# Time trends in prescribing of type 2 diabetes drugs, glycemic response and risk factors: a retrospective analysis of primary care data, 2010-2017

## Running title: Prescribing and patient outcomes in type 2 diabetes

**Authors:** John M Dennis, William E Henley, Andrew P McGovern, Andrew J Farmer, Naveed Sattar, Rury R Holman, Ewan R Pearson, Andrew T Hattersley, Beverley M Shields*, Angus G Jones* on behalf of the MASTERMIND consortium

**Author affiliations:**

John M Dennis, PhD student. University of Exeter Medical School. Address: Health Statistics Group, Institute of Health Research, University of Exeter Medical School, Exeter EX1 2LU, UK

William E Henley, Professor. University of Exeter Medical School. Address: Health Statistics Group, Institute of Health Research, University of Exeter Medical School, Exeter EX1 2LU, UK

Andrew P McGovern. Clinical Research Fellow. University of Exeter Medical School. Address: Institute of Biomedical & Clinical Science, RILD Building, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

Andrew J Farmer, Professor. Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford OX2 6GG, UK

Naveed Sattar, Professor. University of Glasgow. Address: Institute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow G12 8TA, UK

Rury R Holman, Professor. Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford. Oxford NIHR Biomedical Research Centre, Churchill Hospital, Oxford. Address: Diabetes Trials Unit, Oxford Centre for Diabetes, Endocrinology and Metabolism, University of Oxford, Oxford, UK

Ewan R Pearson, Professor. University of Dundee. Address: Division of Molecular & Clinical Medicine, Ninewells Hospital and Medical School, University of Dundee, Dundee DD1 9SY, UK

Andrew T Hattersley, Professor. University of Exeter Medical School. Address: Institute of Biomedical & Clinical Science, RILD Building, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

Beverley M Shields, Senior Lecturer. University of Exeter Medical School. Address: Institute of Biomedical & Clinical Science, RILD Building, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

Angus G Jones, NIHR Clinician Scientist/Honorary Consultant Physician. University of Exeter Medical School. Royal and Devon Exeter Hospital. Address: University of Exeter Medical School. Address: Institute of Biomedical & Clinical Science, RILD Building, Royal Devon & Exeter Hospital, Barrack Road, Exeter EX2 5DW, UK

***Correspondence to:**

Beverley Shields. Email: B.Shields@exeter.ac.uk phone +44 1392 408203
Angus Jones. Email Angus.Jones@exeter.ac.uk, phone +44 1392 408260

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**List of abbreviations**

BMI: Body mass index; CI: Confidence interval; CPRD: Clinical Practice Research Datalink; DPP4: Dipeptidyl peptidase-4; GLP-1: Glucagon-like peptide-1; SGLT2: Sodium–glucose cotransporter 2; UK: United Kingdom; US United States

**Abstract**

**Aim:** Prescribing in type 2 diabetes has changed markedly in recent years, with increasing use of newer, more expensive glucose-lowering drugs. We aimed to describe population-level time trends in both prescribing patterns and short-term patient outcomes (HbA1c, weight, blood pressure, hypoglycemia and treatment discontinuation) after initiating new therapy.

**Materials and methods:** We studied 81,532 UK patients with type 2 diabetes initiating a first to fourth line drug in primary care between 2010-2017 inclusive (Clinical Practice Research Datalink). Trends in new prescriptions and subsequent six and twelve-month adjusted changes in glycemic response (reduction in HbA1c), weight, blood pressure, and rates of hypoglycemia and treatment discontinuation were examined.

**Results:** DPP4-inhibitor use second-line near doubled (41% of new prescriptions in 2017 *vs.* 22% 2010), replacing sulfonylureas as the most common second-line drug (29% 2017 *vs.* 53% 2010). SGLT2-inhibitors, introduced in 2013, comprised 17% of new first-fourth line prescriptions by 2017. First-line use of metformin remained stable (91% of new prescriptions in 2017 vs. 91% 2010). Over the study period there was little change in average glycemic response and treatment discontinuation. There was a modest reduction in weight second and third-line (second line 2017 *vs.* 2010: -1.5 kg (95%CI -1.9;-1.1), p<0.001), and a slight reduction in systolic blood pressure first to third-line (2017 *vs.* 2010 difference range -1.7 to -2.1 mmHg, all p<0.001). Hypoglycemia rates decreased second-line (incidence rate ratio 0.94 per-year (95%CI 0.88;1.00, p=0.04)), mirroring the decline in use of sulfonylureas.

**Conclusions:** Recent changes in prescribing of therapy in type 2 diabetes have not led to a change in glycemic response and have resulted in modest improvements in other population-level short-term patient outcomes.

## Introduction

Prescribing of glucose-lowering therapies for patients with type 2 diabetes has changed markedly in recent years. International guidelines have been updated to include a much greater choice of agents when additional therapies after metformin are required to achieve glycemic control.(1-4) Newer drug classes including DPP4-inhibitors, SGLT2-inhibitors and GLP-1 receptor agonists are now established alongside the longstanding options sulfonylureas, thiazolidinediones and insulin. Choice between these agents is left largely to the clinician and patient. Recent studies show that there have been marked changes in which agents are initiated after metformin, with a declining use of sulfonylureas and increasing and earlier use of DPP4-inhibitors and SGLT2-inhibitors in both the US, Europe and UK.(5-8)

Although studies have suggested the glucose-lowering effectiveness of agents typically added to metformin may be comparable,(1, 9, 10) there are well established differences between the different drug classes in weight change and side-effects. GLP-1 receptor agonists and SGLT2-inhibitors are associated with weight loss whereas DPP4-inhibitors are weight neutral and sulfonylureas can promote weight gain.(9, 10) Hypoglycemia risk is greater with sulfonylureas and insulin relative to other agents.(9) Despite these known differences in non-glycemic effects between agents, evidence of the impact of recent changes in prescribing on population-level patient outcomes is limited.(5, 7, 11, 12) In this study we aimed to describe changes in prescribing of glucose-lowering drugs for patients initiating first to fourth line therapy between 2010 and 2017 in the UK, a setting where prescribing does not reflect the ability of patients to pay. We further examined population-level time trends in the short-term clinical outcomes of glycemic response, weight change, blood pressure change, hypoglycemia, and treatment discontinuation.

