,3] Patricia M Kearney[1]

¹School of Public Health, University College Cork, Cork, Ireland
²Division of Population Health Sciences, Royal College of Surgeons in Ireland, Dublin, Ireland
³Department of Statistics, University College Cork, Cork, Ireland

Correspondence to
Dr Kate N O Neill;
kate.oneill@ucc.ie

ABSTRACT

Objectives To explore trends in pharmaceutical expenditure on diabetes between 2011 and 2015, describing trends in expenditure on blood glucose-lowering medications and estimating the effect of cost-containment measures implemented during this time.

Design Repeated cross-sectional study of national pharmacy claims data in Ireland.

Participants Patients' dispensed items used in the treatment or management of diabetes.

Primary and secondary outcomes Total expenditure associated with diabetes was calculated by extracting data on all diabetes-related items dispensed to eligible patients. Costs were categorised into two groups. Diabetes-specific items include items used directly in diabetes treatment (WHO-Anatomical Therapeutic Chemical (ATC): A10, V07, V04) and diabetes-related include all other condition-related items (WHO-ATC: B01, C, H04, N03, N06). The impacts of two specific cost-containment measures, co-payments and reference pricing, were assessed using segmented linear regression analyses of interrupted time-series.

Results Total expenditure varied over the study period, peaking at €216 994 441 in 2012. Expenditure on diabetes-specific items increased steadily by 18% reaching €153 621 477 in 2015, with blood glucose-lowering medications accounting for 73% of this increase. During the same period, expenditure on diabetes-related items decreased by 32% to €50 835 856. The introduction of reference pricing for atorvastatin in November 2013 resulted in immediate costs savings of €2.4 million per yearly quarter (level-change p<0.001).

Conclusions The increasing expenditure on blood glucose-lowering medications negates the effect of recent cost-containment measures, presenting a significant challenge for the provision of diabetes care. Innovative policies are required to ensure high-quality diabetes care can be provided at an equitable, affordable and sustainable rate.

Strengths and limitations of this study

► This study uses data from a large national pharmacy claims database to analyse trends in pharmaceutical expenditure on diabetes over a 5-year period.
► Cost data from this pharmacy claims database are complete and highly accurate as its primary function is for reimbursement.
► Due to the absence of clinical diagnoses in the database, diabetes diagnosis is defined as having received items used in the management or treatment of diabetes during the study period.
► This study only examines costs of diabetes-associated items according to the definition used by the national reimbursement schemes and thus may underestimate total expenditure attributable to diabetes.

INTRODUCTION

The global burden of diabetes is a growing challenge for national economies.[1–3] By 2030, it is estimated that the cost of diabetes will account for 2.2% of global Gross Domestic Product, increasing from 1.8% in 2015.[1] Direct medical costs account for two-thirds of the costs,[1] with medication costs identified as the primary driver of increasing medical expenditure on diabetes.[4] A combination of increasing diabetes prevalence, advancements in clinical guidelines advocating long-term glycaemic control and the upsurge of new expensive medical treatments contributes to the escalating medication costs.[3–5]

As of 2016, there were at least 171 new drug therapies in development for the treatment and management of diabetes and its related complication.[6] With an emphasis on maintaining glycaemic control, the number of classes of glucose-lowering drugs developed over the past two decades has more than tripled.[7] Such drug classes include glucagon-like peptide-1 receptor (GLP-1) analogues and sodium-glucose co-transporter 2 (SGLT2) inhibitors.[8] Novel and innovative treatments are expensive and concern has been raised about whether the benefits of these medications outweigh their significantly higher costs.[9] While empirical data are scarce, it is predicted these treatments contribute to rising medication costs associated with diabetes and the continued advancement in diabetes-related medical technology will

likely result in increasing per capita medical expenditure per year.[3 4] The most recent American Diabetes Association and European Association for the Study of Diabetes guidelines recommend the use of these newer medications in second-line therapy and although improvements in diabetes care must be promoted, cost-containment measures are necessary to ensure the affordability and sustainability of health systems.[7 10]

Governments have introduced wide-ranging cost-containment strategies aimed at tackling increasing pharmaceutical expenditure.[11] Ireland has one of the highest public expenditures on pharmaceuticals among the Organisation for Economic Co-operation and Development (OECD) countries.[12] Amid concerns over health system sustainability and pressure from the European Union/International Monetary Fund Programme of Financial Support, Ireland introduced an array of cost-containment measures over the last decade.[13] With the goal of achieving better value for money on pharmaceuticals, such measures include the introduction of a co-payment policy and a model for reference pricing.

