Title

Glucose, cholesterol and blood pressure in type II diabetes: a longitudinal observational study comparing patients with and without severe mental illness

Running Title

Diabetes control in severe mental illness

Authors

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Acknowledgements

This project was funded by NIHR CLAHRC Yorkshire and Humber. www.clahrc-yh.nihr.ac.uk. The views expressed are those of the author(s), and not necessarily those of the NHS, the NIHR or the Department of Health. This article/paper/report presents independent research by the National Institute for Health Research Collaboration for Leadership in Applied Health Research and Care Yorkshire and Humber (NIHR CLAHRC YH).

Accessible Summary

What is known on the subject?

- People with severe mental illness (SMI) have a life expectancy 15-20 years less than the general population, partly due to increased risk of physical disease, including type II diabetes (T2DM) and cardiovascular disease.
- Little is known about changes in cardiovascular risk factors over time in people with both T2DM and SMI compared to those with T2DM and no SMI.

What this paper adds to existing knowledge?

- We investigated whether levels of cardiovascular risk factors, cholesterol, $HbA_{1c,}$ systolic and diastolic blood pressure associated with adverse clinical outcomes are different in T2DM patients with and without SMI. We found significant differences in systolic blood pressure and HbA_{1c} between the two groups.
- 55% and 29% of T2DM patients with comorbid SMI are at increased risk of adverse clinical outcomes due to sub-optimal HbA_{1c} and systolic blood pressure levels respectively.

What are the implications for practice?

- Many patients with T2DM and SMI have higher levels of cardiovascular risk compared to patients with T2DM only, and good management of risk factors is therefore particularly important in patients with both conditions.
- Achieving better control of HbA_{1c} levels is likely to be central to addressing inequalities in outcomes for patients with both SMI and T2DM.

Abstract

Introduction: Patients with both severe mental illness (SMI) and type II diabetes (T2DM) have lower life expectancy than patients with T2DM alone, partly due to poor control of cardiovascular risk factors in comorbid patients.

Aim: To compare levels of cholesterol, HbA_{1c} and blood pressure in T2DM patients with and without SMI.

Method: We analysed longitudinal clinical records of 30,353 people with T2DM (657 with SMI;29,696 controls without SMI) between 2001 and 2013 using the Clinical Practice Research Datalink (CPRD). We used mixed effects regression models to compare cardiovascular risk factors between SMI and controls.

Results: Patients with SMI had lower mean systolic blood pressure (SBP) (β -2.49; SE=0.45 P=<0.01) and were more likely to have extreme (high and low) values of HbA_{1c} and SBP (OR 1.38, 95%CI: 1.16,1.64 and 1.76:1.40,2.21 respectively).

Discussion: People with T2DM and SMI have similar average values of cardiovascular risk factors to people with T2DM alone but are more likely to have values of HbA_{1c} and SBP indicating increased risk of adverse clinical outcomes.

Implications for Practice: Improved management of cardiovascular risk factors in general, glycaemic control in particular, is central to addressing the increased risk of adverse outcomes in people with both SMI and T2DM.

Keywords: Epidemiology, Physical Health, Primary Care

Relevance statement

People with comorbid T2DM and SMI are more likely to have extreme values of HbA_{1c} and systolic blood pressure that are associated with adverse clinical outcomes. Better management of these risk

factors should be ensured to address inequalities in physical health outcomes in patients with SMI and T2DM.

Introduction

People with severe mental illness (SMI) including schizophrenia, bipolar disorder and other forms of psychosis have a life expectancy 15-20 years less than the general population (Brown et al., 2010). Reduction of excess mortality in those with mental disorders has been identified as an important global health issue, identifying risk factors for earlier mortality can lead to development of effective interventions to address physical health inequality among those with mental disorder (Liu et al., 2017). Most of the premature deaths are caused by complications of physical health conditions (Reilly et al., 2015, De Hert et al., 2009). These include insulin resistance and relative insulin deficiency forms of diabetes mellitus, type II diabetes mellitus (T2DM), the prevalence of which is twice as great in those with SMI than in the general population (Reilly et al., 2015). This increased prevalence of T2DM is attributed due to a variety of factors including genetic predisposition (De Hert et al., 2009), the metabolic effects of atypical antipsychotics (Smith et al., 2008), higher levels of obesity and poor diet (Osborn et al., 2007), lower levels of physical activity (Daumit et al., 2005) and the greater barriers that disadvantaged or marginalised groups face in navigating the healthcare system (Dixon-Woods et al., 2006). People with the co-occurrence of T2DM and SMI (comorbid T2DM and SMI) have around a 50% increased risk of mortality compared with people with T2DM alone (Kontopantelis et al., 2015, Wu et al., 2015, Vinogradova et al., 2010), but the underlying mechanism for this difference is not well understood. Candidate causes include higher levels of smoking (McDonald, 2000), poor management of cardiovascular risk factors (including glycaemia, cholesterol and blood pressure), and higher prevalence of other comorbid conditions (Vinogradova et al., 2010). Patients with comorbid SMI and T2DM are less likely to receive standard levels of diabetes care, with 45% not receiving any diabetes care and the least chance of receiving specialised interventions for cardiovascular treatments (De Hert et al., 2011). Controlling HbA_{1c} and optimising

