Relative Risk of Cardiovascular and Cancer Mortality in People With Severe Mental Illness From the United Kingdom's General Practice Research Database

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Context: People with severe mental illness (SMI) appear to have an elevated risk of death from cardiovascular disease, but results regarding cancer mortality are conflicting.

Objective: To estimate this excess mortality and the contribution of antipsychotic medication, smoking, and social deprivation.

Design: Retrospective cohort study.

Setting: United Kingdom's General Practice Research Database.

Patients: Two cohorts were compared: people with SMI diagnoses and people without such diagnoses.

Main Outcome Measure: Mortality rates for coronary heart disease (CHD), stroke, and the 7 most common cancers in the United Kingdom.

Results: A total of 46 136 people with SMI and 300 426 without SMI were selected for the study. Hazard ratios (HRs) for CHD mortality in people with SMI compared with controls were 3.22 (95% confidence interval [CI], 1.99-5.21) for people 18 through 49 years old, 1.86 (95% CI, 1.63-2.12) for those 50 through 75 years old, and 1.05 (95% CI, 0.92-1.19) for those older than 75 years. For stroke deaths, the HRs were 2.53 (95% CI, 0.99-6.47) for those younger than 50 years, 1.89 (95% CI, 1.50-2.38) for those 50 through 75 years old, and 1.34 (95% CI, 1.17-1.54) for those older than 75 years. The only significant result for cancer deaths was an unadjusted HR for respiratory tumors of 1.32 (95% CI, 1.04-1.68) for those 50 to 75 years old, which lost statistical significance after controlling for smoking and social deprivation. Increased HRs for CHD mortality occurred irrespective of sex, SMI diagnosis, or prescription of antipsychotic medication during follow-up. However, a higher prescribed dose of antipsychotics predicted greater risk of mortality from CHD and stroke.

Conclusions: This large community sample demonstrates that people with SMI have an increased risk of death from CHD and stroke that is not wholly explained by antipsychotic medication, smoking, or social deprivation scores. Rates of nonrespiratory cancer mortality were not raised. Further research is required concerning prevention of this mortality, including cardiovascular risk assessment, monitoring of antipsychotic medication, and attention to diet and exercise.

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THE PHYSICAL HEALTH OF people with severe mental illness (SMI) is of concern, particularly in relation to possible adverse effects of antipsychotic medication.[1-3] Smoking, lifestyle, and poverty may play equally important roles, and the true burden of physical disease in this group remains unclear. Standardized mortality ratios for cardiovascular disease in schizophrenia are reported to be in the region of 104 (95% confidence interval [CI], 102-116)[3] to 110 (95% CI, 105-115),[2] but these estimates are limited to cohorts of people attending specific services in small geographical areas with short-term follow-up and considerable attrition. The figures are also compromised by small numbers of observed deaths and consequent low precision of the risk estimates. These limitations are summarized in **Table 1**.[2-8] The literature is similarly conflicting regarding cancer mortality. Despite raised risk factors for neoplastic disease, mortality rates for some cancers are similar or even reduced in people with schizophrenia.[3,9,10]

We need robust estimates of the potential role of antipsychotic medication, psychiatric diagnosis, age group, smoking, and social deprivation in any excess death from coronary heart disease (CHD)

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Table 1. Recent Reports of Cardiovascular Mortality in Patients With Severe Mental Illnesses *

Source, y	Study Description	Diagnostic Group	Relative Risk of CVD (95% CI)		
			Both Sexes	Men	Women
Brown,[2] 1997	Meta-analysis	Schizophrenia	**110**† (105-115)	**112**† (105-119)	**109**† (102-116)
Harris and Barraclough,[3] 1998	Meta-analysis	Schizophrenia	**104**† (100-108)	**110**† (104-116)	102† (96-108)
		Bipolar affective disorder	**158**† (139-180)	93† (72-119)	163† (89-274)
Ösby et al, 2000[4]	Inpatients in Sweden‡	Schizophrenia	NR	**1.7-8.3**§ (1.2-17.0)	**1.7-5.0**§ (1.4-4.3)
Hansen et al, 2001[5]	Inpatients in Norway‖	Schizophrenia	NR	**2.1** (1.5-2.8)	**2.1** (1.5-3.0)
Joukamaa et al, 2001[6]	Community in Finland	Schizophrenia	NR	**2.92** (1.65-5.20)	1.63 (0.67-3.95)
Lawrence et al, 2003[7]	Community in Australia	Schizophrenia	NR	**1.78** (1.21-2.61)	0.89 (0.50-1.49)
		Affective psychoses	NR	**1.58** (1.32-1.90)	**1.35** (1.13-1.60)
Enger et al, 2004[8]	US community	Schizophrenia	1.66 (0.34-8.22)	NR	NR

