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# Statin prescribing for prevention of cardiovascular disease amongst people with severe mental illness: Cohort study in UK primary care

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ABSTRACT

*Background:* Severe mental illness (SMI) is associated with excess cardiovascular disease (CVD) morbidity, but little is known on provision of preventative interventions. We investigated statin initiation for primary CVD prevention in individuals with and without SMI.
*Methods:* We used primary care data from The Health Improvement Network from 2006 to 2015 for UK patients aged 30–99 years with no pre-existing CVD conditions and selected individuals with schizophrenia ($n = 13,252$) or bipolar disorder ($n = 11,994$). In addition, we identified samples of individuals without schizophrenia ($n = 66,060$) and bipolar disorder ($n = 59,765$), but with similar age and gender distribution. Missing data on CVD covariates were estimated using multiple imputation. Statin prescribing differences between individuals with and without SMI were investigated using multivariable Poisson regression models.
*Results:* Initiation of statin prescribing was between 2 and 3 fold higher in people aged 30–59 years with SMI than in those without after adjusting for CVD covariates. The rates in those aged 60–74 years with SMI were similar or slightly higher relative to those without SMI. The incidence rate ratio (IRR) was 1.15 (95% CI 1.03–1.28) for bipolar disorder and 1.00 (0.91–1.11) for schizophrenia. The rate of statin prescribing was lower (IRR 0.81 (0.66–0.98)) amongst the oldest (aged 75+ years) with schizophrenia relative to those without schizophrenia.
*Conclusions:* Despite higher rates of new statin prescriptions to younger individuals with SMI relative to individuals without SMI, there was evidence of lower rates of statin initiation for older individuals with schizophrenia, and this group may benefit from additional measures to prevent CVD.


## 1. Introduction

Severe mental illness (SMI) including schizophrenia and bipolar disorder is associated with a high burden of physical comorbidity: rates of cardiovascular disease (CVD) are two to threefold higher in younger people with an SMI diagnosis than comparable individuals without SMI (Osborn et al., 2007; Laursen et al., 2011). CVD-associated mortality is three times higher amongst people with SMI than the general population and makes a sizable contribution to the 15–20 year deficit in life expectancy experienced by this group (Ringen et al., 2014). In the past, both the provision and quality of treatment for existing CVD conditions has been lower for individuals with SMI than the general population (Mitchell et al., 2012; Mitchell and Lord, 2010; Hippisley-Cox et al., 2007): however little is known about the prescribing of statins for primary prevention of CVD.

Guidelines from the National Institute of Healthcare and Clinical Excellence (NICE) identify people with SMI as a specific population for whom statin prescribing for primary prevention should be considered at the same threshold (currently >10% 10 year CVD risk) as the general population (National Institute for Health and Clinical Excellence, 2014b; National Institute for Health and Clinical Excellence, 2014c; National Institute for Health and Clinical Excellence, 2014a). Statins are cost-effective for preventing CVD events within randomised controlled trial (RCT) populations without mental illness (Taylor et al., 2013) and there is growing evidence to suggest that statins are similarly effective in people with SMI (Ojala et al., 2008; De Hert et al., 2006; Hanssens et al., 2007; Vincenzi et al., 2014, Blackburn et al., 2017). Given such evidence of effectiveness there is a need to evaluate statin prescribing in practice and to establish where policy intervention is needed to improve health outcomes for people with SMI.

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Physical health screening to estimate an individual's future risk of CVD should usually precede statin prescribing for primary CVD prevention in both people with and without SMI. Over the past decade, national guidance and financial incentives for physical health screening have been introduced for individuals with SMI (National Institute for Health and Clinical Excellance, 2006; National Institute for Health Clinical Excellence, 2009) (Fig. 1). The specification of these health checks has changed over time, with corresponding increases in CVD screening reported for the period 2000–2007 (Osborn et al., 2011) but little evaluation thereafter. Similar strategies – such as the NHS Health Check (also outlined in Fig. 1) – applied to the general population have tended to result in low levels of uptake (Artac et al., 2013; Dalton and Soljak, 2012) that is inversely correlated with need (Bender et al., 2014; Krogsboll et al., 2012a; Krogsboll et al., 2012b; Waller et al., 1990), thus generating concern that such policies may widen health inequalities (Capewell and Graham, 2010).

To date, there is limited evidence on CVD prevention in people with SMI and a paucity of research with a focus on statin prescribing for primary CVD prevention (Cooper et al., 2016; Tosh et al., 2010). This study therefore aims to evaluate patterns in new statin prescriptions to individuals with SMI, compared to people without SMI, for the period from the 1st January 2006 to 31st December 2015.