lipid and blood pressure management reduces the risks of microvascular and macrovascular complications, which remain the main cause of morbidity and mortality in patients with T2DM (Ray et al., 2009, Khaw et al., 2001, Collaborators, 2008, Group, 1998). However, the evidence for appropriate management of cardiovascular risk factors in patients with diabetes and SMI is inconclusive, particularly in the UK (Dixon et al., 2004, Wake et al., 2016). A small study in the United States showed that patients with SMI had lower levels of HbA_{1c} compared to patients without SMI (Dixon et al., 2004), and a recent larger study suggested that people with T2DM taking antipsychotic medication have lower cholesterol, HbA_{1c} and blood pressure levels compared to matched controls not taking antipsychotic medication (Wake et al., 2016). There is, however, little evidence at a population level on the changes in cardiovascular risk factors over time in those with SMI that develop T2DM compared to those with T2DM and no SMI. Using population level data of clinical records from primary care, we can assess variation in cardiovascular risk factors that may be a contributing factor to the excess mortality for people with SMI and T2DM at a population level. Identification of the candidate causes of the mortality gap can then be targeted through evidence-based interventions (Lawrence and Kisely, 2010).

The aim of this study was to investigate whether there is a difference in cardiovascular risk factors in adults with diabetes and SMI compared with adults with diabetes without SMI, and whether these risk factors change over time.

Materials and Methods

Data Source

We used data from Clinical Practice Research Datalink (CPRD) which contains primary care records for around 6.9% of the UK's patients (Herrett et al., 2015). Clinical care processes, diagnoses, measurements and test results are recorded using a hierarchical set of clinical codes (Read codes).

Prescriptions for medicine are recorded using British National Formulary (BNF) codes. The sample used in this study was taken from 125 out of 674 practices in CPRD (19%), all practice included in the sample were based in England. Practices were selected to be proportionally representative of the proportional distribution of all the 674 practices in CPRD in terms of level of socioeconomic deprivation (using practice postcode linked to Index of Multiple Deprivation) and practice size in terms of number of registered patients. All patients' records at participating practices were added to the CPRD database, the criteria for inclusion in our sample were patients with at least one of the following long-term conditions documented using Read codes in their primary care record: asthma, atrial fibrillation, coronary heart disease (CHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), diabetes, epilepsy, heart failure, hypertension, hyperthyroidism, learning disability, osteoporosis, SMI or stroke. For the purpose of this study, we selected all patients in the sample who had diabetes, with or without other long-term conditions.

Cohort

Patient records were included in the study if they had a Read code indicating a diagnosis of T2DM. Patients with diabetes diagnosis Read codes that did not distinguish diabetes type were excluded. Patients with SMI were identified using Read codes indicating a diagnosis of SMI (schizophrenia, bipolar disorder or other forms of psychoses). Patients with T2DM but without SMI were classified as controls. Patients with diagnosis dates for either condition that matched their date of entry into a CPRD practice (1% of all patients) were excluded from the analysis as their diagnosis date was not deemed reliable, as this suggests the diagnosis was made prior to the patient joining the study practice.

Data were extracted for 1st April 2001 to 31st March 2013. Not all participants entered the study in 2001; for patients with both SMI and type II diabetes (T2DM), patients entered the study on the year of their diagnosis of the second condition, either SMI or T2DM, depending on the order in which the patient was diagnosed. The year of diagnosis of T2DM was the baseline year in patients without SMI.

All eligible patients (18+ years) upon entering the database were followed up until the end of the study (2013), unless they died or moved to a non-study practice.

Outcomes

Diabetes-related measurements included serum cholesterol levels, HbA_{1c} levels, and systolic and diastolic blood pressure (SBP and DBP respectively), which are predictive of future complications (Ray et al., 2009, Khaw et al., 2001, Collaborators, 2008, Group, 1998). National guidelines generally aim to control these parameters below recommended thresholds, but previous studies have suggested that very low levels of these parameters are not always associated with optimal outcomes. We therefore examined both mean levels of these parameters and values identified in previous studies as being associated with increased risk of mortality in patients with diabetes: HbA_{1c} <6.25% or >7.75% (<45 or >61mmol/mol), serum cholesterol <2.5mmol/l or >6.5mmol/l , SBP <115mmHg and DBP <72.5mmHg or >92.5mmHg (Lipska et al., 2013, Kontopantelis et al., 2015). Repeated measures were used for each year for each patient during the study period. When multiple values were available in the same year for the same patient, the mean of the patient's values were used.

Covariates

Data were extracted from patients' records for the following covariates: gender, age, body mass index (BMI) (Bhaskaran et al., 2013), smoking behaviour, comorbid long-term illnesses, prescription of diabetes medication, antipsychotic medication, antidepressant medication and cardiovascular medication were recorded if a prescription code was reported at any time within a given year. Area deprivation for patient postcode was measured in quintiles using Index of Multiple Deprivation (IMD) as a measurement of patients' socioeconomic status (Noble et al., 2006). Ethnic group was identified using Read codes in patients' records but because ethnicity is typically poorly reported in

primary care, for those with missing data in CPRD, we acquired the information using Hospital Episodes Statistics (HES) using a standardised approach (Mathur et al., 2014). Smoking status was taken from the patient's clinical record. If smoking status was missing in the corresponding year, the last recorded smoking status was used from the patient's historical record.

Several comorbid conditions were used to control for differences in underlying risk factors between those with and without SMI. The comorbid conditions included asthma, coronary heart disease (CHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), epilepsy, heart failure, hypertension, hyperthyroidism, osteoarthritis (OA), osteoporosis, or stroke. Read codes to identify all diagnoses of health conditions were taken from previously validated lists (Reilly et al., 2015). All Read code lists used in this study are available to download from www.clinicalcodes.org.