Abbreviation: CI, confidence interval; CVD, cardiovascular disease; NR, not reported.
*Results set in boldface type indicate that the CIs do not cross unity.
†Standarized mortality ratio rather than risk ratio.
‡First admissions to unit followed up.
§Presented in different calendar periods, relative risk worsening over time.
‖Two inpatient units followed up after deinstitutionalization.

or cancer. Precise estimation of the true population risk for cardiovascular disease or cancer mortality requires data from large, representative populations followed up for periods long enough to include sufficient observed deaths. Our primary aim was to estimate the risk of CHD, stroke, and cancer mortality using the United Kingdom's General Practice Research Database (GPRD). Our secondary aim was to assess the relative contribution of antipsychotic medication, psychiatric diagnosis, smoking, and social deprivation to any excess mortality.

METHODS

This historical cohort study compared mortality from CHD, cancer, and stroke between a cohort of patients with SMI (exposed) and a cohort without SMI (unexposed) from the GPRD. This anonymous database covered 741 general practices in the United Kingdom and had 8 million registered patients between its inception in June 1987 and April 2002. It records routine data for clinical and research purposes. The GPRD covers 6.4% of the population in England, 5.1% in Wales, 2.8% in Scotland, and 5.8% in Northern Ireland.

The database is broadly representative of the UK population in age and sex structure. Regarding general practices, smaller practices are slightly underrepresented.[11] Quality of data recording[11,12] and diagnoses for SMI[13] have previously been established in the database, and practices are defined as up to research standard by cross-checking within practices and by comparisons with national statistics. No accurate individual information is available regarding employment, marital status, individual socioeconomic status, or ethnicity.

The GPRD is a clinical data set that comprises real-time patient notes and requires intensive data management and cleaning to produce a numerical data set suitable for statistical analyses. The GPRD is a valuable resource for examining specific associations between carefully defined exposures (such as a specific drug) and outcomes (such as CHD, specific cancers, or a specific adverse effect). This process involves creation of accurate and comprehensive code lists for every exposure, outcome, and covariate of interest. The GPRD is then searched with these code lists to accurately determine whether each patient has received a diagnosis, investigation, or intervention and, if so, when.

Diagnostic information in the GPRD was originally recorded using the Oxford Medical Information System (OXMIS)[14] codes, but more recently the Read classification system was used. We used a systematic approach to accurately identify SMI, main mortality outcomes, and smoking status from patient records, irrespective of type of coding used by individual health care professionals. Read code lists were compiled for each variable of interest using the National Health Service Clinical Terminology Browser. Text word and code stem searches were performed using Microsoft Access (Microsoft Inc, Redmond, Wash) to identify relevant OXMIS codes and missing Read codes. Finally, 2 independent checks were made to exclude irrelevant codes from the resulting list.

INCLUSION CRITERIA

Patients with SMI were identified as those with at least one diagnosis of SMI at any time after their 18th birthday. The SMI category included Read and OXMIS codes for all forms of schizophrenia, schizoaffective disorder, bipolar disorder, delusional disorder, and their synonyms. All other nonorganic psychoses were also included, such as brief psychoses and unipolar depressive psychoses. Psychoses with an organic origin or caused by alcohol and other drugs were excluded. Six controls, who had never been assigned an SMI diagnosis, were selected at random for each SMI patient. These controls formed the comparison group. In both groups, only patients with at least 6 months of data up to research standard were included to ensure data quality. We aimed for both the SMI group and the comparison group to be as representative of the general population as possible. Therefore, we did not apply exclusion criteria (such as other psychiatric diagnoses or drugs) that would render the comparison group an abnormally healthy sample.

OUTCOMES

The main outcomes were deaths from CHD, stroke, and cancer. We included all Read and OXMIS codes for synonyms of CHD and strokes. Because of the large number of different potential cancer codes, we focused on the 7 most common cancers in the United Kingdom, namely, respiratory (including lung, larynx, trachea, and pleura), colorectal, breast, prostate, stomach, esophageal, and pancreas.[15]

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We chose to study death rates rather than incidence rates, because mortality is the most robust outcome since it includes diagnoses made post mortem. Furthermore, mortality has been validated in the GPRD, and its use allows comparability with most previous cardiovascular disease studies, which do not report morbidity (Table 1). On the other hand, incidence rates for a disease may be a less reliable outcome than mortality in the GPRD. Accurate coding of morbidity relies on a pathway that involves presentation of symptoms, then correct investigation, diagnosis, and recording of a disease. All of these steps are susceptible to inaccuracy, perhaps differentially for people with and without SMI, producing possible outcome bias for morbidity coding.