## Materials and methods

### *Data source and data extraction*

We conducted a population-based analysis of anonymized primary care data from the UK's Clinical Practice Research Database (CPRD). CPRD is a population representative database containing demographic, clinical and prescription primary care records of patients.(13) Although CPRD includes full prescription records no data on drug dispensation are available. CPRD has been extensively used to study drug prescribing and patient outcomes in type 2 diabetes.(14) We analyzed data from the January 2018 release of CPRD, including all practices that were still contributing to CPRD in 2017 to ensure that changes in prescribing did not reflect changes in the practices captured in CPRD over the study period. We classified glucose-lowering drugs into drug classes according the British National Formulary sections 6.1.1 and 6.1.2.(15) Drugs were categorised as metformin, sulfonylureas, thiazolidinediones, DPP4-inhibitors, GLP-1 receptor agonists, SGLT2-inhibitors, insulin or Other (Meglitinides and alpha-glucosidase inhibitors, which are prescribed very rarely in the UK). Scientific approval was granted by the CPRD Independent Scientific Advisory Committee (ISAC 13_177RA4R).

***Study population***

We extracted the clinical and prescription records of all patients with type 2 diabetes who started at least one glucose-lowering drug for the first time ever between 1st January 2010 and 31st December 2017 and met CPRD quality assurance criteria (n=78,857). Inclusion criteria and data ascertainment followed our previously reported CPRD cohort profile.(16) Type 2 diabetes was defined largely on the basis of prescriptions for non-insulin diabetes therapies rather than diagnostic medical codes to minimize coding errors.(17) We excluded patients with diagnostic codes for other forms of diabetes or polycystic ovary syndrome which can be treated with metformin. To remove patients with type 1 diabetes, who may be miscoded as Type 2, we excluded patients with an age at diagnosis <35 or on insulin treatment within 12 months of diagnosis. Consequently, patients with type 2 diabetes whose first-line therapy was insulin were not included. We defined date of diabetes diagnosis as the earliest of: first prescription for a non-insulin diabetes therapy; first HbA1c result >=6.5% (48 mmol/mol); or first diabetes diagnostic code.

***Study design***

The study exposure was a new first to fourth line drug prescription record for a patient within the study period. New drug prescriptions (and their corresponding start dates) were defined as the first ever prescription of a drug in a class for a patient. First, second, third or fourth-line prescription categories were defined based on the order of new drug prescriptions for individual patients. Every time a patient started a new drug class we assigned this to the next line of therapy, regardless of whether their concomitant therapy changed at a similar time point.

The primary unit of analysis was line of therapy. This meant individual patients who started more than one new therapy over the study period contributed to the analysis more than once at different lines of therapy (see Supplementary Flowchart).

***Study outcomes***

For each line of therapy, we evaluated annual time trends in the drug classes initiated, and time trends in changes in HbA1c, weight, systolic and diastolic blood pressure, hypoglycemia rates and treatment discontinuation after therapy start. To evaluate all outcomes we used a 'new user' design which mitigated immortal time bias.(18) Patients were followed up from their drug start date until there was any change in diabetes therapy or the end of the study period specific to each outcome. A change in therapy could be the addition of a new glucose-lowering drug or the stopping of the drug of interest or any concomitant glucose-lowering drug. Patients were considered to have stopped a drug if there was a subsequent gap in prescribing of that drug for at least 6 months.(16)

We defined glycemic response (the change in HbA1c), weight change and blood pressure change as the absolute change from baseline to 6 months (6 month measure minus baseline measure). For glycemic response, baseline HbA1c was defined as the closest HbA1c to the drug start date in the 3 months prior to the drug start date. HbA1c at 6 months was defined as the closest HbA1c to 6 months after the drug start date (+/- 3 months). Glycemic response was only valid if there were no changes in glucose-lowering therapy between 2 months prior to the baseline HbA1c and the date of the 6 month HbA1c. The same approach was used for weight change and blood pressure change.

We defined hypoglycemia as the first Read code for hypoglycemia up to 2 years after starting a line of therapy, using a previously published Read code list for hypoglycemia.(19) Due to the low number of hypoglycemia events captured in primary care we grouped data into biannual categories representing four distinct periods (2010-11, 2012-13, 2014-15, 2016-17).

We examined treatment discontinuation by estimating the proportion of patients who stopped a therapy within 3 months, 6 months and 1 year. 6 months follow-up after discontinuation was required to determine no new prescriptions were issued.

***Statistical analysis***

We examined annual time trends for each clinical outcome and each line of therapy in separate analysis. We described trends in baseline clinical characteristics as mean (standard deviation) per calendar year. All outcomes analyses were standardized to the mean baseline values of relevant measures for patients starting that line of therapy in 2017.

To evaluate changes in relative prescribing for each line of therapy we calculated the proportion of new prescriptions for each drug class in each calendar year as the:

$$\frac{total\ number\ of\ new\ prescriptions\ of\ the\ drug}{total\ number\ of\ new\ prescriptions}$$

When describing first-line therapy all drugs except metformin and sulfonylureas were pooled. Within drug class trends for DPP4 inhibitors, GLP-1 receptor agonists, SGLT2-inhibitors and sulfonylureas (2014-2017) were estimated using the same approach.

We evaluated non-linear time trends in glycemic response, weight change and blood pressure change for each calendar year using linear regression with calendar year as a categorical covariate and adjustment for baseline HbA1c, age at therapy, duration of diabetes, and the baseline measure of the outcome for non-glycemic outcomes. We used complete case analysis including patients only if they had both a valid baseline measure and a valid 6 month measure. To assess the potential influence of missing data we compared the characteristics of the patients with missing data with those included in the analysis. Multiple imputation was not conducted as it is only valid under the missing at random assumption (meaning the differences between the observed and missing data could can be explained by other recorded measures), and we felt missing outcome data were likely to depend on their actual value (missing not at random). Hypoglycemia biannual time trends were estimated as rates per 1,000 person-years using Poisson regression, adjusted for age, duration, and baseline HbA1c.

Summary measures for each outcome (including baseline HbA1c) were calculated as follows; 1) the 2017 vs. 2010 marginal contrast from the multivariable linear regression models described above;(20) 2) the linear time trend, as the beta coefficient from a multivariable linear regression treating calendar year as a continuous rather than categorical covariate.

