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Management of dyslipidaemia in individuals with severe mental illness: a population-based study in the Greater Copenhagen Area

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Abstract

Background: Severe mental illness (SMI) is associated with increased cardiovascular risk. Dyslipidaemia is a potentially modifiable risk factor, which may be inadequately managed in patients with SMI.

Objectives: To assess management of dyslipidaemia in patients with SMI *versus* healthy controls (HCs) in 2005 and 2015.

Design and methods: Using Danish registers, we identified adult patients with SMI in the Greater Copenhagen Area (schizophrenia spectrum disorders or bipolar disorder) with ⩾1 general practitioner contact in the year before 2005 and 2015, respectively, and HCs without SMI matched on age and gender (1:5). Outcomes were lipid-profile measurements, presence of dyslipidaemia and redemption of lipid-lowering pharmacotherapy. Differences in outcomes between patients with SMI and controls were measured with multivariable logistic regression.

Results: We identified 7217 patients with SMI in 2005 and 9939 in 2015. After 10 years, patients went from having lower odds of lipid measurements to having higher odds of lipid measurements compared with HCs [odds ratio (OR)$_{2005}$ 0.70 (99% confidence interval (CI) 0.63–0.78) *versus* OR$_{2015}$ 1.34 (99% CI 1.24–1.44); $p_{2005versus2015} < 0.01$]. Patients had higher odds of dyslipidaemia during both years [OR$_{2005}$ 1.43 (99% CI 1.10–1.85) and OR$_{2015}$ 1.23 (99% CI 1.08–1.41)]. Patients went from having lower odds of receiving lipid-lowering pharmacotherapy to having higher odds of receiving lipid-lowering pharmacotherapy [OR$_{2005}$ 0.77 (99% CI 0.66–0.89) *versus* OR$_{2015}$ 1.37 (99% CI 1.24–1.51); $p_{2005versus2015} < 0.01$]. However, among persons at high cardiovascular risk, patients had lower odds of receiving lipid-lowering pharmacotherapy during both years, including subsets with previous acute coronary syndrome [OR$_{2005}$ 0.30 (99% CI 0.15–0.59) and OR$_{2015}$ 0.44 (99% CI 0.24–0.83)] and ischaemic stroke or transient ischaemic attack (TIA) [OR$_{2005}$ 0.43 (99% CI 0.26–0.69) and OR $_{2015}$ 0.61 (99% CI 0.41–0.89)].

Conclusion: These results imply an increased general awareness of managing dyslipidaemia among patients with SMI in the primary prophylaxis of cardiovascular disease. However, secondary prevention with lipid-lowering drugs in patients with SMI at high cardiovascular risk may be lacking.

Keywords: bipolar disorder, dyslipidaemia, lipid-lowering pharmacotherapy, schizophrenia, severe mental illness

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Introduction

Severe mental illness (SMI), such as schizophrenia spectrum disorders (SSDs) and bipolar disorder (BD) affects around 1% of the world population and is associated with a reduced life-expectancy of 10–20 years.[1,2] A recent large meta-analysis estimated that patients with SMI are at 53% higher risk of atherosclerotic cardiovascular disease (CVD) and at 85% higher risk of dying from atherosclerotic CVD compared with healthy controls (HCs).[3] Modifiable cardiovascular risk factors are often under-recognized and under-treated in patients with SMI in both primary and secondary prevention.[4–6] A combination of patient-related factors including cognitive impairment, compromised communication skills, limited comprehension of medical advices, poor self-awareness and social isolation as well as physician-related factors such as stigmatization of mental illness and diagnostic overshadowing may contribute to this treatment-gap,[7] which is likely to account for the premature cardiovascular mortality in patients with SMI compared with the background population.[8–11] Therefore, improvements in the management of modifiable risk factors for atherosclerotic CVD in patients with SMI are crucial.

Dyslipidaemia is an important modifiable risk factor for atherosclerotic CVD and patients with SMI have a higher prevalence of dyslipidaemia compared with the background population.[12–14] Antipsychotics, especially clozapine and olanzapine, have been associated with lipid abnormalities *via* both weight-related and weight-independent mechanisms.[13,15–17] Sedentary lifestyle, poor dietary patterns, low socioeconomic status with regard to educational level, social deprivation, unhealthy living situations and, hereby, increased prevalence of obesity may also contribute to this association.[13,18] Moreover, smoking and alcohol consumption, which are more common among patients with SMI, are also associated with lipid disturbances.[19] In Denmark, the responsibility of managing dyslipidaemia in patients with SMI traditionally lies with the general practitioner (GP), but evidence regarding the assessment and management of dyslipidaemia in patients with SMI in primary care settings is lacking. In this register-based study of individuals with recent contact to a GP in the Greater Copenhagen Area, we investigated lipid profile measurements as well as presence of dyslipidaemia and redemption of lipid-lowering pharmacotherapy in patients with SMI *versus* HCs without SMI in 2005 and 2015.