COVARIATES

General practices in the GPRD were allocated a social deprivation quintile on the basis of the Carstairs Score of the ward in which it is located[16]; the higher the quintile, the greater the deprivation. Antipsychotic medication was defined as typical or atypical (including risperidone, olanzapine, quetiapine, and clozapine) and as oral or depot preparations.

We determined those who had received the highest doses of antipsychotics as follows. Total prescribed dose of antipsychotic medication was calculated using chlorpromazine hydrochloride equivalent[17] conversions for conventional antipsychotics and the percentage of the British National Formulary[18] maximum dose of atypical antipsychotics. Total dose levels for each class of antipsychotic were created by summing all antipsychotic prescriptions during a patient's time in the GPRD cohort. This total dose was then scaled by each patient's follow-up time so that valid comparisons could be made among individuals who contributed differing amounts of time to the GPRD. Three groups of low, medium, and high antipsychotic exposure were identified separated by terciles of this scaled conventional or atypical antipsychotic dose. Patients were assigned to these groups of total antipsychotic exposure (low, medium, or high) based on their highest conventional or atypical exposure group. Thus, if an individual was assigned to the medium conventional antipsychotic exposure group but the low atypical antipsychotic exposure group, we classified him or her in the medium total antipsychotic exposure group. Any bias caused by this method would therefore dilute rather than exacerbate differences seen among the groups.

In the United Kingdom, most continuing prescriptions for antipsychotics are issued in primary care, but additional prescriptions in secondary care (especially those prescribed to people during hospitalizations) may not be accurately recorded in the GPRD.

To assess changes in mortality rates over time, we divided the sample according to whether each individual contributed data in 1987-1992, 1992-1997, or 1997-2002. These periods were chosen to account for possible changes in lifestyle or prescribing habits in either group over time.

STATISTICAL ANALYSIS

Survival analysis techniques were performed using Stata statistical software, version 8.2.[19] Cox regression was used to estimate hazard ratios (HRs) for mortality between the SMI and control groups. This technique provides a measure of excess risk of death, the HR, and is more precise because it corrects for each patient's age and the length of follow-up the patient contributed to the study period. Herein, the hazard is the risk of death at a point in time, assuming survival up to that time. Regression models were estimated to control for the possible contributing effects of age, calendar period, sex, smoking, antipsychotic medication, and social deprivation. Differences among categories of a given variable (for example, comparing diagnostic groups within SMI) were assessed with the Wald tests.

The HRs between the SMI and control groups were significantly different at different ages. The main results were therefore analyzed in 3 age bands (18-49 years, 50-75 years, and ≥75 years). These groupings had 2 benefits. First, they afforded sufficient statistical power to compare mortality between groups at different ages. Second, no evidence of age interaction within the groups themselves was found. We assessed statistical interaction effects among the covariates (for instance, whether sex modified the risk of CHD death in patients with SMI) by using likelihood ratio tests that compared regression models with and without an interaction term. The importance of any possible statistical interaction was then estimated using the corresponding tests for the interaction coefficients in the regression model.

A missing data category was included for smoking and social deprivation status where no information was available in the GPRD. The importance of the missing data was assessed by a sensitivity analysis. We examined the main mortality results in 2 ways: comparing the effect of including and excluding those with missing smoking or social deprivation data. The study protocol of mortality in SMI was reviewed by the Scientific and Ethical Advisory Group of the GPRD. Results were considered statistically significant at the $P < .05$ level.

RESULTS

We identified 46 136 people with SMI from 728 general practices with at least 6 months of data up to research standard. The comparison group without SMI comprised 300 246 people (**Table 2**). The most common diagnoses were schizophrenia (40.2%), bipolar affective disorder (23.3%), and delusional disorder (19.2%). Slight differences were found in the mean age and length of follow-up between people with and without SMI (Table 2). Of those with any smoking information, 50.9% of people with SMI were current smokers compared with 38.7% of the comparison group.

People with SMI experienced a 3-fold increase in CHD mortality at age 18 through 49 years and almost a 2-fold increase between the ages of 50 and 75 years (**Table 3**). Death rates of stroke were 2.5 times greater in those younger than 50 years and almost twice as high in the 50- to 75-year-olds. The magnitude of these differences did not change significantly after adjustment for smoking or deprivation. Although the mortality HR for the top 7 cancers considered as a whole were not significantly raised in SMI in any age group, the HR for respiratory tumors alone was significantly higher (1.32; 95% CI, 1.04-1.68) in the 50- to 75-year-old group. However, this result was no longer statistically significant after adjustment for smoking and social deprivation (Table 3).

