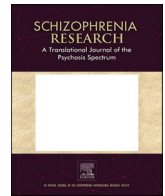




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# Cancer rates and mortality in people with severe mental illness: Further evidence of lack of parity

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## ABSTRACT

**Background:** Severe mental illness (SMI) is associated with poorer physical health, however the relationship between SMI and cancer is complex and previous study findings are inconsistent. Low incidence of cancer in those with SMI has been attributed to premature mortality, though evidence for this is lacking. We aimed to investigate the relationship between SMI and cancer incidence and mortality, and to assess the effect of premature mortality on cancer incidence rates.

**Methods:** In this UK-wide matched cohort study using primary care records we calculated incidence and mortality rates of all-cancer, and bowel, lung, breast or prostate cancer, in patients with SMI, compared to matched patients without SMI. We used competing risks regression to account for mortality from other causes.

**Findings:** 69,632 patients had an SMI diagnosis. The rate of all-cancer diagnoses was reduced in those with SMI (Hazard ratio (HR):0.95; 95%CI 0.93–0.98) compared to those without SMI, and particularly in those with schizophrenia (HR:0.82; 95%CI 0.77–0.88) compared to those without SMI. When accounting for the competing risk of premature mortality, incidence remained lower only in patients with schizophrenia. All-cause mortality after cancer was increased in the SMI group, and cancer-specific mortality was increased in those with schizophrenia (hazard ratio: 1.96; 95%CI 1.57–2.44).

**Interpretation:** Patients with schizophrenia have lower rates of cancer diagnosis but higher all-cause and cancer-specific mortality rates following diagnosis compared to those without SMI. Premature mortality does not explain these differences, suggesting the findings reflect barriers to cancer diagnosis and treatment, which need to be identified and addressed.

## 1. Introduction

Severe mental illness (SMI) is associated with poorer physical health and increased mortality compared to the general population (Hayes et al., 2017). These health disparities may be partially explained by increased adverse health behaviours, such as smoking and poor diet (Liu et al., 2017), as well as prolonged use of antipsychotic medication (Osborn et al., 2007). With around 80 % of lung cancer mortality attributable to tobacco smoking (Anand et al., 2008), it has been hypothesised that the factors contributing to poor physical health in people with SMI may also increase the risk of cancer in this population.

The impact of SMI diagnoses on the incidence and outcomes of cancers is of clinical concern (Howard et al., 2010; Irwin et al., 2014). While studies have consistently reported increased mortality from

cancer in patients with SMI (Ni et al., 2019; Zhuo et al., 2017), findings regarding cancer incidence in people with SMI have been inconsistent. A recent meta-analysis of cohort studies found a decreased incidence of cancer in those with schizophrenia compared to the general population (Li et al., 2018), though the effect size was small and varied by site of cancer, a pattern found in meta-analyses focused on site-specific cancers (Xiping et al., 2019; Zhou et al., 2019; Zhou and Triplett, 2018). In contrast, a recent meta-analysis of cancer incidence in people with bipolar disorder found an increased incidence compared to the general population (Anmella et al., 2021).

It has been suggested that premature aging and death in those with SMI may contribute to lower incidence of cancers of old-age in this population (Lichtermann et al., 2001; Lin et al., 2013), while increased mortality may be explained by factors such as decreased access to cancer

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treatments, diagnostic overshadowing, treatment challenges posed by co-morbidities, drug-drug interactions, and patient compliance (Howard et al., 2010).

In this study, we used data from nationwide primary care records to explore cancer diagnosis rates and mortality in patients with SMI and investigated the four most common cancer types in the UK population: breast, prostate, lung, and bowel cancer (Caul and Broggio, 2019). We used competing risk analysis to investigate the role of premature death on cancer incidence and mortality.

## 2. Methods

The study population for this cohort study was taken from Clinical Practice Research Datalink (CPRD) GOLD and Aurum databases of electronic medical records from UK primary care practices. Data on primary care visits, historical and demographic information, and key diagnoses reported from secondary care, are routinely entered into the system by practice staff. At the time of data extraction, these databases combined included records for over 39 million patients, from all regions of the UK, with a similar age, sex and ethnicity profile to that of the UK population as a whole (Herrett et al., 2015; Wolf et al., 2019). Ethical approval for this study was obtained from the Independent Scientific Advisory Committee of CPRD (protocol no. 18\_288). Informed consent was waived because data are anonymized for research purposes.