Method

Data sources

The CopLab database. In the Greater Copenhagen Area, one laboratory denoted the Copenhagen General Practitioners' Laboratory served the primary sector from 2000 to 2015 with a broad range of laboratory tests. The Copenhagen Primary Care Laboratory (CopLab) database contains all results of these test results from 1.3 million individuals.[20]

National health registries. Individual-level linkage of information between nationwide registries in Denmark is possible due to a unique and permanent civil registration number, which is assigned to all Danish citizens from birth or date of immigration. Age, sex and vital status were identified through the Danish Civil Registration System.[21] Information regarding somatic hospital admissions was identified using the Danish National Patient Registry, which holds information on all Danish inpatient and outpatient hospital contacts in relation to the 10th International Classification of Diseases (ICD-10) since 1994.[22] The Danish Psychiatric Central Research Register includes ICD diagnosis codes for psychiatric hospitalizations (since 1970) and ambulatory contacts (since 1995).[23] The National Prescription Registry contains information on redeemed prescriptions by outpatients from all Danish pharmacies according to the Anatomical Therapeutic Chemical (ATC) system.[24] The National Health Insurance Register contains data on activities that are supported by the National Health Insurance system including contacts to GPs.[25] Data on level of education were obtained from the Registry of Education of Statistics Denmark.[26]

Study sample

From the Danish Psychiatric Central Research Register, we identified adult patients with SMI as individuals who had in- or outpatient contact in hospital settings with primary or secondary diagnosis codes of SSD or BD (see Supplemental Table S1 for ICD-10 codes). Since these diagnoses represent chronic and often lifelong illnesses, we included patients with hospital contacts up to 5 years before 1st January in either 2005 or 2015 (index dates). When more than one diagnosis was registered, the individual patient was assigned to the most severe illness category in relation to the diagnostic hierarchical order in ICD-10, as done

previously.[27,28] Since the CopLab only served the primary care sector in the Greater Copenhagen Area, we included patients with address in the Greater Copenhagen Area at the index dates, who also had at least one contact with a GP up to 1 year before index dates.

Patients with SMI were matched 1:5 on age and gender to HCs, that is, individuals without hospital contacts for any mental disorders up to 5 years before index dates, and who did not redeem prescriptions for antipsychotics, antidepressants or lithium (see Supplemental Table S2 for ATC codes) up to 180 days prior to the index dates. HCs also had addresses in the Greater Copenhagen Area and had at least one contact to a GP within 1 year prior to the index dates. The included contacts from The National Health Insurance Register can be found in Supplemental Table S3.

Measures

Outcomes. The outcomes were measurement of lipid profile and presence of dyslipidaemia as documented in the CopLab database, and redeemed prescriptions for lipid-lowering medication identified through the the National Prescription Registry during 2005 and 2015.

We included the following lipid parameters measured in mmol/l: total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, non-HDL cholesterol and triglycerides (see Supplemental Table S4 for codes for the individual biomarkers). We calculated a yearly median for individuals with the same analysis performed multiple times each year. From such individual medians, a yearly population median ('median of medians') was derived. We also calculated the number of individuals with a measurement or yearly medians above or below clinically relevant thresholds for each lipid parameter during 2005 and 2015 in accordance with treatment targets defined in guidelines by the European Society of Cardiology, European Atherosclerosis Association and the Danish Society of Cardiology.[12,29] Dyslipidaemia was defined as measurements with elevated LDL cholesterol (>3.0 mmol/l) or elevated triglycerides (>1.7 mmol/l) or low HDL cholesterol (<1.0 mmol/l in men and <1.2 mmol/l in women) during 2005 or 2015. The term '*presence of dyslipidaemia*' refers to individuals in our study who received lipid-profile measurements and does not represent the entire study population.

The percentage of the study population on lipid-lowering pharmacotherapy during 2005 and 2015 was identified as redemption of at least one prescription for lipid-lowering drugs (ATC codes C10) within the given year through The National Prescription Registry.

Comorbidities and medication. The somatic comorbidities ischaemic heart disease, congestive heart failure, chronic obstructive pulmonary disease, peripheral artery disease (PAD), cerebrovascular disease and chronic kidney disease were identified using ICD-10 codes for primary and secondary diagnoses from hospital contacts in the Danish National Patient Registry up to 5 years before index dates. Diabetes was defined as (1) at least one redeemed prescription on glucose-lowering medication up to 180 days prior to index dates, (2) a hospital diagnosis up to 5 years prior to index dates or (3) a test result in the CopLab database of plasma or serum glucose ⩾11 mmol/l or haemoglobin A1c ⩾48 mmol/mol (6.5%) up to 5 years before index dates. Substance-induced mental disorders were identified using ICD-10 codes for primary and secondary diagnoses from hospital contacts in the Danish Psychiatric Central Research Register up to 5 years before index dates. Concomitant pharmacotherapy was defined as at least one redeemed prescription up to 90 days before index dates. We included information on use of antithrombotic agents, antihypertensive agents, antipsychotics, lithium, anticonvulsants, antidepressants, benzodiazepines and sedatives/hypnotics. Codes used to define comorbidities and concomitant pharmacotherapy are listed in Supplemental Tables S1 and S5.

