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

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Manuscripts

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3 **1 Title**

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6 2 Glucose, cholesterol and blood pressure in type II diabetes: a longitudinal observational study
7
8 3 comparing patients with and without severe mental illness
9

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11 **4 Accessible Summary**

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14 5 *What is known on the subject?*

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17 6
- 18 • People with severe mental illness (SMI) have a life expectancy 15-20 years less than the
19 general population, partly due to increased risk of physical disease, including type II diabetes
20 (T2DM) and cardiovascular disease.
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 - 22 8
 - 23 • Little is known about changes in cardiovascular risk factors over time in people with both
24 T2DM and SMI compared to those with T2DM and no SMI.
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30 11 *What this paper adds to existing knowledge?*

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33 12
- 34 • We investigated whether levels of cardiovascular risk factors, cholesterol, HbA_{1c}, systolic and
35 diastolic blood pressure associated with adverse clinical outcomes are different in T2DM
36 patients with and without SMI. We found significant differences in systolic blood pressure
37 and HbA_{1c} between the two groups.
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39 15
 - 40 • 55% and 29% of T2DM patients with comorbid SMI are at increased risk of adverse clinical
41 outcomes due to sub-optimal HbA_{1c} and systolic blood pressure levels respectively.
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47 18 *What are the implications for practice?*

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50 19
- 51 • Many patients with T2DM and SMI have higher levels of cardiovascular risk compared to
52 patients with T2DM only, and good management of risk factors is therefore particularly
53 important in patients with both conditions.
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55 21
 - 56 • Achieving better control of HbA_{1c} levels is likely to be central to addressing inequalities in
57 outcomes for patients with both SMI and T2DM.
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- 60

1
2
3 24 **Abstract**
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5

6 25 *Introduction:* Patients with both severe mental illness (SMI) and type II diabetes (T2DM) have lower
7
8 26 life expectancy than patients with T2DM alone, partly due to poor control of cardiovascular risk
9
10 27 factors in comorbid patients.
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13
14 28 *Aim:* To compare levels of cholesterol, HbA_{1c} and blood pressure in T2DM patients with and without
15
16 29 SMI.
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19 30 *Method:* We analysed longitudinal clinical records of 30,353 people with T2DM (657 with SMI;29,696
20
21 31 controls without SMI) between 2001 and 2013 using the Clinical Practice Research Datalink (CPRD).
22
23 32 We used mixed effects regression models to compare cardiovascular risk factors between SMI and
24
25 33 controls.
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28
29 34 *Results:* Patients with SMI had lower mean systolic blood pressure (SBP) (β -2.49; SE=0.45 P=<0.01)
30
31 35 and were more likely to have extreme (high and low) values of HbA_{1c} and SBP (OR 1.38, 95%CI:
32
33 36 1.16,1.64 and 1.76:1.40,2.21 respectively).
34
35

36 37 *Discussion:* People with T2DM and SMI have similar average values of cardiovascular risk factors to
37
38 38 people with T2DM alone but are more likely to have values of HbA_{1c} and SBP indicating increased risk
39
40 39 of adverse clinical outcomes.
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43 40 *Implications for Practice:* Improved management of cardiovascular risk factors in general, glycaemic
44
45 41 control in particular, is central to addressing the increased risk of adverse outcomes in people with
46
47 42 both SMI and T2DM.
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51 43 **Keywords:** Epidemiology, Physical Health, Primary Care
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46 **Relevance statement**

47 People with comorbid T2DM and SMI are more likely to have extreme values of HbA_{1c} and systolic
48 blood pressure that are associated with adverse clinical outcomes. **Better management of these risk**
49 **factors should be ensured to address inequalities in physical health outcomes in patients with SMI**
50 **and T2DM.**

For Peer Review

52 Introduction

53 People with severe mental illness (SMI) including schizophrenia, bipolar disorder and other forms of
54 psychosis have a life expectancy 15-20 years less than the general population (Brown et al., 2010).
55 Reduction of excess mortality in those with mental disorders has been identified as an important
56 global health issue, identifying risk factors for earlier mortality can lead to development of effective
57 interventions to address physical health inequality among those with mental disorder (Liu et al.,
58 2017). Most of the premature deaths are caused by complications of physical health conditions
59 (Reilly et al., 2015, De Hert et al., 2009). These include insulin resistance and relative insulin
60 deficiency forms of diabetes mellitus, type II diabetes mellitus (T2DM), the prevalence of which is
61 twice as great in those with SMI than in the general population (Reilly et al., 2015). This increased
62 prevalence of T2DM is attributed due to a variety of factors including genetic predisposition (De Hert
63 et al., 2009), the metabolic effects of atypical antipsychotics (Smith et al., 2008), higher levels of
64 obesity and poor diet (Osborn et al., 2007), lower levels of physical activity (Daumit et al., 2005) and
65 the greater barriers that disadvantaged or marginalised groups face in navigating the healthcare
66 system (Dixon-Woods et al., 2006). People with the co-occurrence of T2DM and SMI (comorbid
67 T2DM and SMI) have around a 50% increased risk of mortality compared with people with T2DM
68 alone (Kontopantelis et al., 2015, Wu et al., 2015, Vinogradova et al., 2010), but the underlying
69 mechanism for this difference is not well understood. Candidate causes include higher levels of
70 smoking (McDonald, 2000), poor management of cardiovascular risk factors (including glycaemia,
71 cholesterol and blood pressure), and higher prevalence of other comorbid conditions (Vinogradova
72 et al., 2010). Patients with comorbid SMI and T2DM are less likely to receive standard levels of
73 diabetes care, with 45% not receiving any diabetes care and the least chance of receiving specialised
74 interventions for cardiovascular treatments (De Hert et al., 2011). Controlling HbA_{1c} and optimising
75 lipid and blood pressure management reduces the risks of microvascular and macrovascular
76 complications, which remain the main cause of morbidity and mortality in patients with T2DM (Ray
77 et al., 2009, Khaw et al., 2001, Collaborators, 2008, Group, 1998). However, the evidence for

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3 78 appropriate management of cardiovascular risk factors in patients with diabetes and SMI is
4
5 79 inconclusive, particularly in the UK (Dixon et al., 2004, Wake et al., 2016). A small study in the United
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7 80 States showed that patients with SMI had lower levels of HbA_{1c} compared to patients without SMI
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9
10 81 (Dixon et al., 2004), and a recent larger study suggested that people with T2DM taking antipsychotic
11
12 82 medication have lower cholesterol, HbA_{1c} and blood pressure levels compared to matched controls
13
14 83 not taking antipsychotic medication (Wake et al., 2016). **There is, however, little evidence at a**
15
16 84 **population level on the changes in cardiovascular risk factors over time in those with SMI that**
17
18 85 **develop T2DM compared to those with T2DM and no SMI. Using population level data of clinical**
19
20 86 **records from primary care, we can assess variation in cardiovascular risk factors that may be a**
21
22 87 **contributing factor to the excess mortality for people with SMI and T2DM at a population level.**
23
24 88 **Identification of the candidate causes of the mortality gap can then be targeted through evidence-**
25
26 89 **based interventions** (Lawrence and Kisely, 2010).
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31 90 The aim of this study was to investigate whether there is a difference in cardiovascular risk factors in
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33 91 adults with diabetes and SMI compared with adults with diabetes without SMI, and whether these
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35 92 risk factors change over time.
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41 94 **Materials and Methods**

42 43 44 95 *Data Source*

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46
47 96 We used data from Clinical Practice Research Datalink (CPRD) which contains primary care records
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49 97 for around 6.9% of the UK's patients (Herrett et al., 2015). Clinical care processes, diagnoses,
50
51 98 measurements and test results are recorded using a hierarchical set of clinical codes (Read codes).
52
53 99 Prescriptions for medicine are recorded using British National Formulary (BNF) codes. The sample
54
55 100 used in this study was taken from 125 out of 674 practices in CPRD (19%), all practice included in the
56
57 101 sample were based in England. Practices were selected to be proportionally representative of the
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3 102 proportional distribution of all the 674 practices in CPRD in terms of level of socioeconomic
4
5 103 deprivation (using practice postcode linked to Index of Multiple Deprivation) and practice size in
6
7 104 terms of number of registered patients. All patients' records at participating practices were added to
8
9
10 105 the CPRD database, the criteria for inclusion in our sample were patients with at least one of the
11
12 106 following long-term conditions documented using Read codes in their primary care record: asthma,
13
14 107 atrial fibrillation, coronary heart disease (CHD), chronic kidney disease (CKD), chronic obstructive
15
16 108 pulmonary disease (COPD), diabetes, epilepsy, heart failure, hypertension, hyperthyroidism, learning
17
18
19 109 disability, osteoporosis, SMI or stroke. For the purpose of this study, we selected all patients in the
20
21 110 sample who had diabetes, with or without other long-term conditions.
22
23