We aim to explore national trends in pharmaceutical expenditure on diabetes and related medicines between 2011 and 2015, from the perspective of the healthcare system, with objectives to describe trends in expenditure on blood glucose-lowering medications and to estimate the effect of two cost-containment measures implemented during this time; an increasing co-payment policy and reference pricing.

METHODS
Reimbursement of medications
In Ireland, pharmacies are reimbursed for the dispensing of medicines and associated devices through the Health Service Executive- Primary Care Reimbursement Service (HSE-PCRS).[14] HSE-PCRS funds three main community drugs schemes: the General Medical Services (GMS) scheme, the Drugs Payment Scheme (DPS) and the Long-Term Illness (LTI) scheme.[14] The GMS scheme is a means-tested public health insurance scheme which entitles an individual to prescription medications free of charge. In an effort to curtail expenditure and reduce moral hazard, a flat co-payment was introduced in October 2010 at €0.50 per item.[14] This increased to €1.50 per item in January 2013 and further to €2.50 per item in December 2013. In 2015, almost 40% of the population were eligible for the GMS scheme.[14] The remainder of the population are entitled to government-subsidised access to prescription medications through the DPS. Under this scheme, there is a monthly spend threshold of €144 per household. Once a household reaches this threshold, any additional costs are covered by the DPS and are reimbursed to the pharmacy through the HSE-PCRS. The LTI scheme entitles those with 1 of 16 specific chronic conditions to free prescription medications, independent of income. There are no co-payments for items on the LTI scheme. The HSE-PCRS publishes

a core medications list for each of the 16 chronic conditions, listing all the condition-related medications reimbursable under the scheme.[15] Diabetes is one of these 16 conditions and therefore HSE-PCRS defines a core list of medications reimbursable for the treatment and management of diabetes (see online supplemental table S1). It is possible for a person to be eligible for all three schemes simultaneously.

Data source
Data from the national HSE-PCRS pharmacy claims database were analysed. While the primary function of the database is for reimbursement, it has previously been used for pharmacoepidemiological and pharmacoeconomic research.[14] The database contains data on all medications dispensed by community pharmacists under the GMS and LTI schemes. It also contains data on medications reimbursed under the DPS, however, data are only available for items dispensed after the monthly payment threshold is reached. The database contains the date of dispensing, quantity, dose and strength of each medication reimbursed by HSE-PCRS along with information on the ingredient cost, value-added tax (VAT), mark-up and the dispensing fee paid to the pharmacy. Medications are coded using the WHO-Anatomical Therapeutic Chemical (WHO-ATC) classification system. Permission to use the anonymised HSE-PCRS data for research purposes was obtained from the HSE-PCRS.

Participants and prescription items
A repeated cross-sectional study was conducted whereby we identified all individuals who were dispensed items used in the treatment or management of diabetes for each year of the study period (2011–2015). These items were defined as antidiabetic agents (WHO-ATC: A10), monitoring materials used in self-monitoring of blood glucose, blood ketone and urine analysis (WHO-ATC: V07) or needles and lancets used in these devices and for insulin injection (WHO-ATC: V04). To calculate the total expenditure associated with diabetes from the health system perspective, we then extracted data on all diabetes-associated items dispensed to eligible individuals during each year of the study. We define diabetes-associated items as those listed by the HSE-PCRS as reimbursable for the treatment and management of diabetes. This includes all items used in the treatment of diabetes (WHO-ATC: A10, V07, V04) as well as condition-related items such as cardiovascular system drugs (online supplemental appendix table S1). To explore the costs attributable to diabetes, we categorised items into two groups; diabetes-specific items and diabetes-related items (online supplemental appendix table S1). Diabetes-specific items include items used directly in the treatment of diabetes (WHO-ATC: A10, V07, V04). Diabetes-related items include all other condition-related medications not used directly in the treatment of diabetes (WHO-ATC: B01, C, H04, N03, N06).

