Healthcare resource use and costs for people with type 2 diabetes mellitus with and without severe mental illness in England: longitudinal matched-cohort study using the Clinical Practice Research Datalink

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Background
Approximately 60,000 people in England have coexisting type 2 diabetes mellitus (T2DM) and severe mental illness (SMI). They are more likely to have poorer health outcomes and require more complex care pathways compared with those with T2DM alone. Despite increasing prevalence, little is known about the healthcare resource use and costs for people with both conditions.

Aims
To assess the impact of SMI on healthcare resource use and service costs for adults with T2DM, and explore the predictors of healthcare costs and lifetime costs for people with both conditions.

Method
This was a matched-cohort study using data from the Clinical Practice Research Datalink linked to Hospital Episode Statistics for 1620 people with comorbid SMI and T2DM and 4763 people with T2DM alone. Generalised linear models and the Bang and Tsiatis method were used to explore cost predictors and mean lifetime costs respectively.

Results
There were higher average annual costs for people with T2DM and SMI (£1930 higher) than people with T2DM alone, driven primarily by mental health and non-mental health-related hospital admissions. Key predictors of higher total costs were older age, comorbid hypertension, use of antidepressants, use of first-generation antipsychotics, and increased duration of living with both conditions. Expected lifetime costs were approximately £35,000 per person with both SMI and T2DM. Extrapolating nationally, this would generate total annual costs to the National Health Service of around £250 m per year.

Conclusions
Our estimates of resource use and costs for people with both T2DM and SMI will aid policymakers and commissioners in service planning and resource allocation.

Keywords
Severe mental illness; type 2 diabetes; cost; resource use; matched cohort study.

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Background
Severe mental illness (SMI), including bipolar disorder, schizophrenia, and other psychotic disorders, has a dramatic impact on physical health and life expectancy. Studies show that people with SMI die on average 15 to 20 years earlier than the general population, incurring over three times more health service expenditure (including primary and secondary care) than those without SMI. SMI often co-occurs with chronic physical illnesses, including diabetes. In the UK, type 2 diabetes mellitus (T2DM) is twice as common among people with SMI as those without, and each condition influences the severity of the other. Currently, approximately 60,000 people in England live with coexisting diabetes and SMI, and this number is likely to increase.

Although the relationship between T2DM and SMI has been previously explored, little is known about the healthcare resource use and costs for people with both conditions. Having SMI may lead to increased resource use in primary care, admissions to hospital and all-cause readmission and potentially preventable readmissions, but it is unclear how resource consumption and economic costs are split across primary and secondary care settings for people with T2DM and SMI. Also, predictors of healthcare costs for this group remain unknown.

Aims
To address this evidence gap, we aimed to: (a) compare healthcare resource use and costs for people with T2DM and SMI (exposed) with people with T2DM but no SMI (unexposed); (b) investigate the predictors of healthcare costs for people with both T2DM and SMI (exposed); and (c) extrapolate the lifetime costs for people with T2DM and SMI (exposed).

Method
We used a matched-cohort study design. Data were extracted from the Clinical Practice Research Datalink (CPRD) GOLD, a database of individual patient records from UK primary care practices covering 9% of the population and broadly representative in terms of age and gender. Data include patient demographics, symptoms, diagnoses, prescriptions, tests, and referrals from primary care were further linked to the Hospital Episode Statistics (HES) for secondary care information, the Office for National Statistics data for mortality, and the Index of Multiple Deprivation (IMD) for area deprivation. Since HES is England-
based (not UK-based like the CPRD), our sample only includes practices in England.

**Study population**

Patients with a first diagnosis of T2DM and SMI between 1 April 2000 and 31 March 2016, and who were aged 18 or over for both conditions were drawn from the CPRD database. T2DM was classified by the presence of diagnostic codes in primary or secondary care data, and SMI was characterised by the presence of at least one diagnosis for schizophrenia, schizoaffective disorder, bipolar disorder, depression with psychosis, or other affective disorder (such as affective psychoses, unspecified affective psychoses and other affective psychoses) in primary or secondary care data.