Results for incidence of disease (ie, first entry of CHD in the person's case records, which in some cases was the cause of death) were generally similar to the mortality results. For incident CHD, the HRs were smaller in magnitude than the mortality ratios reported in Table 3. The HRs for incident CHD were 1.42 (95% CI, 1.22-1.65) for 18- through 49-year-olds, 1.01 (95% CI, 0.95-1.08) for 50- through 75-year-olds, and 0.92 (95% CI, 0.85-1.00) for those older than 75 years. Similarly, the incident HRs for stroke were as follows: 1.77 (95% CI, 1.39-1.22) for 18- through 49-year-olds, 1.77 (95% CI, 1.59-1.97) for 50-

through 75-year-olds, and 1.47 (95% CI, 1.37-1.58) for those older than 75 years. The incident HRs for all cancers and for respiratory cancers were similar in magnitude to the mortality ratios in Table 3, and none reached statistical significance at the .05 level.

ANTIPSYCHOTIC MEDICATION

We examined the contribution of dose of antipsychotic medication to CHD and stroke mortality rates in SMI using non-SMI comparisons as baseline. For this subanalysis, we did not include comparisons of persons who had ever received an antipsychotic prescription. First, we used 2 levels of antipsychotic exposure, namely, those never taking antipsychotics during their time in the GPRD and those who were prescribed such agents. Second, we created subgroups of those who received antipsychotics with controls, using terciles of dose. People with SMI who were not prescribed any antipsychotics were at increased risk of CHD and stroke than controls, whereas those prescribed such agents were at even greater risk. Those receiving the higher doses were at greatest risk of death from both CHD and stroke (**Table 4**).

Exposure to atypical antipsychotics was not related to CHD mortality. In the 50- through 75-year-olds, 16 CHD deaths occurred in the 2060 people with SMI who ever received atypical antipsychotics (0.8%) compared with 280 CHD deaths in the 17 762 people with SMI who did not receive atypical agents (1.6%). With the non-SMI control group as a baseline, the fully adjusted HRs for CHD death in the SMI subgroups were as follows: 1.38 (95% CI, 1.08-1.76) for those not prescribed any antipsychotics, 0.86 (95% CI, 0.52-1.41) for those ever prescribed atypical antipsychotics, and 2.12 (95% CI, 1.82-2.47) for those receiving conventional antipsychotics only.

Table 2. Age, Sex, Smoking, and Social Deprivation Diagnosis and Medication*

Variable	SMI Group	Control Group
Age, median (IQR), y	46.4 (32.2-63.7)	38.0 (26.3-55.8)†
Follow-up, median (IQR), y	4.7 (2.2-8.2)	4.3 (2.0-8.1)†
Calendar period		
1987-1992	30 942 (13.8)	193 755 (86.2)
1992-1997	37 710 (13.8)	235 291 (86.2)
1997-2002	24 460 (13.1)	162 454 (86.9)
All	46 136 (13.3)	300 246 (86.6)
Sex		
Women	24 608 (53.3)	156 781 (52.2)‡
Men	21 528 (46.7)	143 465 (47.8)
Smoking		
Never smoked	9471 (20.5)	78 614 (26.2)‡
Ex-smoker	2636 (5.7)	18 566 (6.2)
Smoker	12 355 (26.8)	57 209 (19.1)
No information	21 674 (47.0)	148 857 (48.6)
SMI diagnosis		
Schizophrenia	18 555 (40.2)	. . .
Bipolar disorder	10 742 (23.3)	. . .
Schizoaffective disorder	2457 (5.3)	. . .
Depressive psychosis	2715 (5.9)	. . .
Delusional disorders	8835 (19.2)	. . .
Brief psychoses	1585 (3.4)	. . .
Psychoses NOS	1247 (2.7)	. . .
Social deprivation quintile		
0	3536 (8.9)	31 825 (12.4)‡
1	5526 (14.0)	43 456 (16.9)
2	8507 (21.5)	58 486 (22.8)
3	9542 (24.1)	59 917 (23.3)
4	12 469 (31.5)	63 312 (24.6)
Antipsychotic		
Conventional oral	28 358 (61.5)	9280 (3.1)
Atypical oral	6305 (13.7)	439 (0.1)
Depot	7180 (15.6)	146 (0.05)
Any	31 789 (68.9)	9521 (3.2)
None prescribed	14 347 (31.1)	290 725 (96.8)

Abbreviations: IQR, interquartile range; NOS, not otherwise specified; SMI, severe mental illness. Ellipses indicate data not applicable.
*Data are number (percentage) of patients unless otherwise indicated.
†Mann-Whitney *U* test $P<.001$.
‡χ^2 test $P<.001$.