Table 1 Description of diabetes-related prescriptions, 2011–2015

	2011	2012	2013	2014	2015
All items					
Total expenditure (€)	204 092 805	216 994 441	208 702 239	199 279 490	204 457 333
GMS	117 654 990	129 172 992	128 203 076	95 225 066	62 766 810
LTI	79 535 588	81 389 053	75 334 537	99 676 835	137 721 770
DPS	6 902 227	6 432 396	5 164 626	4 377 589	3 968 753
Number of items	6 926 347	7 395 829	7 546 517	7 757 653	8 049 083
Mean cost per item (€) (SD)	29.47 (29.47)	29.34 (29.48)	27.66 (28.50)	25.69 (28.07)	25.40 (28.40)
Diabetes-specific items					
Total expenditure (€)	129 828 301	140 595 029	141 714 991	144 406 885	153 621 477
Number of items	3 256 314	3 513 731	3 621 232	3 761 657	3 952 042
Mean cost per item (€) (SD)	39.87 (38.58)	40.01 (38.39)	39.13 (36.73)	38.39 (35.24)	38.87 (34.89)
Diabetes-related items					
Total expenditure (€)	74 264 504	76 399 412	66 987 248	54 872 605	50 835 856
Number of items	3 670 033	3 882 098	3 925 285	3 995 996	4 097 041
Mean cost per item (€) (SD)	20.24 (11.74)	19.68 (11.19)	17.07 (9.15)	13.75 (8.08)	12.41 (8.13)

DPS, Drugs Payment Scheme; GMS, General Medical Services; LTI, Long-Term Illness.

Statistical analysis

The ingredient cost, dispensing fee, VAT and mark-up were extracted for each prescription item. A prescription item refers to the individual item on each claim. Prescriptions are dispensed and claimed monthly and thus an item refers to one month's supply. The HSE-PCRS will only reimburse one month's supply in a given claim. Where two different doses of the same drug are dispensed in any month they will be two separate items. Total costs were calculated by summing the ingredient cost, dispensing fee and any VAT or mark-up for each item. Data were aggregated by the scheme under which the items were dispensed, WHO-ATC codes and by each yearly quarter. Mean cost per item was calculated by dividing the total costs by the number of items dispensed. Trends over time were explored. The impacts of two specific cost-containment measures implemented over the study period were assessed using segmented regression analyses of interrupted time series.[16 17] First, we analysed the impact of the increasing GMS co-payments on both GMS and LTI expenditure. We assessed the impact of the increase in co-payment to €1.50 in the first quarter of 2013 and the subsequent increase to €2.50 in quarter 4 of 2013. Second, we explored the impact of the introduction of reference pricing. Atorvastatin was the first drug to be subjected to reference pricing. From November 2013, the HSE-PCRS set one price to be reimbursed to pharmacies per each dispensing of atorvastatin.[18] We omitted the time points before the atorvastatin patent expired in quarter 4, 2011. Multiple linear regression models were fitted, containing a dichotomous variable to assess the level change after the implementation of the intervention and an interaction term between time and the intervention to estimate the change in slope after the intervention was implemented.[16 17] The most parsimonious models were selected using stepwise elimination.

Model assumptions were checked and autocorrelation was assessed by plotting the residuals and calculating the Breusch-Godfrey test with a null hypothesis of no autocorrelation.[16 17] The partial autocorrelation function was used to explore if adjustment for seasonality was required. Data management was carried out in SAS V.9.4, data analysis was carried out in R Studio V.3.4.3.

Patient and public involvement

Patients and the public were not involved in the design or conduct of the study.

RESULTS

Total prescription costs varied over the study period, peaking at €216 994 441 in 2012 (table 1). While the total number of items dispensed increased by 16%, the average cost per item fell from €29.47 to €25.40. Diabetes-specific prescription costs increased steadily from €129 828 301 in 2011 to €153 621 478 in 2015. During the same period, costs associated with diabetes-related items decreased by 32% to €50 835 856. Between 2011 and 2015, the average cost per item for diabetes-related items reduced from €20.24 to €12.41, while average cost per item of diabetes-specific items only decreased from €39.87 to €38.97.