Educational level. Educational attainment was classified into three categories according to the International Standard Classification of Education (ISCED) system (UNESCO 1997): ⩽10 years of education = primary or lower secondary education (ISCED level 0–2), 11–12 years of education = upper secondary education (ISCED level, 3) and ⩾13 years of education = post-secondary and tertiary education (ISCED level 4–6).

Statistical analysis

The data were presented descriptively as counts with percentages for categorical variables and as medians with interquartile ranges (IQRs) for continuous variables. Differences in outcomes between patients with SMI and HCs during 2005 and 2015, respectively, were tested by multivariable

logistic regression adjusted for age, gender and level of education. The models for lipid measurements were additionally adjusted for the somatic comorbidities listed in Table 1. Subjects selected in the study, notably SMI patients, could appear up to two times in the data, in 2005 and in 2015. Each SMI case was matched with HCs for each appearance in the data separately. The excess correlation between matched groups and between repeated observations on each study participant was adjusted for with generalized estimation equations. The level of statistical significance was set as $p < 0.01$. All statistical analyses were performed in SAS 9.4 (SAS Institute Inc., Cary, NC, USA).

Subgroup analyses. We performed subgroup analyses using the same methods as described above.

Firstly, we tested for differences in the outcomes between patients with BD *versus* patients with SSD, that is, the analyses as above where the SMI group was subdivided into BD and SSD. Moreover, as a proxy for severity of SMI and since antipsychotic pharmacotherapy is associated with dyslipidaemia, we performed subgroup analyses of outcomes amongst patients with SMI who redeemed antipsychotic medical treatment up to 90 days before index dates using patients with SMI without antipsychotic treatment as reference. Treatment with lipid-lowering medication is strongly recommended in guidelines for individuals at high or very high cardiovascular risk.[12,29] Therefore, we investigated differences in the odds of redeeming lipid-lowering pharmacotherapy in the subsets with diabetes, acute coronary syndrome (ACS), chronic ischaemic heart disease, PAD, chronic kidney disease and ischaemic stroke or transient ischaemic attack (TIA), respectively. A brief description of how secondary prevention of CVD is organized in Denmark is available in Supplemental Material.

Results

Characteristics

We identified 7217 patients with SMI and 36,085 HCs in 2005 and 9939 patients and 49,695 HCs in 2015 (Figure 1). The median age was 46 (IQR 35–58) years in 2005 and 43 years (IQR 30–56) in 2015 (Table 1). At both timepoints, patients with SMI had a higher burden of comorbidity and a lower educational level than HCs. Characteristics of patients with SSD or BD are listed in Supplemental Table S6.

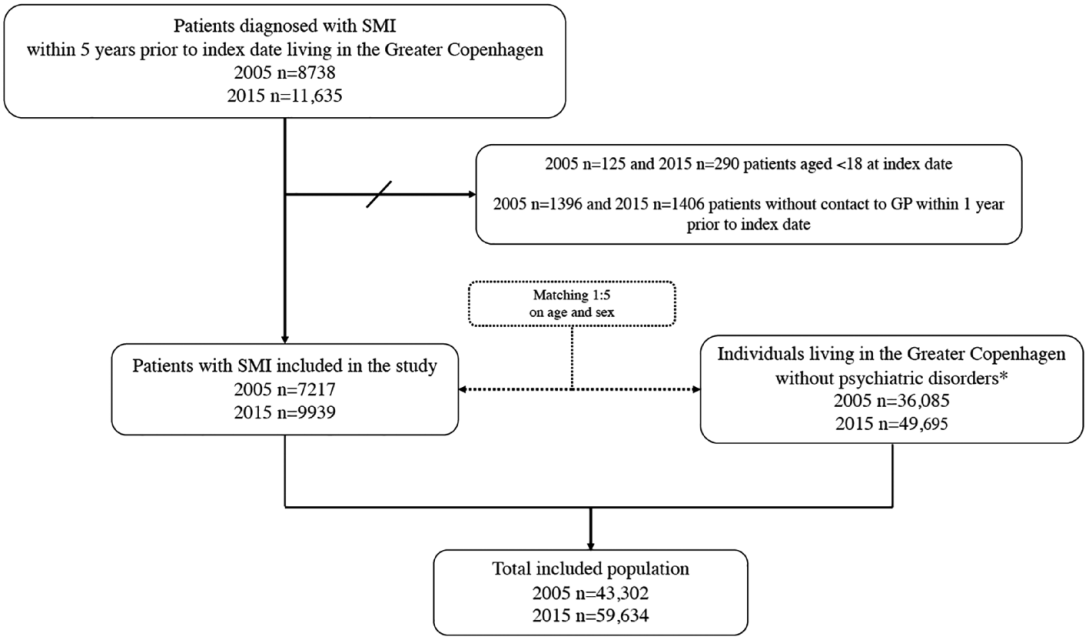

Figure 1. Study design and patient selection during 2005 and 2015.
*Patients without contacts in the Danish Psychiatric Central Register for any mental disorders up to 5 years prior to the index dates and no redeemed prescriptions for antipsychotics, antidepressants, or lithium up to 180 days prior to the index dates.
GP, general practitioner; SMI, severe mental illness.