Statistical analysis

We calculated proportions or means and standard deviations (SD) for each outcome. Median and interquartile ranges (IQR) are reported for skewed data. Characteristics of adults with SMI and controls are presented as measured at baseline year. Between-group differences were assessed over the whole study period using χ^2 test for proportions. Student's paired t-test was used to compare mean values and Wilcoxon rank sum test was used for skewed data. Differences in prevalence of comorbidities were compared using a logistic regression whilst adjusting for age and gender.

We used a two-level linear mixed model for each continuous variable (cholesterol, HbA_{1c}, SBP or DBP), reporting beta (β) and its standard error (SE), and to examine high risk values we used two-level logistic mixed effects models for each outcome, reporting odds ratios (OR) and 95% confidence intervals (95% CI). Results of the regression models are reported over the whole study of all patients. We also describe changes over time in both groups over the course of each year of follow up. The linear and logistic mixed effects models were specified to the following nested structure: nested within different general practices (level 1) and individuals over time (level 2); hence, individual-level

and practice level random intercepts and individual random slopes were specified in the model. We fitted increasingly complex models: 1) bivariate model; 2) multivariate model which also adjusted for mean age (in years), gender, ethnicity, socioeconomic status (the most affluent quintile as the reference group), mean BMI, presence or absence of comorbidities, and smoking status as covariates; 3) as model 2 plus number of years of diabetes diagnosis and presence or absence of cardiovascular medication that interacts with cholesterol (statins and other lipid lowering agents) and blood pressure (ACE inhibitors, α blockers, β blockers, calcium channel blocker, thiazide diuretic, loop diuretics, other lipid lowering and statins). We did not explore the confounding effect of SMI patients taking antipsychotic medication or mood-stabilisers on outcomes because only a very small proportion of our control group had been prescribed antipsychotics or mood-stabilisers, compared to nearly half of those in the SMI group leading to co-linearity between antipsychotic medication or mood-stabilisers and diagnosis of SMI in our cohort.

Due to the nature of the CPRD data and the statistical models used, data were not considered missing for medication and comorbidities, as the absence of a Read code may identify the patients as not having a diagnosis of a condition or prescription of medication in the given year and could not be used to distinguished missing data. Missing data were only considered where records were missing for BMI, smoking, ethnicity, cholesterol, HbA_{1c}, SBP or DBP. There was no difference in the proportion of patients in each group with missing data (**supplement 1**). To account for missing data, we used multiple imputations using a chained command (MICE) and presented the imputed results as the main analysis (White et al., 2011). The MICE repeatedly sampled from the distribution of the four outcome variables: cholesterol, HbA_{1c}, SBP and DBP and all other covariates included in model 3 were entered to the imputation model. Sensitivity analysis was conducted for complete data in all analyses, the statistical significance of analyses was the same in both complete data and imputed data. All analyses were conducted using STATA v14.1. An α level of 5% was used.

Results

Missing data

There was no difference in the proportion of patients in each group with missing measurements of cholesterol (*df*=1, N=3353, X^2=1.0, *P*=0.3), HbA_{1c} (*df*=1, N=3353, X^2=0.6, *P*=0.4), SBP (*df*=1, N=3353, X^2=0.6, *P*=0.4) or DBP (*df*=1, N=3353, (X^2=1.7, *P*=0.2) for the study period (**supplement 1**). Data for ethnicity was missing for 16% of patients with SMI and 17% of controls (*df*=1, N=3353, X^2=0.3, *P*=0.6). For BMI and smoking status; 22% of SMI patients and 24% of controls had at least one missing value in any one year, again this was not different between groups (*df*=1, N=3353, X^2=0.6, *P*=0.4).

Patient characteristics at baseline year

There were 30,353 T2DM patients identified within the dataset, with 657 (2%) having a diagnosis of SMI. For patients with both conditions, most (73%) were diagnosed with SMI first. The characteristics of the cohort are displayed in **table 1**. Compared to controls, people with SMI and T2DM were on average younger, more likely to be female, to live in an area of high deprivation and to smoke, and less likely to be of white British ethnicity. Mean BMI was higher in people with SMI. Those with SMI were diagnosed with diabetes at a younger age (mean 54.7 years compared to 59.6 years for controls) but the number of years since diagnosis with diabetes was not significantly different.

Compared to controls, a higher proportion of people in the SMI group had prescriptions for diabetic medication and antidepressants, but a lower proportion had prescriptions for cardiovascular medication. There was no significant difference in the number of additional comorbidities between groups, but people with SMI and T2DM were more likely to have CKD, dementia, depression, epilepsy, hypothyroidism or stroke and less likely to have CHD, hypertension or osteoarthritis. There

were no significant differences between groups in the prevalence of asthma, cancer, COPD, heart failure, or osteoporosis.

Differences in cardiovascular risk factors

Over the whole follow-up period there were no significant differences between people with SMI and controls in mean level of cholesterol (β=-0.05; SE=0.05, *P*=0.19), HbA_{1c} (-0.08; 0.05, *P*=0.09) or DBP (-0.30; 0.25, *P*=0.21), but mean SBP was significantly lower in people with SMI (-2.50, 0.44 *P*≤0.001) (**table 2**). Over the whole study period and controlling for all covariates, people with SMI and T2DM were more likely to have higher risk for high or low HbA_{1c} (OR 1.38; 95% CI=1.18, 1.64) (**table 2**), a difference between groups observed in low and high HbA_{1c} values with 55% of people with SMI at risk (**table 3**). There were similar findings for SBP, with difference between groups observed in low SBP values (1.76; 1.40, 2.21), with 29% of people with SMI at risk (**table 3**). There was no statistically significant difference between group in cholesterol or DBP in specifications 1, 2 or 3 of the multilevel mixed effect binary logistic regression model. Full results of all three models including covariates are available in the appendix (**supplement 2**).