Diabetes-specific items

Over the time period, the greatest increase in costs was observed in blood glucose-lowering drugs (figure 1). Costs rose from €31 061 768 in 2011 to €48 418 540 in 2015, accounting for 73% of the observed increase in total diabetes-specific costs. The total number of blood glucose-lowering drugs dispensed per year increased by 25% from 1 697 803 in 2011 to 2 115 835 in 2015 (online supplemental figure S1). At the start of the study period, insulins and analogues accounted for 32% of total
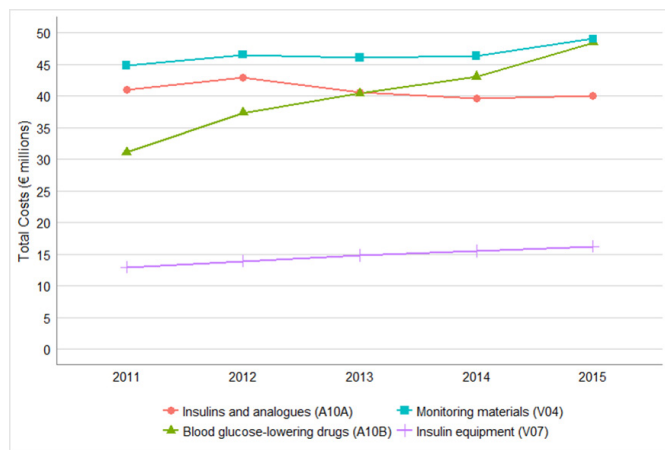
Figure 1 Trends in total costs of diabetes-specific items, 2011–2015.

diabetes-specific costs, with blood glucose-lowering drugs accounting for 24%. By 2015, blood glucose-lowering drugs had overtaken accounting for 32% of diabetes-specific costs, with only 20% of total costs attributable to insulins and analogues. A reduction in the mean cost per item was observed for insulins and analogues (€92.3–€79.6), along with a slower rate of increase in the number of items dispensed per year (online supplemental figure S1).

Of the blood glucose-lowering medications, the largest increase in costs was observed for GLP-1 analogues (figure 2). During the study period, the number of items dispensed for GLP-1 analogues increased from 39 671 in 2011 to 76 181 in 2015 (online supplemental figure S2). The costs attributable to GLP-1 analogues rose from €7 438 338 to €13 396 681, representing an increase of 80%. The number of combination medications dispensed increased by 152% (76 508 in 2011 to 192 590 in 2015) and an increase of 104% was observed for dipeptidyl peptidase-4 (DDP-4) inhibitors (101 952–207 809) (online supplemental figure S2). Total costs attributable to
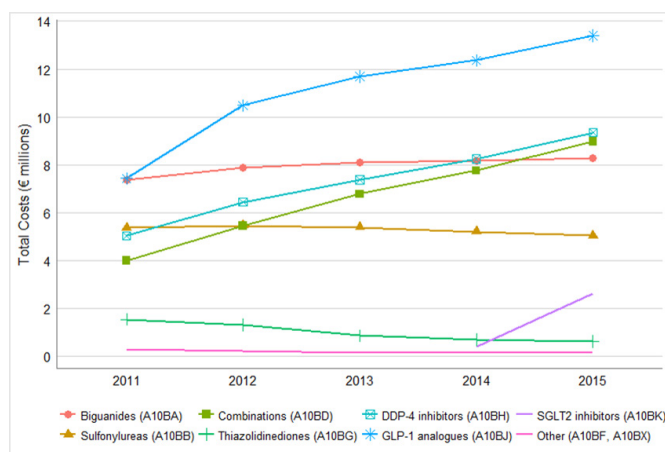
Figure 2 Trends in total costs of blood glucose-lowering drugs, 2011–2015. DDP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; SGLT2, sodium-glucose co-transporter 2.
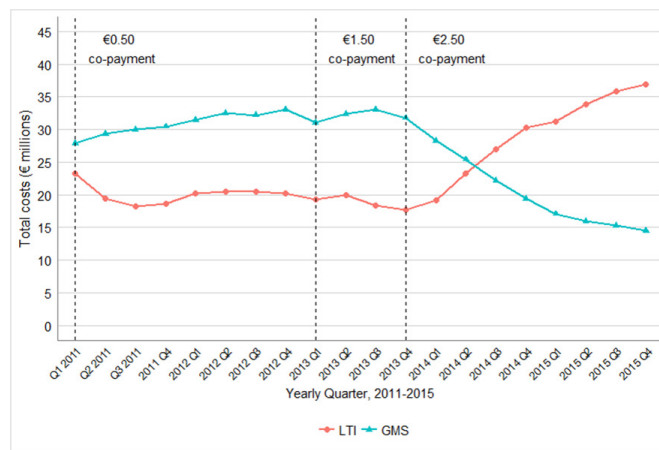
Figure 3 Total costs per yearly quarter, by community scheme, 2011–2015. GMS, General Medical Services; LTI, Long-Term Illness.