To evaluate changes in treatment discontinuation we calculated the proportion of new prescriptions that were stopped within 3 months, 6 months and 1 year for each line of therapy for each calendar year as:

$$\frac{total\ number\ of\ new\ prescriptions\ stopped\ within\ time\ period}{total\ number\ of\ new\ prescriptions}$$

All data extraction and analysis was conducted in Stata v14.0.

***Sensitivity analysis***

We repeated all outcomes analysis using change in each measure from baseline to 12 months as the outcome in a distinct cohort of patients with 12 month measures of each outcome (closest +/-3 months as for the definition of 6 month change). Participants commencing therapy in 2017 were not included in this analysis as 12 months of patient follow-up had not accrued. We also evaluated the sensitivity of results to our definition of line of therapy by repeating all second-line analyses in a subset of patients who were initiated on metformin first-line and then added a different therapy to metformin (rather than stopping metformin). To assess whether changes in outcomes over time were likely to be due to changes in the drugs prescribed we compared time trends in weight change and hypoglycaemia using the same models described above, with drug as an additional covariate.

## Results

123,990 new first to fourth line prescriptions from 81,532 individual patients were eligible for inclusion. 40% (50,215) were for a first-line prescription, 26% (32,071) were second-line, 20% (25,024) were third-line and 13% (16,680) were fourth-line (Supplementary Flowchart). The baseline clinical characteristics of patients starting each line of therapy in 2017 are shown in Supplementary Table 1. Average baseline HbA1c increased second to fourth-line over the study period; average baseline weight increased first-line but there was little difference for other lines of therapy. The proportion of patients with valid data for analysis of each outcome is shown in the Supplementary Flowchart.

***Changing prescribing of glucose lowering therapy***

We found marked changes in relative prescribing of second to fourth-line therapy (Figure 1). DPP4-inhibitors were by 2017 the most commonly initiated second-line therapy (2017 41% of new second-line; 2010 22% of new second-line), whilst second-line prescribing of sulfonylureas decreased (2017 29%; 2010 53%). SGLT2-inhibitors were the most common fourth-line therapy in 2017 (40% prescriptions) and their use second-line (19% of new 2017 prescriptions) and third-line (28% of new 2017 prescriptions) increased rapidly following their introduction in 2013. Fourth-line prescribing of injectable therapy decreased (GLP-1 receptor agonists: 2017 11%, 2010 20%; insulin: 2017 17%, 2010 21%), and remained low second and third-line. First-line use of metformin remained stable (2017 91%; 2010 91%).

Evaluating new first to fourth line drug initiations as a whole (Supplementary Figure 1), we found SGLT2-inhibitors (17% of total new prescriptions in 2017) were more commonly initiated in 2017 than sulfonylureas (14% in 2017). New prescribing of insulin (2017 5%; 2010 5%) and GLP-1 receptor agonists (range 4% to 3%) remained constant over the study period.

***Changes in within class prescribing***

In addition to changes in class of agent there have been marked recent changes in prescription of individual agents within a class. Over 2014 to 2017 for DPP4-inhibitors, there was decreasing use of sitagliptin (2017 37%; 2014 56%), but increasing use of alogliptin (2017 25%; 2014 1%) and linagliptin (2017 31%; 2014 25%) (Supplementary Figure 2a). For GLP-1 receptor agonists use of once-weekly dulaglutide increased to 51% of the class total following its introduction in 2015. For SGLT-2 inhibitors there was increasing use of empagliflozin (2017 46%; 2015 8%) but decreasing use of dapagliflozin (2017 41%; 2014 92%) (Supplementary Figure 2c). Gliclazide use has remained stable (2017 91% of all sulfonylureas; 2010 89%) (Supplementary Figure 2d).

***Reduction in HbA1c***

Average reductions in HbA1c at 6 months were relatively constant over 2010 to 2017 across all lines of therapy (Figure 2). There was no evidence of a change in glycemic response for second-line therapy (2017 *vs.* 2010 change 0.0% (-0.1 mmol/mol), $p=0.80$). For first, third, and fourth-line therapy there was evidence of a statistically significant trend towards improved glycemic response, although this translated to a modest absolute improvement in reduction in HbA1c (2017 *vs.* 2010 change range 0.2-0.3% (1.3 to 2.5 mmol/mol), all $p<0.05$).

***Weight change***

Although there was a trend towards greater weight loss at 6 months for all lines of therapy, this was most marked second and third-line (2017 *vs.* 2010 second-line -1.5kg and third-line -1.2kg, both $p<0.001$; overall time trends for improvement in weight change $p<0.001$ for all lines of therapy) (Figure 3). Patients starting second-line therapy on average lost rather than gained weight when comparing 2017 with 2010.

***Blood pressure***

We found a trend towards a modest improvement in systolic blood pressure at 6 months for all lines of therapy (2017 *vs.* 2010 range -1.7 to -2.1 mmHg, all $p<0.001$, Supplementary Figure 3a). There was no change in diastolic blood pressure (Supplementary Figure 3b).

***Hypoglycemia***

We observed a decrease in hypoglycemia rates for patients starting second-line therapy (2017 rate 5.7 (95% CI 3.5; 7.9) per 1,000 person-years; 2010 rate 8.2 (95% CI 6.3; 10.1) per 1,000 person-years (Figure 4, Supplementary Table 2).

***Treatment discontinuation***

Treatment discontinuation at 3 months, 6 months and 1 year after initiating therapy was stable over 2010-2017 (Supplementary Table 3). The proportion of patients discontinuing within 3 months in 2017 compared to 2010 was as follows: first-line 4% vs 3%; second-line 7% vs 9%; third-line 12% vs 9%; fourth-line 10% vs 9%.

***Sensitivity analysis***

Baseline characteristics of patients excluded as they did not have valid clinical measures were similar to those included in analysis (Supplementary Table 4). Time trends for outcomes at 12 months were similar to at 6 months for glycemic response (Supplementary Figure 4), weight change (Supplementary Figure 5), and blood pressure (Supplementary Figure 6). Second-line prescribing trends and patient outcomes in the subset of patients adding a second-line drug to continued first-line metformin therapy (73% of patients included in the primary analysis) were near identical to the primary analysis (Supplementary Figure 7). Differences in weight change trends became minimal when models were adjusted for drug therapy as a covariate (Supplementary Table 5a), and after adjustment for drug there was no evidence of a difference in risk of hypoglycemia over time (Supplementary Table 5b).