Changes over time in groups

Differences for some outcomes, however, changed over time. For cholesterol, mean levels fell in both groups over study period (**figure 1a**). For HBA_{1c}, mean levels in both groups increased over time from similar baselines, but levels in the control group increased at a faster rate; after 12 years mean levels were higher for controls compared to SMI patients, but this difference failed to reach statistical significance (**figure 1b**). For SBP, mean levels changed over time in both groups, but levels were similar in both groups after 12 years (**figure 1c**). For DBP, mean levels decreased over time in both groups, and were not significantly different at any time (**figure 1d**). The proportion of all

patients in both groups with levels of outcomes associated with a higher risk of adverse events decreased over time of follow-up for cholesterol and HbA_{1c} and increased for SBP and DBP (**figure 2**).

Discussion

Main findings

When examining differences between groups in the values of cardiovascular risk factors, we found that people with SMI had similar mean values of blood cholesterol, HbA_{1c} and DBP. After controlling for the confounding effect of difference in patient characteristics, socioeconomic level, medication and comorbidities, people with SMI had significantly lower values of SDP compared to controls. In relation to values of cardiovascular risk factors associated with increased risk of diabetes complications or mortality, people with SMI appear to be more likely to have at-risk values of HbA_{1c} due to high and low levels, and SBP due to low levels compared to controls. This suggests that, despite similar values in mean scores, a higher proportion of those with low values of cardiovascular risk factors in HbA_{1c} and SBP may contribute to the health inequalities in physical health outcomes observed for people with SMI and T2DM.

Study Strengths and limitations

We analysed a longitudinal dataset containing rich information on individual patients and their management within primary care, adjusting for important comorbidities and differences in characteristics of the groups of interest. In addition to exploring differences in mean values of cardiovascular risk factors, we also examined differences in proportions of patients with risk factor levels associated with increased risk of complications and mortality (Kontopantelis et al., 2015). Lower values below thresholds of cardiovascular risk factors appear to indicate similar risks for microvascular and macrovascular complications in T2DM patients as has been shown in cardiovascular factors used for this study, we selected thresholds that represented a significant

increased risk of earlier mortality compared to a reference value in a study of 246,544 T2DM patients (Kontopantelis et al., 2015). While we considered values of cardiovascular risk factors, it is possible that cardiovascular risk factor variability differs between our study groups, glycaemic variability, which has been associated with adverse outcome (Cardoso et al., 2018) possibly contributes to health inequality in people with SMI and T2DM could be an area of future research. This study is the first to explore if those with SMI and T2DM are at increased risk to adverse clinical outcomes due to a combination of low or high levels of HBA_{1c} and SBP, compared to only higher as previously reported.

The study has several limitations. First, the number of adults with comorbid SMI and diabetes was relatively small and fell during follow-up. Only 5.0% of the SMI cohort remained at 12 years of follow-up, compared to 8.9% in the control group. Attrition in this study is primarily due to patients entering into the study after 2001, leading to fewer follow up years in these patients. For example, a patient with a T2DM diagnosis in 2010 only had a maximum follow-up of 3 years to 2013 (i.e. the date of data cut). Other contributions to attrition were patients dropping out from the practice, due to mortality or leaving the practice. In addition, two practices included in our sample did not have data uploaded to CPRD for the final year of follow up. With a larger sample, we may have been able to identify statistically significant differences in markers of cardiovascular risk between the two groups, although we would have to consider whether any such differences were clinically meaningful. Similarly, our results with respect to the increased risk of extreme values of risk factors in patients with SMI may be affected by the relatively small sample. Second, our dataset depends on accurate and complete recording by primary care practices and missing data is a particular issue for some important covariates, for example ethnicity (Mathur et al., 2014), smoking behaviour, and body mass index (Bhaskaran et al., 2013). The proportion of missing data was not found to be different between groups. We used multiple imputation to infer robust variances and no differences were detected comparing findings drawn from imputed and non-imputed results. Third, although the sampled practices were nationally representative in terms of patient demographics, they might

not be nationally representative in terms of the quality of management of patients with T2DM and/or SMI, although we have no reason to believe that they were not. Fourth, we do not know whether the data we analysed were differentially recorded between our study groups, and it is possible that adjustment for differences in patient characteristics resulted in residual confounding. Fifth, we could only adjust for area-level deprivation which will not have accounted for individual differences in socio-economic status. Finally, in our main analysis, duration of follow-up for patients without SMI began at the time of diagnosis with diabetes, whereas a quarter of patients with SMI had pre-existing diabetes. However, we retained comorbid SMI patients who developed diabetes first to analyse all patients with both diagnoses and controlled for duration of illness in our regression models. Despite limitations relating to attrition and sample size of comorbid SMI patients in the study, the results of differences between groups appears to be robust; where there were no statistical differences between groups in the regression models, mean beta and OR suggest no differences of clinical importance.