24 111 *Cohort*

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26
27 112 Patient records were included in the study if they had a Read code indicating a diagnosis of T2DM.
28
29 113 Patients with diabetes diagnosis Read codes that did not distinguish diabetes type were excluded.
30
31 114 Patients with SMI were identified using Read codes indicating a diagnosis of SMI (schizophrenia,
32
33 115 bipolar disorder or other forms of psychoses). Patients with T2DM but without SMI were classified as
34
35
36 116 controls. Patients with diagnosis dates for either condition that matched their date of entry into a
37
38 117 CPRD practice (1% of all patients) were excluded from the analysis as their diagnosis date was not
39
40 118 deemed reliable, as this suggests the diagnosis was made prior to the patient joining the study
41
42
43 119 practice.
44
45

46 120 Data were extracted for 1st April 2001 to 31st March 2013. Not all participants entered the study in
47
48 121 2001; for patients with both SMI and type II diabetes (T2DM), patients entered the study on the year
49
50 122 of their diagnosis of the second condition, either SMI or T2DM, depending on the order in which the
51
52 123 patient was diagnosed. The year of diagnosis of T2DM was the baseline year in patients without SMI.
53
54
55 124 All eligible patients (18+ years) upon entering the database were followed up until the end of the
56
57 125 study (2013), unless they died or moved to a non-study practice.
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3 127 *Outcomes*
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6 128 Diabetes-related measurements included serum cholesterol levels, HbA_{1c} levels, and systolic and
7
8 129 diastolic blood pressure (SBP and DBP respectively), which are predictive of future complications (Ray
9
10 130 et al., 2009, Khaw et al., 2001, Collaborators, 2008, Group, 1998). National guidelines generally aim
11
12 131 to control these parameters below recommended thresholds, but previous studies have suggested
13
14 132 that very low levels of these parameters are not always associated with optimal outcomes. We
15
16 133 therefore examined both mean levels of these parameters and values identified in previous studies
17
18 134 as being associated with increased risk of mortality in patients with diabetes: HbA_{1c} <6.25% or
19
20 135 >7.75% (<45 or >61mmol/mol), serum cholesterol <2.5mmol/l or >6.5mmol/l , SBP <115mmHg and
21
22 136 DBP <72.5mmHg or >92.5mmHg (Lipska et al., 2013, Kontopantelis et al., 2015). Repeated measures
23
24 137 were used for each year for each patient during the study period. When multiple values were
25
26 138 available in the same year for the same patient, the mean of the patient's values were used.
27
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29
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31 139 *Covariates*
32
33

34 140 Data were extracted from patients' records for the following covariates: gender, age, body mass
35
36 141 index (BMI) (Bhaskaran et al., 2013), smoking behaviour, comorbid long-term illnesses, prescription
37
38 142 of diabetes medication, antipsychotic medication, antidepressant medication and cardiovascular
39
40 143 medication were recorded if a prescription code was reported at any time within a given year. Area
41
42 144 deprivation for patient postcode was measured in quintiles using Index of Multiple Deprivation (IMD)
43
44 145 as a measurement of patients' socioeconomic status (Noble et al., 2006). Ethnic group was identified
45
46 146 using Read codes in patients' records but because ethnicity is typically poorly reported in primary
47
48 147 care, for those with missing data in CPRD, we acquired the information using Hospital Episodes
49
50 148 Statistics (HES) using a standardised approach (Mathur et al., 2014). Smoking status was taken from
51
52 149 the patient's clinical record. If smoking status was missing in the corresponding year, the last
53
54 150 recorded smoking status was used from the patient's historical record.
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3 151 Several comorbid conditions were used to control for differences in underlying risk factors between
4
5 152 those with and without SMI. The comorbid conditions included asthma, coronary heart disease
6
7 153 (CHD), chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), epilepsy, heart
8
9 154 failure, hypertension, hyperthyroidism, osteoarthritis (OA), osteoporosis, or stroke. Read codes to
10
11 155 identify all diagnoses of health conditions were taken from previously validated lists (Reilly et al.,
12
13 156 2015). All Read code lists used in this study are available to download from www.clinicalcodes.org.

17 157 *Statistical analysis*

20 158 We calculated proportions or means and standard deviations (SD) for each outcome. Median and
21
22 159 interquartile ranges (IQR) are reported for skewed data. Characteristics of adults with SMI and
23
24 160 controls are presented as measured at baseline year. Between-group differences were assessed over
25
26 161 the whole study period using χ^2 test for proportions. Student's paired t-test was used to compare
27
28 162 mean values and Wilcoxon rank sum test was used for skewed data. Differences in prevalence of
29
30 163 comorbidities were compared using a logistic regression whilst adjusting for age and gender.

33
34 164 We used a two-level linear mixed model for each continuous variable (cholesterol, HbA_{1c}, SBP or
35
36 165 DBP), reporting beta (β) and its standard error (SE), and to examine high risk values we used two-
37
38 166 level logistic mixed effects models for each outcome, reporting odds ratios (OR) and 95% confidence
39
40 167 intervals (95% CI). Results of the regression models are reported over the whole study of all patients.

43 168 We also describe changes over time in both groups over the course of each year of follow up. The
44
45 169 linear and logistic mixed effects models were specified to the following nested structure: nested
46
47 170 within different general **practices** (level 1) and individuals over time (level 2); hence, individual-level
48
49 171 and practice level random intercepts and individual random slopes were specified in the model. We
50
51 172 fitted increasingly complex models: 1) bivariate model; 2) multivariate model which also adjusted for
52
53 173 mean age (in years), gender, ethnicity, socioeconomic status (**the most affluent quintile as the**
54
55 174 **reference group**), mean BMI, presence or absence of comorbidities, and smoking status as
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57 175 covariates; 3) as model 2 plus number of years of diabetes diagnosis and presence or absence of
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3 176 cardiovascular medication that interacts with cholesterol (statins and other lipid lowering agents)
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5 177 and blood pressure (ACE inhibitors, α blockers, β blockers, calcium channel blocker, thiazide diuretic,
6
7 178 loop diuretics, other lipid lowering and statins). We did not explore the confounding effect of SMI
8
9 179 patients taking antipsychotic medication or mood-stabilisers on outcomes because only a very small
10
11 180 proportion of our control group had been prescribed antipsychotics or mood-stabilisers, compared to
12
13 181 nearly half of those in the SMI group leading to co-linearity between antipsychotic medication or
14
15 182 mood-stabilisers and diagnosis of SMI in our cohort.

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19 183 Due to the nature of the CPRD data and the statistical models used, data were not considered
20
21 184 missing for medication and comorbidities, as the absence of a Read code may identify the patients as
22
23 185 not having a diagnosis of a condition or prescription of medication in the given year and could not be
24
25 186 used to distinguished missing data. Missing data were only considered where records were missing
26
27 187 for BMI, smoking, ethnicity, cholesterol, HbA_{1c}, SBP or DBP. There was no difference in the
28
29 188 proportion of patients in each group with missing data (**supplement 1**). To account for missing data,
30
31 189 we used multiple imputations using a chained command (MICE) and presented the imputed results
32
33 190 as the main analysis (White et al., 2011). The MICE repeatedly sampled from the distribution of the
34
35 191 four outcome variables: cholesterol, HbA_{1c}, SBP and DBP and **all other covariates included in model 3**
36
37 192 **were** entered to the imputation model. Sensitivity analysis was conducted for complete data in all
38
39 193 analyses, the statistical significance of analyses was the same in both complete data and imputed
40
41 194 data. All analyses were conducted using STATA v14.1. An α level of 5% was used.

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48 49 50 196 **Results**

51 52 53 197 *Missing data*

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56 198 There was no difference in the proportion of patients in each group with missing measurements of
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58 199 cholesterol ($df=1$, $N=3353$, $\chi^2=1.0$, $P=0.3$), HbA_{1c} ($df=1$, $N=3353$, $\chi^2=0.6$, $P=0.4$), SBP ($df=1$, $N=3353$,

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3 200 $\chi^2=0.6, P=0.4$) or DBP ($df=1, N=3353, \chi^2=1.7, P=0.2$) for the study period (**supplement 1**). Data for
4
5 201 ethnicity was missing for 16% of patients with SMI and 17% of controls ($df=1, N=3353, \chi^2=0.3, P=0.6$).
6
7 202 For BMI and smoking status; 22% of SMI patients and 24% of controls had at least one missing value
8
9 203 in any one year, again this was not different between groups ($df=1, N=3353, \chi^2=0.6, P=0.4$).
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13 204 *****Insert table 1*****
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19 206 *Patient characteristics at baseline year*
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22 207 There were 30,353 T2DM patients identified within the dataset, with 657 (2%) having a diagnosis of
23
24 208 SMI. For patients with both conditions, most (73%) were diagnosed with SMI first. The characteristics
25
26 209 of the cohort are displayed in **table 1**. Compared to controls, people with SMI and T2DM were on
27
28 210 average younger, more likely to be female, to live in an area of high deprivation and to smoke, and
29
30 211 less likely to be of white British ethnicity. Mean BMI was higher in people with SMI. Those with SMI
31
32 212 were diagnosed with diabetes at a younger age (mean 54.7 years compared to 59.6 years for
33
34 213 controls) but the number of years since diagnosis with diabetes was not significantly different.
35
36
37
38 214 Compared to controls, a higher proportion of people in the SMI group had prescriptions for diabetic
39
40 215 medication and antidepressants, but a lower proportion had prescriptions for cardiovascular
41
42 216 medication. There was no significant difference in the number of additional comorbidities between
43
44 217 groups, but people with SMI and T2DM were more likely to have CKD, dementia, depression,
45
46 218 epilepsy, hypothyroidism or stroke and less likely to have CHD, hypertension or osteoarthritis. There
47
48 219 were no significant differences between groups in the prevalence of asthma, cancer, COPD, heart
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50 220 failure, or osteoporosis.
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55 221 *****Insert table 2*****
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57