## Discussion

Our study describes, for the first time, recent population-level time trends in patient outcomes after initiating glucose-lowering therapy over 2010 to 2017, a period where there was drastic changes in type 2 diabetes prescribing patterns. There were modest population-level improvements in weight change and rates of hypoglycemia for patients starting additional therapy after metformin, but little change in glycemic response, blood pressure change or treatment discontinuation. Data on these important short-term clinical outcomes provide timely context to the worldwide trend towards prescribing of newer more costly glucose-lowering agents. We also provide updated information on UK prescribing trends: 1) increased and earlier initiation of DPP4-inhibitors; 2) reduced initiation of sulfonylureas second-line; 3) a rapid increase in initiation of SGLT2-inhibitors; and 4) decreased initiation of injectable therapy (GLP-1 receptor agonists and insulin).

Whilst our retrospective analysis precludes causal inference and can only show temporal correlation, the time trends in patient outcomes reflect the known effects of the different drug classes on clinical outcomes. As might be expected from previous comparative analysis,(9, 10) there was an improvement in weight change and reduction in rates of hypoglycemia where there was a rapid increase in the use of SGLT2-inhibitors and DPP4 inhibitors in place of sulfonylureas. These changes were attenuated by adjustment for drug, supporting the suggestion that the population-level improvements relate to changes in prescribing. Although recent meta-analyses have found little difference in glycemic response when comparing therapies added to metformin,(1, 9) some studies have reported increased response with sulfonylureas compared with other agents,(21-23) or lower response with DPP4-inhibitors,(10) and so it is reassuring that we found second-line glycemic response was stable despite the shift in prescribing. Newer agents, in particular SGLT2-inhibitors, have been associated with modestly lower blood pressure.(24-27) However whilst there were small improvements over time in blood pressure change with second to fourth-line therapy there were also improvements first-line where prescribing was unaltered. This suggests that improvements do not solely reflect prescribing changes.

The trends in new prescribing in this study are consistent with previous studies of UK primary care data,(7) including a recent analysis which documented extensive geographical variation in UK prescribing.(6) Comparison with US data suggest newer therapies have been adopted more quickly in the UK than in the US; in the US sulfonylureas remain the most common second-line therapy.(5) However, trends in new prescribing are similar in the US, with decreasing second-line use of sulfonylureas (46% of new second-line prescribing in 2016 compared to 55% in 2010) and increasing use of DPP4-inhibitors (20% in 2016; 14% in 2010). The increased cost of newer agents may explain their relatively slower uptake in the US.(5)

There are limited recent studies in time trends of patient outcomes. A recent analysis of 1.7 million US Medicare patients found no overall change in glycemic control or rates of hypoglycemia over 2006 to 2013, but unlike our study did not study patients initiating new therapy.(12) Declining overall rates of hypoglycemia requiring hospitalization were observed in UK patients over, but not under, 65 from 2009 to 2013 in the context of declining use of sulfonylureas in this older age group.(28) The changes observed in these studies examining the overall population of patients with type 2 diabetes will lag considerably behind those observed in our analysis of new therapy initiation, as once initiated a glucose lowering therapy may be continued for decades.

Strengths of the study include our approach examining new prescribing, which allowed interrogation of time trends whilst accounting for the increasing prevalence of type 2 diabetes, which in the UK is due more recently to declining mortality rather than increasing incidence,(29, 30) and means prescribing of glucose-lowering therapy is increasing in absolute terms.(6, 31) Our definition of type 2 diabetes should minimize misclassification.(16) Our study provides a near complete picture of UK prescribing, as in the UK type 2 diabetes is largely managed in primary care. Even new therapy initiated on the advice of a specialist will usually be prescribed by the patients' primary care physician. A limitation of this study is the weakness in the way hypoglycemia is recorded. It is likely that many episodes of hypoglycemia will be missing from a patients' primary care record, as mild hypoglycemia or more severe hypoglycemia requiring attendance in secondary care are poorly recorded. However, previous studies have provided useful insight into hypoglycemia using similar definitions in the same dataset.(32) Although the missing records mean the absolute rates of hypoglycemia in this study will be an underestimate, the specificity of our key finding, a relative decrease in hypoglycemia rates second-line where use of sulfonylureas has markedly declined, is reassuring. Whilst our study provides timely information on population-level trends, further observational studies, building on recent work, will be needed to establish the real-world comparative effectiveness of individual drug classes at different lines of therapy.(10, 33)

Our results show that prescribing of glucose lowering therapy in Type 2 diabetes is rapidly changing towards newer, more expensive agents. Changes in prescribing appear to have pre-empted rather than reflected changes to clinical guidelines.(1) In particular second-line prescribing of DPP4-inhibitors increased rapidly long before treatment guidelines were updated to position them along sulfonylureas and pioglitazone as second-line options.(1) The positive trends in weight change, hypoglycemia and blood pressure are likely to have improved the quality of life for patients, and a reduction in hypoglycemia is also likely to have a cost benefit.(34) However, given the much higher cost of newer drug options, the modest improvement we observed in patient outcomes suggests further studies are needed to evaluate cost-effectiveness of the newer glucose-lowering agents. Recent evidence suggests there may be potential for a more stratified approach to prescribing of type 2 diabetes therapy, meaning prescribing decisions can be better informed through identification of patients or subgroups who differ in their likely glycemic response or risk of side-effects with individual agents.(2, 35, 36)

We did not evaluate microvascular or macrovascular outcomes in this study, but a cardiovascular benefit in select participants with established cardiovascular disease or at high risk, has recently been demonstrated in individual trials for the SGLT2-inhibitors empagliflozin and canagliflozin, and GLP-1 receptor agonist liraglutide.(24, 37, 38) A recent meta-analysis of randomized trials suggested that in contrast to SGLT2-inhibitors and GLP-1 receptor agonists there is no short term mortality benefit with DPP4-inhibitors.(39) Given the recent changes in treatment guidelines to consider cardiovascular risk when choosing therapy,(4) and the fact all three classes have now been prescribed in significant numbers for some years, an evaluation of longer-term trends in microvascular and macrovascular complications would be of considerable interest.