## 2. Experimental/materials and methods

A retrospective cohort study was developed using data extracted from The Health Improvement Network (THIN) primary care database (IMS Health, 2015). THIN captures anonymised data from electronic health records from patients registered at 587 general practice (GP) surgeries across the United Kingdom (UK); reflecting 5.7% of the total population (IMS Health, 2015). The majority of individuals with SMI routinely access primary care (Reilly et al., 2012) and the validity of these diagnoses in computer records has been established (Hardoon et al., 2013; Nazareth et al., 1993). THIN data are recorded as hierarchical medical codes (Read codes), free text comments, drug codes for prescribed medications, referrals and additional health information such as laboratory test results and biometrics (Chisholm, 1990; Stuart-Buttle et al., 1996). Townsend score for the quintile of deprivation is recorded in THIN and is assigned on the basis of deprivation at the level of the corresponding enumeration district (areas of approximately 150 households) for a patient's address (Townsend et al., 1986). All data management and analysis were undertaken with Stata v14 (StataCorp., 2015).

### 2.1. Study population

Data for all GP surgeries were extracted for eligible individuals for the period 1st January 2006 to 31st December 2015. Individuals with a diagnosis of schizophrenia or bipolar disorder were categorised as having SMI. The sample was stratified on age and gender and for each strata, up to 5 times as many people from the same practice who were similar in terms of age at baseline (±5 years) and gender but without an SMI diagnosis were selected for inclusion in a parallel cohort.

Entry into the study was at the latest of; i) 30th birthday, ii) date of GP registration plus 6 months and iii) 1st January 2006. In addition, data were censored for time points prior to the GP surgery meeting acceptable levels of data quality, which were assessed in terms of mortality rate and computer usage (Horsfall et al., 2012; Maguire et al., 2009). Exit from the study occurred at the earliest of i) 100th birthday ii) out of practice transfer iii) death iv) first statin prescription, v) CVD event or vi) 31st December 2015. Individuals were excluded from the study if they had a diagnosis of CVD prior to enrolment in the study or had a record of a statin prescription prior to the study start date. Thus, individuals were not eligible to enter the study until six months after the date of registration: this was in order to exclude people with prevalent diagnoses of cardiovascular disease or who were continuing statin treatment (Lewis et al., 2005). Patient data were extracted on SMI diagnoses, patient age, gender, Townsend score and physical health data (blood pressure, height, weight, total cholesterol, high density lipoprotein cholesterol (HDL-C), diabetes, smoking status and antihypertensive prescribing) and statin prescriptions. Body mass index (BMI) was estimated from weight and adult height. Measurements of blood pressure, height, weight, total cholesterol, HDL-C and smoking status recorded within the same calendar year were combined (as a mean or mode). Data on time-varying characteristics (e.g. blood pressure) were summarised for three 1 year calendar time points (2007, 2011 and 2015) and differences examined by unpaired *t*-test (or Mann–Whitney *U* test if not normally distributed) for continuous data and Chi-squared test for categorical data.

Some data were missing for smoking, height, weight, blood pressure, total cholesterol and HDL—C. Missing values were estimated using multiple imputation with the twofold Fully Conditional Specification method, which makes use of the full longitudinal health record (Nevalainen et al., 2009; Welch et al., 2014; Osborn et al., 2015). The imputation model included variables for all patient data outlined above including the outcome (statin prescribing) and associated Nelson Aalen cumulative hazard function. We created 10 imputed datasets from which combined effect estimates and associated standard errors were derived using appropriate statistical methods (Welch et al., 2014). Greater numbers of imputations were not feasible given the large size of the dataset. Height, weight, blood pressure, total cholesterol and HDL-C were included in the imputation model in log form.

### 2.2. Analysis of statin prescribing

Analyses were stratified into four pre-specified age groups (30–39, 40–59, 60–74, 75–99 years), which are compatible with screening

