Drugs for Diabetes in England 1998-2017

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Abstract

Aims: UK guidelines for type II diabetes leave the choice of glucose lowering therapies after metformin largely to prescribers. They vary greatly in cost, and comparative effectiveness data is lacking. We set out to measure the variation in prescribing of these second-line non-insulin diabetes drugs.

Materials and Methods: We evaluated time trends 1998-2016, using England's publicly available prescribing datasets, and stratified by the order prescribed to patients using the Clinical Practice Research Datalink (CPRD). We calculated the proportion of each class of diabetes drug as a percentage of the total per year. We evaluated geographical variation in prescribing using

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general practice-level data for the latest 12-months (to August 2017), with aggregation to Clinical Commissioning Groups (CCGs). We calculated percentiles, ranges and plotted maps.
Results: Prescribing of therapy after metformin is changing rapidly. DPP4-inhibitor use has increased markedly, now the most common second-line drug (43% prescriptions in 2016). Use of SGLT-2 inhibitors also increased rapidly (14% new second-line, 27% new third-line prescriptions in 2016). There is wide geographical variation in choice of therapies and average spend per patient. In contrast, metformin is consistently used first-line in accordance with guidelines.
Conclusions: In England there is extensive geographical variation in the prescribing of diabetes drugs after metformin, and increasing use of higher-cost DPP4-inhibitors and SGLT-2 inhibitors over low-cost sulfonylureas. Our findings strongly support the case for comparative effectiveness trials of current diabetes drugs.

Abbreviations

BNF - British National Formulary
BSA - NHS Business Services Authority
CCG - NHS Clinical Commissioning Group
CPRD - Clinical Practice Research Datalink
DPP-4 - Dipeptidyl peptidase-4 inhibitor (also known as gliptins)
GLP-1 - Glucagon-like peptide 1 analogue
GP - General Medical Practitioner
NHS - National Health Service
NIC - Net Ingredient Cost
NICE - National Institute for Health and Care Excellence
ONS - Office for National Statistics
PCA - Prescription Cost Analysis
QOF - Quality Outcomes Framework
SGLT-2 - Sodium-glucose cotransporter-2 inhibitor
SU - Sulfonylurea
TZD - Thiazolidinedione

Introduction

The prevalence of diabetes recorded across England in 2015-16 was 6.55% of the population, or 3.03m people[1]. Good control of blood glucose in patients with diabetes is important to reduce the risk of complications, and is measured primarily by maintenance of haemoglobin A1c (HbA1c) levels. Most patients with diabetes are prescribed glucose lowering medication to achieve adequate glucose control[2]. In 2016, anti-diabetes drugs were identified as the section of National Health Service (NHS) prescribing with the greatest spend[3]. In 2016-17, 11.0% of England's total primary care net ingredient costs (NIC) were spent on diabetes, costing £984m[4]. While 54.9% of this was spent on insulin and diagnostic/monitoring items, the remaining £444m went on the subset of "other anti-diabetic drugs" (paragraph 6.1.2 of the British National Formulary, BNF). These are drugs largely used to control type II diabetes, including metformin, sulfonylureas and several newer classes.

Metformin is recommended by the National Institute for Health and Care Excellence (NICE) as a first-line treatment, but for many patients this is not sufficient to control the disease, and they are prescribed an additional, "second-line" treatment[2]. The optimal drug choice after metformin is unclear, with four different treatments recommended by NICE to form a dual therapy with metformin[5]: sulfonylureas, pioglitazone (a thiazolidinedione, "TZD"), DPP-4 inhibitors and SGLT-2 inhibitors. The latter are recommended mainly if other therapies are contraindicated, but for the former three there is no particular order, and there is limited guidance on how they may be selected for different patients, except for some contraindications for pioglitazone. For patients requiring further intensification, triple therapy should comprise metformin and one of three possible combinations of two of the aforementioned drugs, or a fifth class, GLP-1 analogues, to be considered for obese patients.

Based upon a sample of over 400,000 type II diabetes patients on medication, in 2013, 83.6% of them were receiving metformin, including 91.0% of patients receiving their first treatment[2]. For patients requiring second-line therapy after metformin, 61.7% received a sulfonylurea and 26.9% a DPP-4. However, since then SGLT-2 inhibitors have become available and 2015 NICE guidelines markedly departed from previous guidance which recommended sulfonylureas as preferred therapy after metformin.

It is unclear how this situation is evolving and whether the different available medications are offered to patients in a consistent manner across the country. There is wide variation in cost between these treatment options, with metformin and sulfonylureas averaging around £4-6 per item prescribed in 2015/16, and SGLT-2s and DPP-4s around £40 per item[1].

We therefore aimed to determine variation in prescribing and prescribing costs of anti-diabetic treatments both geographically, across practices in England; and over time; by using three different datasets, summarised in Table S1.