## Conclusions

The trend towards prescribing of newer, more expensive, glucose-lowering medication in the UK has coincided, for patients initiating new therapy, with a likely reduction in hypoglycemia rates and a modest improvement in weight and blood pressure, but little change in glycaemic response or treatment discontinuation. These results demonstrate the potential population-level impact of the rapid changes which are occurring in prescribing of glucose-lowering therapy worldwide.

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**Authors' contributions:** JMD, ATH, BMS, and AGJ designed the study. JMD and BMS analysed the data. JMD, BMS and AGJ drafted the article. ATH, APM, AJF, ERP, NS, WEH and RHH provided support for the analysis and interpretation of results, and critically revised the article. All authors had full access to all of the data and take responsibility for the integrity of the data and the accuracy of the data analysis. BMS and AGJ are the guarantors.

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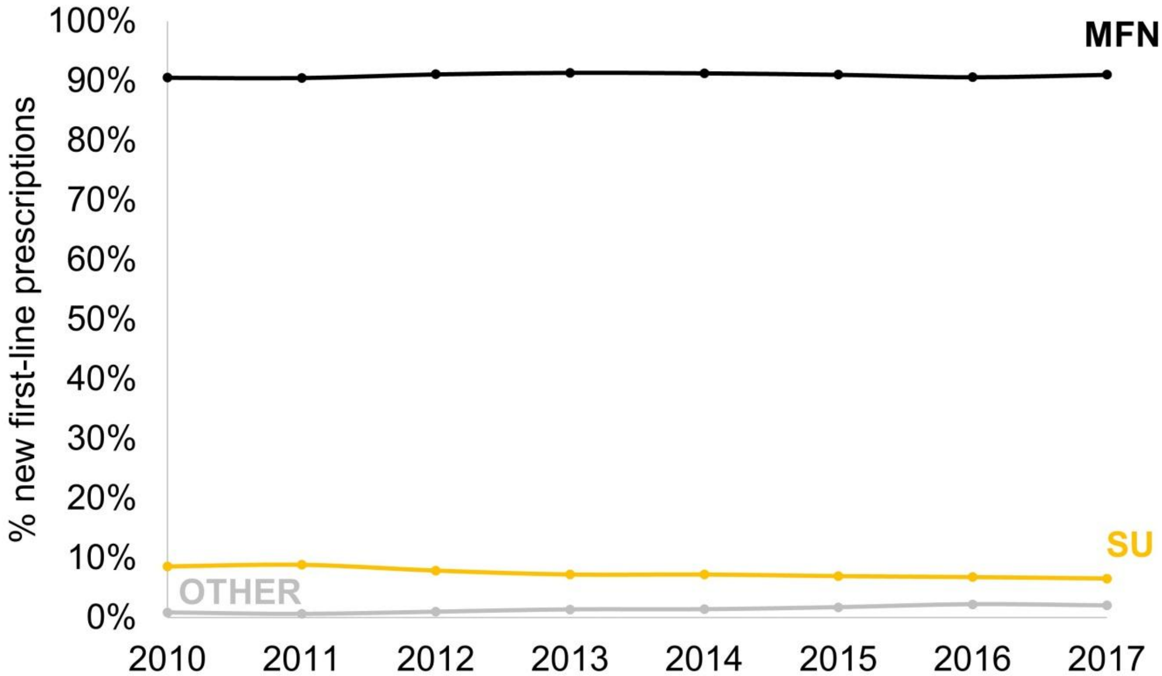
**Figure Legends**

**Figure 1: Time trends in new drug prescriptions for a) first-line b) second-line c) third-line d) fourth-line therapy.** The prescriptions for each drug class each year are given as a percentage of total new drug prescriptions for that year.

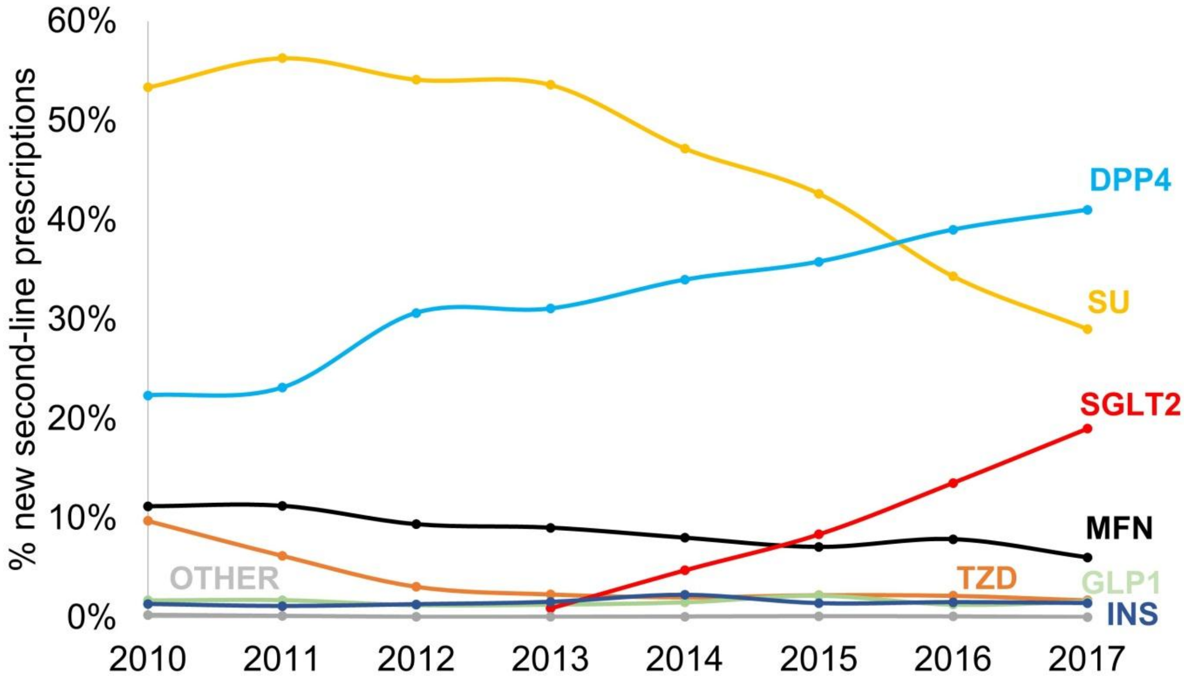
**Figure 2: Mean HbA1c response at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line.** Error bars are 95% confidence intervals. Data are standardised to the average baseline HbA1c, age at diagnosis and duration of diabetes, specific to each drug line in 2017.