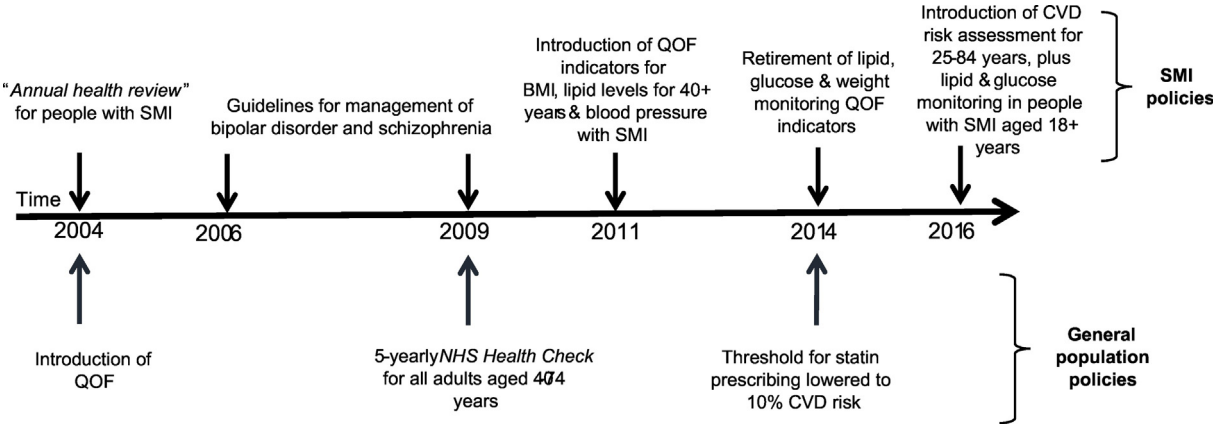


**Fig. 1.** Cardiovascular screening and prescribing policy developments in individuals with SMI and the UK general population.

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policies for the general population (Department of Health, 2016) or individuals with SMI (National Institute for Health Clinical Excellence, 2009; National Institute for Health and Clinical Excellance, 2006). Annual rates of new statin prescriptions were calculated for each year by dividing the number of individuals in the 12 month period with a first statin prescription by the total person-time at risk.

Evidence of differences in statin prescribing between people with and without SMI diagnoses (the exposure of interest) were assessed using multivariable Poisson regression models with new statin prescriptions as the outcome. Models accounted for follow-up time and were adjusted for patient characteristics during the calendar year in which an individual started follow-up. Model 1 included data that were complete (five year age band, gender and Townsend quintile of deprivation). We also examined the impact of characteristics associated with CVD risk on statin prescribing (Model 2); diabetes status, antihypertensive prescribing, smoking status, BMI, total cholesterol and HDL-C in addition to age, gender and Townsend score. Model fitting within the subset of individuals with complete data was used to guide inclusion of continuous variables in linear or log-linear form.

As a sensitivity analysis we applied a different modelling strategy (Model 3) which adjusted for strata of estimated 10 year CVD risk (<5%, 5–10%, 11–20%, 21–40%, >50%) in addition to the variables in Model 1. The sensitivity analysis was included to assess whether different approaches for adjusting for cardiovascular risk as a confounding factor changed the interpretation of our results from the main analyses. CVD risk was estimated using the office version of the Framingham risk score (D'Agostino et al., 2008): age, gender, diabetes status, antihypertensive prescribing, BMI, systolic blood pressure and smoking status.

## 3. Results

A total of 25,246 individuals with an SMI diagnosis were identified. Of these 13,252 (52%) had a diagnosis of schizophrenia and 11,994 (48%) a diagnosis of bipolar disorder. We identified 66,060 individuals without a diagnosis of SMI but with a similar age and gender distribution as the individuals with schizophrenia. Likewise, we identified 59,765 individuals without SMI but with a similar age and gender distribution as the individuals with bipolar disorder. The characteristics of individuals included in the SMI and non-SMI cohorts are outlined in Table 1. The number of individuals entering and exiting the cohort at each time point is outlined in the supplementary material (Supplementary Table 1). The median age at the start of follow up was 48 years for schizophrenia and 45 years for bipolar disorder. Diagnoses of schizophrenia were more common amongst men (60% males), whereas bipolar disorder was more frequently diagnosed amongst women (61% females).

Time-varying characteristics recorded for the study population (at three separate time points) are summarised in Table 2a, Table 2b and Table 2c. These illustrate that patterns of physical health monitoring vary across the time points and that measured characteristics generally suggest a higher cardiovascular risk profile amongst people with SMI in terms of higher smoking and diabetes prevalence, and lower HDL-C concentration. By contrast, systolic blood pressure was generally lower amongst people with SMI relative to comparison groups. Imputed estimates for variables with missing data are outlined in the supplementary material (Supplementary Tables 2a–c).

The absolute rate of statin initiation between 2006 and 2015 was 23.7 (95% CI 22.5–25.1) and 28.3 (26.9–39.7) per 1000 person years for people with bipolar disorder and schizophrenia, relative to 17.1 (16.8–17.4) and 20.7 (20.3–21.0) in the respective comparison groups. Within age groups temporal patterns of statin prescribing were similar for individuals with schizophrenia and bipolar disorder: rates of new statin prescriptions have therefore been combined for both SMI conditions as well as the associated comparison groups. For all years the initiation rate of statin prescribing was substantially higher in younger (those aged 30–39 and 40–59 years) individuals with SMI than for individuals in the comparison cohorts (Fig. 2). Amongst older individuals (60–74 and 75–99 years), rates of initiation prescribing were more similar for individuals with and without SMI. Rates of statin prescribing initiation to people with SMI aged 40 + years increased between 2010 and 2012 to a highs of 33 (40–59 year olds), 57 (60–74 year olds) and 31 (75 + year olds) prescriptions per 1000 person years, with a decline in initiation thereafter (Fig. 2). Initiation of prescribing rates to comparison people without SMI showed a consistent decline throughout the study period, except for those aged 30–39 years where there was less temporal variation. In more recent years, the gap between initiation of prescribing to people aged 30–74 years with and without SMI has reduced and now appears similar to 2010 levels.