Table 3. Relative Risk of Death From CHD, Stroke, and Cancer*

Cause of Death by Age Group, y	Deaths, No. (%) of Controls/ No. (%) of Persons With SMI	HR (95% CI)†	
		Effect of SMI Adjusted for Age, Sex, and Calendar Period	Models Adjusted for Age, Sex, Calendar Period, Smoking Status, and Social Deprivation
CHD			
18-49	49 (0.02)/25 (0.10)	**3.22** (1.99-5.21)	**2.88** (1.77-4.70)
50-75	896 (0.89)/296 (1.49)	**1.86** (1.63-2.12)	**1.76** (1.54-2.01)
≥75	1348 (3.37)/297 (3.75)	1.05 (0.92-1.19)	1.04 (0.91-1.18)
Stroke			
18-49	16 (0.01)/6 (0.02)	2.53 (0.99-6.47)	2.39 (0.92-6.17)
50-75	275 (0.27)/100 (0.31)	**1.89** (1.50-2.38)	**1.83** (1.45-2.31)
≥75	908 (2.56)/279 (3.52)	**1.34** (1.17-1.54)	**1.33** (1.16-1.52)
Cancer, 7 most common types			
18-49	84 (0.04)/15 (0.06)	1.10 (0.63-1.90)	1.04 (0.60-1.82)
50-75	835 (0.83)/179 (0.90)	1.16 (0.99-1.36)	1.10 (0.93-1.29)
≥75	739 (2.08)/130 (1.64)	0.90 (0.75-1.09)	0.89 (0.73-1.07)
Respiratory tumor			
18-49	18 (0.01)/4 (0.02)	1.38 (0.47-4.07)	1.05 (0.35-3.11)
50-75	351 (0.35)/82 (0.41)	**1.32** (1.04-1.68)	1.19 (0.93-1.51)
≥75	263 (0.74)/34 (0.43)	0.74 (0.51-1.06)	0.70 (0.49-1.00)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; SMI, severe mental illness.
*Results set in boldface type indicate that the CIs do not cross unity.
†Hazard ratios for mortality comparing those with SMI to baseline controls without SMI from separate Cox regression models for different age groups.

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Table 4. Role of Antipsychotic Medication and Dose in Cardiovascular Mortality*

Cause of Death by Age and Patient Groups	CHD			Stroke		
	Deaths, No. (%)	HR (95% CI) Adjusted for Sex, Age, Period, and Social Deprivation	*P* Value (Test Within SMI Groups)†	Deaths, No. (%)	HR (95% CI) Adjusted for Sex, Age, Period, and Social Deprivation	*P* Value (Test Within SMI Groups)†
18-49 y	73 (0.03)‡			22 (0.01)‡		
Control	48 (0.02)	1.00		16 (<0.01)	NA	
SMI patients not taking APs§	6 (0.08)	**2.75** (1.17-6.44)		1 (0.01)	NA	
SMI patients taking APs	19 (0.10)	**3.13** (1.84-5.35)	.78	5 (0.01)	NA	NA
Lowest dose	4 (0.05)	**3.08** (1.11-8.55)	.86		NA	NA
Medium dose	4 (0.03)	1.92 (0.69-5.33)	.58		NA	NA
Highest dose‖	11 (0.08)	**4.11** (2.13-7.96)	.43		NA	NA
50-75 y	1151 (0.99)‡			347 (0.30)‡		
Control	855 (0.89)	1.00		247 (0.26)	1.00	
SMI patients not taking APs	69 (0.61)	**1.40** (1.10-1.79)		27 (0.24)	**1.80** (1.21-2.68)	
SMI patients taking APs	227 (0.86)	**2.01** (1.73-2.33)	.009	73 (0.28)	**2.01** (1.55-2.62)	.62
Lowest dose	41 (0.69)	**1.46** (1.06-1.99)	.85	21 (0.35)	**2.26** (1.45-3.54)	.43
Medium dose	82 (0.87)	**1.90** (1.51-2.39)	.06	26 (0.28)	**1.84** (1.23-2.77)	.93
Highest dose	104 (0.96)	**2.49** (2.03-3.05)	<.001	26 (0.24)	**2.02** (1.35-3.03)	.68
≥75 y	1496 (3.76)‡			978 (2.46)‡		
Control	1199 (3.76)	1.00		699 (1.25)	1.00	
SMI patients not taking APs	84 (2.18)	1.17 (0.94-1.46)		**54 (1.40)**	1.23 (0.93-1.63)	
SMI patients taking APs	213 (2.13)	0.98 (0.84-1.13)	.16	**225 (2.25)**	**1.58** (1.35-1.84)	.10
Lowest dose	55 (1.68)	**0.68** (0.52-0.90)	.002	**60 (1.84)**	1.13 (0.87-1.47)	.64
Medium dose	99 (2.21)	1.02 (0.83-1.25)	.35	**110 (2.46)**	**1.70** (1.38-2.08)	.06
Highest dose	59 (2.62)	**1.43** (1.10-1.86)	.24	**55 (2.44)**	**2.21** (1.68-2.92)	.002

Abbreviations: AP, antipsychotic; CHD, coronary heart disease; CI, confidence interval; GPRD, United Kingdom's General Practice Research Database; HR, hazard ratio; NA, not applicable; SMI, severe mental illness.