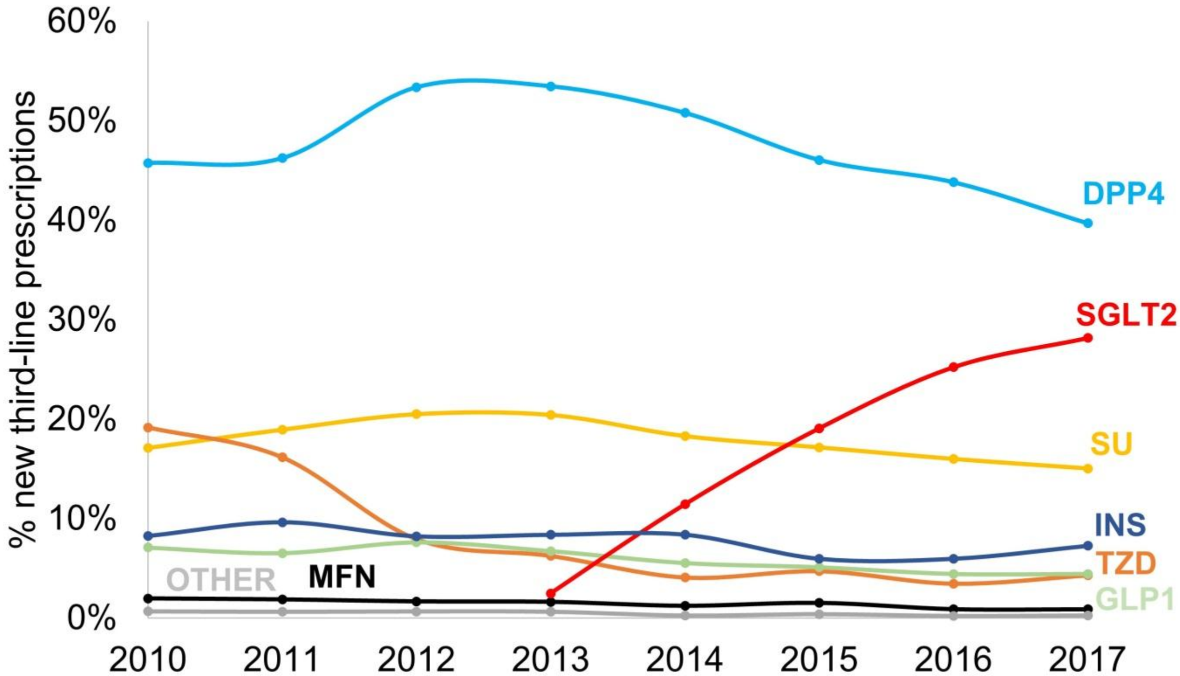
**Figure 3: Mean change in weight at 6 months, 2010-2017 for a) first-line b) second-line c) third-line d) fourth-line.** Error bars are 95% confidence intervals. Data are standardized to the average baseline weight, baseline HbA1c, age at diagnosis and duration of diabetes, specific to each drug line in 2017.

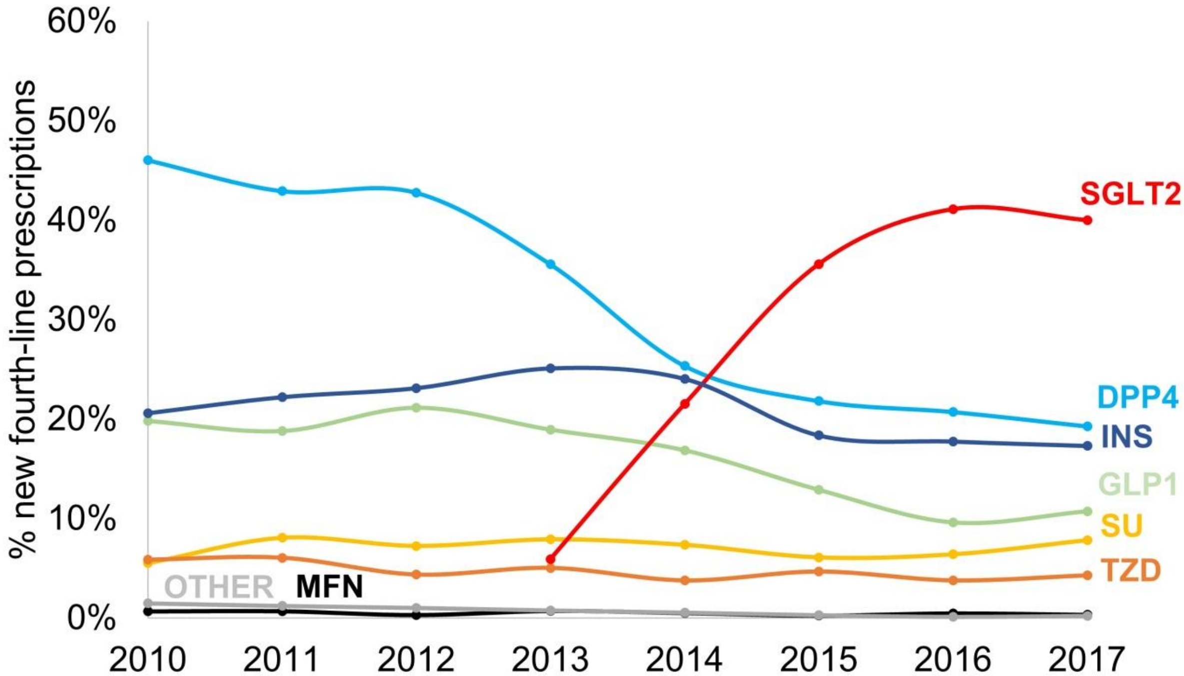
**Figure 4: Hypoglycaemia rates per 1,000 person-years by 2 year period for a) first-line b) second-line c) third-line d) fourth-line therapy.** Rates represent the occurrence of hypoglycaemia over the first two years after starting a line of therapy.