We defined patients with SMI as patients receiving a diagnosis of schizophrenia, bipolar disorder or other non-organic psychoses, identified by Read codes, as recorded in their primary care health record. These diagnoses will have been made by psychiatrists in secondary care (using International Classification of Diseases criteria) and communicated to the primary care practice, where the General Practitioner is responsible for long-term prescribing and physical health monitoring (Reilly et al., 2012). Inclusion criteria for the exposure group comprised any patient over the age of 18 who received a diagnosis of SMI between 1 January 2000 and 31 December 2018. These patients were matched 1:4 by sex, age (in 5-year age bands), primary care practice, and year of registration at the practice, to patients without a diagnosis of SMI, who formed the comparison group. We excluded patients who were under 18 at study exit or at cancer diagnosis ( $n = 2101$ ), those with an uncertain cancer diagnosis date ( $n = 12$ ), and those who could not be matched 1:4 (3904). Patients reaching aged 18 during follow up were included only after they became 18. A subset of patients from England had linked death certificate information (from Office of National Statistics).

### 2.1. Outcomes

The primary outcomes were adult lifetime cancer diagnosis rate and cancer-related mortality rate. To measure cancer diagnosis incidence, cancer was defined as any cancer occurring over the age of 18. We looked historically for cancer diagnoses at any time point after age 18, with follow up ending at the earliest of: death date, cancer diagnosis date, date of transfer out of practice or 31 December 2018. Cancers of the bowel, lung, breast, and prostate were investigated separately. For patients with multiple cancer medical codes, the code with the earliest date was selected.

Cancer-related mortality was defined as any death following cancer diagnosis, while cancer-specific mortality was defined as ICD-9 codes 140–239 or ICD-10 codes C00–D48 recorded as a cause of death in death certificate records, where available. Follow up began at the date of first cancer diagnosis over aged 18, and ended at the earliest of: death date, date of transfer out of practice or 31 December 2018. Analysis of cancer-specific mortality was limited to events prior to 31 January 2018 as no record linkage was available after that date.

### 2.2. Covariates

We considered age, sex, clustering by primary care practice,

ethnicity, smoking status, body mass index (BMI) and calendar time as covariates. Ethnicity was categorised as White, Black, Asian, Mixed, or other. Smoking status was defined as ‘ever smoked’ and included smokers and ex-smokers. Data on height, weight, and BMI was extracted and supplemented with code lists for ‘overweight’ and ‘obese’ to define the highest BMI category ever recorded. Patients with missing smoking or BMI data were coded as non-smoker or normal range BMI respectively, since general practitioners are less likely to report a value that is within the norm (Hippisley-Cox et al., 2008; Marston et al., 2014). Patients with missing ethnicity data were recorded as White ethnicity (Hippisley-Cox et al., 2008). The resulting proportions in the comparison group were compared to those reported in Health Survey for England 2017 (Conolly and Davies, 2019; Osborne and Cooper, 2019) to ensure representativeness.

### 2.3. Analysis

Cancer diagnosis incidence rates and all-cause mortality rates following cancer were calculated for the SMI and non-SMI comparison group, and schizophrenia, bipolar disorder, or other non-affective psychotic illness subgroups.

#### 2.3.1. Cancer incidence

We used Cox proportional hazard regression to calculate hazard ratios for the incidence of each cancer type from age 18 to study exit, adjusting for sex, ethnicity and calendar year, and clustering within primary care practices (partially adjusted model). We repeated the analyses additionally adjusting for smoking status and BMI (fully adjusted model). Finally, we carried out a competing risks analysis (Lambert, 2017) to examine cumulative cancer incidence with all-cause mortality as the competing risk. Sex, ethnicity and year were controlled for in the analysis and predictive cumulative incidence function curves plotted at average values for these variables. This method accounts for the fact that an individual is censored in an informative manner (i.e., death) and gives a more accurate estimation of the cumulative incidence of cancer diagnoses (Schuster et al., 2020).

#### 2.3.2. Cancer mortality

We used Cox hazard regression analysis to calculate hazard ratios for the all-cause and cancer-specific death rate following diagnosis of each cancer type, adjusting for age, sex, ethnicity and calendar year, and clustering of primary care practices (partially adjusted model), and additionally with smoking status and BMI included (fully adjusted model). We carried out a competing risks analysis (Lambert, 2017) to examine cancer specific mortality, with mortality from other causes as the competing risk while adjusting for age, sex, ethnicity and year.