What the study adds to the existing evidence

We estimate that approximately 55% of T2DM patients with comorbid SMI are at increased risk of microvascular and macrovascular complications due to high or low HbA_{1c} levels. This represents a higher risk compared to T2DM patients with no SMI. Our analysis of longitudinal data suggests this risk remains stable for SMI patients from onset of diagnosis. Approximately 29% of T2DM patients with comorbid SMI are also at increased risk due to levels of SBP associated with adverse outcomes, again a higher proportion of those at risk compared to T2DM patients with no SMI. To our knowledge, this is the first study to explore extreme (high and low) values related to cardiovascular risk, the presence of which may be obscured when mean values are examined.

Implications

Our study is the first to comparatively evaluate markers of cardiovascular risk factors in people with SMI using longitudinal data. Two previous studies, one a case-control study (matching patients with schizophrenia with controls on factors including BMI) and one a cross-sectional study, observed significantly lower HbA_{1c} levels in SMI groups compared to non SMI groups (Dixon et al., 2004, Wake et al., 2016). We observed no significant initial difference in mean HbA_{1c} between groups, but we included patients without schizophrenia and did not follow the same matching approach. We also found that over time, HbA_{1c} levels in patients with SMI increased at a slower rate than for patients without. The case-control study also compared serum cholesterol levels and blood pressure in patients with schizophrenia to controls. The findings were similar to our study; compared with controls, average blood pressure was lower in patients with schizophrenia but there were no differences for serum cholesterol.

People with SMI face a greater risk of developing several chronic physical diseases, including diabetes, and tend to have poorer outcomes for those conditions compared to the general population. Both SMI and diabetes are mainly managed in the community setting in the England, and primary care has a central role in coordination and continuity of care for patients with multiple conditions (Ricci-Cabello et al., 2015). It is therefore crucial that mental health nurses are aware that a higher proportion of their patients with T2DM and SMI are at risk of adverse outcomes due to their cardiovascular risk factors. Better management of all cardiovascular risk factors should be ensured, particularly controlling of extreme (high and low) values of HbA_{1c}, to address inequalities in physical health outcomes in patients with SMI and T2DM. We found that overall the management of cardiovascular risk factors was similar in diabetes patients with and without SMI, although those with SMI appear to be at increased risk of HbA_{1c} and SBP values associated with increased risk of adverse clinical outcomes. However, further investigation of the contributors to the physical health gap in patients with SMI and diabetes is needed.

Conclusions

Overall, our findings suggest that people with SMI are more likely to have HbA_{1c} and SBP values associated with poor cardiovascular outcomes in the context of diabetes. They are also more likely to live in deprived areas, to smoke, and to be obese. Conversely, they are less likely to have hypertension or coronary heart disease. After controlling for such risk factors, patients with SMI have similar average levels of cholesterol, HbA_{1c} and DBP but lower SBP. This suggests that patients with SMI and diabetes are managed to a similar standard to other patients with diabetes, and that other factors are maybe responsible for the gross inequalities in physical health outcomes observed for people with SMI. However, both HbA_{1c} and SBP in patients with SMI may be over-treated, which may increase the risk of adverse clinical outcomes. This warrants further investigation, including the contributing factors that increase risk of mortality, microvascular events, macrovascular events and diabetes-related hospital admissions in patients with comorbid SMI.

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Table 1 Characteristics of cohort at baseline year

Characteristics	SMI (n=657)	Control (n=29 696)	*P* value
Age years, mean (SD)	59.1 (14.1)	63.6 (13.4)	<0.001*
Females, n (%)	356 (54)	13267 (45)	<0.001**
Ethnicity, n (%)			
White	448 (68)	21299 (72)	<0.001**
Mixed	6 (1)	147 (1)	
South Asian	45 (7)	1846 (6)	
Black	42 (6)	1028 (4)	
Chinese/other	12 (2)	451 (2)	
unknown	104 (16)	4925 (17)	
IMD quintile, n (%)			
1 (most affluent)	88 (13)	5647 (19)	<0.001**
2	97 (15)	6151 (21)	
3	113 (17)	5732 (19)	
4	154 (23)	6062 (20)	
5 (most deprived)	195 (30)	5930 (20)	
Missing	10 (2)	274 (1)	
Mean BMI (kg.m^2), mean (SD)	31.6 (6.8)	30.7 (6.6)	<0.001*
Missing n (%)	10 (1.5)	411 (1.4)	
Smoking status, n (%)			
Current smoker	252 (38)	5442 (18)	<0.001**
Never smoked	227 (35)	11798 (40)	
Ex-smoker	139 (21)	10634 (36)	
missing	39 (6)	1822 (6)	
Age at diabetes diagnosis, mean years(SD)	54.3 (14.5)	56.9 (16.9)	<0.001*
Years since diabetes diagnosis, median (IQR)	1 (1-6)	1(1-5)	Z=0.001***
SMI type, n (%)			
Schizophrenia	295 (45)		
Bipolar disorder	194 (30)		
Other psychosis	115 (18)		
More than one type	53 (8)		
Age at SMI diagnosis, mean years(SD)	45.9 (16.6)		
years since onset of SMI diagnosis, median years (IQR)	10 (2-20)		
Diabetes medication, n (%)			
None	168 (26)	9074 (31)	0.001**
Insulin only	38 (7)	1509 (5)	
Oral medication only	4.03 (61)	16983 (57)	
Both	48 (7)	2130 (7)	
Cardiovascular medication, n (%)			
None	129 (20)	4348 (15)	<0.001**
ACE inhibitors	265 (40)	15988 (54)	
α blockers	29 (4)	2307 (8)	
Anticoagulant	21 (3)	1424 (5)	
Antiplatelet	218 (23)	11807 (40)	