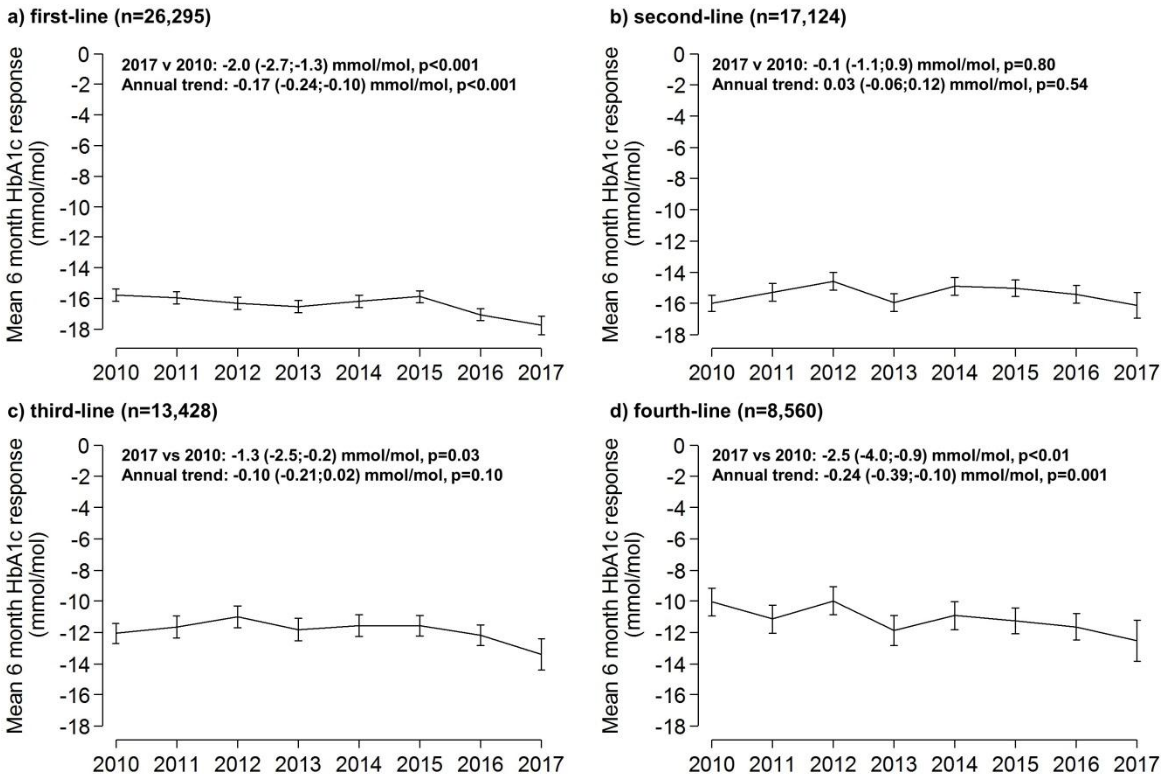


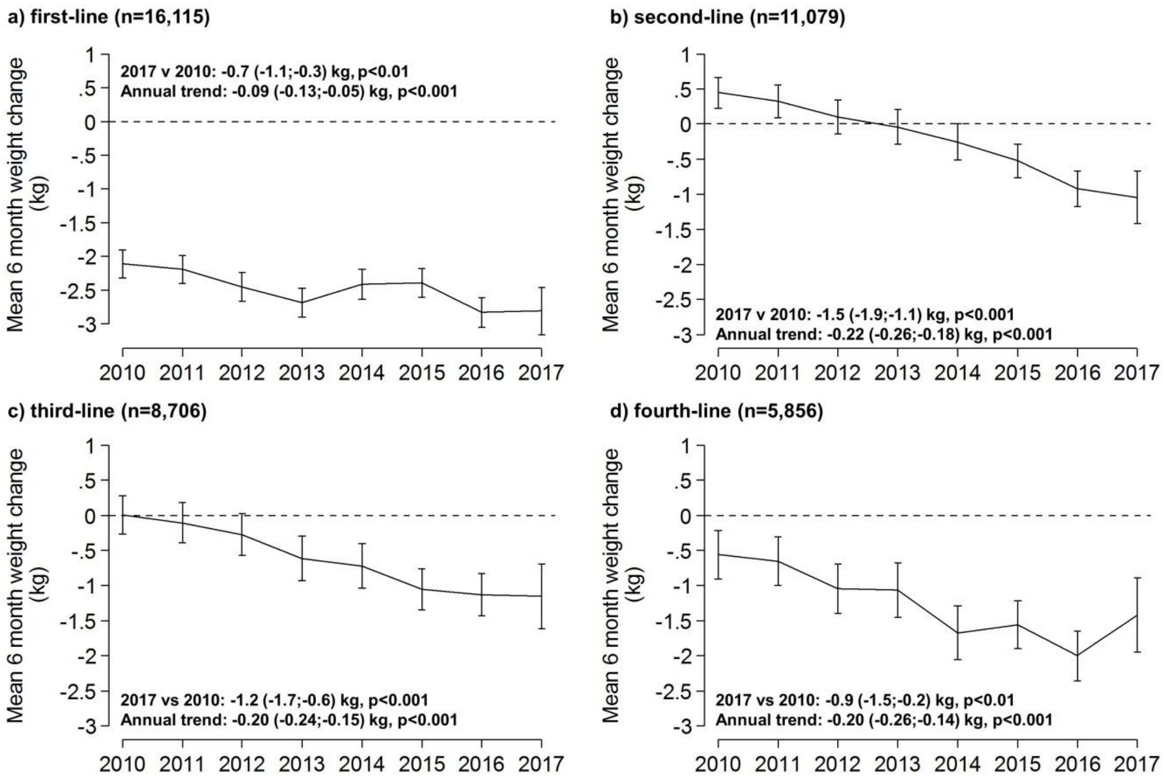
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
% new first-line prescriptions
MFN
SU
OTHER
2010
2011
2012
2013
2014
2015
2016
2017