58 222 *****Insert table 3*****
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223

224 *Differences in cardiovascular risk factors*

225 Over the whole follow-up period there were no significant differences between people with SMI and
226 controls in mean level of cholesterol ($\beta=-0.05$; $SE=0.05$, $P=0.19$), HbA_{1c} (-0.08 ; 0.05 , $P=0.09$) or DBP ($-$
227 0.30 ; 0.25 , $P=0.21$), but mean SBP was significantly lower in people with SMI (-2.50 , 0.44 $P\leq 0.001$)
228 (**table 2**). Over the whole study period and controlling for all covariates, people with SMI and T2DM
229 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
230 difference between groups observed in low and high HbA_{1c} values with 55% of people with SMI at
231 risk (**table 3**). There were similar findings for SBP, with difference between groups observed in low
232 SBP values (1.76; 1.40, 2.21), with 29% of people with SMI at risk (**table 3**). There was no statistically
233 significant difference between group in cholesterol or DBP in specifications 1, 2 or 3 of the multilevel
234 mixed effect binary logistic regression model. Full results of all three models including covariates are
235 available in the appendix (**supplement 2**).

236 ***Insert figure 1***

237 ***Insert figure 2***

238 *Changes over time in groups*

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

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

248

249 **Discussion**

250 *Main findings*

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

261 *Study Strengths and limitations*

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

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3 270 increased risk of earlier mortality compared to a reference value in a study of 246,544 T2DM patients
4
5 271 (Kontopantelis et al., 2015). While we considered values of cardiovascular risk factors, it is possible
6
7 272 that cardiovascular risk factor variability differs between our study groups, glycaemic variability,
8
9 273 which has been associated with adverse outcome (Cardoso et al., 2018) possibly contributes to
10
11 274 health inequality in people with SMI and T2DM could be an area of future research. This study is the
12
13 275 first to explore if those with SMI and T2DM are at increased risk to adverse clinical outcomes due to a
14
15 276 combination of low or high levels of HBA_{1c} and SBP, compared to only higher as previously reported.
16
17
18
19 277 The study has several limitations. First, the number of adults with comorbid SMI and diabetes was
20
21 278 relatively small and fell during follow-up. Only 5.0% of the SMI cohort remained at 12 years of follow-
22
23 279 up, compared to 8.9% in the control group. Attrition in this study is primarily due to patients entering
24
25 280 into the study after 2001, leading to fewer follow up years in these patients. For example, a patient
26
27 281 with a T2DM diagnosis in 2010 only had a maximum follow-up of 3 years to 2013 (i.e. the date of
28
29 282 data cut). Other contributions to attrition were patients dropping out from the practice, due to
30
31 283 mortality or leaving the practice. In addition, two practices included in our sample did not have data
32
33 284 uploaded to CPRD for the final year of follow up. With a larger sample, we may have been able to
34
35 285 identify statistically significant differences in markers of cardiovascular risk between the two groups,
36
37 286 although we would have to consider whether any such differences were clinically meaningful.
38
39
40 287 Similarly, our results with respect to the increased risk of extreme values of risk factors in patients
41
42 288 with SMI may be affected by the relatively small sample. Second, our dataset depends on accurate
43
44 289 and complete recording by primary care practices and missing data is a particular issue for some
45
46 290 important covariates, for example ethnicity (Mathur et al., 2014), smoking behaviour, and body mass
47
48 291 index (Bhaskaran et al., 2013). The proportion of missing data was not found to be different between
49
50 292 groups. We used multiple imputation to infer robust variances and no differences were detected
51
52 293 comparing findings drawn from imputed and non-imputed results. Third, although the sampled
53
54 294 practices were nationally representative in terms of patient demographics, they might not be
55
56 295 nationally representative in terms of the quality of management of patients with T2DM and/or SMI,
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3 296 although we have no reason to believe that they were not. Fourth, we do not know whether the data
4
5 297 we analysed were differentially recorded between our study groups, and it is possible that
6
7 298 adjustment for differences in patient characteristics resulted in residual confounding. Fifth, we could
8
9 299 only adjust for area-level deprivation which will not have accounted for individual differences in
10
11 300 socio-economic status. Finally, in our main analysis, duration of follow-up for patients without SMI
12
13 301 began at the time of diagnosis with diabetes, whereas a quarter of patients with SMI had pre-existing
14
15 302 diabetes. However, we retained comorbid SMI patients who developed diabetes first to analyse all
16
17 303 patients with both diagnoses and controlled for duration of illness in our regression models. Despite
18
19 304 limitations relating to attrition and sample size of comorbid SMI patients in the study, the results of
20
21 305 differences between groups appears to be robust; where there were no statistical differences
22
23 306 between groups in the regression models, mean beta and OR suggest no differences of clinical
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25 307 importance.
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309 *What the study adds to the existing evidence*

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

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319 *Implications*

320 Our study is the first to comparatively evaluate markers of cardiovascular risk factors in people with
321 SMI using longitudinal data. Two previous studies, one a case-control study (matching patients with
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3 322 schizophrenia with controls on factors including BMI) and one a cross-sectional study, observed
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5 323 significantly lower HbA_{1c} levels in SMI groups compared to non SMI groups (Dixon et al., 2004, Wake
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7 324 et al., 2016). We observed no significant initial difference in mean HbA_{1c} between groups, but we
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9 325 included patients without schizophrenia and did not follow the same matching approach. We also
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11 326 found that over time, HbA_{1c} levels in patients with SMI increased at a slower rate than for patients
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13 327 without. The case-control study also compared serum cholesterol levels and blood pressure in
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15 328 patients with schizophrenia to controls. The findings were similar to our study; compared with
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17 329 controls, average blood pressure was lower in patients with schizophrenia but there were no
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19 330 differences for serum cholesterol.
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24 331 People with SMI face a greater risk of developing several chronic physical diseases, including
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26 332 diabetes, and tend to have poorer outcomes for those conditions compared to the general
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28 333 population. Both SMI and diabetes are mainly managed in the community setting in the England, and
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30 334 primary care has a central role in coordination and continuity of care for patients with multiple
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32 335 conditions (Ricci-Cabello et al., 2015). **It is therefore crucial that mental health nurses are aware that**
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34 336 **a higher proportion of their patients with T2DM and SMI are at risk of adverse outcomes due to their**
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36 337 **cardiovascular risk factors. Better management of all cardiovascular risk factors should be ensured,**
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38 338 **particularly controlling of extreme (high and low) values of HbA_{1c}, to address inequalities in physical**
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40 339 **health outcomes in patients with SMI and T2DM.** We found that overall the management of
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42 340 cardiovascular risk factors was similar in diabetes patients with and without SMI, although those with
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44 341 SMI appear to be at increased risk of HbA_{1c} and SBP values associated with increased risk of adverse
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46 342 clinical outcomes. However, further investigation of the contributors to the physical health gap in
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48 343 patients with SMI and diabetes is needed.
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54 344 **Conclusions**

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57 345 Overall, our findings suggest that people with SMI are more likely to have HbA_{1c} and SBP values
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59 346 associated with poor cardiovascular outcomes in the context of diabetes. They are also more likely to
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3 347 live in deprived areas, to smoke, and to be obese. Conversely, they are less likely to have
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5 348 hypertension or coronary heart disease. After controlling for such risk factors, patients with SMI have
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7 349 similar average levels of cholesterol, HbA_{1c} and DBP but lower SBP. This suggests that patients with
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9 350 SMI and diabetes are managed to a similar standard to other patients with diabetes, and that other
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11 351 factors are maybe responsible for the gross inequalities in physical health outcomes observed for
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13 352 people with SMI. However, both HbA_{1c} and SBP in patients with SMI may be over-treated, which may
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15 353 increase the risk of adverse clinical outcomes. This warrants further investigation, including the
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17 354 contributing factors that increase risk of mortality, microvascular events, macrovascular events and
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19 355 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.m²), 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)