β blockers	96 (15)	6644 (22)	
Calcium channel blocker	116 (18)	8577 (29)	
Thiazide diuretic	69 (11)	5765 (19)	
Loop diuretics	80 (12)	4091 (14)	
Other lipid lowering	38 (6)	1458 (5)	
Statins	399 (61)	18131 (61)	
Antipsychotic medication, n (%)			
None	276 (42)	28994 (98)	<0.001**
Typical	107 (16)	153 (2)	
Atypical	254 (39)	253 (1)	
Depot	42 (7)	1 (0)	
Other	19 (3)	333 (1)	
Lithium or other mood stabilizer medication, n (%)	170(26)	421 (1)	<0.001**
Antidepressant medication, n (%)			
None	342 (52)	24727 (83)	<0.001**
Tricyclic antidepressants	93 (14)	2420 (8)	
Selective serotonin reuptake inhibitors	178 (27)	2498 (8)	
Other antidepressant	96 (15)	645 (2)	
Additional comorbidities count, median (IQR)	1 (0-2)	1 (0-2)	Z=0.08***
Comorbidities, n (%)			
Asthma	81 (12.)	3578 (12)	0.56 ****
Cancer	37 (6)	2255 (8)	0.55 ****
Coronary heart disease	73 (11)	5317 (18)	0.02 ****
Chronic kidney disease	45 (7)	1640 (6)	0.01 ****
Chronic obstructive pulmonary disease	25 (4)	1252 (4)	0.67 ****
Dementia	25 (4)	374 (1)	0.01 ****
Depression	48 (7)	820 (3)	0.01 ****
Epilepsy	37 (6)	404 (1)	0.01 ****
Heart failure	24 (4)	1394 (5)	0.96 ****
Hypertension	250 (38)	15925 (54)	<0.001 ****
Hypothyroidism	94 (14)	2190 (7)	<0.001 ****
Osteoarthritis	89 (14)	5676 (19)	0.02 ****
Osteoporosis	18 (3)	622 (2)	0.19 ****
Stroke	54 (8)	1965 (7)	<0.001 ****

SMI severe mental illness, BMI body mass index, SD standard deviation, IQR inter quartile range, IMD index of multiple deprivation, * t-test, ** χ^2 test, *** Wilcoxon rank sum test, **** logistic regression adjusting for age and gender. Data for medication categories are not mutually exclusive as patients could be prescribed more than one. Comparisons of medication between groups were made in those with no reported medication compared to those with at least one medication.

Table 2 Beta coefficients and odds ratios for patients with SMI compared to controls from univariate and multivariate multilevel mixed effect regression models for cardiovascular risk factors

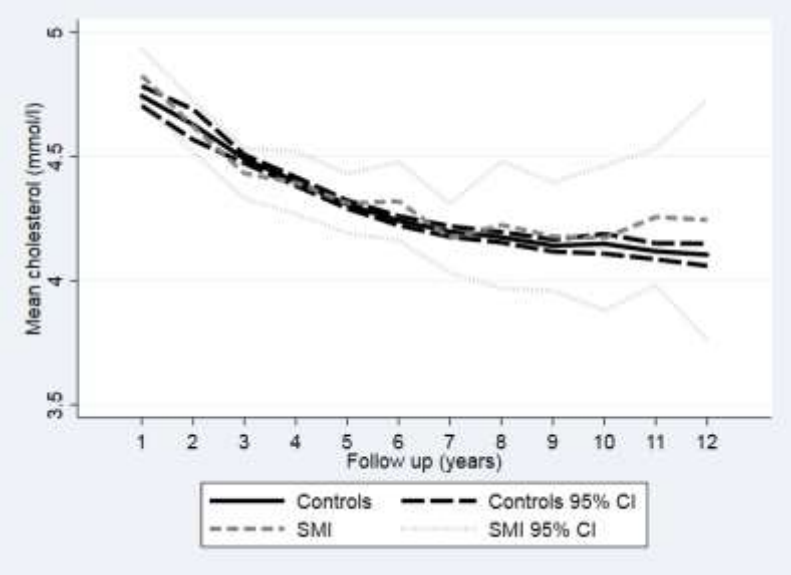
Regression Model	Cholesterol	HbA_{1c}	Systolic Blood Pressure	Diastolic blood Pressure
Multilevel mixed effect linear regression model, Beta (SE, *P*)				
Model 1	0.05 (0.05, 0.31)	0.04 (0.05, 0.41)	**-4.32 (0.49, <0.001)**	0.10 (0.29, 0.74)
Model 2	-0.08 (0.05, 0.13)	-0.05 (0.05, 0.32)	**-3.06 (0.46, <0.001)**	**-0.51 (0.25, 0.04)**
Model 3	-0.07 (0.05, 0.19)	-0.08 (0.05, 0.09)	**-2.49 (0.45, <0.001)**	-0.30 (0.25, 0.22)
Multilevel mixed effect binary logistic regression model, OR (95% CI)				
Model 1	1.28 (0.91-1.78)	**1.60 (1.34-1.90)**	**2.60 (2.01-3.34)**	0.95 (0.82-1.12)
Model 2	0.93 (0.67-1.31)	**1.40 (1.18-1.66)**	**1.83 (1.45-2.32)**	1.02 (0.88-1.19)
Model 3	0.94 (0.68-1.33)	**1.38 (1.16-1.64)**	**1.76 (1.40-2.21)**	1.02 (0.87-1.18)