Table 1. Characteristics of patients with SMI and the control population.

Characteristics	2005		2015	
	Patients with SMI (7217)	Healthy Controls (36,085)	Patients with SMI (9939)	Healthy Controls (49,695)
Median age, year (IQR)	46 (35–58)	46 (35–58)	43 (30–56)	43 (30–56)
Men, no. (%)	3477 (48.2%)	17,385 (48.2%)	4929 (49.6%)	24,645 (49.6%)
Comorbidities				
Ischaemic heart disease, no. (%)	193 (2.7%)	983 (2.7%)	263 (2.7%)	1033 (2.1%)
Congestive heart failure, no. (%)	130 (1.8%)	440 (1.2%)	120 (1.2%)	411 (0.8%)
COPD, no. (%)	203 (2.8%)	550 (1.5%)	409 (4.1%)	580 (1.2%)
PAD, no. (%)	61 (0.9%)	272 (0.8%)	82 (0.8%)	334 (0.7%)
Cerebrovascular disease, no. (%)	214 (3.0%)	599 (1.7%)	291 (2.9%)	670 (1.4%)
Diabetes, no. (%)	539 (7.5%)	1536 (4.3%)	944 (9.5%)	2428 (4.9%)
Chronic kidney disease, no. (%)	91 (1.3%)	188 (0.5%)	129 (1.3%)	352 (0.7%)
Substance-induced mental disorders, no. (%)	1734 (24.0%)	405 (1.1%)	3064 (30.8%)	953 (1.9%)
Educational position				
Missing, no. (%)	533 (7.4%)	2107 (5.8%)	445 (4.5%)	2254 (4.5%)
Low, no. (%)	3125 (43.3%)	9027 (25.0%)	4380 (44.0%)	10,354 (20.8%)
Medium, no. (%)	2361 (32.7%)	14,639 (40.6%)	3241 (32.6%)	19,166 (38.6%)
High, no. (%)	1198 (16.6%)	10,312 (28.6%)	1873 (18.8%)	17,921 (36.1%)
Concomitant pharmacotherapy				
Antithrombotic agents, no. (%)	461 (6.4%)	2205 (6.1%)	649 (6.5%)	2600 (5.2%)
Antihypertensive agents, no. (%)	837 (11.6%)	5060 (14.0%)	1195 (12.0%)	6273 (12.6%)
Antipsychotics, no. (%)	3599 (50.0%)	0	4381 (44.1%)	0
Lithium, no. (%)	514 (7.1%)	0	721 (7.3%)	0
Anticonvulsants, no. (%)	353 (4.9%)	122 (0.3%)	1008 (10.1%)	185 (0.4%)
Antidepressants, no. (%)	2063 (28.6%)	0	2113 (21.3%)	0
Benzodiazepines, no. (%)	1275 (17.7%)	1136 (3.2%)	965 (9.7%)	520 (1.1%)
Sedatives/hypnotics, no. (%)	1293 (17.9%)	1318 (3.7%)	1104 (11.1%)	991 (2.0%)

COPD, chronic obstructive pulmonary disease; IQR, interquartile range; PAD, peripheral artery disease; SMI, severe mental illness.

Lipid profile measurements

In adjusted logistic regression analyses, patients with SMI went from having lower odds of lipid profile measurements to having higher odds of lipid profile measurements compared with HCs after 10 years [odds ratio $(OR)_{2005}$ 0.70 (99% confidence interval (CI) 0.63–0.78) *versus* OR_{2015} 1.34 (99% CI 1.24–1.44); $p_{2005versus2015} < 0.01$] (Figure 2 and Supplemental Table S7). Compared with HCs, patients with SMI had higher odds of