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3 **Figure 1 Mean levels of outcomes in diabetes patients with comorbid SMI and in non-SMI controls by year of follow-up**
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6 **(a) Cholesterol**
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9 **(b) HbA_{1c}**
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12 **(c) Systolic blood pressure**
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15 **(d) Diastolic blood pressure**
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18 **Figure 2 Percentage of diabetes patients with 'high risk' levels of outcomes by year of follow-up**
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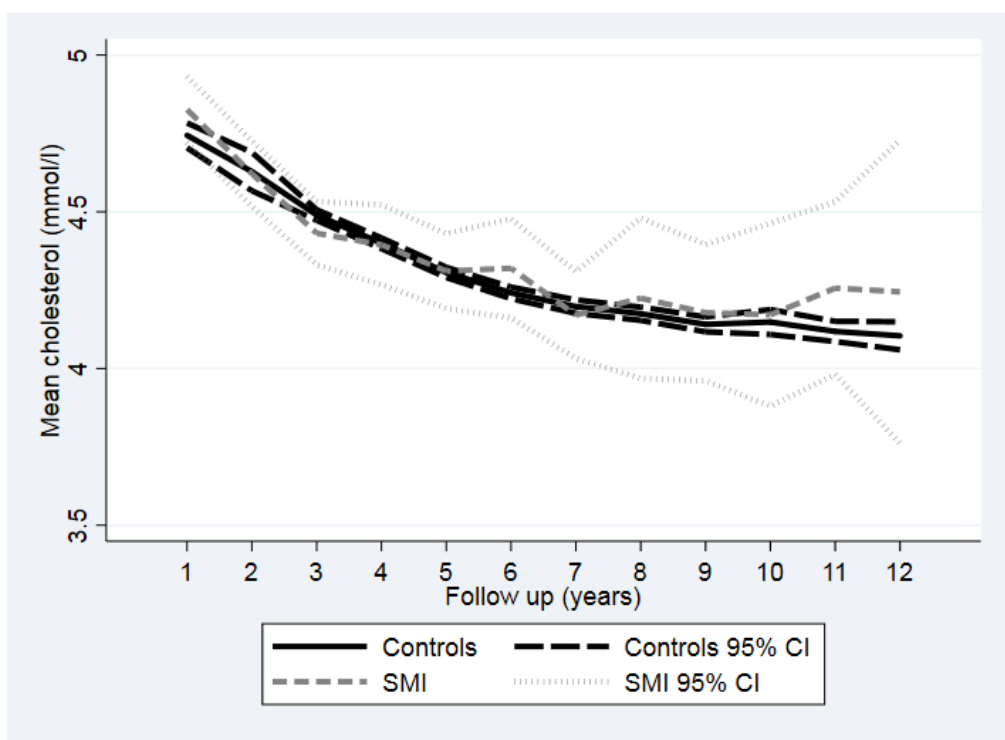
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22 **(a) Cholesterol <2.5mmol/l or >6.5mmol/l**
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25 **(b) HbA_{1c} <6.25% or >7.75% (<45 or >61mmol/mol)**
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28 **(c) Systolic blood pressure <115mmHg**
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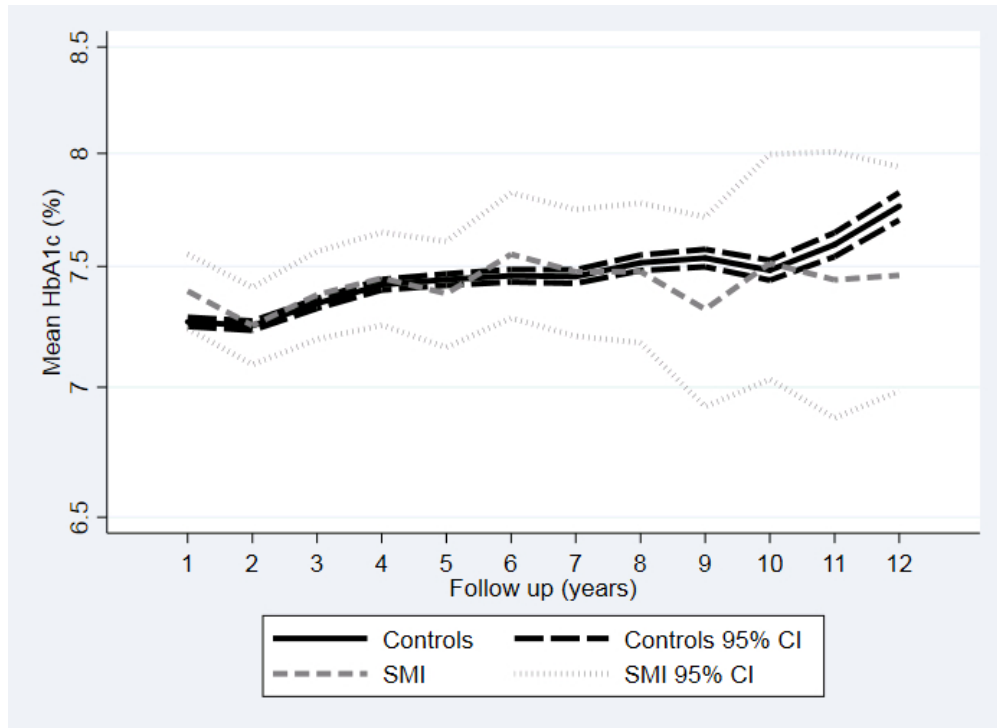
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31 **(d) Diastolic blood pressure <72.5mmHg or >92.5mmHg**
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(a) Cholesterol

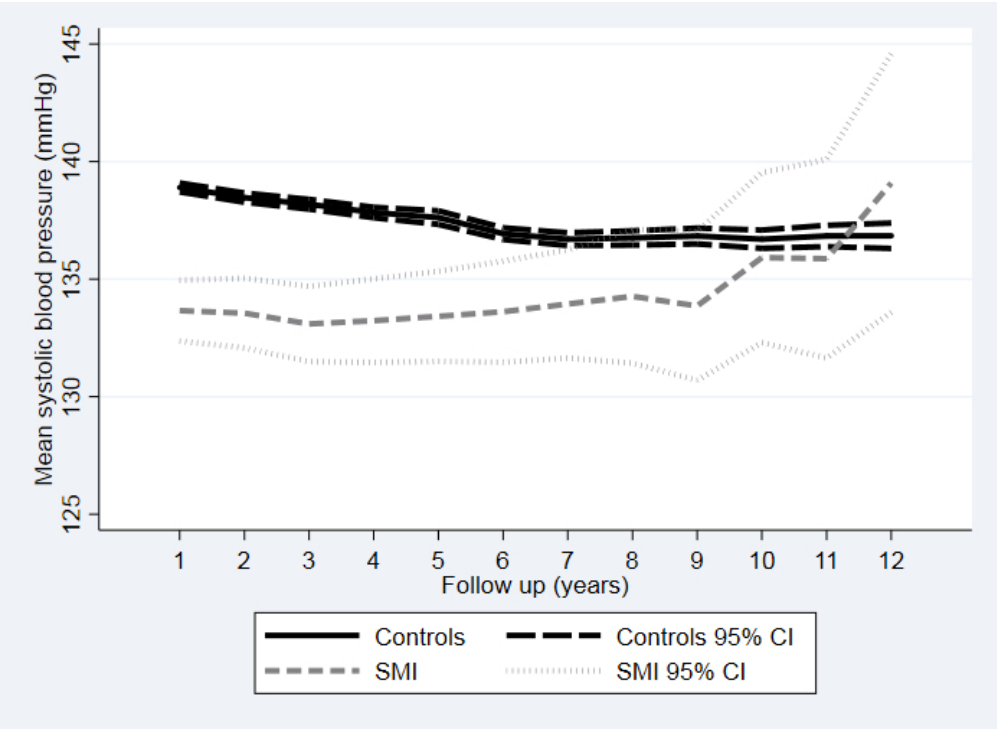
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(b) HbA1c

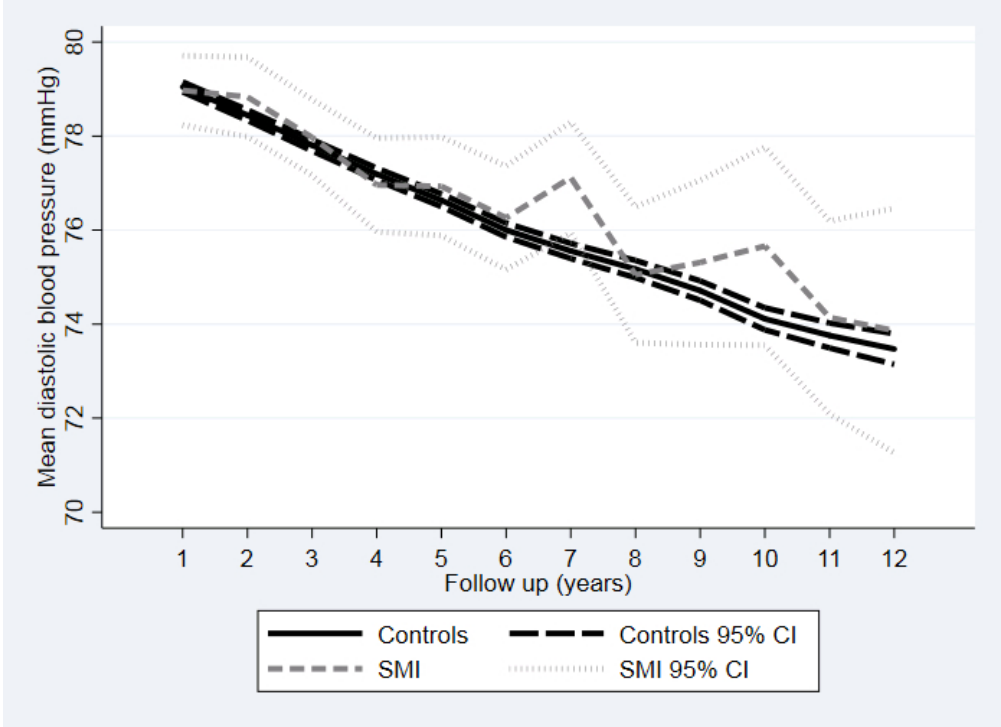
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(c) Systolic blood pressure