*Results set in boldface type indicate that the CIs do not cross unity.

†Wald tests comparing those with SMI not prescribed antipsychotics with those with SMI who were taking antipsychotics.

‡Indicates total number (percentage) of deaths for that age group.

§Not taking APs indicates that the person was not prescribed an antipsychotic in general practice according to the GPRD.

‖Highest doses were highest tercile of antipsychotic using chlorpromazine equivalents or percentages of British National Formulary maximum, as appropriate.

INTERACTIONS

Age was the only covariate that had a significant interaction with SMI status in prediction of mortality. **Table 5** provides the HRs for CHD and stroke, comparing the effects of different calendar periods, SMI diagnoses, and sex. Persons with schizophrenia who were younger than 75 years had higher rates of CHD than people with other SMI diagnoses, such as bipolar affective disorder, but these differences were not statistically significant. Contrary to existing literature (Table 1), CHD risk is of similar magnitude in both sexes with SMI. A trend for increasing HRs over calendar time was not statistically significant.

IMPACT OF MISSING DATA

Since the GPRD is a working clinical database, some variables inevitably have missing data. Although most deaths were allocated a cause, not every death received a specific code. Causes of death were available for 4178 (75.4%) of 5544 SMI deaths and 12 982 (75.4%) of 17 219 non-SMI deaths. Although the most common missing data concerned smoking, no systematic difference was found between the 2 patient groups (Table 2). Assessment of the GPRD smoking variable confirmed its clinical validity as a risk factor for CHD. In the whole sample of 50- through 75-year-olds, using nonsmokers as a baseline, the HR for CHD was 1.84 (95% CI, 1.56-2.18) in smokers, 1.20 (95% CI, 0.95-1.51) in ex-smokers, and 1.41 (95% CI, 1.22-1.64) in those with missing smoking information. Social deprivation data were available for 618 of the 728 practices or 85.6% of patients. A sensitivity analysis, which excluded patients with missing data, revealed no systematic differences in the point estimates for mortality outcomes such as CHD in SMI.

COMMENT

Our main finding is a marked excess of deaths from cardiovascular disease in people of all ages with SMI. Although the 3-fold risk of death from CHD in persons younger than 50 years is the most worrying, the 2-fold risk of dying of heart disease and stroke in 50- through 75-year-olds is also of concern. A significant but lower magnitude of risk exists in persons older than 75 years. Compared with previous reports (Table 1), this overall CHD mortality risk is of greater magnitude, seen in both sexes, and statistically more robust.

With the exception of respiratory tumors, people with SMI were not at increased risk of dying from the 7 most common cancers in the United Kingdom. However, our data did not confirm other evidence that they were protected from cancers.[3,9,10] Neither smoking nor social deprivation fully explains this increased CHD and stroke mortality in SMI. Antipsychotic medication is only part of

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Table 5. Mortality for CHD and Stroke by Age, SMI Diagnoses, Calendar Period, and Sex*