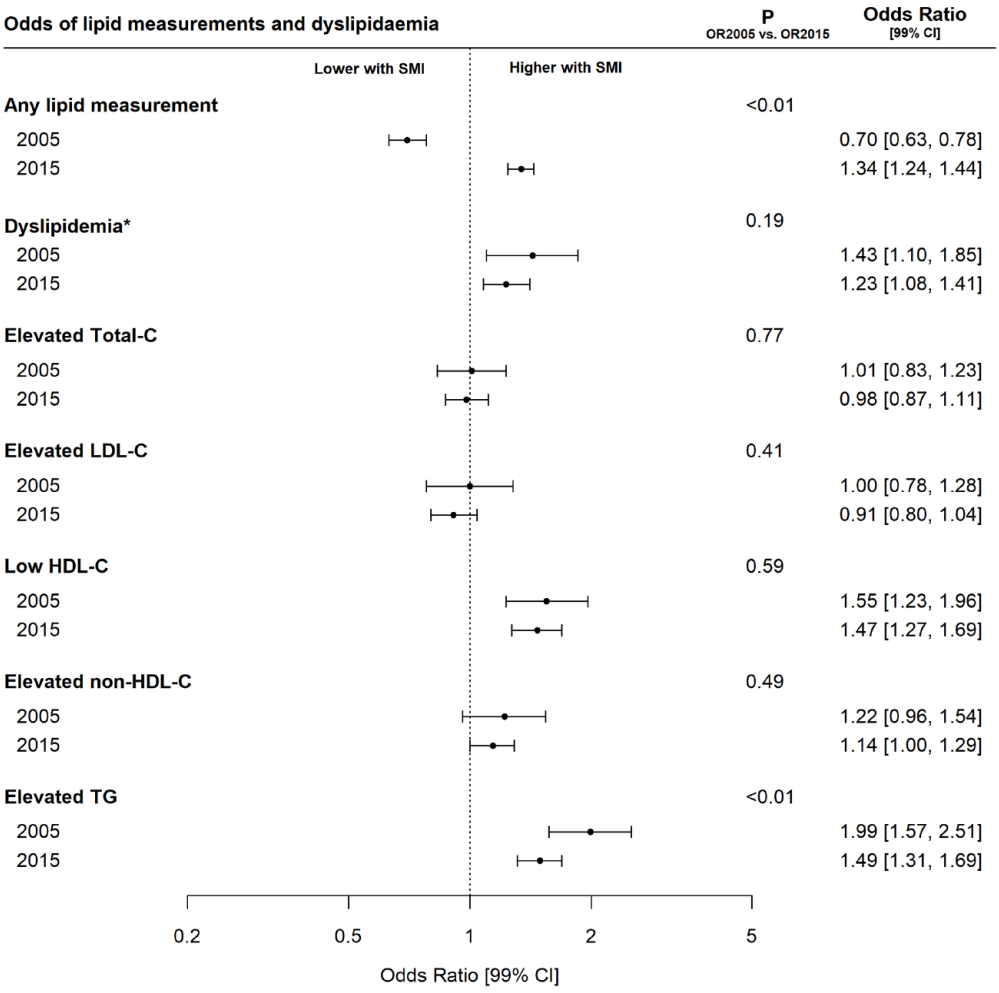

Figure 2. Odds of having lipid biomarker measurements and dyslipidaemia in patients with SMI *versus* healthy controls without SMI during 2005 and 2015. The logistic regression models were adjusted for age, gender and the somatic comorbidities listed in Table 1 and educational position. Information regarding number of persons contributing to the analyses, biochemical thresholds for elevated/low lipid parameters and odds of having measured the individual lipid profile parameters is available in Supplemental Table S7.
*Defined as individuals with elevated LDL-C, elevated triglycerides, or low HDL-C.
C, Cholesterol; CI, confidence interval; HDL, high-density lipoprotein; LDL, low-density lipoprotein; OR, odds ratio; SMI, severe mental illness; TG, triglycerides.

dyslipidaemia during both years [OR_{2005} 1.43 (99% CI 1.10–1.85) *versus* OR_{2015} 1.23 (99% CI 1.08–1.41); $p_{2005versus2015} = 0.19$]. There was no evidence of differences in the odds of having elevated total cholesterol, elevated non-HDL-cholesterol or elevated LDL-cholesterol between patients with SMI and HCs. However, during both years patients with SMI as compared with HCs had higher odds of low HDL-cholesterol [OR_{2005} 1.55 (99% CI 1.23–1.96) *versus* OR_{2015} 1.47 (99% CI 1.27–1.69); $p_{2005versus2015} = 0.59$] and elevated triglycerides [OR_{2005} 1.99 (99% CI 1.57–2.51) *versus* OR_{2015} 1.49 (99% CI 1.31–1.69); $p_{2005versus2015} < 0.01$].

Patients with SSD had lower odds of having lipid profile measurements compared with patients with BD. There was no evidence of a difference in the odds of dyslipidaemia in patients with SSD as compared with patients with BD (Supplemental Table S8). Patients in treatment with antipsychotics had higher odds of having lipid profile measurements compared with patients not in treatment with

antipsychotics, but there was no evidence of a difference in the odds of dyslipidaemia during both years (Supplemental Table S9).

The median values and corresponding IQR of all lipid profile parameters in patients with SMI and HCs are listed in Supplemental Table S10.

Lipid-lowering pharmacotherapy

In adjusted logistic regression analyses, patients with SMI as compared with HCs went from having lower odds of receiving lipid-lowering pharmacotherapy to having higher odds of receiving lipid-lowering pharmacotherapy after 10 years [OR_{2005} 0.77 (99% CI 0.66–0.89) *versus* OR_{2015} 1.37 (99% CI 1.24–1.51); $p_{2005versus2015} < 0.01$] (Figure 3 and Supplemental Table S11). Among the subsets at high or very high cardiovascular risk, patients with SMI had lower odds of receiving lipid-lowering pharmacotherapy compared with HCs, for example, amongst the subsets with previous ACS [OR_{2005} 0.30 (99% CI 0.15–0.59) *versus* OR_{2015} 0.44 (99% CI 0.24–0.83); $p_{2005versus2015} = 0.26$] and ischaemic stroke or TIA [OR_{2005} 0.43 (99% CI 0.26–0.69) *versus* OR_{2015} 0.61 (99% CI 0.41–0.89); $p_{2005versus2015} = 0.14$]. There was only evidence of a significant increase in the odds of receiving lipid-lowering pharmacotherapy in patients with SMI as compared