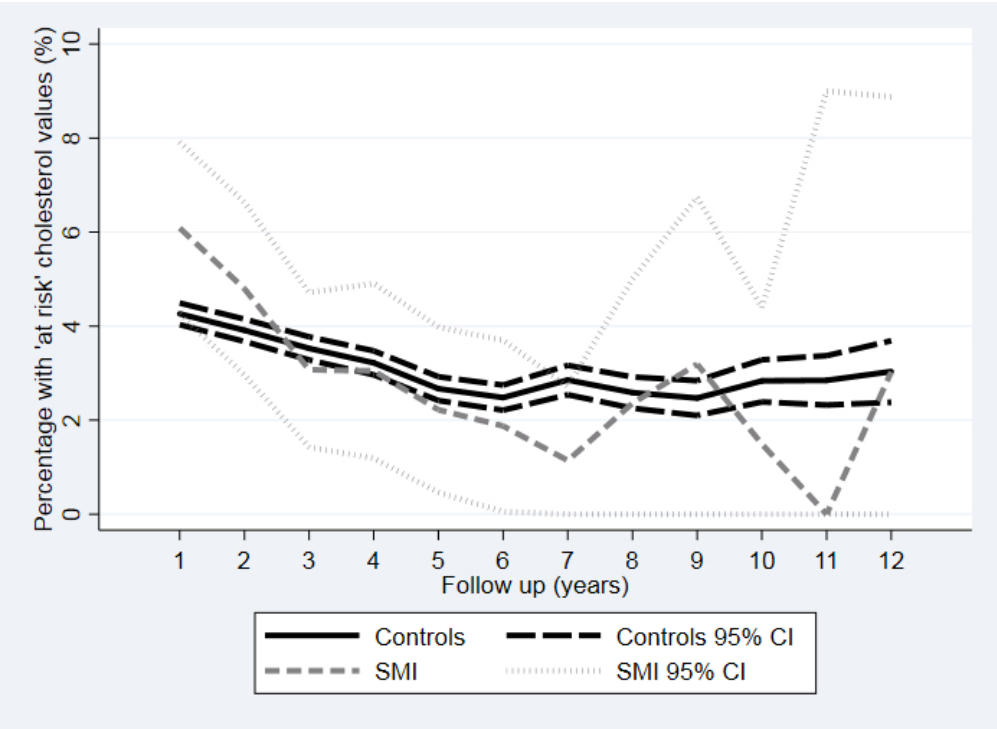
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(d) Diastolic blood pressure

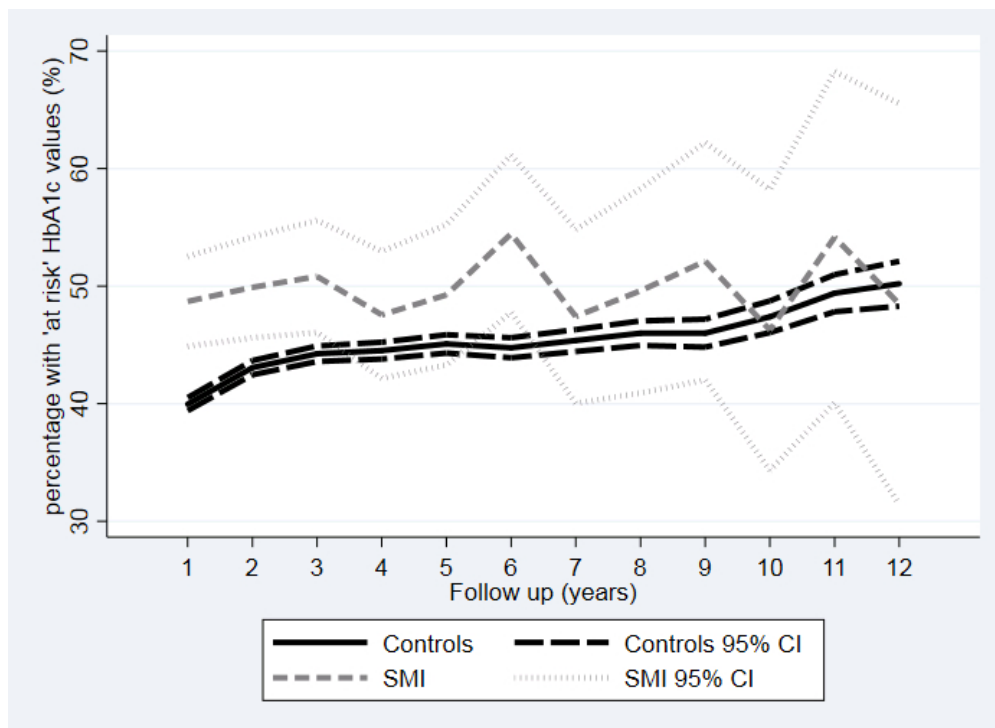
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(a) Cholesterol <math>< 2.5\text{mmol/l}</math> or $> 6.5\text{mmol/l}$

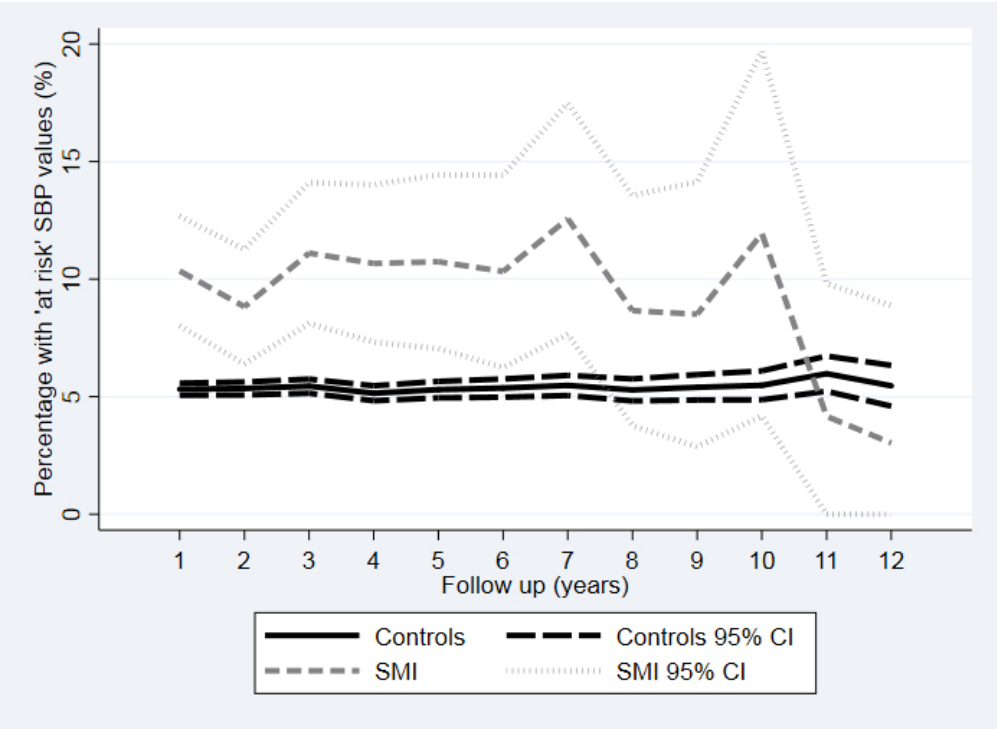
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(b) HbA1c <6.25% or >7.75% (<45 or >61mmol/mol)