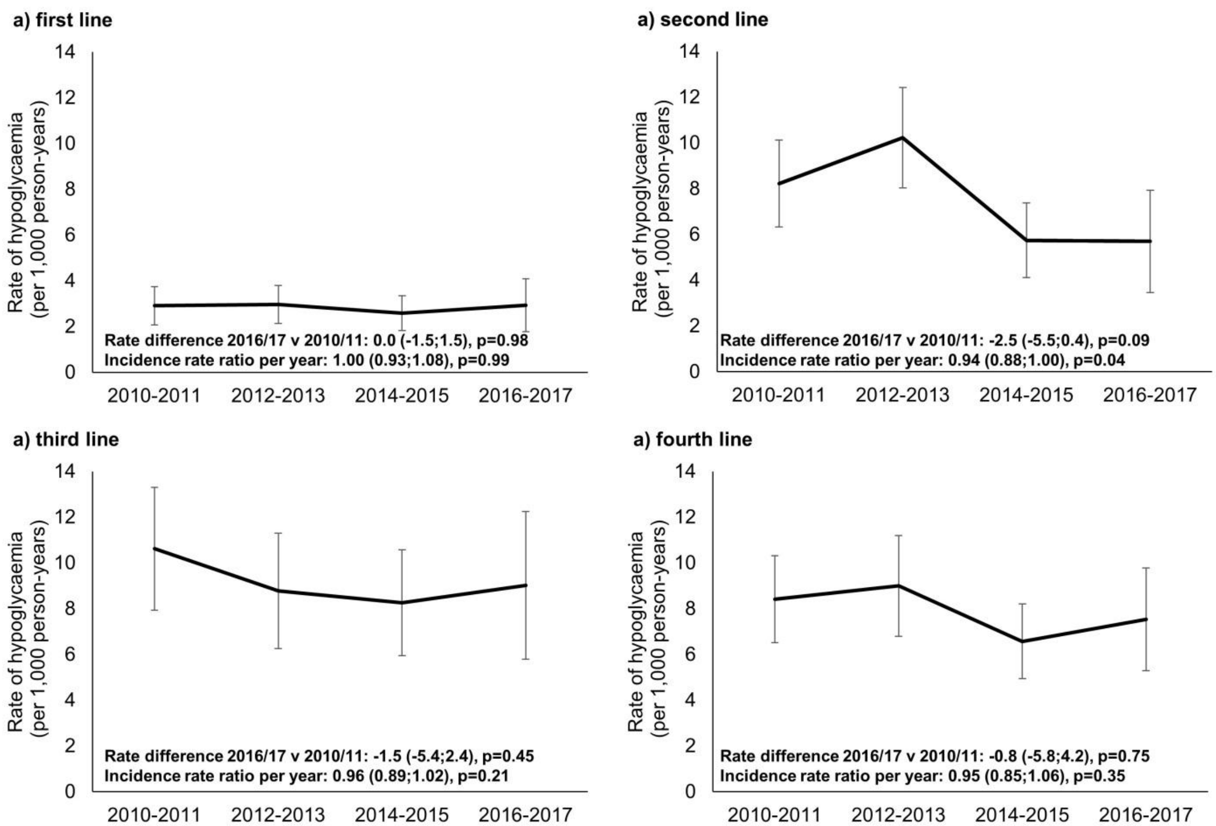

60%
50%
40%
30%
20%
10%
0%
% new second-line prescriptions
2010
2011
2012
2013
2014
2015
2016
2017
DPP4
SU
SGLT2
MFN
OTHER
TZD
GLP1
INS


60%
50%
40%
30%
20%
10%
0%
% new third-line prescriptions
DPP4
SGLT2
SU
INS
TZD
GLP1
OTHER
MFN
2010
2011
2012
2013
2014
2015
2016
2017


% new fourth-line prescriptions
60%
50%
40%
30%
20%
10%
0%
2010
2011
2012
2013
2014
2015
2016
2017
SGLT2
DPP4
INS
GLP1
SU
TZD
OTHER
MFN


a) first-line (n=26,295)
2017 v 2010: -2.0 (-2.7;-1.3) mmol/mol, p<0.001
Annual trend: -0.17 (-0.24;-0.10) mmol/mol, p<0.001
b) second-line (n=17,124)
2017 v 2010: -0.1 (-1.1;0.9) mmol/mol, p=0.80
Annual trend: 0.03 (-0.06;0.12) mmol/mol, p=0.54
c) third-line (n=13,428)
2017 vs 2010: -1.3 (-2.5;-0.2) mmol/mol, p=0.03
Annual trend: -0.10 (-0.21;0.02) mmol/mol, p=0.10
d) fourth-line (n=8,560)
2017 vs 2010: -2.5 (-4.0;-0.9) mmol/mol, p<0.01
Annual trend: -0.24 (-0.39;-0.10) mmol/mol, p=0.001
Mean 6 month HbA1c response (mmol/mol)
0
-2
-4
-6
-8
-10
-12
-14
-16
-18
2010
2011
2012
2013
2014
2015
2016
2017


a) first-line (n=16,115)
2017 v 2010: -0.7 (-1.1;-0.3) kg, p<0.01
Annual trend: -0.09 (-0.13;-0.05) kg, p<0.001
b) second-line (n=11,079)
2017 v 2010: -1.5 (-1.9;-1.1) kg, p<0.001
Annual trend: -0.22 (-0.26;-0.18) kg, p<0.001
c) third-line (n=8,706)
2017 vs 2010: -1.2 (-1.7;-0.6) kg, p<0.001
Annual trend: -0.20 (-0.24;-0.15) kg, p<0.001
d) fourth-line (n=5,856)
2017 vs 2010: -0.9 (-1.5;-0.2) kg, p<0.01
Annual trend: -0.20 (-0.26;-0.14) kg, p<0.001
Mean 6 month weight change (kg)
2010 2011 2012 2013 2014 2015 2016 2017


a) first line
Rate of hypoglycaemia (per 1,000 person-years)
14
12
10
8
6
4
2
0
2010-2011
2012-2013
2014-2015
2016-2017
Rate difference 2016/17 v 2010/11: 0.0 (-1.5;1.5), p=0.98
Incidence rate ratio per year: 1.00 (0.93;1.08), p=0.99
a) second line
Rate difference 2016/17 v 2010/11: -2.5 (-5.5;0.4), p=0.09
Incidence rate ratio per year: 0.94 (0.88;1.00), p=0.04
a) third line
Rate difference 2016/17 v 2010/11: -1.5 (-5.4;2.4), p=0.45
Incidence rate ratio per year: 0.96 (0.89;1.02), p=0.21
a) fourth line
Rate difference 2016/17 v 2010/11: -0.8 (-5.8;4.2), p=0.75
Incidence rate ratio per year: 0.95 (0.85;1.06), p=0.35