Diagnoses were based on Read codes20 in CPRD and ICD-10 codes21 in HES. Detailed code lists are described in Lister et al.22 People with SMI and T2DM were matched, with a maximum ratio of 1:4, to people diagnosed with T2DM between 1 April 2000 and 31 March 2016 but without SMI, on age (plus or minus 2 years), gender and primary care practice. Matching methods have been described in more detailed elsewhere.23 All participants had at least 15 months' continuous health records up to research standard, and at least 1 year of follow-up. All the resource utilisation within the follow-up period was considered for the analysis. The methods for determining the start and end dates of follow-up and the baseline characteristics identification period (15-month window) are presented in Supplementary Appendix 1 available at https://doi.org/10.1192/bjp.2021.131.

Baseline characteristics included age at diagnosis of T2DM, gender, ethnicity, area deprivation, comorbidity and medication use. Details about derivation of variables and resolving disagreements between CPRD and HES have been described elsewhere.22,23 Area deprivation was categorised in five quintiles based on residential postcode using IMD 2010 calculated at the Lower layer Super Output Area level.

Cardiovascular comorbidities at baseline were measured by the clinical diagnosis of cardiovascular disease (CVD) and hypertension. Comorbidity was summarised by the number of Charlson comorbidities,24 excluding diabetes and diabetes with complications. Medication was defined based on prescription of three types of medications (antidiabetes drugs, antidepressants and antipsychotics) at least once within a 15-month window. Identified baseline characteristics were used to adjust analyses for sample heterogeneity or to explore potential cost predictors.

**Resource use and cost estimation**

Resource use and cost estimation included both primary and secondary care services. Primary care services included general practitioner (GP) or primary care physician consultations, practice nurse consultations, prescriptions and diagnostic tests. Secondary care services comprised in-patient stays in general hospitals. All included resources were costed using a bottom-up costing approach, and calculated costs were expressed in 2018 British pounds. An overview of all the sources of healthcare utilisation data and unit costs (both primary and secondary care) is shown in Supplementary Appendix 2.

**Primary care costs**

Data relating to primary care utilisation were extracted from CPRD based on Read codes,20 a clinical coding system that classifies diagnoses, patient characteristics, procedures and tests for primary care in the UK. Our study included costs associated with primary care consultations, prescriptions and diagnostic tests. Following the approach proposed by Ride et al,25 consultation costs were calculated by the duration multiplied by the costs per minute of staff time. Different members of staff, such as doctors and practice nurses, attracted different unit costs. Data about the latter were extracted from the Unit Costs of Health and Social Care (2018).26 Multiple visits to the same staff on the same day were considered as duplicates and discarded, whereas visits to different staff on the same day were counted separately.

Prescription data were derived from the Therapy data-set of CPRD. Prescription costs were calculated by the number of prescriptions multiplied by unit costs from the Prescription Cost Analysis 2018.27 Prescription records were costed at British National Formulary subparagraph level, which provides detailed information about a drug, including chemical substance, strength and formulation. Higher hierarchy levels (paragraph, section, or chapter) were used where subparagraph codes were unavailable.

Diagnostic test data were derived from the test data-set of CPRD and included diagnostic imaging, diagnostic services and pathology services. Following the costing approach proposed in Ride et al,25 the test records were first grouped into Healthcare Resource Groups (HRGs) that are also used in National Health Service (NHS) Reference Costs 2017/18.28 HRGs are the NHS equivalent of the diagnosis-related groups in the USA, and the NHS Reference Costs are average unit costs for NHS activities. Costs were estimated using the type of tests multiplied by the unit costs from the NHS Reference Costs. Details of the grouping method, including the Read codes and corresponding HRGs appear in Supplementary Appendix 3.

Secondary care/hospital care costs

The use and cost of secondary care was calculated only for admissions to general hospitals (including non-specialist mental health providers). Admissions to specialist mental health hospitals such as psychiatric hospitals were not included due to data constraint. Both number of admissions and number of in-patient days were reported as secondary care resource use. Hospital activities, such as diagnoses and procedures, were first grouped into HRGs using HRG4 + 2017/18 Reference Costs Grouper29 and then linked to the national average costs from the NHS Reference Costs 2017/18 at spell level. Hospital admissions and associated costs were further split into mental and physical health-related admissions using HRG codes.30