Methods

Data Sources and Preparation

We used three sources of data: Clinical Practice Research Datalink (CPRD), a UK-representative database of anonymised primary care electronic health records[6]; annual Prescription Cost Analysis (PCA) data, aggregated nationally, covering 1998-2016; and monthly practice-level prescribing data, September 2010- August 2017.

CPRD data

We extracted clinical and prescription records for 207,338 patients with type II diabetes from CPRD (download date 19/01/2017) who were prescribed a first to fourth line oral diabetes drug in BNF 6.1.2 “other anti-diabetic drugs” over 1998-2016 and had not previously been prescribed insulin. A detailed description of CRPD data ascertainment has been previously reported[7]. Briefly, we positively identified type II diabetes patients largely on the basis of prescriptions rather than diagnostic medical codes due to known problems with coding errors[8]. However, we excluded patients with diagnostic codes for other forms of diabetes (e.g. steroid induced, monogenic etc.) or polycystic ovary syndrome (which can be treated with metformin). To remove patients with type I diabetes, we excluded patients with an age at diagnosis <35 or on insulin treatment within 12 months of diagnosis. We defined the date of diabetes diagnosis as the earliest of: first prescription for a non-insulin diabetes therapy; first HbA1c result >47.5 mmol/mol (6.5%); or first diabetes diagnostic code. Ethics approval was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177RA4R).

Annual PCA data

The annual PCA datasets contain one row for each treatment and dose, for all prescriptions issued in NHS primary care and dispensed in community settings in England, describing the number of prescriptions dispensed and the total cost. PCA data was processed as previously described[9,10]. Briefly, data for each year between 1998 and 2016 was obtained from NHS Digital or Government archives and compiled. To correct for changes in drug names, spellings and classifications over time, each drug was assigned its full BNF code, chemical and product name from the current BNF. Drug names not matched exactly to a currently available product were assigned appropriate classifications via approximate matching. Data were normalised by converting number of prescriptions and costs to relative figures per thousand population, using mid-year populations for England[11]. Number of *items* represents the number of times each drug was prescribed; costs are NIC, which represent the basic price of the medicine, i.e. the price listed in the Drug Tariff or published by the manufacturer or supplier. NIC may be subject to further charges and/or discounts. Costs were also corrected for inflation using the consumer price index compared to 2016[12].

Practice-level data

The monthly prescribing datasets published by NHS Digital contain one row for each treatment and dose, in each prescribing organisation in NHS primary care in England, describing the number of prescriptions issued and the total cost. We limited to organisations with setting code "4" - general practices (GPs), according to the NHS Digital dataset of practice characteristics[13], to exclude all other organisations such as prisons and out-of-hours services. Practices with a current status of "closed" or "dormant" were also excluded from the latest 12 months analysis. Each practice in England belongs to one of 207 Clinical Commissioning Groups (CCGs) which are responsible for commissioning health care services in their local area, so we aggregated this data for CCG-level analyses. We used number of *items* which represents the number of

times each drug was prescribed, and Actual Costs, which are the full cost to the NHS including NIC and any further charges and discounts.

Prevalence data

Estimates of national type II diabetes percentage prevalence for 2000-2013 were obtained from an analysis of practices in The Health Improvement Network (THIN) database[2], extrapolated to cover 1998-2016 using a straight line estimation in Excel ($R^2 = 0.9965$). We calculated items prescribed/cost per person with diabetes for England by dividing prescribing figures per 1,000 population by the prevalence rate per 1,000. CCG and practice-level prevalence figures were obtained from Quality Outcomes Framework (QOF)[14], for financial year 2016-17 (April-March) and including all types of diabetes. To estimate number of diabetics per CCG, accounting for missing practice registrations, we multiplied the adult prevalence rate from QOF by the population (aged 15+) of each CCG, using each CCG's latest practice membership, at August 2017. We then calculated rates of items prescribed per person with diabetes by dividing prescribing figures by the number of people registered with diabetes in the corresponding population.

Extraction and classification of diabetes drug data

In CPRD we categorised drug prescriptions using BNF codes and Medcode keyword searches of "product name" and "drug substance name". CPRD includes full prescription records but no data on drug dispensation. New drug prescriptions (and their corresponding start dates) were defined as the first ever prescription of a drug in each class for each patient, even if only prescribed once. Patients were considered to have stopped a drug if there was a gap in prescribing of that drug for at least 6 months[7]. We defined first, second, third or fourth-line prescription categories based on the order of new drug prescriptions for individual patients.

Every time a patient started a new drug we assigned this to the next line of therapy, regardless of whether their concomitant therapy changed at a similar time point.

In the PCA and practice-level datasets we extracted the prescribing data for paragraph 6.1.2, "other anti-diabetic drugs". Drugs were each assigned to the appropriate class (metformin, sulfonylureas, TZD, gliptins/DPP-4 inhibitors (DPP-4), GLP-1 analogues and SGLT-2 inhibitors) based on their chemical name (Table S2). In CPRD, we assigned combination drug prescriptions containing metformin and one other to both constituent classes; in the PCA and practice-level datasets these combination drugs were counted only as the non-metformin drug (e.g. Metformin Hydrochloride/Rosiglitazone was assigned to the class of Rosiglitazone, i.e. TZD). In all datasets, drugs containing a mixture of any other two classes were counted as "other".