In the fully adjusted model (Model 2) the incident rate ratio (IRR) for initiation of statin prescribing to the oldest individuals (75–99 years) with schizophrenia were lower than people without SMI (IRR 0.81 (95% CI 0.66–0.98)), whereas rates of statin prescribing to individuals with bipolar disorder for the same age group were comparable to people without (IRR 0.92 (0.74–1.15)) (Table 3). In contrast, initiation of statins to people with SMI was higher in individuals aged 30–39 years (IRR 2.24 (1.64–3.07) for bipolar disorder and 3.26 (2.48–4.29) for schizophrenia) and for 40–59 year olds (IRR 1.68 (1.53–1.84) for bipolar disorder and 1.68 (1.53–1.82) for schizophrenia) than those without SMI. Amongst individuals aged 60–74 years, rates of statin initiation were similar for people with a diagnosis of schizophrenia (IRR 1.00 (0.91–1.11), but higher for bipolar disorder (IRR 1.15 (1.03–1.28)) compared to people without SMI. There were small (ranging from 0.5% in people aged 30–39 years to 1.9% in people aged 60–74 years) but statistically significant differences in the estimated CVD risk scores of people with and without SMI who were in the same age band. At ages 30–74 years people with SMI had relatively higher estimated risk scores

**Table 1**
Characteristics of the study population during the period January 2006 to December 2015.

| Characteristic | | n = 13,252 | | n = 66,060 | | n = 11,994 | | n = 59,765 | |
|---|---|---|---|---|---|---|---|---|---|
| | | Schizophrenia | (%) | No SMI | (%) | Bipolar disorder | (%) | No SMI | (%) |
| Age at study entry | 30–39 years | 4134 | 31% | 20,670 | 31% | 4379 | 37% | 21,883 | 37% |
| | 40–59 years | 5717 | 43% | 28,585 | 43% | 5254 | 44% | 26,231 | 44% |
| | 60–74 years | 2305 | 17% | 11,429 | 17% | 1670 | 14% | 8277 | 14% |
| | 75–99 years | 1096 | 8% | 5376 | 8% | 691 | 6% | 3374 | 6% |
| Median age at start in years [IQR] | | 47.5 | [37.5–60.5] | 47.5 | [37.5–60.5] | 44.5 | [35.9–56.5] | 44.5 | [35.9–56.5] |
| Sex | Males | 7901 | 60% | 39,365 | 60% | 4727 | 39% | 23,549 | 39% |
| Townsend score | | | | | | | | | |
| 1 | Least deprived | 1472 | 11% | 13,317 | 20% | 2165 | 18% | 13,849 | 23% |
| 2 | | 1856 | 14% | 13,000 | 20% | 2245 | 19% | 12,996 | 22% |
| 3 | | 2682 | 20% | 14,565 | 22% | 2655 | 22% | 13,211 | 22% |
| 4 | | 3451 | 26% | 13,746 | 21% | 2767 | 23% | 11,544 | 19% |
| 5 | Most deprived | 3791 | 29% | 11,432 | 17% | 2162 | 18% | 8165 | 14% |

SMI; severe mental illness, CVD; cardiovascular disease, QOF; Quality and Outcomes Framework, BMI; body mass index.

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**Table 2a**
Characteristics of the study population measured during the period January 2007 to December 2007.