combination drugs more than doubled from €4 004 687 to €8 965 514, while a similar increase from €5 035 011 to €9 348 434 was observed for DDP-4 inhibitors. While the mean cost of biguanides remained constant over the time period, the number of items dispensed increased gradually from 899 148 in 2011 to 1 034 512 in 2015 (online supplemental figure S2). The costs increased by €1 335 311. Between 2014 and 2015, the number of SGLT2 inhibitors dispensed increased by sixfold (9208–55 096) resulting in costs rising from €423 118 to €2 615 442.

Diabetes-related items

Total expenditure on diabetes-related items is stratified by WHO-ATC classification in online supplementary table S2. While the number of lipid-modifying agents dispensed increased by 155 989, the mean cost per item fell from €30.8 to €13.5. The total costs of lipid-modifying agents halved from €34 225 615 to €17 094 079 over the study period.

Impact of cost-containment measures

The total expenditures (diabetes-specific and diabetes-related) per yearly quarter for the GMS and LTI schemes are displayed in figure 3. Before the increase in co-payment to €1.50 in the first quarter of 2013, GMS expenditure was increasing significantly by €694 892 per quarter (p=0.001). While the increase of the co-payment to €1.50 did not impact significantly on this trend, expenditure dropped by €2 822 770 (p=0.03) when the increase was implemented (Q1 2013). The increase in co-payments to €2.50 resulted in a significant change in slope, with costs reducing by €2 968 017 per quarter (p<0.001). There was no significant trend in LTI expenditure before the increase in GMS co-payment to €2.50. When the GMS co-payments were increased to €2.50 in quarter 4 of 2013, there is a statistically significant trend thereafter, with costs now increasing by €2 298 667 per quarter (p<0.001).

During the time period, expenditure on atorvastatin fell from €28 870 808 to €12 609 525. Before reference pricing was introduced, there was a significant decreasing
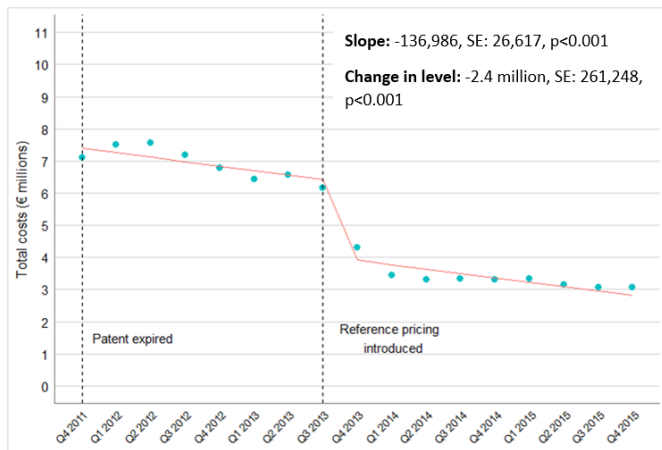
Figure 4 Total costs of atorvastatin per yearly quarter, 2013–2015.

trend of €136986 per quarter (p<0.001) (figure 4). Directly after the reference pricing was implemented in the third quarter of 2013, total costs per quarter dropped significantly by €2.4 million (p<0.001). There was no evidence of a change in slope after the introduction of reference pricing (p=0.2).