Analysis

We calculated prescribing rates per class of drug by dividing the number of items prescribed by the total number of anti-diabetic items (BNF 6.1.2) prescribed. Trend charts from PCA data were produced in Excel by summing items or cost per patient with type II diabetes over each class per year. In CPRD, we calculated the proportion of new prescriptions of each drug for each calendar year and line of therapy as the total number of new prescriptions of the drug / total number of new prescriptions. CPRD data extraction and analysis was conducted in Stata v14.0, and trends charts were produced using Excel. Deciles of practice-level prescribing trends across all practices were calculated for each available month and plotted as time trend charts using Python. After limiting to and aggregating the latest available 12 months, summary tables of CCG and practice prescribing were produced in Python.

Maps

Maps of anti-diabetic items prescribed by all CCGs in England for a single month snapshot were created using OpenPrescribing.net/analyse, by selecting all the chemicals within each class as numerator and BNF Paragraph 6.1.2 as denominator. The results were converted to percentages (from per 1000). The data source for OpenPrescribing.net is the monthly practice-level prescribing dataset described above. It includes all practices with status "4" (standard GP practices) but does not exclude closed and dormant practices. The map of spend per patient across CCGs was produced using Tableau Open software.

Data and Code

PCA and practice-level data were extracted using SQL in Google BigQuery. The links to each map for CCG prescribing on OpenPrescribing.net are provided in the Supplementary Information. The Tableau workbook mapping the costs per patient is available online at https://public.tableau.com/views/Diabetesmap/Dashboard1?:embed=y&:display_count=yes. Practice-level data were analysed and charts produced using Python *scipy.stats*, *matplotlib.pyplot* and *seaborn* modules. Complete code provided in Supplementary Information and PCA data extract in FigShare[15].

Results

Data Sources and Preparation

In CPRD we included data on 392,764 new first to fourth-line anti-diabetic drug prescriptions for 207,338 unique patients over 1998-2016. Of these, 48% (191,550) were for a first-line drug, 31% (124,673) second-line, 14% (57,679) third-line and 5% (18,862) for a fourth-line drug. Metformin was the most common newly initiated drug prescribed (48% of total new prescriptions), followed by sulfonylureas (27%), TZDs (10%), DPP-4s (10%), GLP-1 analogues (2%) and SGLT-2 inhibitors (2%). All PCA data were extracted successfully. From the practice-level data for the latest 12 months, 7,261 practices belonging to all 207 current CCGs were included, after excluding 342 with a status of closed (68) or dormant (274). In total this covered 48m registered patients (aged 15+), of which approximately 3.1m were registered as diabetic. For decile calculations across 2010-2017, in total 8,155 practices were included.

DPP-4 inhibitors are now the most commonly prescribed second line diabetes therapy, with sulfonylurea use rapidly declining

CPRD data shows that metformin has been favoured as first-line treatment since 2001 (Figure 1), with a majority of over 90% for the past 10 years. Sulfonylureas were the most common second-line therapy, prescribed in 40-64% of cases from 2004 to 2015. In 2016, the most common became DPP-4, with second-line sulfonylurea use rapidly declining to 34%. Metformin use in second-line therapy has declined over time (from 60 to 5%) as most patients began to receive it as first-line. In third-line therapies, DPP-4 has remained the most common since 2010, but declined slightly since reaching a peak of 60% in 2012. The use of SGLT-2 as second, third and fourth-line is rising rapidly. It has been the most common fourth-line therapy since 2015, prescribed to almost half of patients requiring a fourth drug. GLP-1 drugs appear to be largely reserved for third or fourth-line therapy only.

The cost of prescribing for diabetes in the UK is rapidly increasing

Figure 2 shows national prescribing of non-insulin glucose lowering therapy in PCA data between 1998 and 2016. Trends in overall prescribing (Figure 2a) are similar to CPRD. The total number of non-metformin items dispensed relative to the number of patients with diabetes was relatively stable, until increasing only modestly since 2008 (4.1 to 4.8 items per year, 17%). Costs per patient, however, have risen by 55% since 2008, from £66 to £102.

From 2014 to 2016, a 32% increase in cost per patient (£78 to £102) was accompanied by only a 5% increase in items dispensed (4.6 to 4.8). This rise corresponds with increased usage of DPP-4s and SGLT-2. An increase in price of TZDs also contributed, caused by a shortage of generic pioglitazone[16] and subsequent price volatility.