| Characteristic | | $n = 7503$ | | $n = 38,683$ | | | $n = 6603$ | | $n = 33,268$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Schizophrenia | (%) | No SMI | (%) | $p$ | Bipolar disorder | (%) | No SMI | (%) | $p$ |
| Median age at startin years [IQR] | | 51 | [41–63] | 52 | [41–63] | 0.48 | 48 | [40–60] | 49 | [40–60] | 0.52 |
| Sex | Males | 4298 | 57% | 22,124 | 57% | 0.99 | 2551 | 39% | 12,906 | 39% | 0.98 |
| Diabetes | Yes | 331 | 4% | 868 | 2% | <0.001 | 204 | 3% | 680 | 2% | <0.001 |
| Antihypertensive | Yes | 1111 | 15% | 6488 | 17% | <0.001 | 1096 | 17% | 4918 | 15% | <0.001 |
| Smoker | | 2491 | 57% | 5097 | 31% | <0.001 | 1812 | 48% | 4466 | 32% | <0.001 |
| Not recorded | | 3094 | 41% | 22,337 | 58% | | 2822 | 43% | 19,117 | 57% | |
| Mean cholesterol (mmol/L) | | 5.4 | (1.2)[a] | 5.5 | (1.1)[a] | 0.001 | 5.6 | (1.2)[a] | 5.6 | (1.3)[a] | 0.65 |
| Not recorded | | 5763 | 77% | 32,088 | 83% | | 5063 | 77% | 28,172 | 85% | |
| Mean HDL-C (mmol/L) | | 1.3 | (0.4)[a] | 1.4 | (0.5)[a] | <0.001 | 1.4 | (0.4)[a] | 1.5 | (0.4)[a] | <0.001[a] |
| Not recorded | | 6178 | 82% | 33,386 | 86% | | 5415 | 82% | 29,155 | 88% | |
| Mean SBP (mmHg) | | 130 | (17)[a] | 135 | (17)[a] | <0.001 | 130 | (16)[a] | 132 | (17)[a] | <0.001 |
| Not recorded | | 3237 | 43% | 22,212 | 57% | | 2729 | 41% | 18,798 | 57% | |
| Mean BMI (kg/m$^2$) | | 28.1 | (6.3)[a] | 27.3 | (5.7)[a] | <0.001 | 27.9 | (5.9)[a] | 27.2 | (5.8)[a] | <0.001 |
| Not recorded | | 4342 | 58% | 28,686 | 74% | | 3828 | 58% | 24,598 | 74% | |

$p$ indicates the $p$ value for a Chi-square or $t$-test (categorical or continuous variables, respectively) for people with versus without SMI.
[a] Indicates reporting of a standard deviation in place of a percentage.

than comparison people, whereas people aged over 75 with SMI had estimated risk scores that were approximately 1% lower (1.01% (0.50–1.52) for schizophrenia and 0.82% (0.17–1.46) for bipolar disorder) than comparison people.

Adjustment for strata of risk score (sensitivity analysis) produced similar results to Model 2, except amongst 60–74 year olds with bipolar disorder where the rate of statin initiation no longer differed relative to people without SMI (IRR 1.08 (0.98–1.19)). Modelling continuous CVD covariates in linear (as reported) or log linear form (data not shown) had negligible impact on the association between SMI status and statin prescribing in either the complete cases or imputed data.

## 4. Discussion

This study presents the first UK data on the initiation of statins prescribed to people with SMI for primary prevention of cardiovascular disease. The key findings are that rates of new statin prescribing to people with SMI are at or above levels in people without SMI, with the exception of elderly people with schizophrenia who were less frequently initiated on statins relative to those without SMI. Although the rates of initiation of statins remain higher amongst people aged 30–74 with SMI this has decreased in recent years relative to people without SMI, potentially reflecting increased numbers of prevalent statin users (O'Keeffe et al., 2016) and/or issues with continued engagement of this group with CVD screening and subsequent interventions. The decline in the initiation of statins prescribed to people without SMI after 2006 is in line with other studies and may reflect the initiation of statins at earlier time points (as this study excluded people with prior statin use) or increased reporting of adverse effects of these drugs (O'Keeffe et al., 2016).

Our finding that 30–59 year olds with SMI were more frequently initiated a statin than those without SMI differs markedly to historic studies that have reported lower levels of use amongst this group. For example, meta-analysis of 61 comparative studies estimated that people with SMI were 40% (OR 0.61 (0.39–0.94)) less likely than people without mental illness to be prescribed a statin (Mitchell et al., 2012). However, this estimate includes people with prior CVD diagnoses and combines data from a wide-variety of geographical locations and health systems (Mitchell et al., 2012) and there have been marked temporal changes in both the initiation of statins and the pool of people with on-going use (O'Keeffe et al., 2016), thus direct comparison is difficult. The relatively higher rate of statin initiation to younger people with SMI (compared to people without SMI of a similar age) identified in this study was not fully explained by differences in CVD risk amongst this group. However, our study confirms well-documented reports that people with SMI are more likely to have greater levels of socioeconomic deprivation and to have characteristics – such as a higher prevalence of diabetes (Osborn et al., 2008) and smoking than those without SMI (de Leon and Diaz, 2005) - that are associated with greater risk of CVD events and may warrant statin prescribing.

Despite twofold or higher rates of statin initiation amongst younger individuals with SMI, our results suggest that the oldest people with