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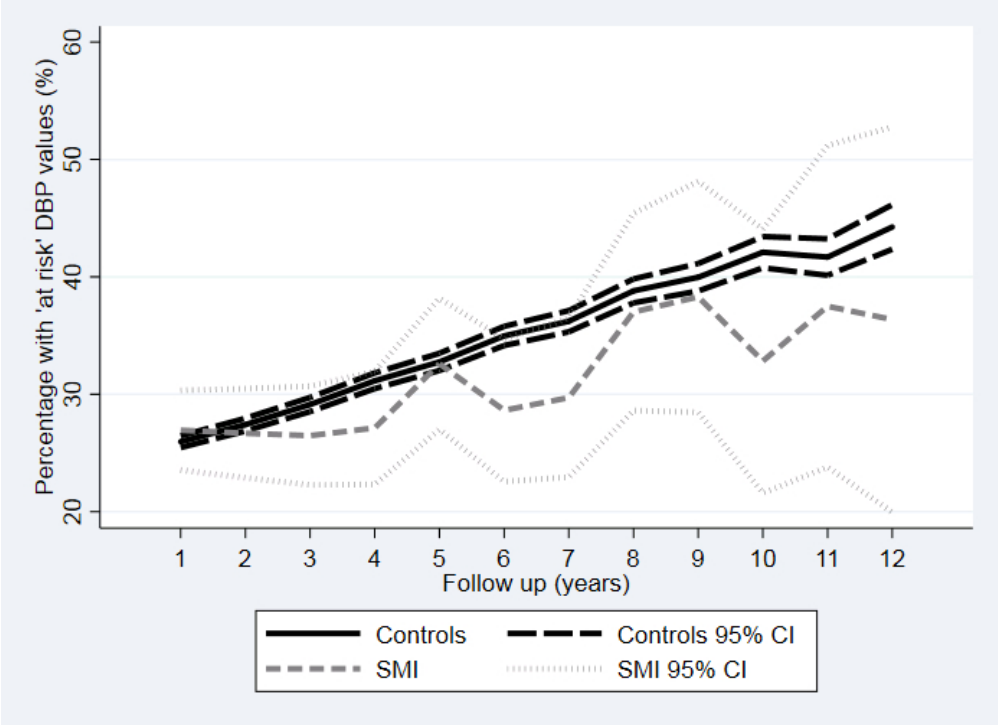
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(c) Systolic blood pressure <115mmHg

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Diastolic blood pressure <72.5mmHg or >92.5mmHg

244x177mm (72 x 72 DPI)

Table S1. Cohort characteristics across follow-up from baseline year

Follow-up (years)	1	2	3	4	5	6	7	8	9	10	11	12
SMI, n (%)	657 (100)	521 (79.3)	423 (64.4)	328 (49.9)	270 (41.1)	213 (32.4)	175 (26.6)	127 (19.3)	94 (14.3)	67 (10.2)	48 (7.3)	33 (5.0)
Control n (%)	29696 (100)	25679 (86.5)	21766 (73.3)	18473 (62.2)	15611 (52.6)	13059 (44.0)	10893 (36.7)	8771 (29.5)	6758 (22.8)	5287 (17.8)	3862 (13.0)	2635 (8.9)
Serum cholesterol measurement, n (%)												
SMI	537 (81.7)	403 (77.4)	338 (79.9)	275 (83.8)	229 (84.8)	172 (80.8)	152 (86.9)	106 (83.5)	84(89.4)	56(83.4)	40 (83.3)	24 (72.7)
Control	23816 (80.2)	20949 (81.5)	18295 (84.1)	15839 (85.7)	13475 (86.3)	11275 (86.3)	9416 (86.4)	7594 (86.6)	5838 (86.4)	4546 (86.0)	3322 (86.0)	2234 (84.8)
HbA_{1c} measurement, n (%)												
SMI	527 (80.2)	434 (83.3)	368 (87.0)	285 (86.9)	236 (87.4)	187 (87.8)	155 (88.6)	110 (86.6)	89 (94.7)	60 (89.6)	45(93.8)	28 (84.9)
Control	23334 (78.6)	21677 (84.4)	19321 (88.8)	16742 (90.6)	14269 (91.4)	11989 (91.8)	10037 (92.1)	8077 (92.1)	6269 (92.8)	4895 (92.6)	3597 (93.1)	2427 (92.1)
Blood pressure measurement, n (%)												
SMI	598 (91.0)	462 (88.9)	395 (93.4)	296 (90.2)	246 (91.1)	199 (93.4)	164 (93.7)	119 (93.7)	89 (94.7)	63 (94.0)	45 (93.8)	29 (87.8)
Control	27399 (92.2)	23769 (92.6)	20357 (93.5)	17511 (94.8)	14848 (95.1)	12378 (94.8)	10342 (95.0)	8327 (95.0)	6423 (95.0)	3646 (94.4)	3646 (94.4)	2505 (95.0)

Percentages of patients in groups are displayed in relation to follow up year 1. Percentages of vascular risk factor measurements are displayed in relation to total number of patients in corresponding year.

1 **Table S2. Beta coefficients of independent variable and covariates in multilevel mixed effect linear regression model for vascular risk factors**

	Cholesterol			HbAa1c		
	Model 1 β (95%CI)	Model 2 β (95%CI)	Model 3 β (95% CI)	Model 1 β (95%CI)	Model 2 β (95%CI)	Model 3 β (95%CI)
Control	REF	REF	REF	REF	REF	REF
SMI	0.05 (-0.05, 0.16)	-0.08 (-0.18, 0.24)	-0.07 (-0.17, 0.03)	0.04 (-0.05, 0.14)	-0.05 (-0.15, 0.05)	-0.08 (-0.18, 0.01)
Gender						
Males		REF	REF		REF	REF
Females		0.39 (0.36, 0.42)	0.38 (0.35, 0.41)		-0.04 (-0.07, -0.02)	-0.02 (-0.04, 0.01)
Age		-0.01 (-0.01, -0.01)	-0.01 (-0.01, -0.01)		-0.01 (-0.01, -0.01)	-0.02 (-0.01, -0.02)
BMI		-0.01 (-0.01, -0.01)	-0.01 (-0.01, -0.01)		0.01 (0.01, 0.01)	0.01 (0.01, 0.01)
Smoking status						
Never		REF	REF		REF	REF
Current		0.05 (0.01, 0.09)	0.06 (-0.01, 0.10)		0.08 (0.05, 0.11)	0.08 (0.05, 0.11)
Ex-smoker		-0.02 (-0.01, 0.02)	-0.01 (-0.04, 0.02)		0.01 (-0.01, 0.03)	0.01 (-0.01, 0.03)
Ethnicity						
White		REF	REF		REF	REF
Mixed		-0.04 (0.02, 0.07)	-0.08 (-0.28, 0.12)		0.08 (-0.11, 0.27)	0.08 (-0.11, 0.26)
South Asian		-0.15 (-0.21, -0.09)	-0.13 (-0.20, -0.07)		0.17 (0.12, 0.22)	0.12 (0.09, 0.18)
Black		-0.03 (-0.11, 0.57)	-0.04 (-0.12, 0.04)		0.19 (0.11, 0.27)	0.16 (0.09, 0.24)
Chinese/other		-0.09 (-0.21, 0.22)	-0.09 (-0.21, 0.02)		0.20 (0.10, 0.30)	0.18 (0.08, 0.27)
IMD quintile						
1 (most affluent)		REF	REF		REF	REF
2		-0.04 (-0.09, 0.01)	-0.04 (-0.08, 0.01)		0.04 (-0.01, 0.09)	0.03 (-0.01, 0.08)
3		-0.02 (-0.07, 0.03)	-0.02 (-0.07, 0.30)		0.09 (0.04, 0.14)	0.07 (0.02, 0.11)
4		-0.05 (-0.10, -0.01)	-0.04 (-0.09, 0.01)		0.11 (0.06, 0.17)	0.09 (0.04, 0.14)
5 (most deprived)		-0.04 (-0.10, 0.01)	-0.03 (-0.09, 0.02)		0.19 (0.14, 0.25)	0.17 (0.11, 0.23)
Comorbidities						
Asthma		0.03 (-0.2, 0.07)	0.03 (-0.02, 0.07)		-0.01 (-0.04, 0.04)	-0.01 (-0.04, 0.03)
Cancer		-0.06 (-0.11, -0.01)	-0.06 (-0.11, -0.01)		-0.03 (-0.07, 0.04)	-0.06 (-0.09, -0.01)
CHD		-0.19 (-0.23, -0.15)	-0.13 (-0.17, -0.09)		0.06 (0.02, 0.09)	0.03 (-0.01, 0.06)
CKD		-0.18 (-0.22, -0.14)	-0.14 (-0.18, -0.09)		-0.06 (-0.08, -0.03)	-0.13 (-0.16, -0.11)
COPD		-0.05 (-0.12, 0.24)	-0.05 (-0.11, 0.02)		0.02 (-0.03, 0.07)	0.03 (-0.02, 0.07)
Dementia		-0.03 (-0.17, 0.11)	-0.07 (-0.21, 0.07)		-0.03 (-0.12, 0.06)	-0.07 (-0.17, 0.02)
Depression		0.09 (0.01, 0.17)	0.09 (0.01, 0.18)		0.02 (-0.02, 0.07)	-0.02 (-0.02, 0.06)
Epilepsy		0.08 (-0.04, 0.20)	0.10 (-0.02, 0.21)		-0.13 (-0.22, -0.02)	-0.16 (-0.26, -0.07)
Heart failure		-0.09 (-0.15, -0.02)	-0.10 (-0.16, -0.03)		0.14 (0.09, 0.19)	0.12 (0.07, 0.17)
Hypertension		-0.13 (-0.16, -0.10)	-0.09 (-0.12, -0.06)		-0.13 (-0.15, -0.11)	-0.16 (-0.18, -0.13)
Hypothyroidism		-0.01 (-0.06, -0.04)	-0.01 (-0.05, 0.05)		0.04 (-0.01, 0.08)	0.02 (-0.02, 0.05)
Osteoarthritis		-0.04 (-0.07, -0.01)	-0.03 (-0.06, 0.01)		-0.08 (-0.10, -0.04)	-0.09 (-0.11, -0.06)
Osteoporosis		0.01 (-0.08, 0.09)	0.01 (-0.08, 0.08)		-0.07 (-0.13, -0.01)	-0.10 (-0.16, -0.04)
Stroke		-0.02 (-0.08, 0.03)	0.01 (-0.05, 0.06)		-0.04 (-0.08, 0.01)	-0.07 (-0.11, -0.03)
Years since diabetes diagnosis			-0.01 (-0.01, -0.01)			0.04 (0.04, 0.05)
Cardiovascular medication						
Statin			-0.43 (-0.46, -0.40)			
Other lipid lowering			0.29 (0.24, 0.34)			