Despite remaining the most widely used second-line therapy, sulfonylureas contribute less to total cost per patient than most of the other classes, due to their generic availability (Figure 2b-c). Recently, use of sulfonylureas is declining, apparently in favour of the newer therapies. Spend on TZDs has dropped substantially since its peak in 2007, due to both the decline in their usage and expiry of the patent. The spend on DPP-4, SGLT-2 and GLP-1 classes is increasing in line with their usage. Despite the slow uptake of GLP-1 drugs, they represent the second highest cost burden: in 2016, four times as many DPP-4s as GLP-1s were prescribed, but the expenditure only differed by a factor close to two. National trends in prescribing of individual agents within each class are shown in Figure S1.

National Variation in prescribing by CCG

We investigated how the level of prescribing of each anti-diabetic drug class varied across England, summarising the proportions prescribed by each CCG over a 12-month period (Table 1) and mapping them geographically for a single-month snapshot (Figure 3). There was

relatively low variation in metformin items as a proportion of all anti-diabetic drugs (55.6% ± 2.9, Table 1, Figure 3), but more marked differences in the other available therapies favoured in each region. In the TZD class, the mean level of prescribing across CCGs was 2.5% ± 1.4 (Table 1), but one CCG consistently prescribed more (12% in May 2017, Figure 3).

The spend on anti-diabetic drugs per patient with diabetes over the latest 12-months ranged from £60 to £200 across CCGs (Figure S2). Lower cost per patient generally corresponded to lower rates of prescribing of non-metformin, non-sulfonylurea classes (Figure S2), but the variation in total prescribing level per patient (11.6 ± 2.0) may also contribute (Table 1). The total spend was £414m in total over this period; however, if every CCG could have prescribed at the lowest decile cost per patient (£95pp) this would represent a saving of £113m, over a quarter of the total costs for this area of prescribing.

National Variation in prescribing at practice level

As expected, variation is greater across practices than when aggregated to CCGs (Table S3); the proportion of metformin prescribed extends to a range of approximately 40-70%, but with interquartile range (IQR) restricted to 52-59%. This range of variation has remained roughly constant since 2010 (Figure 4). Almost all practices prescribe at least some sulfonylureas and DPP-4 drugs, with IQRs 17.9-25.5% and 9.8-16.8% respectively. The remaining three classes are commonly prescribed in small proportions with medians close to zero and for 75% of practices they each make up less than 6% of anti-diabetic medications (Table S3). The rise of the SGLT-2 class is highly variable across practices (Figure 4).

Discussion

Summary

We have assessed variation in NHS primary care prescribing of diabetes treatments both geographically, across CCGs and practices in England; and over time. There is wide regional variation in choice of second-line therapy, reflecting the absence of clear evidence or guidelines to inform treatment choice. The more specific guidelines concerning metformin are well adhered to overall, with relatively little variation in metformin use across regions and over time. Recent prescribing increasingly favours the newer more expensive treatments, leading to a rapid increase in cost of prescribing over recent years.

Strengths and Limitations

A key strength of our analysis is that it uses three datasets, with overlapping strengths and weaknesses. CPRD contains data on individual patients, which permits selection of only type II diabetes patients, and investigation of the order in which medicines were prescribed for individual patients. However, CPRD covers only a small subset of all prescribing, and does not permit exploration of individual institutions' prescribing at the level of identifiable CCGs and practices; while the PCA and practice-level datasets cover the complete data for all primary care prescribing in England, not a sample, down to the level of all practices and CCGs; and PCA data covers all national level prescribing back to 1998.

While prescriptions issued by a hospital clinic or private practice, or dispensed in hospital, are not included in our data, almost all prescriptions for glucose lowering agents in the UK are issued through a general practice. Even agents started on the recommendation of a hospital or community endocrinologist or other specialist will almost always be prescribed through general practice and captured in our data, with the exception being inpatient and emergency prescribing. Therefore our data is an accurate representation of UK prescribing practice. Using number of items prescribed in PCA and practice-level data does not distinguish between different lengths of courses being prescribed (e.g. one month's supply versus three), therefore

drugs prescribed in shorter courses may amount to a greater total number of items. Converting into Average Daily Quantities (ADQs) or Defined Daily Doses (DDDs) would be an improvement, but a comprehensive dataset to render this calculation for all medications does not exist, and anti-diabetes drugs may be given in different dosages. Using quantity instead would help to overcome this problem, but does not allow fair comparison between drugs given in different dosing regimens, or between items prescribed in different units of measurement such as liquids (ml) and tablets. In CPRD individual prescribing data were available, including dose and prescription frequency, and the finding of consistent results across CPRD and PCA data is a strength of this study. Although the data do not indicate adherence to therapy, the focus of our study was on prescribing choices.