#### 2.3.3. Other considerations

Breast and prostate cancer were only examined in women and men, respectively, and we tested for interaction between sex and SMI diagnosis for lung, bowel, and all-cancer analyses. The results of the competing risk analysis were presented as predictive cumulative incidence function curves, plotted at average values for these variables. All analysis was completed using Stata 16.1 (StataCorp, 2019), R version 3.5.1 (R Core Team, 2018), and RStudio version 1.1.456 (RStudio Team, 2015).

## 3. Results

### 3.1. Clinical and demographic features

We identified 69,632 patients with a diagnosis of SMI, who were matched to 278,528 patients without SMI. The median year of birth of the cohort was 1968 (IQR 1953–1981) and 51.0 % were male. Of those with an SMI diagnosis, 15,271 (21.9 %) had a diagnosis of schizophrenia, 24,601 (35.3 %) of bipolar disorder, and 29,760 (42.7 %) of

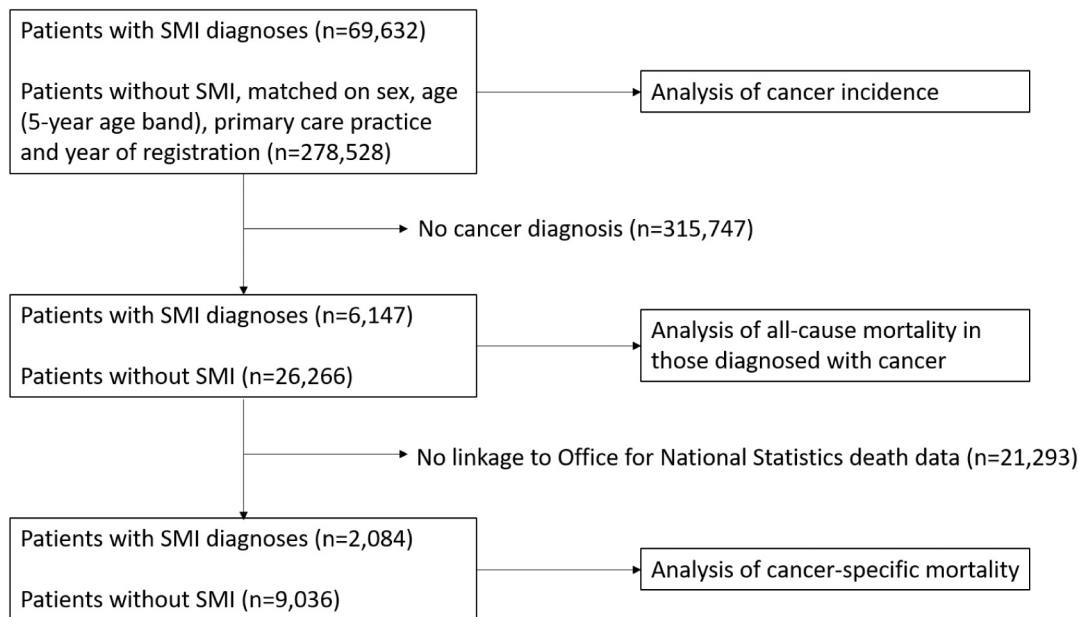


Fig. 1. Cohort selection.

**Table 1**  
Characteristics and demographics, n = 348,160.

	No SMI	SMI	Schizophrenia	Bipolar	Other psychoses
Total, n	278,528	69,632	15,271	24,601	29,760
Year of birth, median (IQR)	1968 (1953–1980)	1968 (1953–1980)	1969 (1956–1980)	1967 (1954–1979)	1968 (1949–1981)
Male, n (%)	142,136 (51.0)	35,534 (51.0)	9862 (64.6)	10,034 (40.8)	15,638 (52.6)
Ever smoked, n (%)	128,012 (46.0)	45,729 (65.7)	10,475 (68.6)	16,325 (66.4)	18,929 (63.6)
BMI, median (IQR)	26.8 (23.5–31.1)	28.6 (24.6–33.5)	29.2 (24.9–34.2)	29.2 (25.2–34.2)	27.8 (24.0–32.4)
Overweight (BMI ≥ 25), n (%)	74,547 (26.8)	19,209 (27.6)	3957 (25.9)	7040 (28.6)	8212 (27.6)
Obese (BMI > 30), n (%)	68,408 (24.6)	26,346 (37.8)	6108 (40.0)	10,435 (42.4)	9803 (32.9)
Ethnicity, n (%)					
White	247,019 (88.7)	60,209 (86.5)	12,150 (79.6)	22,462 (91.3)	25,594 (86.0)
Black	9044 (3.3)	3646 (5.2)	1443 (9.5)	541 (2.2)	1662 (5.6)
Asian	14,027 (5.0)	3309 (4.8)	1079 (7.1)	798 (3.2)	1432 (4.8)
Mixed	2149 (0.8)	862 (1.2)	244 (1.6)	255 (1.0)	363 (1.2)
Other	6289 (2.3)	1609 (2.3)	355 (2.3)	545 (2.2)	709 (2.4)
All-cancer diagnoses, n (%)	26,266 (9.4)	6147 (8.8)	926 (6.1)	2334 (9.5)	2887 (9.7)
Age at cancer diagnoses, median (IQR)	64 (51–75)	63 (50–74)	60 (49–71)	60 (47–70)	66 (52–77)
Cancer diagnosis before 50y, n (%)	5891 (22.4)	1536 (25.0)	245 (26.5)	673 (28.8)	618 (21.4)
All-cause deaths (as registered in CPRD)	19,907 (7.2)	7682 (11.0)	1647 (10.8)	2168 (8.8)	3867 (13.0)