3 Table S2 continue

	Systolic blood pressure			Diastolic blood pressure		
	Model 1 β (95%CI)	Model 2 β (95%CI)	Model 3 β (95%CI)	Model 1 β (95%CI)	Model 2 β (95%CI)	Model 3 β (95%CI)
Control	REF	REF	REF	REF	REF	REF
SMI	-4.32 (-5.30, 3.36)	-3.06 (-3.96, -2.16)	-2.50 (-3.37, -1.62)	0.09 (-0.46, 0.66)	-0.51 (-1.02, -0.02)	-0.30 (-0.80, 0.18)
Gender						
Males		REF	REF		REF	REF
Females		0.59 (0.32, 0.86)	0.72 (0.46, 0.98)		-0.37 (-0.53, -0.22)	-0.44 (-0.59, -0.29)
Age		0.18 (0.17, 0.19)	0.18 (0.17, 0.19)		-0.17 (-0.18, -0.16)	-0.14 (-0.15, -0.13)
BMI		0.13 (0.11, 0.15)	0.12 (0.10, 0.13)		0.14 (0.14, 0.15)	0.15 (0.14, 0.16)
Smoking status						
Never		REF	REF		REF	REF
Current		-0.25 (-0.57, 0.75)	-0.14 (-0.45, 0.18)		-0.33 (-0.53, -0.14)	-0.30 (-0.49, -0.11)
Ex-smoker		-0.20 (-0.45, 0.04)	-0.19 (-0.43, 0.05)		-0.36 (-0.50, -0.21)	-0.36 (-0.50, -0.22)
Ethnicity						
White		REF	REF		REF	REF
Mixed		-1.53 (-3.55, 0.50)	-1.60 (-3.54, 0.34)		0.51 (-0.53, 1.54)	0.48 (-0.55, 1.51)
South Asian		-1.45 (-1.94, -0.96)	-1.33 (-1.81, -0.84)		0.08 (-0.23, 0.38)	0.25 (-0.06, 0.55)
Black		0.89 (0.18, 1.60)	0.54 (-0.15, 1.22)		1.28 (0.93, 1.64)	1.36 (1.01, 1.72)
Chinese/other		-1.73 (-2.73, -0.74)	-1.68 (-2.65, -0.70)		0.35 (-0.25, 0.94)	0.43 (-0.15, 1.02)
IMD quintile						
1 (most affluent)		REF	REF		REF	REF
2		0.09 (-0.35, 0.53)	0.15 (-0.28, 0.57)		0.08 (-0.16, 0.32)	0.14 (-0.09, 0.37)
3		0.64 (-0.41, 0.54)	0.01 (-0.36, 0.56)		-0.12 (-0.38, 0.13)	-0.03 (-0.28, 0.22)
4		0.07 (-0.41, 0.56)	0.16 (-0.31, 0.63)		-0.40 (-0.67, -0.13)	-0.23 (-0.49, 0.03)
5 (most deprived)		0.09 (-0.45, 0.63)	0.16 (-0.37, 0.69)		-0.39 (-0.69, -0.09)	-0.26 (-0.55, 0.04)
Comorbidities						
Asthma		-0.45 (-0.82, -0.08)	-0.43 (-0.79, -0.07)		-0.22 (-0.42, -0.02)	-0.21 (-0.41, -0.01)
Cancer		-1.20 (-1.58, -0.83)	-1.02 (-1.39, -0.66)		-0.68 (-0.88, -0.47)	-0.55 (-0.75, -0.35)
CHD		-2.07 (-2.38, -1.76)	-1.78 (-2.09, -1.46)		-1.94 (-2.11, -1.77)	-1.45 (-1.63, -1.28)
CKD		-3.94 (-4.21, -3.67)	-3.53 (-3.80, -3.27)		-2.00 (-2.15, -1.85)	-1.52 (-1.67, -1.38)
COPD		-2.47 (-2.97, -1.97)	-2.19 (-2.68, -1.71)		-1.22 (-1.50, -0.95)	-1.18 (-1.45, -0.91)
Dementia		-6.02 (-6.86, -5.18)	-5.20 (-6.03, -4.38)		-0.88 (-1.36, -0.40)	-0.61 (-1.08, -0.14)
Depression		-0.39 (-0.83, 0.04)	-0.34 (-0.91, 0.09)		0.17 (-0.05, 0.40)	0.20 (-0.02, 0.43)
Epilepsy		-0.23 (-1.19, 0.73)	0.03 (-0.90, 0.96)		-0.21 (-0.75, 0.33)	-0.05 (-0.48, 0.58)
Heart failure		-3.57 (-4.24, -3.10)	-2.67 (-3.14, -2.19)		-1.45 (-1.72, -1.19)	-1.06 (-1.32, -0.80)
Hypertension		4.12 (3.88, 4.36)	2.14 (1.88, 2.40)		1.18 (1.05, 1.31)	1.04 (0.90, 1.18)
Hypothyroidism		-1.53 (-1.94, -1.12)	-1.16 (-1.56, -0.77)		-0.65 (-0.88, -0.42)	-0.46 (-0.68, -0.23)
Osteoarthritis		-0.85 (-1.13, -0.56)	-0.72 (-0.99, -0.45)		-0.47 (-0.62, -0.32)	-0.37 (-0.52, -0.22)
Osteoporosis		-1.20 (-2.11, -1.27)	-0.85 (-1.46, -0.22)		-0.33 (-0.67, 0.02)	-0.10 (-0.45, 0.24)

1	Stroke	-1.69 (0.22, <0.01)	-1.49 (1.90, -1.08)	-0.70 (-0.94, -0.47)	-0.39 (-0.62, -0.17)
2	Years since diabetes diagnosis		-0.14 (-0.16, -0.12)		-0.22 (-0.23, -0.21)
3	Cardiovascular medication				
4	ACE inhibitors		2.64 (2.42, 2.84)		0.90 (0.79, 1.02)
5	α blockers		3.60 (3.28, 3.92)		-0.08 (-0.22, 0.09)
6	β blockers		0.26 (0.01, 0.50)		-0.30 (-0.43, -0.16)
7	Calcium channel blocker		2.63 (2.41, 2.84)		-0.08 (-0.19, 0.03)
8	Thiazide diuretic		1.59 (1.36-1.83)		0.39 (0.26, 0.52)
9	Loop diuretics		-1.90 (-2.17, -1.63)		-0.87 (-1.02, -0.73)
10	Other lipid lowering		-1.21 (-1.58, -0.87)		-0.74 (-0.94, -0.54)
11	Statins		-2.29 (-2.49, -2.08)		-1.01 (-1.12, -0.90)

For Peer Review

Table S3. Odds ratios of at 'high risk' levels and covariates in multilevel mixed effect binary regression model for vascular risk factors