Correcting for diabetes prevalence allowed us to investigate variation in prescribing independently from the increasing number of people living with the condition. National type II diabetes prevalence data for 1998-2016 was extrapolated from estimates from THIN practices[2]. The advantage of this data is that the coverage of the sample is comprehensive, including secondary care data. The figures reported in the National Diabetes Audit (NDA) were lower, but prevalence in NDA is lower than predicted from epidemiological studies due to some patients not being registered as diabetic by practices[17]. QOF figures were approximately 0.7-0.8 percentage points lower than the figures used, likely because QOF includes all types of diabetes and excludes under-17s, the age group with lowest prevalence. On the other hand, like the NDA, QOF data also depends upon practice registrations which may be incomplete. QOF figures were the best available source of practice and CCG-level data on prevalence.

Similarly to the UK, type II diabetes guidelines from the American College of Physicians, European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) all leave the choice of therapy after metformin largely to the practitioner[18–20]. Therefore,

our key findings, that the use of therapy after metformin is changing dramatically and that there is geographical variation in drug prescribing in England, are likely to be generalisable to other countries.

Findings in context of other research

We found that metformin has been favoured as first-line treatment since 2001, reflecting guidance and previous reports[2]. The rise in metformin use has been attributed to the publication of several UK-based studies on the efficacy of metformin from 1998, which had a high level of media publicity, with the later NICE guidance having no clear additional effect[21]. DPP-4 drugs are thought to have a similar efficacy to sulfonylureas but cause fewer side effects[22]. The increasing use of SGLT-2s may relate to a favourable side effect profile in previous trials, which includes weight loss, oral administration (in comparison to injected GLP-1 inhibitors, the only other class associated with clinically significant weight loss), and (for empagliflozin), positive cardiovascular outcome[23]. However, empagliflozin was only the third most common SGLT-2 prescribed in England in 2015 and 2016. If they succeed in reducing serious side-effects and complications, additional spend on newer anti-diabetic drugs may lead to reduced spend on other related healthcare costs, and also improve patient experience. Indeed, the spend on anti-diabetic drugs in 2010 was estimated to make up just 6.1% of the total cost of drugs and care for people with type II diabetes in the UK[24].

The relationship between type II diabetes prescribing levels and HbA1c control across practices participating in the NDA (>50%) has recently been studied[25]. Greater HbA1c control was correlated with higher levels of metformin and DPP-4 prescribing, lower prescribing of sulfonylureas, and lower overall spend on diabetes medication per patient (including estimated quantities of blood testing strips and insulin used for type II diabetics). Greater achievement on non-pharmaceutical targets was also correlated with better HbA1c control[25]. Such variability in

care and outcomes have led to the initiation of trials studying interventions targeted at primary care practitioners, including their prescribing behaviour[26,27].

Previous work has shown that responses to unclear guidelines can be variable. When a common antipsychotic drug had its licence severely restricted but no specific advice was given on which alternative drug should be prescribed, in Scotland chlorpromazine was the most common replacement, whereas in England it was a combination of chlorpromazine and two newer drugs[28], however regional variation within England was not studied. Similarly, the removal of the licence for co-proxamol was followed by an increase in several other analgesics[29]. In addition, while safety concerns around prescribing tend to be acted upon quickly, evidence-based guidelines have less impact, even when the prescribing advice is clear, suggesting that dissemination could be improved[30,31].

Policy implications and future research

We found unexplained variation in choice of non-metformin treatment, in the context of absence of clear advice in guidelines and current evidence. Aside from clinicians' personal choices, there may be a variety of external influences, including local policy, price changes, marketing, financial arrangements with drug companies, media reports, access to educational material, and drug safety alerts. However, our findings raise various prospects and opportunities in diabetes research. Firstly, it suggests that a randomised trial of choice of second-line medication would be clinically useful, to resolve outstanding uncertainty on the best treatment for an extremely common clinical presentation. There is no such study ongoing in the UK, which seems a remarkable oversight, given that diabetes is the single biggest cost area for prescribing in NHS England. The one such study ongoing in the US, GRADE, does not include SGLT-2 therapy[32]. Secondly, it suggests that a pragmatic low-cost cluster randomised trial, randomising practices

or CCGs to a prescribing policy that prefers a particular second-line treatment, would be justifiable on grounds of costs and ethics, as there is already existing unexplained variation[33].

Thirdly, in the absence of guidance on which second line treatment is best, and with guidance only suggesting that the lowest cost options within each class are preferred, we found extensive variation in prescribing costs between CCGs. The total spend was £414m over 12 months, but with a potential saving of £113m if all CCGs had prescribed at the same per-patient cost as the most efficient decile of CCGs. However, a full cost-effectiveness analysis would require consideration of differences in side-effect and cardiovascular outcomes across the different drug classes as well as consideration of non-medicinal treatments. Our OpenPrescribing.net project is an openly accessible data service which highlights prescribing variation in primary care, and allows practices and commissioners to monitor their own prescribing behaviour for key prescribing measures and any chemical of interest, using statistical process control techniques to automatically send alerts to practices when they deviate from national changes in behaviour (including on diabetes prescribing). We have previously argued that greater investment in disseminating evidence, auditing its implementation, and using variation in practice to target clinicians for educational interventions may all prove to be cost effective mechanisms to ensure that health services use treatments effectively and cost-effectively.