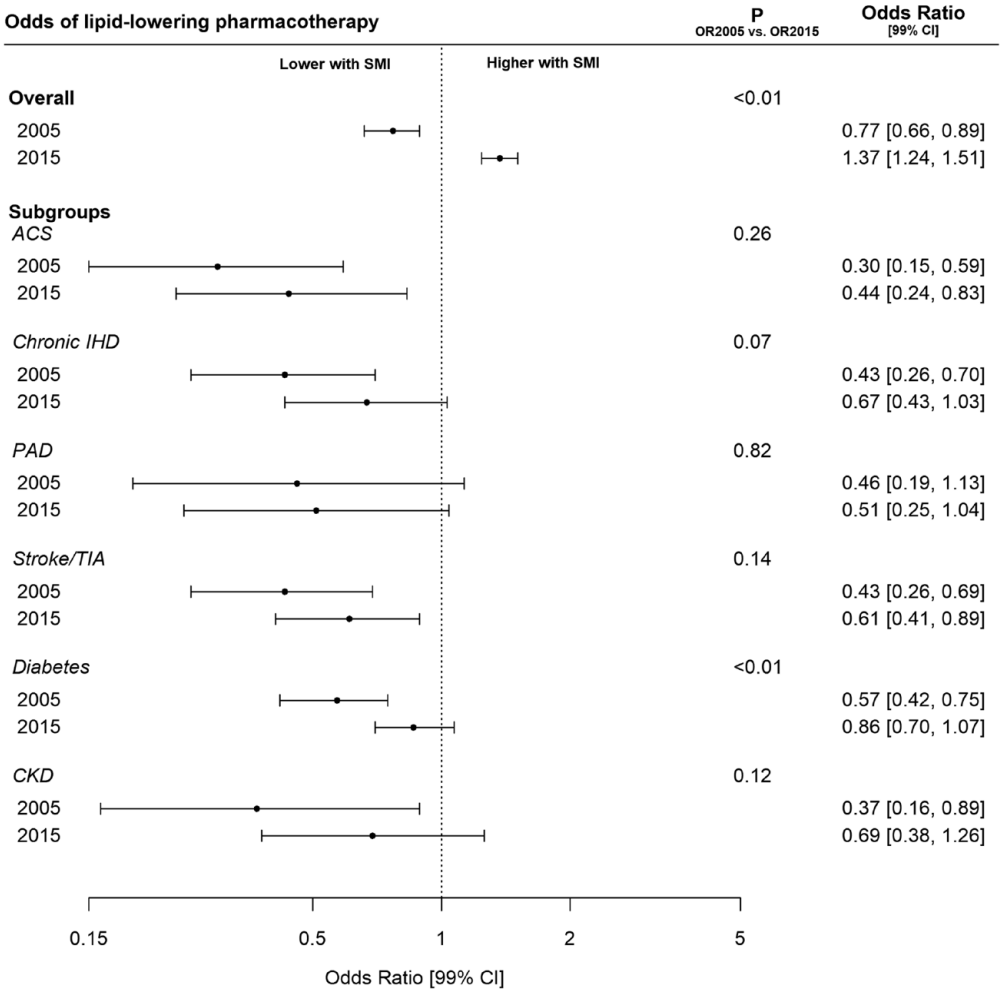

Figure 3. Odds of redeeming prescriptions on lipid-lowering pharmacotherapy in patients with SMI *versus* healthy controls without SMI during 2005 and 2015. The logistic regression models were adjusted for age, gender and educational position. Subgroups are defined as persons with previous hospital contacts for the individual diseases up to 5 years before January 1st in 2005 and 2015, respectively. Information regarding number of persons contributing to the analyses is available in Supplemental Table S11.
ACS, acute coronary syndrome; CKD, chronic kidney disease; CI, confidence interval; IHD, ischaemic heart disease; OR, odds ratio; PAD, peripheral artery disease; SMI, severe mental illness; Stroke/TIA, ischaemic stroke or transient ischaemic attack.

with HCs amongst the subsets who had diabetes from 2005 to 2015.

Patients with SSD had lower odds of receiving lipid-lowering pharmacotherapy as compared with patients with BD in 2015 amongst the subsets with previous ischaemic stroke or TIA. There was no other evidence of statistically significant differences in the odds of receiving lipid-lowering pharmacotherapy between patients with SSD *versus* BD (Supplemental Table S12). Patients in treatment with antipsychotics went from having no evidence of a difference to having higher odds of receiving lipid-lowering pharmacotherapy as compared with patients not in treatment with antipsychotics from 2005 to 2015 (Supplemental Table S13).

