**Title:**

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

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**Declaration of Interest**

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**Author contributions**

NS, RIGH, DS, SG, RJ, TD, CH, SLP, JT, and SLA designed and directed the project. SB and CEWK contributed to project management. HW and LH processed the data, designed and performed the data analyses. RJ verified the analytical methods. HW took the lead in writing the manuscript. All authors provided critical feedback and helped shape the research, analysis and manuscript.

**Data Availability**

Researchers can apply to access Clinical Practice Research Datalink (CPRD) data with linkage to Hospital Episode Statistics (HES) through [https://www.cprd.com/]. Data sharing agreements with 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 SAS and stata code for cleaning and analysing the data can be provided upon reasonable request.

## Abstract

**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 to 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**

Matched cohort study using data from Clinical Practice Research Datalink (CPRD) linked to Hospital Episode Statistics (HES) for 1,620 people with comorbid SMI and T2DM and 4,763 people with T2DM alone. Generalised linear models (GLMs) and the Bang and Tsiatis method were used to explore cost predictors and mean lifetime costs respectively.

**Results**

People with T2DM and SMI had higher average annual costs (£1,930) than people with T2DM alone, driven primarily by mental health and non-mental health-related hospitalisations. Key predictors of higher total costs were older age, comorbid hypertension, use of antidepressants and 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 NHS of around £250m per year.

**Conclusions**

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

## Introduction

Severe mental illness (SMI), including bipolar disorder and schizophrenia, 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 (1,2), incurring over three times more health service expenditure (including primary and secondary care) than those without SMI (3,4). SMI often co-occurs with chronic physical illnesses, including diabetes (5–7). In the UK, type 2 diabetes mellitus (T2DM) is twice as common amongst people with SMI as those without (8), and each condition influences the severity of the other (7). Currently, approximately 60,000 people in England live with coexisting diabetes and SMI (9), and this number is likely to increase (8,10).

While the relationship between T2DM and SMI has been previously explored (7), 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 (11), hospitalisations (12–14), and all-cause re-admission and potentially preventable readmissions (15–17), 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.

To address this evidence gap, we aimed to: 1) compare healthcare resource use and costs for people with T2DM and SMI (exposed) with people with T2DM but no SMI (unexposed); 2) investigate the predictors of healthcare costs for people with both T2DM and SMI (exposed); and 3) extrapolate the lifetime costs for people with T2DM and SMI (exposed).

## Methods

### Data source and study population

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 (18) covering 9% of the population and broadly representative in terms of age and sex (19). 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 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, while SMI was characterised by the presence of at least one diagnosis for schizophrenia, schizoaffective disorder, bipolar disorder, depression with psychosis, or other affective disorder (e.g. affective psychoses, unspecified affective psychoses, and other affective psychoses) in primary or secondary care data. Diagnoses were based on Read codes (20) in CPRD and ICD-10 codes (21) 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 (± 2 years of age), sex, 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 one 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 Appendix 1.

Baseline characteristics included age at diagnosis of T2DM, sex, ethnicity, area deprivation, comorbidity and medication use. Details about derivation of variables and resolving disagreements between CRPD and HES have been described elsewhere (22,23). Area deprivation was categorised in 5 quintiles based on residential postcodes using IMD 2010 calculated at the Lower layer Super Output Area (LSOA) 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 inpatient 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 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 (PSSRU 2018, (26)). Multiple visits to the same staff on the same day were considered as duplicates and discarded, while visits to different staff on the same day were counted separately.

Prescription data were derived from the Therapy dataset of CPRD. Prescription costs were calculated by the number of prescriptions multiplied by unit costs from the Prescription Cost Analysis (PCA) 2018 (27). Prescription records were costed at British National Formulary (BNF) 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 dataset 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 (DRGs) 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 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). Both number of admissions and number of inpatient 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 Grouper (29) and then linked to the national average costs from the NHS Reference Costs 2017/18 (28) 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), sex, 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 test (32) 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 (34). 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 NHS each year, prevalence-based healthcare costs were calculated based on the prevalence reported in the National Diabetes Audit (9) 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). Individual patient consent is not required for observational CPRD studies, but patients have the opportunity to opt out of contributing to the database.

## Results

### Descriptive statistics

A total of 6,383 people (1,620 exposed and 4,763 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 (SD 12.6). Overall, 48.3% were male, 82.5% were white, 55.0% had hypertension, 33.5% had cardiovascular diseases, 26.6% were prescribed antidepressants, and 17.5% received antipsychotics.

People with both T2DM and SMI (exposed) and people with T2DM but no SMI (unexposed) were similar on age, sex and ethnicity. As expected, those with SMI were more likely to have been prescribed psychotropic medications (antidepressants and antipsychotics) (chi-square, p<0.001).