Conclusions

In the absence of good evidence to guide choice of second-line treatment for diabetes, we found evidence of extensive variation in choice of drug; and prescription volumes for new treatments rising as they appear on the market, in the absence of good comparative effectiveness data.

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Titles and legends to figures

Figure 1. *Time trends in anti-diabetic medication prescribed across the UK, 1998-2016, separated by line of therapy (i.e. the order in which additional drugs were prescribed to each patient), based upon CPRD data. The prescriptions for each class of anti-diabetic drug each year are given as a percentage of all anti-diabetic prescriptions (BNF 6.1.2). In (a) all classes other than metformin and sulfonylurea are grouped into "Other".*

Figure 2*. Time trends in anti-diabetic medications dispensed in English primary care in PCA data, 1998-2016. (a) Proportion of each class of drug dispensed in England each year, taking items prescribed of each as a percentage of all anti-diabetic items (BNF 6.1.2). (b) Number of items and (c) Inflation-corrected cost of each class of (and total) non-metformin diabetes drug dispensed in England per person with type II diabetes.*

Figure 3. *Geographical variation in prescribing of anti-diabetic drugs by all CCGs in England, May 2017. Numbers represent number of items of each class prescribed as a percentage of all anti-diabetic drugs prescribed (BNF 6.1.2). Updated versions of each map may be accessed at OpenPrescribing.net using links provided in Table S4.*

Figure 4*. Decile charts summarising the proportion of each drug class of all anti-diabetic items prescribed (BNF paragraph 6.1.2) across England's general practices, between October 2010 and August 2017. Solid lines represent the median, dashed lines are 10-90th percentiles.*