DISCUSSION

This study documents the substantial national pharmaceutical expenditure on diabetes and provides an insight into the trends in expenditure patterns over time. Diabetes-specific items account for the majority of expenditure, increasing year on year. By 2015, expenditure reached almost €154 million, having increased by 18% since 2011. Conversely, spending on diabetes-related items reduced by 32% to €51 million in 2015. Successful cost-containment measures, such as the introduction of reference pricing for atorvastatin, were largely responsible for the observed cost curtailment.

The steady increase in pharmaceutical expenditure on diabetes-specific items is in line with international trends.[4 19] Our findings identify blood glucose-lowering drugs as the primary driver of increasing costs. By 2015, expenditure on blood glucose-lowering drugs had surpassed the costs of insulins and accounted for one-third of all expenditure on diabetes-specific items. This was explained by a sharp increase in the number of items dispensed and also a rise in the mean cost per blood glucose-lowering drug. While the rise in volume of blood glucose-lowering drugs may be explained by increasing prevalence of diabetes over the study period,[20] guidelines advocating tight glycaemic control combined with the introduction of new classes of blood glucose-lowering medications for dual and triple combination therapy may also contribute to the expedited increase in volume compared with that observed for insulins.[7 21 22] Similar patterns have been observed across Europe, with insulin use remaining relatively stable in recent years.[23–25] In the UK, expenditure on blood glucose-lowering drugs now

also exceeds the costs of all insulins.[19] In contrast, over a similar time period in Poland, insulins remained responsible for the majority of expenditure on diabetes-specific items.[26] This can be explained by reimbursement policies in Poland. For instance, newer drug classes such as DDP-4 inhibitors are not reimbursable due to insufficient evidence on the impact of their long-term use and the high cost per item.[26]

The increasing expenditure on blood glucose-lowering drugs is driven by the increasing volume of newer drug classes; DDP-4 inhibitors, GLP-1 analogues and SGLT2 inhibitors.[8] For instance, one-third of the increase in expenditure is attributable to GLP-1 analogues. By 2015, GLP-1 analogues accounted for over a quarter (28%) of blood glucose-lowering medication costs, despite only representing 3.6% of items dispensed. Expenditure on SGLT2 inhibitors has risen to over €2 million in the 1-year period since their introduction to the market in 2014, suggesting the beginning of a similar trend to that observed for GLP-1 analogues. The most recent international guidelines published by the American Diabetes Association and European Association for the Study of Diabetes advocate for the use of GLP-1 analogues and SGLT2 inhibitors in second line therapy.[7] Our findings show the impact of the increasing volume of these two drugs classes on pharmaceutical expenditure at a national level and thus raise a concern about how to ensure their accessibility while maintaining affordable and sustainable health systems, particularly in lower-resource settings.

Concern exists about whether the advantages of such blood glucose-lowering drugs outweigh their significantly higher costs.[9 27–29] Position statements advocate a patient-centred approach to treatment considering many factors including efficacy, hypoglycaemic risk, impact on weight and cost.[7 30] However, with little evidence available on which subgroups of patients may have better outcomes with specific treatments, implementation of such recommendations is challenging.[31] A large comparative effectiveness study is currently underway, but with results not due until 2020 and with more new drugs in development, an innovative approach is required to ensure the provision of cost-effective diabetes care.[31]

As observed in other OECD countries, our findings support the introduction of reference pricing as a successful mechanism for inducing immediate reductions in expenditure.[32] The increase of co-payments had a profound impact on the GMS and LTI schemes expenditure, demonstrating the power of moral hazard. All people with diabetes in Ireland are entitled to receive their medications free of charge on the LTI scheme. Prior to the introduction of co-payments, people with diabetes with GMS cover could also receive their medications free of charge through the GMS scheme. Our findings show that the increase in co-payment to €2.50 per item dispensed under the GMS, resulted in people switching schemes to avail of prescription items free of charge under the LTI scheme.