Study Group	CHD Mortality, No. (%)	HR (95% CI)†	Stroke Mortality, No. (%)	HR (95% CI)†
		SMI Diagnosis		
18-49 y				
Controls	49 (0.01)	1.00	16 (<0.01)	1.00
Schizophrenia	15 (0.07)	**3.61** (2.00-6.49)	3 (0.01)	2.87 (0.82-10.04)
Bipolar affective disorder	4 (0.04)	2.13 (0.77-5.93)	2 (0.02)	3.34 (0.76-14.66)
Other SMI	6 (0.03)	2.29 (0.98-5.36)	1 (0.01)	1.15 (0.15-8.74)
50-75 y				
Controls	896 (0.47)	1.00	275 (0.14)	1.00
Schizophrenia	135 (0.89)	**1.96** (1.63-2.35)	44 (0.29)	**2.00** (1.45-2.76)
Bipolar affective disorder	66 (0.65)	**1.52** (1.18-1.95)	23 (0.23	**1.63** (1.07-2.50)
Other SMI	95 (0.77)	**1.72** (1.39-2.13)	33 (0.27)	**1.77** (1.23-2.55)
≥75 y				
Controls	1348 (2.16)	1.00	908 (1.45)	1.00
Schizophrenia	92 (2.06)	1.03 (0.83-1.27)	85 (1.90)	**1.31** (1.05-1.63)
Bipolar affective disorder	58 (2.13)	1.13 (0.86-1.46)	40 (1.47)	1.13 (0.82-1.55)
Other SMI	147 (2.20)	1.01 (0.85-1.20)	154 (2.31)	**1.41** (1.19-1.68)
		Calendar Periods‡		
18-49 y				
1987-1992	8 (0.01)/4 (0.03)	2.84 (0.84-9.60)	6 (<0.01)/0 (0)	Too few events
1992-1997	34 (0.02)/15 (0.07)	**2.48** (1.34-4.61)	7 (<0.01)/3 (0.01)	**2.41** (6.12-9.52)
1997-2002	7 (0.01)/6 (0.05)	**4.64** (1.54-13.97)	3 (<0.01)/3 (0.02)	**8.39** (1.67-42.22)
50-75 y				
1987-1992	163 (0.27)/44 (0.35)	1.31 (0.93-1.83)	48 (0.08)/18 (0.14)	1.65 (0.95-2.85)
1992-1997	576 (0.76)/191 (1.25)	**1.75** (1.48-2.06)	176 (0.23)/62 (0.41)	**1.78** (1.33-2.39)
1997-2002	157 (0.28)/61 (0.61)	**2.35** (1.74-3.16)	51 (0.09)/20 (0.20)	**2.12** (1.26-3.57)
≥75 y				
1987-1992	260 (1.38)/34 (0.79)	**0.58** (0.40-0.83)	151 (0.80)/52 (1.20)	**1.43** (1.04-1.96)
1992-1997	862 (3.34)/212 (3.55)	1.12 (0.97-1.31)	538 (2.08)/159 (2.66)	**1.22** (1.02-1.46)
1997-2002	226 (1.27)/51 (1.43)	1.29 (0.95-1.76)	219 (1.23)/68 (1.91)	**1.58** (1.20-2.08)
		Sex‡		
18-49 y				
Women	11 (0.01)/5 (0.02)	2.80 (0.96-8.19)	9 (<0.01)/2 (0.01)	1.57 (0.33-7.39)
Men	38 (0.02)/20 (0.07)	**2.93** (1.69-5.08)	7 (<0.01)/4 (0.01)	3.34 (0.96-11.60)
50-75 y				
Women	272 (0.28)/124 (0.55)	**1.79** (1.44-2.21)	129 (0.13)/58 (0.26)	**1.81** (1.32-2.46)
Men	624 (0.67)/172 (1.15)	**1.76** (1.48-2.09)	146 (0.16)/42 (0.28)	**1.87** (1.32-2.64)
≥75 y				
Women	724 (1.82)/207 (1.96)	1.04 (0.89-1.21)	614 (1.54)/232 (2.19)	**1.38** (1.19-1.61)
Men	624 (2.75)/90 (2.75)	1.03 (0.83-1.29)	294 (1.30)/47 (1.44)	1.13 (0.83-1.54)

Abbreviations: CHD, coronary heart disease; CI, confidence interval; HR, hazard ratio; SMI, severe mental illness.

*For SMI diagnosis, all models are adjusted for age, sex, 5-year calendar period, smoking, and social deprivation. For calendar periods, all models are adjusted for age, sex, smoking, and social deprivation. For sex, all models are adjusted for age, 5-year calendar period, smoking, and social deprivation. Results set in boldface type indicate that the CIs do not cross unity.

†All HRs compare patients with SMI with controls, with controls as the baseline group.

‡Data in columns 2 and 4 are given as number (percentage) of controls/number (percentage) of patients with SMI.

the explanation; people with SMI who received no antipsychotics during their follow-up in the database were still more likely than control patients to die of heart disease or stroke. However, risk was greater for those prescribed antipsychotics, and this result was statistically significant for CHD in the 50- through 75-year-old group. Evidence was also found that patients who received the highest doses of antipsychotic medication during the follow-up period were more likely to die of heart disease. No increased risk of CHD death due to atypical agents was observed, perhaps because of limited length of exposure by 2002. We found an increased risk of death from CHD and stroke in both sexes and in the main diagnostic groups.

STRENGTHS AND LIMITATIONS

In contrast to previous studies, our data are based on a large, national, representative community sample of people with SMI. The size of the sample enabled a systematic examination of the size of the effect across age groups and geographical areas and the contribution of antipsychotic medication and smoking. Although these results pertain to people registered with general practitioners, this sample includes almost all people with SMI in the United Kingdom, including those in long-term care. However, because homeless people may not be well represented in our sample, the risk of CHD death may be even greater than we have demonstrated.

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We chose mortality rather than morbidity as the most robust GPRD outcome. Mortality reflects both the incidence of a disease and its outcome. We acknowledge that choosing death as an indicator of disease incidence can be complicated by potential inaccuracy in the recorded cause of death.