other non-affective psychotic illness. A total of 32,413 patients had a cancer diagnosis as an adult (6147 with an SMI diagnosis), of which 11,120 (2084 with an SMI diagnosis) were eligible for linkage with death certificate records (Fig. 1).

There was a higher proportion of people of Black ethnicity (5.2 % vs. 3.3 %) and ever-smokers (65.7 % vs. 46.0 %) in the SMI cohort. People with SMI diagnoses were more likely to be obese (37.8 %) compared to the no-SMI group (24.6 %) but the proportion of overweight individuals was similar (27.6 % vs 26.8 %). Within the SMI cohort, a higher proportion of those diagnosed with schizophrenia were male, a smoker, or of Black ethnicity than those diagnosed with bipolar or other psychoses, while those with bipolar disorder were more often obese (Table 1).

### 3.2. Cancer incidence

In the SMI group the rate of all-cancer diagnoses was 28.04 (95 % CI 27.35–28.75) per 10,000 person-years at risk (PYR) and 30.11 (95 % CI 29.75–30.48) per 10,000 PYR in the non-SMI group. Patients with schizophrenia had a lower rate (20.53 cases per 10,000 PYR) of cancer than those with bipolar disorder or other psychoses (30.20/29.83 cases per 10,000 PYR, respectively).

In the fully adjusted model, patients with schizophrenia or other psychoses had lower incidence of any recorded cancer (aHR 0.82, 95%CI 0.77–0.88; aHR 0.92 (95%CI 0.89–0.96)), and of bowel and prostate cancer (Table 2) than those without SMI. Incidence of lung cancer was similar in those with schizophrenia or other psychosis compared to the general population, though incidence was raised in patients with schizophrenia in the partially adjusted model which did not control for smoking or BMI (aHR: 1.38; 95%CI 1.09–1.75). Those with bipolar disorder had slightly higher all-cancer diagnosis rates than those without SMI (aHR 1.07; 1.02–1.11), though there was no difference in incidence of recorded bowel, lung, breast, or prostate cancer (Table 2).

When accounting for the competing risk of any other cause of death, cancer diagnosis in patients with schizophrenia and other psychoses was consistently lower than in patients with bipolar disorder or no SMI (Fig. 2). At 50 years old people with schizophrenia had a 1.49 fewer cancer diagnoses per 100 patients than the non-SMI group, after accounting for the premature mortality, by age 80 those with schizophrenia had a 9.49 fewer diagnoses per 100 patients.

An interaction was found between sex and bipolar disorder diagnosis in the all-cancer diagnoses model. The hazard ratio for males with bipolar disorder was 1.00 (95%CI: 0.94–1.08, p = 0.885), while for

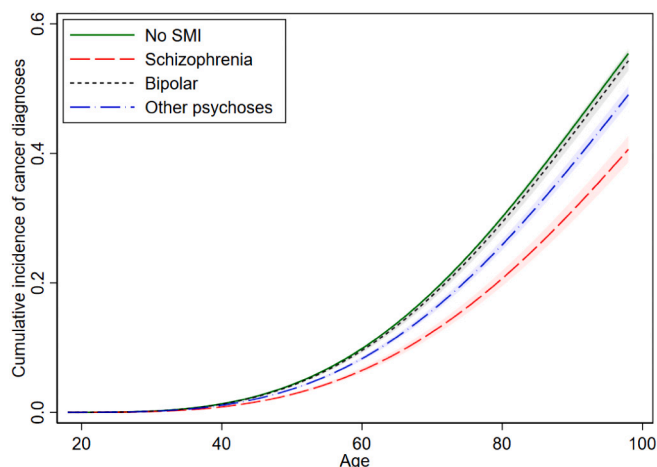
**Table 2**  
Cancer incidence, n = 348,160.