Discussion

In this population-based study, we investigated lipid profile measurements as well as presence and medical treatment of dyslipidaemia during 2005 and 2015 in patients with SMI and HCs without SMI who had a recent contact to a GP and who were living in the Greater Copenhagen Area. Over a 10-year period, patients with SMI as compared with HCs went from having lower odds to having higher odds of lipid profile measurements and lipid-lowering pharmacotherapy. However, patients with SMI were less likely to receive lipid-lowering pharmacotherapy for secondary prevention, and this did not improve after 10 years – particularly among persons with ACS and ischaemic stroke or TIA. The odds of dyslipidaemia were significantly higher among patients with SMI compared to HCs during both 2005 and 2015. This was due to lower levels of HDL-cholesterol and higher levels of triglycerides. We did not find evidence of differences in the level of total cholesterol, non-HDL-cholesterol or elevated LDL-cholesterol between the two groups.

Measurements of lipid-profile

During the last two decades, specific guidelines and treatment recommendations for dyslipidaemia with special awareness on patients with SMI have been developed.[1,14,30–33] Concordantly, our study showed that the odds of having lipid profile measurements in 2015 compared to 2005 went from being significantly lower to significantly higher among patients with SMI as compared with HCs. Moreover, in contrast with the current literature,[1,30,34,35] we also found that the odds of having lipid profile measurements in patients treated with antipsychotics increased. Several factors may explain these encouraging observations. Our population was composed of individuals who had at least one contact to a GP within 1 year prior to the index date. This could have selected a group of patients with SMI and good compliance. The number of primary care provider visits has been identified as a strong predictor for lipid monitoring.[34] It may be speculated that the implementation of standard screening protocols and the numerous studies showing the negative effect of dyslipidaemia on cardiovascular outcomes in patients with SMI have raised awareness in more recent years with regards to lipid monitoring in these patients.[1,3] Moreover, differences in the healthcare system between Denmark and the USA, where the vast majority of previous studies have been carried out, may also have played a role.[36]

Patients with SSD had lower probability of having their blood lipid profile measured in both 2005 and 2015 compared to patients with BD. However, we found no evidence that the odds of dyslipidaemia differed in patients with SSD and BD. This may indicate differences in the screening strategies for dyslipidaemia between the two groups. It may be hypothesized that, in our population, a larger proportion of patients with BD get screened for dyslipidaemia, while only patients with a baseline higher risk receive lipid-measurements in SSD, since these two disorders seem to have a similar overall presence of dyslipidaemia.

Presence of dyslipidaemia

The overall presence of dyslipidaemia in our psychiatric population was higher compared with previous estimates.[37–40] Compared to a previous Danish study including patients at first-time schizophrenia diagnosis,[37] we found an approximately 20% higher presence of dyslipidaemia (70–80% *versus* 58%), which may be explained by an overall older population with longer duration of mental illness and different cut-off for LDL- and HDL-cholesterol. Similarly, the use of ICD-codes to define dyslipidaemia in a study from China may account for the much lower estimates compared to ours.[39] Moreover, we speculate that the high presence of dyslipidaemia, which we observed, may be primarily caused by the fact that the included patients had contact with their

GP in the preceding year and were further selected by the GP to have their lipid profile measured. Our estimates for dyslipidaemia were similar to a retrospective study from Poland including patients with SSD and BD hospitalised in the acute phase of their disorder, where they reported hyperlipidaemia in 80–85% of the included population.[41]

As in previous studies,[17,39,42] we found that patients with SMI as compared to HCs were more likely to have dyslipidaemia. In addition, we observed that SMI was associated with higher odds of having lower level of HDL-cholesterol and a higher level of triglycerides compared with HCs. Importantly, these two are core components of the metabolic syndrome, which is strongly associated with CVD.[40] Conversely, we did not find evidence of significant differences in the level of total cholesterol and LDL-cholesterol between the groups. This is in line with findings of previous meta-analyses and may be explained by similar pathophysiology underlying SMI and metabolic syndrome.[17,40] Furthermore, this lipid profile (high triglycerides and low HDL) has been associated with antipsychotic treatment.[16]

Lipid-lowering pharmacotherapy

Along with an increase in the odds of having lipid measurements over 10 years among patients with SMI, we found that they went from having lower to having higher odds of receiving lipid-lowering pharmacotherapy compared with HCs from 2005 to 2015. Notably, this also applied patients treated with antipsychotics. Dyslipidaemia alone is rarely an indication for prescription of lipid-lowering pharmacotherapy in primary prophylaxis according to current European guidelines,[12] but the treatment is indicated if other risk factors for CVD are present. Therefore, we also assessed changes in the odds of redeeming lipid-lowering pharmacotherapy among patients at high or very high cardiovascular risk. Although we found a considerable overall increase in the odds of receiving lipid-lowering pharmacotherapy in patients with SMI compared with HCs, the odds of receiving this medication remained lower in patients with SMI amongst the subsets with previous ACS and ischaemic stroke or TIA. This gap in secondary prevention is in line with previous articles and it has been advocated as one of the main cause of excess cardiovascular mortality in patients with SMI compared with the general population.[1,27,43]