**Statistical methods**

The resource utilisation and costs of both people with T2DM, with and without SMI, were presented at aggregate annual level. A two-phase analysis was conducted. The first phase estimated differences in resource use and costs between groups using a matched-cohort design. Unadjusted comparisons compared simple averages of annual resource utilisation and costs. Adjusted comparisons were performed using a series of generalised linear models (GLMs), appropriate for non-negative and highly skewed cost and resource data.31 All GLM regressions were adjusted for age at diagnosis of T2DM (continuous variable), gender, ethnic group, time since diagnosis of T2DM (continuous variable) and characteristics at diagnosis of T2DM, including area deprivation, comorbid hypertension, comorbid CVD, number of Charlson comorbidities (continuous variable), medications (antidepressant and antidiabetes drugs) and financial year in order to account for sample heterogeneity. Choices of distributional family and link functions of all GLMs were informed by the Park test32 and the Pregibon link test.33 To ensure robustness of GLM results, a sensitivity analysis without extreme values, defined as those over the 99th percentile, was also conducted.
The second phase focused on people with both T2DM and SMI only. The cost predictors of total, primary care and secondary care costs were explored using the multivariate GLM method as described above. Lifetime costs (costs from having T2DM and SMI to death) were estimated using the Bang and Tsiatis partition method, which estimates mean costs by adjusting survival when these costs are right censored. Average lifetime cost for those that died within the follow-up period was also calculated for the purposes of comparison. Furthermore, to estimate the economic impact of people with T2DM and SMI to the NHS each year, prevalence-based healthcare costs were calculated based on the prevalence reported in the National Diabetes Audit and the average annual cost estimated in this study. All analyses were performed using SAS software, version 9.4 (SAS Institute, North Carolina, US) and Stata version 15 (StataCorp LP, College Station, TX, USA).

Ethics approval and consent to participate

A data-use agreement for CPRD records and linked HES and Office for National Statistics mortality data was granted by the Independent Scientific Advisory Committee (ref: 17_161R).

Results

Descriptive statistics

A total of 6383 people (1620 exposed and 4763 matched unexposed participants) were included in the analysis with 1 023 257 primary care contacts and 22 253 hospital admission spells. Table 1 shows baseline characteristics for the total sample, and the two groups. The mean age of the sample population was 57.9 years (s.d. = 12.6). Overall, 48.3% were male, 82.5% were White, 55.0% had hypertension, 35.7% had depression and psychosis, 32.3% had bipolar disorder and 52.5% had schizophrenia.

The annual resource use and costs for the two groups are presented in Table 2. People with SMI used more primary and secondary care services on average every year compared with those without SMI. On average, people with SMI received 2141 (33.5) primary care consultations, 158 (9.8) secondary care contacts and 22 253 hospital admission spells. Table 1 shows baseline characteristics for the total sample, and the two groups. The mean age of the sample population was 57.9 years (s.d. = 12.6). Overall, 48.3% were male, 82.5% were White, 55.0% had hypertension, 35.7% had depression and psychosis, 32.3% had bipolar disorder and 52.5% had schizophrenia.
hospital in-patient days (10.2 and 2.9 days for exposed and unexposed individuals, respectively), the annual number of consultations (12.1 contacts for exposed versus 8.7 contacts for unexposed individuals) and the all-cause annual number of admissions (0.8 admissions for people with SMI versus 0.6 for those without SMI). The differences remained significant even after extreme values were removed (Supplementary Appendix 5).

Unadjusted mean annual costs per patient were £4459 (s.d. = 12 231) for people with SMI. This is £1930 higher compared with those without SMI, with £2129 (s.d. = 4238). Admission to hospital was the main contributor to the annual costs, accounting for 80.2% and 73.9% of overall healthcare expenditure for those with and without SMI, respectively.

Table 2 summarises the results of the GLM models adjusting for age at diagnosis of T2DM, gender, ethnic group, time since diagnosis of T2DM and characteristics at diagnosis of T2DM, including area deprivation, comorbid hypertension, comorbid CVD, number of Charlson comorbidities and medications (antidepressant and antidiabetes drugs) and financial year.