	Cholesterol			HbAa1c		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Control	REF	REF	REF	REF	REF	REF
SMI	1.28 (0.91, 1.78)	0.93 (0.67, 1.31)	0.95 (0.68, 1.32)	1.60 (1.34, 1.90)	1.40 (1.18, 1.67)	1.38 (1.16, 1.64)
Gender						
Males		REF	REF		REF	REF
Females		1.99 (1.79, 2.21)	1.95 (1.76, 2.16)		1.01 (0.96, 1.07)	1.02 (0.97, 1.06)
Age		0.98 (0.97, 0.99)	0.98 (0.97, 0.99)		0.98 (0.97, 0.99)	0.97 (0.96, 0.98)
BMI		0.98 (0.97, 0.99)	0.98 (0.97, 0.99)		0.98 (0.97, 0.99)	0.98 (0.97, 0.99)
Smoking status						
Never		REF	REF		REF	REF
Current		1.49 (1.32, 1.67)	1.50 (1.33, 1.69)		1.11 (1.05, 1.17)	1.11 (1.05, 1.18)
Ex-smoker		1.01 (0.92, 1.10)	1.01 (0.91, 1.11)		1.06 (1.01, 1.10)	1.06 (1.01, 1.11)
Ethnicity						
White		REF	REF		REF	REF
Mixed		1.00 (0.57, 1.75)	0.98 (0.56, 1.70)		0.98 (0.72, 1.32)	0.98 (0.73, 1.32)
South Asian		0.72 (0.57, 0.92)	0.74 (0.58, 0.95)		0.97 (0.89, 1.06)	0.94 (0.86, 1.03)
Black		0.73 (0.56, 0.94)	0.72 (0.56, 0.94)		1.07 (0.96, 1.20)	1.05 (0.94, 1.17)
Chinese/other		0.83 (0.56, 1.22)	0.84 (0.57, 1.23)		0.99 (0.83, 1.21)	0.98 (0.81, 1.19)
IMD quintile						
1 (most affluent)		REF	REF		REF	REF
2		1.00 (0.86, 1.16)	1.01 (0.87, 1.17)		1.02 (0.95, 1.09)	1.01 (0.94, 1.08)
3		1.07 (0.91, 1.25)	1.08 (0.82, 1.30)		1.13 (1.04, 1.23)	1.11 (1.03, 1.21)
4		1.08 (0.91, 1.27)	1.11 (0.93, 1.30)		1.09 (1.01, 1.19)	1.07 (1.00, 1.16)
5 (most deprived)		1.06 (0.89, 1.26)	1.09 (0.92, 1.29)		1.16 (1.06, 1.27)	1.14 (1.05, 1.25)
Comorbidities						
Asthma		0.90 (0.79, 1.04)	0.90 (0.79, 1.03)		0.95 (0.88, 1.01)	0.95 (0.89, 1.01)
Cancer		1.11 (0.94, 1.32)	1.09 (0.93, 1.30)		0.93 (0.87, 0.99)	0.92 (0.86, 0.99)
CHD		0.90 (0.79, 1.02)	0.95 (0.84, 1.08)		0.98 (0.94, 1.04)	0.96 (0.91, 1.02)
CKD		0.77 (0.68, 0.87)	0.79 (0.69, 0.89)		1.02 (0.97, 1.08)	0.97 (0.92, 1.03)
COPD		1.06 (0.86, 1.30)	1.04 (0.85, 1.28)		1.00 (0.92, 1.10)	1.01 (0.93, 1.11)
Dementia		1.33 (0.92, 1.92)	1.30 (0.90, 1.88)		1.64 (1.40, 1.94)	1.59 (1.34, 1.87)
Depression		1.19 (0.98, 1.43)	1.19 (1.00, 1.43)		1.07 (0.98, 1.18)	1.07 (0.98, 1.17)
Epilepsy		1.04 (0.73, 1.48)	1.07 (0.76, 1.54)		1.04 (0.88, 1.24)	1.02 (0.86, 1.21)
Heart failure		1.42 (1.18, 1.71)	1.42 (1.19, 1.72)		1.17 (1.01, 1.28)	1.15 (1.06, 1.26)
Hypertension		0.75 (0.68, 0.82)	0.79 (0.72, 0.86)		0.93 (0.89, 0.97)	0.92 (0.88, 0.96)
Hypothyroidism		1.21 (1.03, 1.42)	1.23 (1.05, 1.44)		1.09 (1.01, 1.18)	1.08 (0.99, 1.16)

Osteoarthritis	0.95 (0.85, 1.06)	0.95 (0.85, 1.06)	0.95 (0.90, 1.00)	0.95 (0.90, 0.99)
Osteoporosis	1.26 (0.97, 1.64)	1.26 (0.97, 1.63)	1.16 (1.03, 1.31)	1.13 (1.00, 1.28)
Stroke	1.05 (0.88, 1.25)	1.10 (0.93, 1.32)	1.13 (1.04, 1.22)	1.10 (1.01, 1.19)
Years since diabetes diagnosis		0.97 (0.96, 0.98)		1.03 (1.02, 1.04)
Cardiovascular medication				
Statin		0.62 (0.57, 0.67)		
Other lipid lowering		1.78 (1.56, 2.01)		

Table S3 continued

	Systolic blood pressure			Diastolic blood pressure		
	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)	Model 1 OR (95% CI)	Model 2 OR (95% CI)	Model 3 OR (95% CI)
Control	REF	REF	REF	REF	REF	REF
SMI	2.60 (2.01, 3.34)	1.83 (1.45, 2.31)	1.76 (1.40, 2.21)	0.95 (0.82, 1.12)	1.02 (0.88, 1.19)	1.02 (0.84, 1.18)
Gender						
Males		REF	REF		REF	REF
Females		1.16 (1.06, 1.25)	1.06 (0.96, 1.16)		1.02 (0.98, 1.07)	1.04 (0.99, 1.08)
Age		0.97 (0.96, 0.98)	0.97 (0.96, 0.98)		1.02 (1.01, 1.03)	1.02 (1.01, 1.03)
BMI		0.95 (0.94, 0.96)	0.95 (0.94, 0.96)		0.97 (0.96, 0.98)	0.97 (0.96, 0.98)
Smoking status						
Never		REF	REF		REF	REF
Current		1.25 (1.14, 1.39)	1.26 (1.15, 1.39)		1.14 (1.07, 1.20)	1.14 (1.08, 1.21)
Ex-smoker		1.08 (0.99, 1.18)	1.08 (0.95, 1.17)		1.04 (1.01, 1.10)	1.05 (1.01, 1.09)
Ethnicity						
White		REF	REF		REF	REF
Mixed		1.08 (0.62, 1.88)	1.08 (0.62, 1.87)		0.79 (0.57, 1.10)	0.80 (0.58, 1.11)
South Asian		1.26 (1.06, 1.51)	1.27 (1.06, 1.51)		0.98 (0.88, 1.08)	0.94 (0.86, 1.05)
Black		0.82 (0.64, 1.05)	0.88 (0.70, 1.12)		0.89 (0.78, 1.06)	0.85 (0.75, 0.96)
Chinese/other		1.27 (0.92, 1.76)	1.31 (0.95, 1.80)		0.80 (0.68, 0.97)	0.80 (0.67, 0.95)
IMD quintile						
1 (most affluent)		REF	REF		REF	REF
2		1.06 (0.94, 1.21)	1.05 (0.93, 1.19)		0.96 (0.90, 1.03)	0.95 (0.89, 1.02)
3		1.05 (0.91, 1.20)	1.03 (0.90, 1.18)		1.04 (0.97, 1.12)	1.02 (0.95, 1.10)
4		1.11 (0.97, 1.29)	1.10 (0.96, 1.27)		1.12 (1.04, 1.21)	1.08 (1.01, 1.18)
5 (most deprived)		1.21 (1.03, 1.41)	1.20 (1.03, 1.39)		1.14 (1.05, 1.24)	1.12 (1.02, 1.21)
Comorbidities						
Asthma		0.93 (0.83, 1.04)	0.96 (0.86, 1.08)		1.01 (0.95, 1.07)	1.01 (0.95, 1.07)

1				
2				
3	Cancer	1.11 (0.98, 1.25)	1.08 (0.96, 1.23)	1.10 (1.04, 1.18)
4	CHD	1.76 (1.61, 1.93)	1.58 (1.43, 1.75)	1.50 (1.43, 1.57)
5	CKD	1.46 (1.31, 1.61)	1.41 (1.28, 1.56)	1.65 (1.57, 1.73)
6	COPD	1.43 (1.23, 1.67)	1.37 (1.17, 1.60)	1.27 (1.17, 1.38)
7	Dementia	4.16 (3.29, 5.25)	3.93 (3.11, 4.94)	1.39 (1.19, 1.61)
8	Depression	1.18 (1.01, 1.37)	1.16 (1.00, 1.35)	1.02 (0.94, 1.12)
9	Epilepsy	1.08 (0.81, 1.46)	1.05 (0.79, 1.41)	0.98 (0.83, 1.15)
10	Heart failure	2.90 (2.54, 3.31)	2.02 (1.76, 2.32)	1.60 (1.47, 1.72)
11	Hypertension	0.30 (0.28, 0.33)	0.39 (0.36, 0.42)	0.77 (0.73, 0.80)
12	Hypothyroidism	1.19 (1.05, 1.35)	1.15 (1.01, 1.30)	1.12 (1.05, 1.21)
13	Osteoarthritis	1.08 (0.99, 1.20)	1.07 (0.98, 1.17)	1.06 (1.01, 1.11)
14	Osteoporosis	1.18 (0.96, 1.45)	1.14 (0.94, 1.40)	1.07 (0.96, 1.18)
15	Stroke	1.50 (1.31, 1.70)	1.49 (1.31, 1.70)	1.16 (1.08, 1.25)
16	Years since diabetes diagnosis		1.00 (0.99, 1.01)	1.03 (1.02, 1.04)
17	Cardiovascular medication			
18	ACE inhibitors		0.85 (0.79, 0.92)	1.06 (1.02, 1.10)
19	α blockers		0.67 (0.58, 0.77)	1.22 (1.15, 1.29)
20	β blockers		1.29 (1.18, 1.40)	1.10 (1.05, 1.15)
21	Calcium channel blocker		0.57 (0.52, 0.62)	1.16 (1.12, 1.21)
22	Thiazide diuretic		0.85 (0.77, 0.94)	0.96 (0.92, 0.99)
23	Loop diuretics		1.91 (1.74, 2.10)	1.28 (1.22, 1.35)
24	Other lipid lowering		0.98 (0.86, 1.11)	1.02 (0.95, 1.08)
25	Statins		0.98 (0.91, 1.06)	1.03 (0.98, 1.06)

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