**Table 2b**
Characteristics of the study population measured during the period January 2011 to December 2011.

| Characteristic | | $n = 6962$ | | $n = 38,910$ | | | $n = 6761$ | | $n = 36,029$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Schizophrenia | (%) | No SMI | (%) | $p$ | Bipolar disorder | (%) | No SMI | (%) | $p$ |
| Median age at start in years [IQR] | | 50 | [41–63] | 51 | [42–63] | 0.01 | 48 | [40–59] | 49 | [40–60] | 0.01 |
| Sex | Males | 4141 | 59% | 22,945 | 59% | 0.85 | 2554 | 38% | 13,771 | 38% | 0.64 |
| Diabetes | Yes | 448 | 6% | 1247 | 3% | <0.001 | 340 | 5% | 1054 | 3% | <0.001 |
| Antihypertensive | Yes | 1170 | 17% | 7123 | 18% | 0.003 | 1349 | 20% | 5887 | 16% | <0.001 |
| Smoker | | 2633 | 57% | 4817 | 33% | <0.001 | 2045 | 47% | 4280 | 31% | <0.001 |
| Not recorded | | 2344 | 34% | 24,193 | 62% | | 2412 | 36% | 22,143 | 61% | |
| Mean cholesterol (mmol/L) | | 5.3 | (1.1)[a] | 5.5 | (1.1)[a] | <0.001 | 5.5 | (1.1)[a] | 5.5 | (1.0)[a] | 0.09 |
| Not recorded | | 4112 | 59% | 31,349 | 81% | | 4170 | 62% | 29,699 | 82% | |
| Mean HDL-C (mmol/L) | | 1.3 | (0.5)[a] | 1.4 | (0.4)[a] | <0.001 | 1.4 | (0.5)[a] | 1.5 | (0.5)[a] | <0.001 |
| Not recorded | | 4435 | 64% | 32,230 | 83% | | 4437 | 66% | 30,453 | 85% | |
| Mean SBP (mmHg) | | 128 | (16)[a] | 133 | (16)[a] | <0.001 | 128 | (16)[a] | 131 | (16)[a] | <0.001 |
| Not recorded | | 2521 | 36% | 23,053 | 59% | | 2463 | 36% | 20,885 | 58% | |
| Mean BMI (kg/m$^2$) | | 28.1 | (6.3)[a] | 27.5 | (5.9)[a] | <0.001 | 28.1 | (6.0)[a] | 27.6 | (6.1)[a] | <0.001 |
| Not recorded | | 3136 | 45% | 29,251 | 75% | | 3174 | 47% | 26,915 | 75% | |

$p$ indicates the $p$ value for a Chi-square or $t$-test (categorical or continuous variables, respectively) for people with versus without SMI.
[a] Indicates reporting of a standard deviation in place of a percentage.

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**Table 2c**
Characteristics of the study population measured during the period January 2015 to December 2015.

| Characteristic | | $n = 4647$ | | $n = 28,522$ | | | $n = 4943$ | | $n = 28,075$ | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Schizophrenia | (%) | No SMI | (%) | p | Bipolar disorder | (%) | No SMI | (%) | p |
| Median age at start in years [IQR] | | 51 | [41–62] | 52 | [43–64] | <0.001 | 49 | [41–59] | 50 | [41–60] | <0.001 |
| Sex | Males | 2833 | 61% | 17,343 | 61% | 0.44 | 1816 | 37% | 10,636 | 38% | 0.45 |
| Diabetes | Yes | 406 | 9% | 1215 | 4% | <0.001 | 360 | 7% | 1071 | 4% | <0.001 |
| Antihypertensive | Yes | 930 | 20% | 5893 | 21% | 0.31 | 1253 | 25% | 5402 | 19% | <0.001 |
| Smoker | | 1583 | 57% | 3178 | 35% | <0.001 | 1371 | 45% | 3053 | 33% | <0.001 |
| Not recorded | | 1861 | 40% | 19,444 | 68% | | 1902 | 38% | 18,845 | 67% | |
| Mean cholesterol (mmol/L) | | 5.3 | (1.4)[a] | 5.3 | (1.1)[a] | <0.001 | 5.4 | (1.1)[a] | 5.4 | (1.0)[a] | 0.04 |
| Not recorded | | 2932 | 63% | 23,152 | 81% | | 3092 | 63% | 23,083 | 82% | |
| Mean HDL-C (mmol/L) | | 1.3 | (0.4)[a] | 1.5 | (0.4)[a] | <0.001 | 1.4 | (0.7)[a] | 1.5 | (0.5)[a] | <0.001 |
| Not recorded | | 3030 | 65% | 23,469 | 82% | | 3182 | 64% | 23,375 | 83% | |
| Mean SBP (mmHg) | | 127 | (15)[a] | 133 | (16)[a] | <0.001 | 126 | (15)[a] | 130 | (16)[a] | <0.001 |
| Not recorded | | 1807 | 39% | 18,162 | 64% | | 1715 | 35% | 17,500 | 62% | |
| Mean BMI (kg/m$^2$) | | 28.5 | (6.7)[a] | 27.8 | (6.2)[a] | <0.001 | 28.5 | (6.6)[a] | 27.8 | (6.4)[a] | <0.001 |
| Not recorded | | 2539 | 55% | 22,450 | 78% | | 2627 | 53% | 21,832 | 78% | |