Limitations

Firstly, lifestyle interventions are often first-line therapy for metabolic disorders such as dyslipidaemia in patients who are not at very high cardiovascular risk. Unfortunately, the included registries do not have information on lifestyle parameters such as smoking habits, alcohol intake, body mass index and dietary habits, which we therefore could not consider in this study. Secondly, the fact that the study was not nationwide may impede the generalizability of our findings. Important geographical differences exist in healthcare systems, ethnicity of the population and presence of dyslipidaemia.[12] Thirdly, the CopLab database only includes blood samples until 2015, which prevents us to detect more recent temporal changes in lipid profile measurement. However, we find that the current blood sample measurements from 2005 to 2015 will constitute highly relevant risk profiles, which will aid interpretation of future analyses on mortality rates in patients with SMI. Fourthly, the indication for lipid-profile measurements or prescription of lipid-lowering pharmacotherapy was not known in all individuals. Notably, several studies have shown contrasting patterns of screening and medical treatment of dyslipidaemia according to diverse indications.[30,36,44] However, to investigate individuals with indication for lipid-lowering pharmacotherapy, we included analyses in subsets of patients with baseline comorbidities associated with high or very high cardiovascular risk. Fifthly, we only included patients with SMI with a recent contact to their GP, thereby selecting a subgroup of patients who probably had a better adherence to both lipid measurements and redemption of lipid-lowering pharmacotherapy. Nevertheless, this group constituted >80% of our eligible adult population with SMI (in 2005 83.8% and in 2015 87.6%). Sixthly, we classified dyslipidaemia only according to the results of blood lipid profile without considering the concomitant use of lipid-lowering pharmacotherapy.

Implications

Conventional ‘silo’ working between mental health on one side and physical health on the other side has been suggested as an obstruction for lowering the mortality gap between individuals with and without SMI. However, our results imply that a considerable increased awareness towards screening and treatment of dyslipidaemia in patients with SMI with recent contact to a GP

occurred between 2005 and 2015. Particularly, we observed a substantial increase in the odds of having lipid-profile measurements and redeeming lipid-lowering pharmacotherapy in patients with SMI compared with HCs who did not have SMI.

Our study may reflect that programmes focusing on increased detection of dyslipidaemia to some extend also transfer to patients with SMI. However, there is still room for improvement, especially in patients with SMI at high cardiovascular risk, among whom we showed a consistently large difference in the odds of receiving lipid-lowering pharmacotherapy compared with HCs. Considering that previous studies have shown that for each 1 mmol/l reduction in LDL-cholesterol with lipid-lowering drugs, the risk of death due to coronary artery disease declines by 20% over a 5-year period,[12] our findings importantly highlight a potentially modifiable cause of the increased mortality gap between individuals with and without SMI. Also, patients with SMI often receive fragmented care and guidelines are often not consistent when stating whether the treatment of cardiovascular risk factors should be approached by primary care settings, somatic hospital sectors or psychiatric services.[17,45] A recent European Delphi expert consensus study concluded that psychiatrists should act as the central coordination professional in metabolic care of patients with SMI, assisted as needed by other specialists and the GP.[17] The formation of multidisciplinary teams composed by GPs, specialists in endocrinology and cardiology along with psychiatrists, to whom GPs/psychiatrists may refer patients requiring a close follow-up and integrative approach, may optimize the treatment of patients with SMI at high cardiovascular risk.

Finally, more research is warranted to determine the prevalence, monitoring and treatment of dyslipidaemia in individuals with SMI, who do not have attachment to primary care settings.

Conclusion

Across 10 years, we observed that the odds of having lipid profile measurements and redeeming lipid-lowering medication increased markedly among patients with SMI as compared with HCs. However, patients with SMI had higher odds of dyslipidaemia as compared with HCs without evidence of a difference from 2005 to 2015. Moreover, odds of redeeming lipid-lowering pharmacotherapy in individuals with SMI and concomitant comorbidities such as ACS and ischaemic stroke or TIA were lower than in HCs who also had these comorbidities during 2005 and 2015.

Declarations

Ethics approval and consent to participate

The CopLab database and its activities are approved by the Danish Data Protection Agency through the joint notification of the Faculty of Health and Medical Sciences at the University of Copenhagen (journal no. 2015-57-0121).

Consent for publication

According to Danish legislation, no ethical approval or patient consent was required because the patients were not approached at any time during the conduct of the study.

Author contributions

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Competing interests
BE is part of the Advisory Board of Eli Lilly Denmark A/S, Janssen-Cilag, Lundbeck Pharma A/S, and Takeda Pharmaceutical Company Ltd, and has received lecture fees from Bristol-Myers Squibb, Boehringer Ingelheim, Otsuka Pharma Scandinavia AB, Eli Lilly Company and Lundbeck Pharma A/S. FKK has served on scientific advisory panels and/or been part of speaker's bureaus for, served as a consultant to and/or received research support from Amgen, AstraZeneca, Boehringer Ingelheim, Carmot Therapeutics, Eli Lilly, Gubra, MedImmune, MSD/Merck, Mundipharma, Norgine, Novo Nordisk, Sanofi, ShouTi, Zealand Pharma and Zucara. The other authors declare no conflict of interests.

Availability of data and materials
The data, analytical methods and study materials cannot be made available to other researchers for purposes of reproducing the results or replicating the procedure.

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Supplemental material

Supplemental material for this article is available online.

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