This study has a number of strengths. Most noteworthy, we use a large national pharmacy claims database and, as a result, we provide complete and robust data on all diabetes-related pharmaceutical expenditure funded by the Irish government. Cost data from the HSE-PCRS database are highly accurate as its primary function is for reimbursement.[14] This study provides data on recent pharmaceutical expenditure, allowing us to explore the impact of newer more expensive diabetes medications. There are some important limitations to our study. Due to the absence of clinical diagnoses in the HSE-PCRS database, we make the assumption that anyone receiving items used in the management or treatment of diabetes had a diagnosis of diabetes. This is a sensitive measure. For instance, metformin is also used in the treatment of polycystic ovarian syndrome (PCOS). However, only a small proportion of women of reproductive age are affected by PCOS, with many also having a diabetes diagnosis.[33] Furthermore, the costs of metformin are low and any effect on total expenditure would be negligible. We estimated costs of items reimbursed for the treatment and management of diabetes as defined by the HSE-PCRS. However, we acknowledge that the sequelae of diabetes are not limited to cardiovascular disease, depression or neuropathy. As a result, our estimates reflect pharmaceutical expenditure on diabetes as defined by the HSE but are an underestimation of the total expenditure attributable to diabetes. It was not possible to identify these costs using HSE-PCRS. In the absence of a unique identifier across reimbursement schemes in our data, it was not possible to determine whether the increase in blood glucose-lowering drugs was due to an increase in the number of people with diabetes or to an increase in the number of people taking a combination of blood glucose-lowering medications.

In conclusion, our findings provide timely and stark evidence of the impact of newer drug classes on pharmaceutical expenditure associated with diabetes. Novel blood glucose-lowering drugs classes, DDP-4 inhibitors, GLP-1 analogues and more recently SGLT2 inhibitors, are driving increasing expenditure. Cost-containment measures, namely reference pricing, have resulted in significant savings in expenditure on diabetes-related items used in the prevention and management of diabetes-related complications. However, the increasing cost of blood glucose-lowering medications threatens to negate the effect of these cost-saving interventions and presents a significant challenge for the provision of diabetes care globally. Innovative policies will be required to ensure quality diabetes care can be provided at an equitable, affordable and sustainable rate.

ORCID iDs
Kate N O Neill http://orcid.org/0000-0003-4843-4265
Kathleen E Bennett http://orcid.org/0000-0002-2861-7665

REFERENCES

1 Bommer C, Sagalova V, Heesemann E, *et al*. Global economic burden of diabetes in adults: projections from 2015 to 2030. *Diabetes Care* 2018;41:963–70.
2 Bommer C, Heesemann E, Sagalova V, *et al*. The global economic burden of diabetes in adults aged 20–79 years: a cost-of-illness study. *Lancet Diabetes Endocrinol* 2017;3633:423–30.
3 Zhang P, Gregg E. Global economic burden of diabetes and its implications. *Lancet Diabetes Endocrinol* 2017;5:404–5.
4 Zhuo X, Zhang P, Kahn HS, *et al*. Change in medical spending attributable to diabetes: national data from 1987 to 2011. *Diabetes Care* 2015;38:dc141687.
5 American Diabetes Association. Economic costs of diabetes in the U.S. in 2017. *Diabetes Care* 2018;41:dci180007.
6 Medicines in Development. Medicines in development for diabetes. Washington, 2016. Available: http://phrma-docs.phrma.org/files/dmfile/medicines-in-development-report-diabetes.pdf [Accessed 12 Jun 2018].
7 Davies MJ, D'Alessio DA, Fradkin J, *et al*. Management of hyperglycemia in type 2 diabetes, 2018. A consensus report by the American diabetes association (ADA) and the European association for the study of diabetes (EASD). *Diabetes Care* 2018;41:2669–701.
8 Nathan DM. Diabetes: advances in diagnosis and treatment. *JAMA* 2015;314:1052–62.
9 Qaseem A, Barry MJ, Humphrey LL, *et al*. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline update from the American College of physicians. *Ann Intern Med* 2017;166:279–90.
10 Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. *Nature* 2001;414:782–7.
11 Lee I-H, Bloor K, Hewitt C, *et al*. International experience in controlling pharmaceutical expenditure: influencing patients and providers and regulating industry - a systematic review. *J Health Serv Res Policy* 2015;20:52–9.
12 OECD. Health at a glance 2015 - How does Ireland compare? 2015. Available: http://www.oecd-ilibrary.org/social-issues-migration-health/health-at-a-glance-2009_health_glance-2009-en [Accessed 13 Jun 2018].