*p* indicates the *p* value for a Chi-square or *t*-test (categorical or continuous variables, respectively) for people with versus without SMI.
[a] Indicates reporting of a standard deviation in place of a percentage.

schizophrenia have lower rates than people without SMI. Explanation of these lower rates of prescribing to people with SMI could reflect a number of scenarios including differences in those already prescribed a statin or lower uptake of CVD screening amongst older people with SMI than older people without SMI, or a lack of clarity regarding prescribing to individuals aged over 75 years. Other studies investigating provision of cardiovascular medication for secondary prevention to people with SMI suggest that greater severity of mental illness and schizophrenia as associated with lower frequency of prescribing (Woodhead et al., 2016; Mitchell et al., 2012). In our study there was some evidence that older people (75+ years) with SMI might have slightly lower CVD risk than comparison people, potentially reflecting a healthy survivor effect of those with less severe mental illness. However, the rate of statin initiation to the oldest people with schizophrenia remained lower than for comparison people after statistical adjustment for these differences. Furthermore, it should be noted that the Framingham risk score is not validated for ages >74 years and thus results for older ages should be interpreted with caution.

Numerous policy changes and delays between their publication and official implementation makes establishing the impact of individual policies on statin prescribing difficult to establish. However, our study indicates that fluctuations in new statin prescribing to people with SMI coincide with some policy changes. In particular, the rise in statin initiation to people with SMI between 2010 and 2012 corresponds with introduction of an incentive scheme for GPs in England to screen for cholesterol and CVD risk in people with SMI (Qureshi et al., 2016). Perhaps surprisingly, our results (Fig. 2) provide no indication that the decreased threshold of CVD risk for statin prescribing for primary prevention (reducing the risk threshold from 20% ten year risk to 10% in 2014) (National Institute for Health and Clinical Excellence, 2014b; National Institute for Health and Clinical Excellence, 2008) has been accompanied by increased prescribing rates. Future research evaluating of the impact of primary prevention strategies on CVD events in people with and without SMI is needed and could help optimise future policy for prevention.

Our study has some important limitations. In particular, because our data do not routinely capture CVD risk scores that were estimated by the GP it was not possible to examine the proportion of people who were screened, subsequently determined to have high risk (i.e. >10% after 2014) and who then received statins. Given the excess CVD

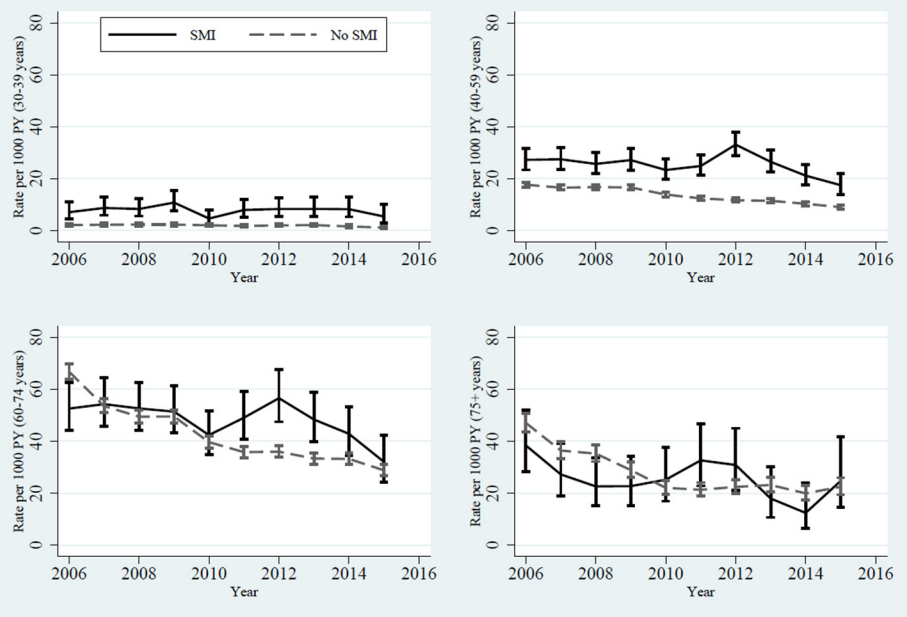


**Fig. 2.** The crude rate of new statin prescribing to individuals with and without SMI by calendar year between January 2006 and December 2015.