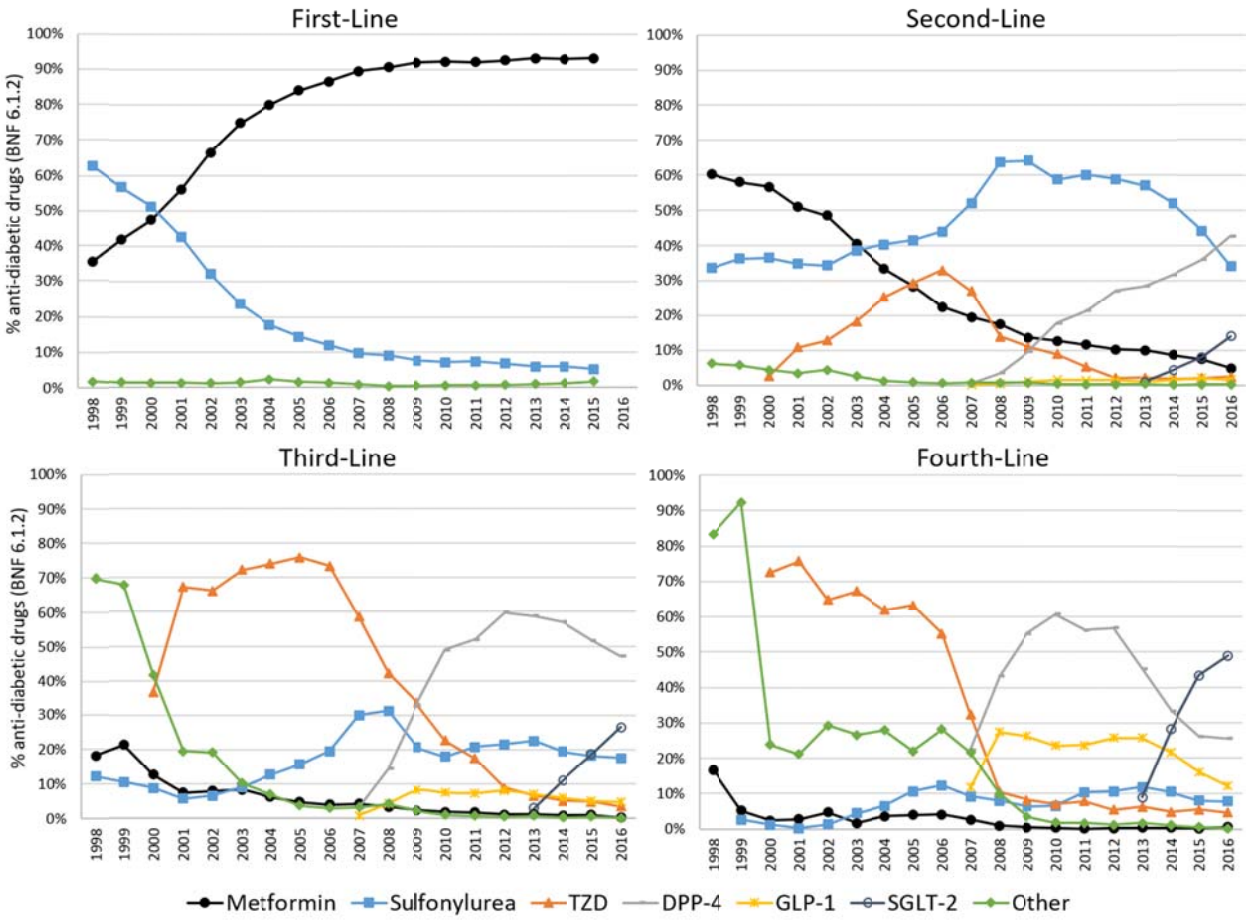
Tables

Table 1. *Volumes and cost of anti-diabetic drugs prescribed across England's CCGs over a 12-month period, Sept 2016-Aug 2017. Percentages represent the proportion of items for each drug class out of all anti-diabetic items prescribed (BNF paragraph 6.1.2). The total number of items and cost of anti-diabetic prescribing per patient are also given. Standard deviation (and kurtosis for percentage measures) are included as metrics of variation in between regions. Non-Met Non-SU = Non-metformin, non-sulfonylurea.*

	Mean	Std Dev	Median	Lower Quartile	Upper Quartile	IQR	Kurtosis
Metformin (%)	55.6	2.9	55.2	53.6	57.6	4.0	8.0
Sulfonylurea (%)	21.6	3.5	21.6	19.2	24.0	4.9	5.0
DPP-4 (%)	13.5	3.3	13.9	11.3	16.0	4.7	2.7
TZD (%)	2.5	1.4	2.2	1.5	3.0	1.5	8.7
SGLT-2 (%)	4.1	1.6	4.2	2.9	5.2	2.3	10.2
GLP-1 (%)	2.4	0.9	2.4	1.8	2.9	1.1	46.2
Non-Met Non-SU (%)	22.8	4.7	23.6	20.0	26.2	6.2	
Items per diabetic	11.6	2.0	11.4	10.4	12.8	2.5	
Cost per diabetic	£130	£25	£131	£114	£148	£35	

Figures

Figure_1



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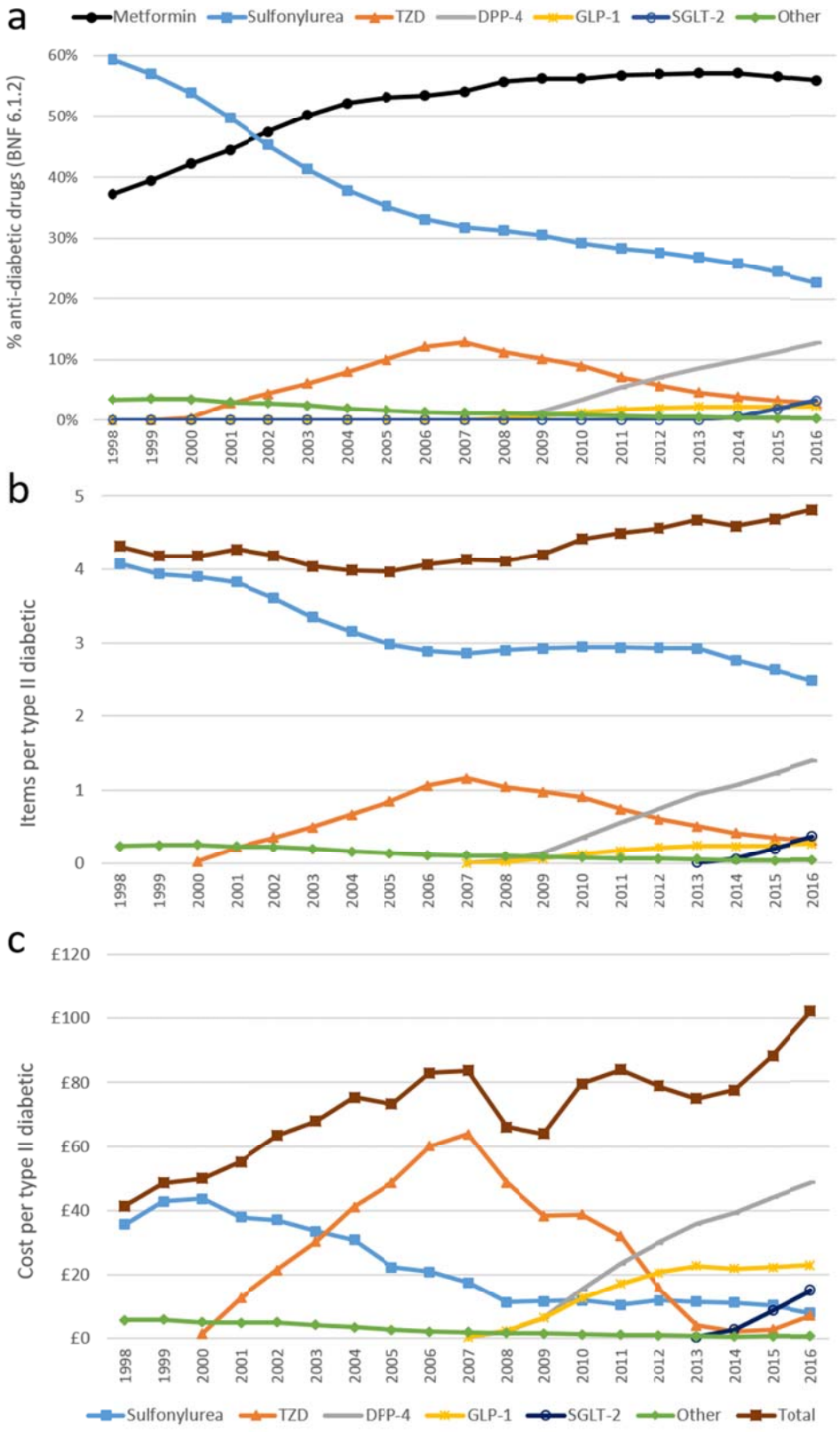