Cost predictors of total costs for people with T2DM and SMI

The results of the analysis using GLM models for predictors of total, primary and secondary care costs for those with T2DM and SMI can be found in Table 3. Key predictors of higher total costs for those who were older at diagnosis (for the latest of SMI or T2DM), comorbid hypertension, use of antidepressants, use of first-generation antipsychotics, and longer duration of both T2DM and SMI. For example, the average marginal effect of time since having T2DM and SMI is £1666 (95% CI 1160–2172), suggesting that the total cost was increased by £1666 (95% CI 1160–2172) when people lived one additional year of living with both conditions. In addition, younger age, female gender, White ethnicity, diagnosis with bipolar disorder or depression and psychosis, comorbid hypertension, increased number of Charlson comorbidities, and use of antidepressants, antipsychotics or antidiabetes drugs were associated with higher primary care costs. For secondary care costs, the significant cost predictors were age, comorbid hypertension and duration of illness.

Lifetime and prevalence-based costs for people with T2DM and SMI

Of the 1620 people with T2DM and SMI, 234 (14.4%) died within the follow-up period, leaving 85.6% of people with cost data censored. The average lifetime cost for those that died within the follow-up period was estimated at £26 354. The average lifetime cost increased to £34 518 when living participants were included, and censored cost data were considered using the Bang and Tsiatis partition method. The study time period was partitioned into 1-year time intervals, and average costs incurred in each interval were multiplied by the inverse probability of not being censored. Weighted costs were summed across intervals and divided by the sample size to account for censoring. Regarding prevalence-based costs, it was estimated that people with SMI and T2DM cost NHS (England) £268 380 000 per year based on the prevalence reported in the National Diabetes Audit, and the adjusted average annual cost of £4473 (s.d. = 3767) reported in Table 2.

Discussion

Main findings

This study, to the best of our knowledge, is the first to estimate the resource use and costs of people with T2DM and SMI using information from both primary and secondary care sources. The presence of SMI was associated with increased resource use and costs.
for people with diabetes. The significant cost differences were mainly driven by secondary care services, and were related to higher numbers of admissions and days in hospital. As expected, people with SMI had higher numbers of admissions and days in hospital. As expected, people with T2DM and SMI also had, on average, more

Table 3  Cost drivers of total cost for people with severe mental illness (SMI) and type 2 diabetes mellitus (T2DM) (exposed)\textsuperscript{a}\textsuperscript{b}

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>Total (n = 1620)</th>
<th>Primary care (n = 1620)</th>
<th>Secondary care (n = 1620)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis of having both T2DM and SMI</td>
<td>140** (34 to 245)</td>
<td>–22** (–39 to –6)</td>
<td>202*** (101 to 304)</td>
</tr>
<tr>
<td>Type of SMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>Reference</td>
<td>917*** (537 to 1297)</td>
<td>728 (–1531 to 2988)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>–262</td>
<td>–251* (–500 to –2)</td>
<td>2172 (–2661 to 7005)</td>
</tr>
<tr>
<td>Depression and psychosis</td>
<td>26</td>
<td>–1806*** (–2580 to –1140)</td>
<td>–12 198*** (–13 852 to –10 544)</td>
</tr>
<tr>
<td>Other \textsuperscript{a}</td>
<td>3363 (–8021 to 14 746)</td>
<td>1979 (–207 to 4164)</td>
<td>2003 (–6193 to 10 198)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>–547</td>
<td>–2877* (–5171 to –580)</td>
<td>–13 397*** (–16 945 to –9849)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2820* (190 to 541)</td>
<td>639*** (234 to 1043)</td>
<td>2137* (87 to 4187)</td>
</tr>
<tr>
<td>Number of Charlson Comorbidities</td>
<td>1660 (–11 to 3431)</td>
<td>603*** (321 to 885)</td>
<td>1150 (–287 to 2587)</td>
</tr>
<tr>
<td>Medication</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antidepressants</td>
<td>2836* (241 to 5431)</td>
<td>1056*** (645 to 1467)</td>
<td>1952 (–595 to 4458)</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First generation</td>
<td>339* (195 to 659)</td>
<td>1332*** (826 to 1839)</td>
<td>1993 (–1013 to 4998)</td>
</tr>
<tr>
<td>Second generation</td>
<td>2308</td>
<td>649*** (247 to 1051)</td>
<td>2214 (–274 to 4702)</td>
</tr>
<tr>
<td>Antidiabetes</td>
<td>1206 (–224 to 4841)</td>
<td>708* (163 to 252)</td>
<td>410 (–2571 to 3490)</td>
</tr>
<tr>
<td>Time since having T2DM and SMI (years)</td>
<td>1666*** (1160 to 2172)</td>
<td>875*** (752 to 963)</td>
<td>947*** (524 to 1370)</td>
</tr>
<tr>
<td>Family Link \textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Link \textsuperscript{c}</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a. The financial year at T2DM or SMI diagnosis (whichever was the latest) was adjusted in all the analyses.

b. Other included other affective disorder and mixed conditions.

c. Both family and link functions are the model specifications of corresponding generalised linear model. Also please add some extra spacing between “Time since having T2DM and SMI (years)” and “Family Link”.