	No SMI	SMI	Schizophrenia	Bipolar disorder	Other psychoses
<b>All-cancer</b>					
Number/person-years at risk (10,000s)	26,266/872.23	6147/219.24	926/45.12	2334/77.34	2887/96.79
Rate <sup>a</sup> (95%CI)	30.11 (29.75–30.48)	28.04 (27.35–28.75)	20.53 (19.25–21.89)	30.20 (28.98–31.43)	29.83 (28.76–30.94)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.97 (0.94–0.99)	0.84 (0.78–0.90)	1.10 (1.05–1.15)	0.93 (0.90–0.97)
p-value		0.039	<0.001	<0.001	<0.001
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.95 (0.93–0.98)	0.82 (0.77–0.88)	1.07 (1.02–1.11)	0.92 (0.89–0.96)
p-value		0.001	<0.001	0.004	<0.001
<b>Bowel cancer</b>					
Number/person-years at risk (10,000s)	1841/895.26	376/224.44	54/45.75	149/79.28	173/99.42
Rate <sup>a</sup> (95%CI)	2.06 (1.96–2.15)	1.68 (1.51–1.85)	1.18 (0.90–1.54)	1.88 (1.60–2.20)	1.74 (1.50–2.02)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.86 (0.77–0.96)	0.76 (0.58–1.00)	1.07 (0.90–1.26)	0.77 (0.66–0.90)
p-value		0.009	0.052	0.455	0.001
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.86 (0.77–0.96)	0.76 (0.57–0.997)	1.05 (0.89–1.24)	0.77 (0.66–0.90)
p-value		0.006	0.047	0.578	0.001
<b>Lung cancer</b>					
Number/person-years at risk (10,000s)	1403/896.38	334/224.62	77/45.76	119/79.35	138/99.51
Rate <sup>a</sup> (95%CI)	1.56 (1.49–1.65)	1.49 (1.34–1.66)	1.68 (1.35–2.10)	1.50 (1.25–1.79)	1.39 (1.17–1.64)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.07 (0.95–1.20)	1.38 (1.09–1.75)	1.10 (0.91–1.33)	0.92 (0.77–1.10)
p-value		0.294	0.007	0.305	0.352
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.01 (0.90–1.14)	1.26 (0.99–1.61)	1.05 (0.87–1.27)	0.88 (0.74–1.05)
p-value		0.861	0.055	0.591	0.154
<b>Breast cancer (females only, n = 170,490)</b>					
Number/person-years at risk (10,000s)	4276/489.56	1000/122.78	146/19.59	386/46.78	468/56.41
Rate <sup>a</sup> (95%CI)	8.73 (8.48–9.00)	8.15 (7.66–8.67)	7.45 (6.34–8.77)	8.25 (7.47–9.12)	8.29 (7.58–9.08)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.96 (0.90–1.03)	0.94 (0.80–1.11)	1.09 (0.98–1.21)	0.89 (0.81–0.98)
p-value		0.292	0.496	0.117	0.013
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.95 (0.89–1.02)	0.93 (0.79–1.10)	1.07 (0.96–1.18)	0.89 (0.80–0.97)
p-value		0.180	0.423	0.240	0.012
<b>Prostate cancer (males only, n = 177,670)</b>					
Number/person-years at risk (10,000s)	1875/401.44	368/100.63	53/26.02	149/32.11	166/42.50
Rate <sup>a</sup> (95%CI)	4.67 (4.46–4.89)	3.66 (3.30–4.05)	2.04 (1.56–2.67)	4.64 (3.95–5.45)	3.91 (3.35–4.55)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.86 (0.77–0.96)	0.65 (0.49–0.85)	1.00 (0.85–1.19)	0.83 (0.71–0.97)
p-value		0.006	0.002	0.959	0.023
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.86 (0.77–0.96)	0.67 (0.51–0.88)	1.00 (0.85–1.18)	0.84 (0.71–0.98)
p-value		0.009	0.004	0.985	0.028

<sup>a</sup> Rate per 10,000 PYR (person years at risk).