Figure_3

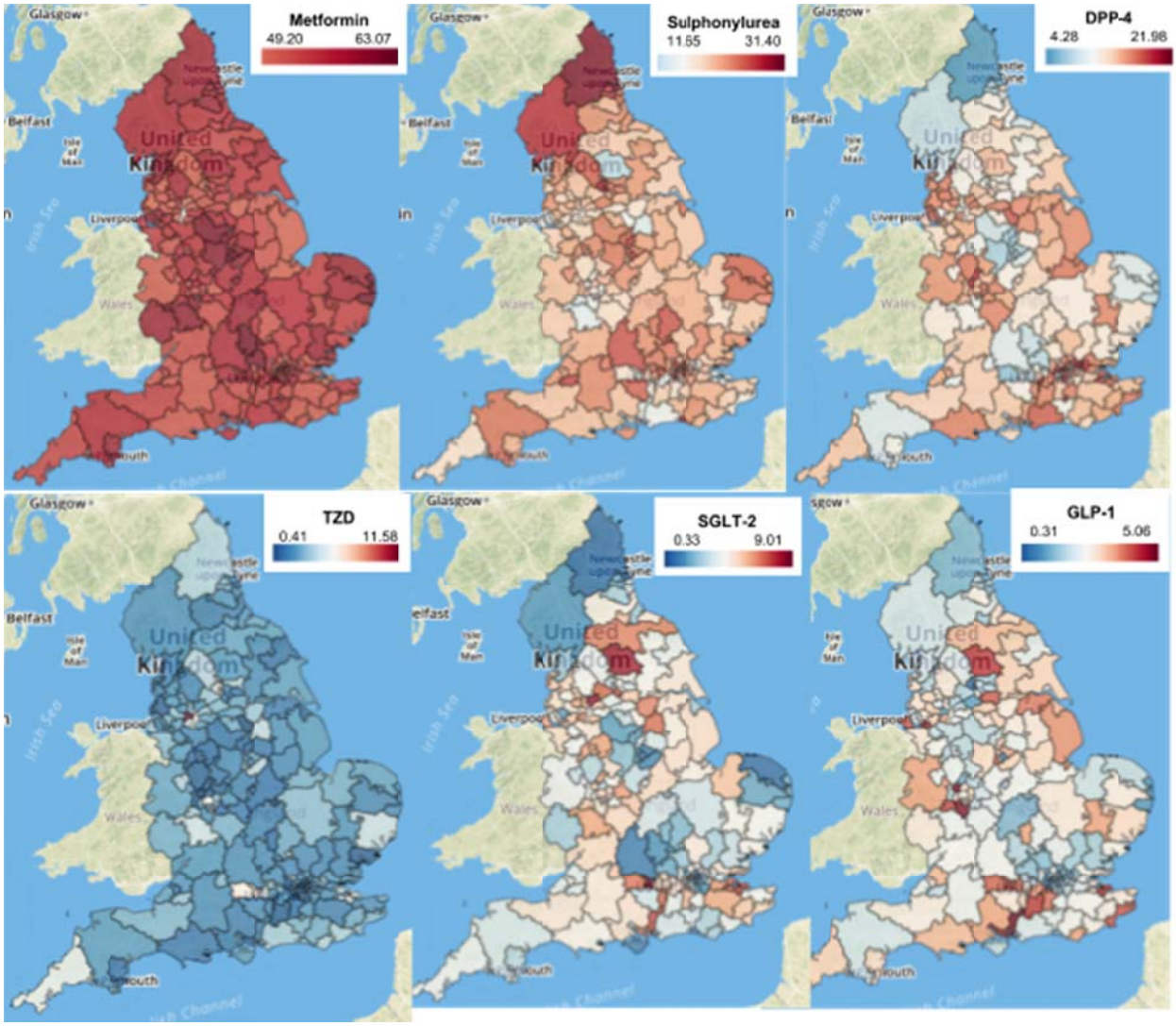

Figure_4