Table 3 Percentage of patient-years with 'high risk' levels of outcomes over all patient-years

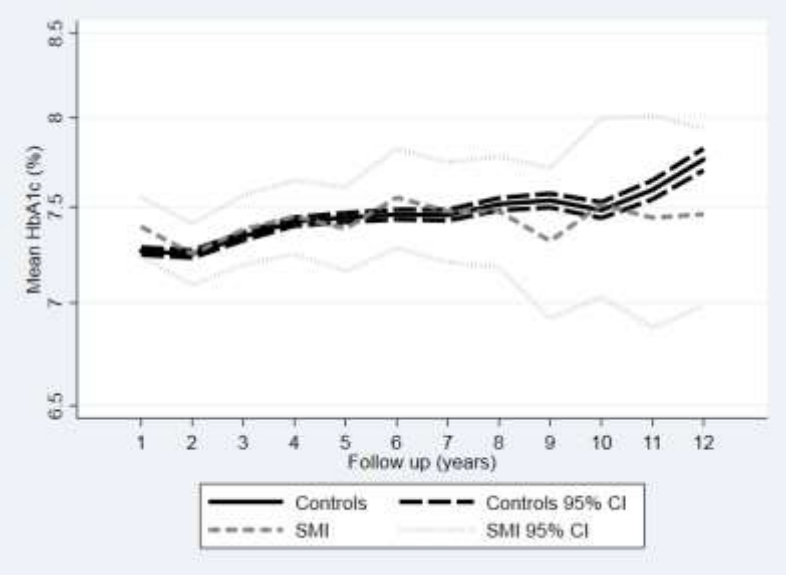
	SMI	Controls
Cholesterol, % (95% CI)		
Below 2.5mmol/l	0 (0, 1)	1 (1, 1)
Above 6.5mmol/l	4 (3, 5.)	3 (3, 3)
HbA_{1c}, % (95% CI)		
Below 6.25% (<45 mmol/mol)	27 (25, 28)	19 (19, 20)
Above 7.75% (61mmol/mol)	32 (30, 34)	31 (30, 31)
Systolic, % (95% CI)		
Below 115mmHg	29 (26, 29)	18 (17, 18)
Diastolic, % (95% CI)		
Below 72.5mmHg	28 (26, 30)	30 (30, 30)
Above 92.5mmHg	4 (3, 4)	4 (3, 4)

Figure 1 Mean levels of outcomes in diabetes patients with comorbid SMI and in non-SMI controls by year of follow-up

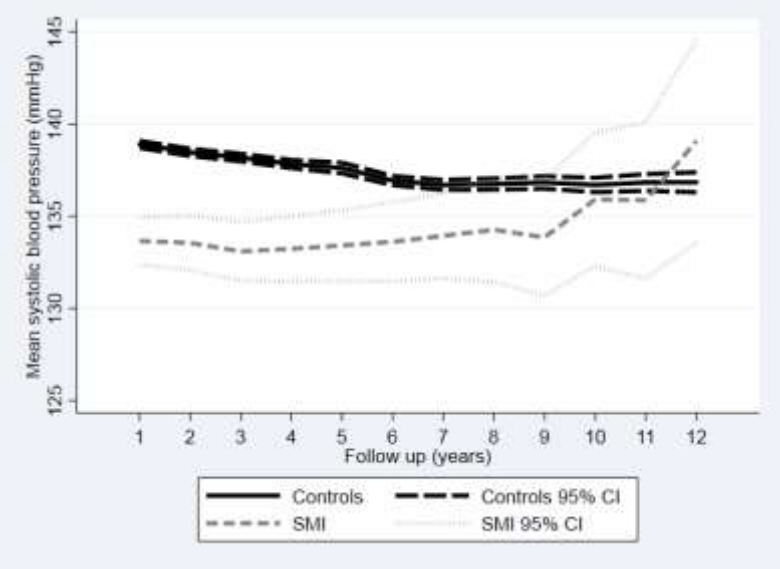
(a) Cholesterol



(b) HbA_{1c}


Mean HbA1c (%)
6.5
7
7.5
8
8.5
1
2
3
4
5
6
7
8
9
10
11
12
Follow up (years)
Controls
Controls 95% CI
SMI
SMI 95% CI