Importantly, some non-mental health admissions and in-patient days are unrelated to diabetes and may benefit from further investigation.

Another possible explanation for the long average non-mental health-related in-patient days is that managing a greater number of comorbidities (SMI) is associated with lengthier admissions.\textsuperscript{39,40}

For our study group, this could be exacerbated because of lack of continuity of care, poor coordination with secondary care or lack of person-centred care. Further investigation of the underlying mechanisms behind this finding is needed.

For people with T2DM and SMI, older age, White ethnicity, female gender, more comorbidities (including hypertension), use of antidepressants or antipsychotics and increased duration of living with both T2DM and SMI were associated with higher healthcare costs. Among these cost predictors, ethnicity, gender, use of antidepressants or antipsychotics, and number of Charlson comorbidities only had a significant impact on costs in primary care. This finding complements previous findings showing that people with T2DM
and SMI had higher average annual costs than those with T2DM alone, and indicates that more attention should be given to coordination of care for people with these characteristics, in order to reduce healthcare costs and improve outcomes. These cost predictors may also help policymakers to project future costs and to manage costs.

Findings related to cost predictors also reveal some probable interacting drivers of inequalities. Complementing previously found inequalities in prevalence and health outcomes for people with T2DM and SMI, our study indicates that inequality in healthcare costs also exists in relation to ethnicity, gender and age. For example, female gender and White ethnicity were associated with higher primary care costs, suggesting that males and those from a minority ethnic background may have less access to primary care or may be less engaged. This aligns with findings for individuals with SMI alone.

Our results also show that older age is associated with higher costs (lower costs in primary care, but higher costs in secondary care), suggesting that older people may have less access to essential primary care, resulting in increased risk of complications, and require more secondary care resources. Similar findings have been observed for individuals with T2DM alone, whereas Ride et al presented a reverse directional effect of age in people with SMI alone. Data limitations prevented us exploring whether inequalities were because of the severity of illness, complications of T2DM, problems navigating the healthcare system or synergies between these circumstances. Future studies might untangle these observations to map the relationship between disadvantage, discrimination and health outcomes in order to create an environment that can more fairly meet the health needs of individuals with T2DM and SMI.

Finally, the study demonstrated the substantial economic costs associated with people with both T2DM and SMI in England. In terms of incidence-based healthcare costs, the average total cost from diagnosis to death was around £35 000. Regarding prevalence-based healthcare costs, SMI and diabetes multimorbidity costs the NHS approximately a quarter of a billion pounds per year. Moreover, the prevalence of both conditions is rising. Thus, the annual economic impact is likely to increase, which should make management of this comorbidity an NHS priority. Interventions aimed at minimising the impact of SMI (for example, integrated care and supporting patient empowerment) or improving T2DM care (for example, weight reduction and non-pharmacologic interventions) may help to reduce healthcare costs and improve patient outcomes.

Comparison with findings from other studies

Several studies found that individuals with T2DM and SMI were more likely to experience in-patient admissions compared with people with just T2DM. Both Kurdyak et al and Guerrero Fernández de Alba et al used data from single-payer health insurance systems to study resource use in the population, but their findings were subject to limitations, such as short-term resource-use data (1-year admission to hospital data in Kurdyak et al and 2-year admission to hospital data in Guerrero Fernández de Alba et al), geographic area (Ontario in Kurdyak et al and Aragón in Guerrero Fernández de Alba et al) and specific type of SMI (such as schizophrenia). By contrast, Krein et al examined 1-year all-cause hospital admissions in people with T2DM and all types of SMI in the USA. However, the use of data from the US Department of Veterans Affairs healthcare system may limit its generalisability to health services outside the Department of Veterans Affairs system. Nonetheless, our study findings are in line with these three studies. As with Krein et al’s study, our study focused on all types of SMI. Furthermore, the use of cohort data from CPRD and HES ensured all the resource use was captured, and the long-term effects were examined (mean follow-up time: 6.4 years, Table 1).