It is possible that the high CHD mortality in younger people with SMI reflects both high incidence and poor management of CHD. The HRs for overall CHD incidence were smaller than the HRs for CHD death. People with SMI may be less likely to present with CHD symptoms, to receive a diagnosis of CHD, to receive correct treatment, and to adhere to this treatment, resulting in lower survival. Little evidence was found of differences between incidence and mortality for cancers or strokes to systematically support this argument. Estimating the effect of antipsychotic medication is complex when so many different agents are prescribed nationally, and we cannot rule out the possibility that additional agents were prescribed in secondary care without being recorded on the GPRD.

Our estimation of antipsychotic dose level is admittedly crude, relying on conversions to relative doses of different medications, which are imprecise estimates. However, our finding of an association between CHD risk and antipsychotics is robust. The lack of association between atypical antipsychotics and CHD death, however, is counterintuitive given the interest in metabolic effects of such agents.[1]

Channeling bias cannot be discounted, whereby people most at risk of cardiovascular disease such as those who are older or overweight may be prescribed atypical agents less frequently. However, prescriptions for such agents increased greatly toward the latter part of our follow-up period, and it is possible that any effect on CHD mortality may not have occurred within the period of our study.

This study of clinical data does not answer questions regarding individual antipsychotics; more detailed pharmacological mortality studies would be required for this purpose. We did not aim to assess the additional contribution of other psychotropic medications, such as mood stabilizers.

Despite the large size of our sample, numbers of deaths in some categories are still relatively small, particularly for those younger than 50 years, for different diagnostic groups within the SMI category, and for those prescribed atypical antipsychotics.

As with any clinical database, missing data are a problem. In this study, only data on smoking were missing. Our results, however, confirm the strong relationship between smoking and CHD outcomes and were stable given 2 methods of managing the missing data. Our smoking data have external validity given their similarity with previously published smoking rates in community studies of SMI.[20]

Our social deprivation score concerns the neighborhood of each general practice rather than each individual's status and thus may not be sensitive enough to evaluate the impact of deprivation on the association between SMI and CHD or stroke. We did not aim to assess risk factors for CHD, such as hyperlipidemia, diabetes, or hypertension, and so did not extract such data. Such work might be possible in the GPRD, although not all patients will have been screened for these conditions.

AGE AND RISK

The lower magnitude of risk in the people older than 75 years may represent a healthy survivor effect in older people with SMI or may reflect lower lifetime smoking prevalence compared with younger patients. Alternatively it may represent a cohort effect whereby older people in the general population have not made the protective changes in lifestyle and smoking that are seen in middle-aged people and thus remain closer to the risk of CHD and respiratory cancer seen in people with SMI.

ANTIPSYCHOTIC MEDICATION

The dose response observed in the relationship between antipsychotic medication and CHD mortality might be due to adverse effects of higher doses. Alternatively, dose could be an indicator of the severity of the mental illness, which might in turn affect mortality through diet and exercise, intensity of tobacco use,[21,22] or the stresses of psychiatric symptoms. The reliability of other potential markers of illness severity (such as hospitalizations) is not established in the GPRD, and we did not extract these data.

CONCLUSIONS

Severe mental illnesses, including schizophrenia and bipolar affective disorder, are associated with excess deaths from CHD and stroke in persons younger than 75 years. This mortality is only partly explained by antipsychotic medication, smoking, and social deprivation based on the location of the general practice. The mortality is associated with higher doses of antipsychotic medication but not with prescription of atypical antipsychotics in this sample. Rates of cancer mortality were not raised in SMI with the exception of deaths from respiratory tumors, which were partly explained by smoking and deprivation.

More research into the primary and secondary prevention of cardiovascular disease in people with SMI is needed. Clinically, a holistic approach to the care of people with SMI is still frequently overlooked. Such an approach requires monitoring for somatic conditions and demands effective communication between primary and secondary care to provide coherent physical health care. The focus should include factors, possibly best managed in primary care, such as monitoring of blood pressure, glucose level, cholesterol level, and smoking. However, psychiatric health care professionals cannot be viewed as exempt from responsibility for physical health monitoring. Furthermore, CHD lifestyle risk factors such as poor diet and exercise, which are more prevalent in people with SMI, provide another important focus for intervention.

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Correction

Error in Table. In the Original Article by Osborn et al titled "Relative Risk of Cardiovascular and Cancer Mortality in People With Severe Mental Illness From the United Kingdom's General Practice Research Database," published in the February issue of the *Archives* (2007;64:242-249), an error appeared in Table 3. The final category under "Cause of Death by Age Group, y" should have been "Respiratory tumor," and the age groups of 18-49, 50-75, and ≥75, along with their corresponding data, should have appeared directly underneath. We regret the error. This article was corrected online for typographical errors on April 11, 2007.