(c) Systolic blood pressure



(d) Diastolic blood pressure

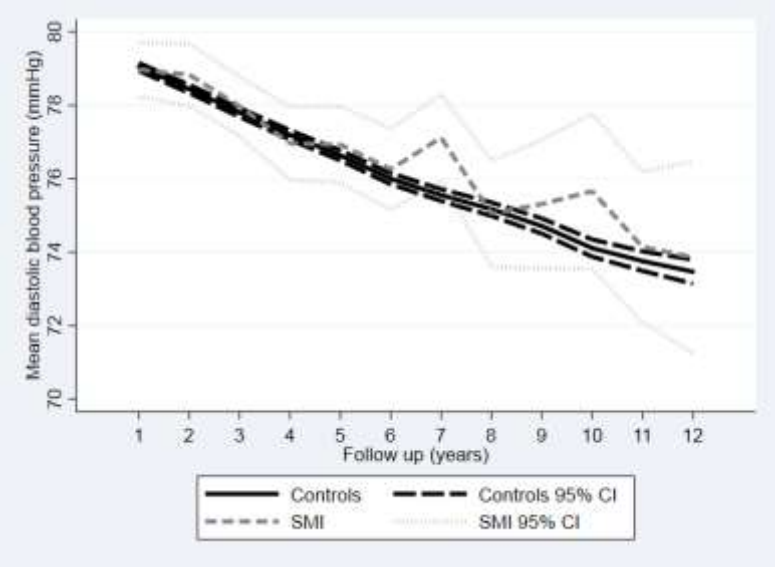
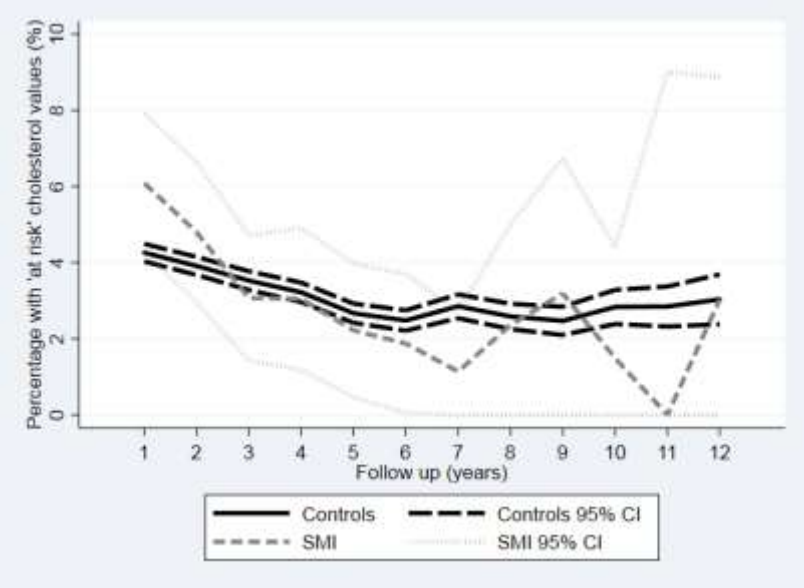
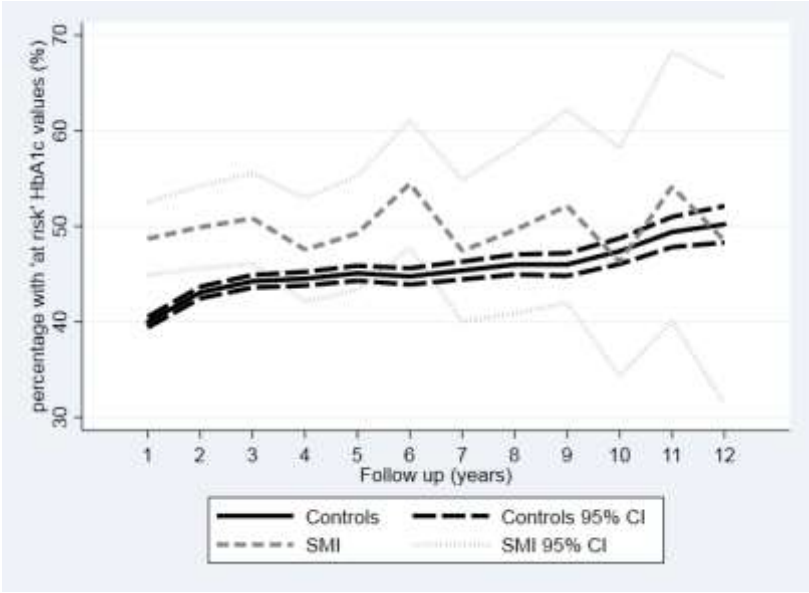


Figure 2 Percentage of diabetes patients with 'high risk' levels of outcomes by year of follow-up

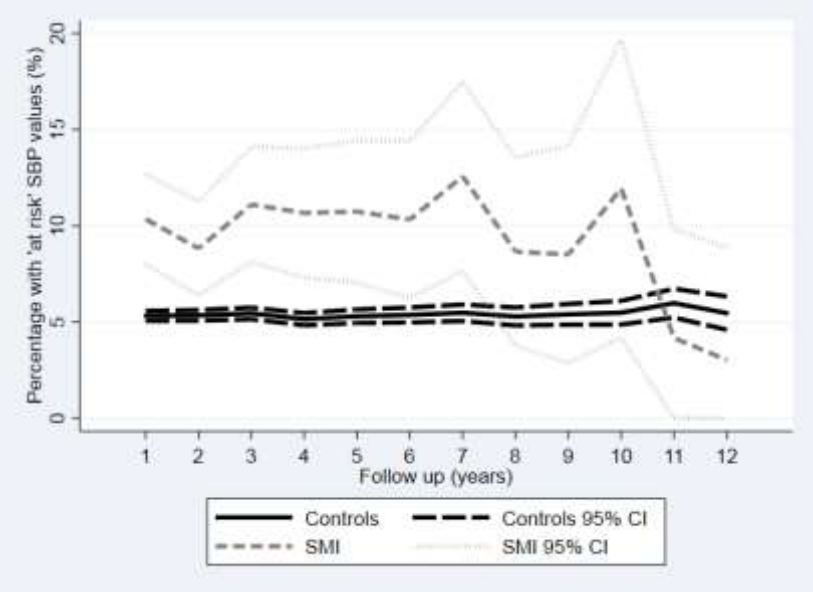
(a) Cholesterol <2.5mmol/l or >6.5mmol/l



(b) HbA_{1c} <6.25% or >7.75% (<45 or >61mmol/mol



(c) Systolic blood pressure <115mmHg



(d) Diastolic blood pressure <72.5mmHg or >92.5mmHg