### Annual resource utilisation and costs

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 20 primary care contacts every year, and the majority were non-prescription or test-related consultations. They spent a mean of 10.2 (SD 29.1) days in hospital per annum, and the majority were non-mental health related (details in Appendix 4). The main differences between the two groups were the all-cause annual number of hospital inpatient days (10.2 and 2.9 days for exposed and unexposed individuals respectively), the annual number of consultations (12.1 contacts for exposed vs. 8.7 contacts for unexposed individuals), and the all-cause annual number of admissions (0.8 admissions for people with SMI vs. 0.6 for those without SMI). The differences remained significant even after extreme values were removed (Appendix 5). Unadjusted mean annual costs per patient were £4,059 (SD 12,231) for people with SMI compared to £2,129 (SD 4,238) for those without SMI. Hospitalisation 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, sex, 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). Adjusted differences in resource utilisation and costs between those with and without SMI were significant, with the exception of differences in the numbers of prescription-related and test-related consultations (further details in Appendix 6).

### 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 were older age at diagnosis (for the latest of SMI or T2DM), comorbid hypertension, use of antidepressants and first-generation antipsychotics, and longer duration of both T2DM and SMI. For example, the total cost of one additional year of living with both conditions was £1,666 (95% CI: 1,160 to 2,172). In addition, younger age, female sex, 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 (27). The study time period was partitioned into one 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 (9), and the adjusted average annual cost of £4,473 (SD 3,767) measured in section 3.2 (Table 2).

## Discussion

This study 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 mental health-related admissions and inpatient days compared to those without. However, people with T2DM and SMI also had, on average, more non-mental health admissions and inpatient days. One possible explanation for this is ‘diagnostic overshadowing’; previous studies have shown that having a SMI diagnosis can overshadow diabetes care (35,36) leading to later presentations of physical illnesses which are then more likely to require a non-mental health hospital admission. Regular physical health checks, appropriate treatment for diabetes and greater support for diabetes self-management have been proposed for people with T2DM and SMI, in order to improve health outcomes and reduce healthcare costs (37). Similarly, since the majority (78.3%) of individuals with T2DM and SMI developed diabetes after SMI, such health checks and treatments may also delay or prevent the onset of diabetes and provide clinical and economic benefits (38). Importantly, some non-mental health admissions and inpatient days are unrelated to diabetes and may benefit from further investigation. Another possible explanation for the long average non-mental health-related inpatient days is that managing a greater number of comorbidities (SMI) is associated with lengthier admissions (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 fidning is needed.

For people with T2DM and SMI, older age, white ethnicity, female sex, 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, sex, use of antidepressants or antipsychotics, and number of Charlson comorbidities only had significant impacts 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 policy makers 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 (9,41), our study indicates that inequality in healthcare costs also exists in relation to ethnicity, sex, and age. For example, female sex and white ethnicity were associated with higher primary care costs, suggesting that males and those from a non-white ethnic background may have less access to primary care or may be less engaged. This aligns with findings for individuals with SMI alone (25). 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 (42), while Ride et al. (25) presented a reverse directional effect of age in people with SMI alone. Data limitations prevented us exploring whether inequalities were due to 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 (8). 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 (43)) or improving T2DM care (for example, weight reduction (44) and non-pharmacologic interventions (45)) may help to reduce healthcare costs and improve patient outcomes.

Several studies found that individuals with T2DM and SMI were more likely to experience inpatient admissions compared to people with just T2DM (12–14). Both Kurdyak et al. (14) and IGF de Alba et al. (12) used data from single-payer health insurance systems to study the resource use in the population, but their findings were subject to limitations, such as short-term resource use data (1-year hosipitalisation data in Kurdyak et al.and 2-year in IGF de Alba et al.), geographic area (Ontario in Kurdyak et al. and Aragón in IGF de Alba et al.) and specific type of SMI (e.g. schizophrenia). By contrast, Krein et al. examined 1-year all-cause hospitalisations in people with T2DM and all types of SMI in the U.S (13). However, the use of data from the U.S. Department of Veterans Affairs (VA) health care system may limit its generalisibility to health services outside the VA system. Nonetheless, our study findings are in line with these three studies. As in Krein et al. (13), 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).

Our study was subject to certain limitations in terms of representativeness. Although patients in CPRD broadly represent the general population (18), 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 (46) . Furthermore, people with SMI often have undiagnosed diabetes due to difficulties accessing the health care system (47). 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 Appendix 6, people with missing ethnicity were associated with low resource use and costs. While 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 under-estimation 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 (9) that reported a similar distribution to our study group by characteristics such as age at T2DM diagnosis, sex, 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 due to data constraints preventing us including costs of outpatient services, Emergency Department, and community mental health care, the latter being one of the main components of total annual costs for individuals with SMI (25). In the current matched cohort analysis, only the resource use and costs of secondary care have been stratified by mental-health/non-mental health. Since 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 costs results and relevant information can provide valuable information for decision modelling, especially for Markov model construction.

## Conclusion

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 hospitalisations, highlighting the need for better coordination of care. The findings can support policy makers and commissioners in service planning and resource allocation. Furthermore, the mechanisms leading to more frequent hospitalisations should be investigated. Finally, strategies to delay the onset of T2DM should be adopted by policy makers, in order to reduce the healthcare costs and improve patient outcomes.

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