13 Kenneally M, Walshe V. Pharmaceutical cost-containment policies and sustainability: recent Irish experience. *Value Health* 2012;15:389–93.

14 Sinnott S-J, Bennett K, Cahir C. Pharmacoepidemiology resources in Ireland-an introduction to pharmacy claims data. *Eur J Clin Pharmacol* 2017;73:1449–55.

15 Health Service Executtive. Long term illness (LTI) scheme: reference guide as to what is covered in the health service executive for each of the 16 scheduled LTI illnesses, 2016. Available: http://www.hse.ie/eng/services/list/1/schemes/lti/aprovmed/ [Accessed 13 Jun 2018].

16 Wagner AK, Soumerai SB, Zhang F, *et al*. Segmented regression analysis of interrupted time series studies in medication use research. *J Clin Pharm Ther* 2002;27:299–309.

17 Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. *Int J Epidemiol* 2017;46:348–55.

18 Department of Health. Reference pricing, 2014. Available: https://health.gov.ie/future-health/reforming-primary-care-2/reference-pricing/ [Accessed 13 Jun 2018].

19 Prescribing and medicines team NHS digital. prescribing for diabetes England 2006/07 to 2016/17. *Can Med Assoc J* 2017:1–24.

20 Tracey ML, Gilmartin M, O'Neill K, *et al*. Epidemiology of diabetes and complications among adults in the Republic of Ireland 1998-2015: a systematic review and meta-analysis. *BMC Public Health* 2016;16:132.

21 McCoy RG, Zhang Y, Herrin J, *et al*. Changing trends in type 2 diabetes mellitus treatment intensification, 2002-2010. *Am J Manag Care* 2015;21:e288–96.

22 Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American diabetes association and the European association for the study of diabetes. *Diabetes Care* 2015;38:140–9.

23 Overbeek JA, Heintjes EM, Prieto-Alhambra D, *et al*. Type 2 diabetes mellitus treatment patterns across Europe: a population-based Multi-database study. *Clin Ther* 2017;39:759–70.

24 Sharma M, Nazareth I, Petersen I. Trends in incidence, prevalence and prescribing in type 2 diabetes mellitus between 2000 and 2013 in primary care: a retrospective cohort study. *BMJ Open* 2016;6:e010210.

25 Torre C, Guerreiro J, de Oliveira Martins S, *et al*. Patterns of glucose lowering drugs utilization in Portugal and in the Netherlands. trends over time. *Prim Care Diabetes* 2015;9:482–9.

26 Śliwczyński A, Brzozowska M, Jacyna A, *et al*. Drug-class-specific changes in the volume and cost of antidiabetic medications in Poland between 2012 and 2015. *PLoS One* 2017;12:e0178764:1–11.

27 Palmer SC, Mavridis D, Nicolucci A, *et al*. Comparison of clinical outcomes and adverse events associated with glucose-lowering drugs in patients with type 2 diabetes: a meta-analysis. *JAMA* 2016;316:313–24.

28 Lipska KJ, Yao X, Herrin J, *et al*. Trends in drug utilization, glycemic control, and rates of severe hypoglycemia, 2006-2013. *Diabetes Care* 2017;40:468–75.

29 Butler PC, Elashoff M, Elashoff R, *et al*. A critical analysis of the clinical use of incretin-based therapies: are the GLP-1 therapies safe? *Diabetes Care* 2013;36:2118–25.

30 American Diabetes Association. Standards of medical care in diabetes: pharmacologic approaches to glycemic treatment. *Diabetes Care* 2017;40:S64–74.

31 Nathan DM, Buse JB, Kahn SE, *et al*. Rationale and design of the glycemia reduction approaches in diabetes: a comparative effectiveness study (grade). *Diabetes Care* 2013;36:2254–61.

32 Galizzi MM, Ghislandi S, Miraldo M. Effects of reference pricing in pharmaceutical markets: a review. *Pharmacoeconomics* 2011;29:17–33.

33 Pate KA. Epidemiology,Diagnosis, and management of polycystic ovary syndrome. *Clin Epidemiol* 2014;6:1–13.