Limitations

Our study was subject to certain limitations in terms of representativeness. Although patients in CPRD broadly represent the general population, we cannot ascertain the representativeness of people with T2DM and SMI. This is because our inclusion criteria required individuals to be registered with the practice for at least 15 months, whereas some people with SMI may have transient care relationships with general practice. Also, the representativeness of our study sample can be affected by undetected T2DM or SMI; previous analyses have shown that SMI is often unrecognised among individuals treated for diabetes. Furthermore, people with SMI often have undiagnosed diabetes because of difficulties accessing the healthcare system. Additionally, the data linkage of UK-based CPRD and England-based HES data may have restricted our sampling to individuals registered to CPRD general practices in England that participated in HES data linkage, potentially differing from the average practice. Finally, although people with missing ethnicity data accounted for a small proportion of the study population (Table 1), they played an important role in the matched-cohort analysis. As shown in Table 2 and Supplementary Appendix 6, people with missing ethnicity were associated with low resource use and costs. Although it is possible that care providers are less likely to record ethnicity for individuals not attending services, the missing ethnicity value is likely to cause an underestimation of the difference between those with and without SMI. Notwithstanding these limitations, the generalisability of our findings was supported by the UK National Diabetes Audit that reported a similar distribution to our study group for characteristics such as age at T2DM diagnosis, gender, deprivation and ethnicity.

Our study was also subject to limitations for our cost and resource-use analyses. We are likely to have underestimated some costs because of data constraints preventing us including costs for out-patient services, emergency department and community mental healthcare, the latter being one of the main components of total annual costs for individuals with SMI. In the current matched-cohort analysis, only the resource use and costs of secondary care have been stratified by mental-health/non-mental health. As important differences of resource use could also occur in primary care, the stratification of primary care resource use should be considered in future studies. Finally, averaging costs over multiple years for the matched cohort analysis can limit appreciation of cost trajectories (i.e. costs peak around the time of diagnosis and then tail off). Nevertheless, annual cost results and relevant information can provide valuable information for decision modelling, especially for Markov model construction.

Implications

Our findings indicate that the healthcare costs for people with both T2DM and SMI are substantial. Costs were influenced by age, ethnicity, number of comorbidities and the length of time living with both T2DM and SMI. The results also confirmed that the presence of SMI is associated with increased resource use and costs among people with T2DM. Such differences were primarily driven by secondary care and were related not only to mental health-related but also non-mental health-related hospital admissions, highlighting the need for better coordination of care. The findings can support policymakers and commissioners in service planning and resource allocation. Furthermore, the mechanisms leading to more frequent hospital admissions should be investigated. Finally, strategies to

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delay the onset of T2DM should be adopted by policymakers, in order to reduce healthcare costs and improve patient outcomes.

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First received 19 Mar 2021, final revision 4 Aug 2021, accepted 08 Aug 2021.

Supplementary material

To view supplementary material for this article, please visit https://doi.org/10.1191/2021.131

Funding

This publication presents independent research funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research (HS&D) programme (ref 15/70/26). S.G., N.S., S.L.P, and R.J. were also funded by the NIHR Yorkshire and Humber (YH) Research Collaboration (NIHR YH-ARC), https://www.arc-yh.nihr.ac.uk/. The views expressed are those of the authors and not necessarily those of the HS&DR programme, the NHS, the NICHR or the Department of Health and Social Care.

Acknowledgements

We would like to express our appreciation to John RAFORD and DiAMONDS Voice Patient and Public Involvement group for providing advice and insight into auditing L.H. processed the data, designed and performed the data analyses. R.J. verified the analytical methods. H.-I.W. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Author contributions

N.S., R.I.G.H., D.S., S.G., R.J., T.D., C.H., S.L.P., J.T., and S.A. designed and directed the project. S.B. and C.E.W.K. led the project management group for providing advice and insights to augmented L.H. processed the data, designed and performed the data analyses. R.J. verified the analytical methods. H.-I.W. took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

Declaration of interest

Research and development on Clinical Practice Research Datalink (CPRD) data with linkage to CPRD do not permit data sharing with third parties. All formulae and additional sources of information are presented in the paper and supplementary materials. The SAGA and state code for cleaning and analysing the data can be provided upon reasonable request.

References