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**Table 3**
Crude rates of statin initiation and adjusted incident rate ratios for statin prescribing in people with (versus without) severe mental illness.

| SMI type | Age group (yrs) | SMI | | No SMI | | Adjusted IRR: Model 1 | | | Adjusted IRR: Model 2 | | | Sensitivity analysis Adjusted IRR: Model 3 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Crude rate | 95% CI | Crude rate | 95% CI | aIRR | 95% CI | *p* value | aIRR | 95% CI | *p* value | aIRR | 95% CI | *p* value |
| Schizophrenia | 30–39 | 11.4 (9.53–13.6) | | 2.33 (2.07–2.63) | | 4.77 (3.84–5.93) | | <0.001 | 3.26 (2.48–4.29) | | <0.001 | 3.54 (2.75–4.54) | | <0.001 |
| | 40–59 | 30.1 (28.1–32.3) | | 16.54 (16.1–17.0) | | 1.70 (1.58–1.84) | | <0.001 | 1.68 (1.53–1.82) | | <0.001 | 1.50 (1.38–1.63) | | <0.001 |
| | 60–74 | 53.0 (49.1–51.4) | | 50.29 (49.1–57.2) | | 1.00 (0.92–1.08) | | 0.94 | 1.00 (0.91–1.11) | | 0.93 | 0.92 (0.84–1.01) | | 0.08 |
| | 75–99 | 31.8 (27.3–36.9) | | 37.87 (36.5–39.3) | | 0.69 (0.60–0.81) | | <0.001 | 0.81 (0.66–0.98) | | 0.03 | 0.76 (0.63–0.92) | | 0.005 |
| Bipolar disorder | 30–39 | 5.79 (4.58–7.30) | | 1.97 (1.73–2.25) | | 2.86 (2.22–3.70) | | <0.001 | 2.24 (1.64–3.07) | | <0.001 | 2.29 (1.69–3.08) | | <0.001 |
| | 40–59 | 25.4 (23.6–27.4) | | 13.69 (13.2–14.1) | | 1.70 (1.57–1.83) | | <0.001 | 1.68 (1.53–1.84) | | <0.001 | 1.46 (1.34–1.60) | | <0.001 |
| | 60–74 | 57.1 (44.1–46.6) | | 45.35 (52.6–62.1) | | 1.22 (1.12–1.33) | | <0.001 | 1.15 (1.03–1.28) | | 0.01 | 1.08 (0.98–1.19) | | 0.12 |
| | 75–99 | 35.7 (30.1–42.2) | | 37.86 (36.2–39.6) | | 0.86 (0.72–1.02) | | 0.09 | 0.92 (0.74–1.15) | | 0.47 | 0.92 (0.74–1.13) | | 0.44 |

Model 1 covariates: age, gender, Townsend score.
Model 2 covariates: age, gender, Townsend score, diabetes, antihypertensive use, smoking status, total cholesterol, HDL-C, BMI, systolic blood pressure.
Model 3 covariates: age, gender, Townsend score, CVD risk score.

morbidity in this group, it is important to keep emphasising the need for early CVD screening and intervention in this group and future studies could focus on this pathway. We were also not able to investigate uptake of other interventions such as lifestyle modifications including dietary changes or over the counter sales of low-dose simvastatin, although uptake via this route is likely to be low due to unfavourable costs relative to prescribed medication. Our study was restricted to the analysis of data for people registered with a general practice. Whilst this population is largely representative of the UK, certain groups at high risk of mental illness (e.g. prisoners and the homeless) are likely to be missed.

Due to substantial missing data it was necessary to use multiple imputation prior to statistical adjustment for differences in cardiovascular characteristics between people with and without SMI. Whilst multiple imputation is the best available method for estimating values that are not missing completely at random it is possible that some residual confounding may remain, which could conceivably bias our estimates in either direction. Conventional CVD risk scores such as Framingham do not reliably predict CVD risk in people with SMI and may underestimate the risk of CVD events relative to people without SMI (Osborn et al., 2015). In our study differentially underestimating CVD risk for SMI groups relative to the comparison groups would tend to mask unmet prescribing needs amongst the SMI group. However, differences in age and sex (key predictors of CVD (D'Agostino et al., 2008; Hippisley-Cox et al., 2008)) were controlled for at both the study design and analysis stage and data on diabetes and antihypertensive medication were fully observed, thereby improving control for confounding.

We conclude that for primary prevention of CVD younger people with SMI have comparable or higher rates of statin initiation than people without SMI; however, the magnitude of this difference appears to be in decline in recent years. For older people with schizophrenia there are lower rates of statin initiation, and this requires further attention to determine whether opportunities - such as screening - to prevent CVD are being missed.

## Ethical approval

The THIN scheme for obtaining and providing anonymous patient data to researchers was approved by the National Health Service South-East Multicentre Research Ethics Committee (MREC) in 2002. Approval for this study was obtained from the Scientific Review Committee on 11th July 2013.

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### Contributors

RB, IP, KW and DO developed the study design and protocol, RB developed the statistical code, extracted and analysed the data under the supervision of IP, KW and DO. DO, KW and IN advised on context and clinical interpretation of the findings. RB drafted the manuscript for further development and review by all co-authors. RB is the guarantor for the study.

## Conflicts of interest

There are no conflicts of interest to report for any of the authors.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2017.05.028.

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