<sup>b</sup> A Partially adjusted model: Adjusted for calendar year and sociodemographic factors (sex [except for breast and prostate cancer], primary care practice, ethnicity).

<sup>c</sup> B Fully adjusted model: Additionally adjusted for smoking status (ever smoked) and BMI (underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (≥30)).



**Fig. 2.** Cumulative incidence of any cancer diagnosis, accounting for death.

females it was 1.11 (95%CI: 1.05–1.17,  $p < 0.001$ ). No interactions between sex and diagnosis were found for other models.

### 3.3. Cancer mortality

All-cause mortality after all-cancer diagnoses was 373.43 per 10,000PYR (95 % CI 357.54–390.02) in those diagnosed with SMI compared to 328.64 per 10,000PYR (95 % CI 321.53–335.91) in the group without SMI. The incidence of all-cause mortality after cancer was increased in the SMI group compared to the non-SMI group in the partially adjusted model (aHR 1.20; 95%CI 1.14–1.26), and the addition of smoking and BMI in the fully adjusted model did not alter the hazard ratio. Incidence of mortality following cancer diagnosis was increased in all SMI groups, particularly in those with schizophrenia (aHR 1.64; 95% CI 1.42–1.83; Table 3).

There was an increased mortality rate in patients with SMI and breast (aHR 1.43; 95%CI 1.21–1.70) or bowel cancer (aHR 1.38; 95%CI 1.08–1.76), relative to the group with no SMI, which held true across all SMI subgroups. For both breast and bowel cancer the highest hazard ratios were in those with schizophrenia (aHR 2.74; 95%CI 1.88–4.00 and aHR 2.56 95%CI 1.41–4.65). For lung and prostate cancer, there was no difference in mortality rates between the group with and group without SMI, however patients with schizophrenia did have increased

**Table 3**  
All-cause mortality in patients diagnosed with cancer (n = 32,413).

	No SMI	SMI	Schizophrenia	Bipolar disorder	Other psychoses
Cancer diagnosis	26,266	6147	926	2334	2887
<b>All-cause mortality</b>					
Number/person-years at risk (10,000s)	8027/24.42	2033/5.44	321/0.65	671/2.04	1041/2.76
Rate <sup>a</sup> (95%CI)	328.64 (321.53–335.91)	373.43 (357.54–390.02)	491.90 (440.93–548.76)	329.58 (305.56–355.48)	377.77 (355.51–401.43)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.20 (1.14–1.26)	1.64 (1.45–1.86)	1.23 (1.14–1.34)	1.08 (1.01–1.16)
p-value		<0.001	<0.001	<0.001	0.022
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.20 (1.14–1.26)	1.61 (1.42–1.83)	1.24 (1.14–1.35)	1.08 (1.01–1.16)
p-value		<0.001	<0.001	<0.001	0.021
<b>Bowel cancer</b>					
Number/person-years at risk (10,000s)	781/1.40	191/0.25	27/0.02	76/0.09	88/0.13
Rate <sup>a</sup> (95%CI)	558.69 (520.85–599.28)	774.72 (672.28–892.76)	1189.27 (815.58–1734.17)	825.85 (659.57–1034.04)	667.62 (541.74–822.75)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.38 (1.08–1.76)	2.56 (1.41–4.65)	1.68 (1.14–2.49)	1.05 (0.68–1.33)
p-value		0.010	0.002	0.009	0.765
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.38 (1.08–1.75)	2.62 (1.47–4.69)	1.65 (1.12–2.44)	0.95 (0.67–1.33)
p-value		0.010	0.001	0.011	0.748
<b>Lung cancer</b>					
Number/person-years at risk (10,000s)	1060/0.28	224/0.07	53/0.01	82/0.02	89/0.03
Rate <sup>a</sup> (95%CI)	3823.1 (3599.8–4060.3)	3386.7 (2971.0–3860.5)	4327.5 (3306.1–5664.5)	3617.0 (2913.1–4491.0)	2850.4 (2315.7–3508.6)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.99 (0.81–1.22)	1.69 (1.18–2.41)	0.74 (0.53–1.02)	0.95 (0.71–1.27)
p-value		0.933	0.004	0.069	0.714
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.97 (0.79–1.20)	1.74 (1.23–2.48)	0.71 (0.51–0.99)	0.92 (0.68–1.24)
p-value		0.783	0.002	0.042	0.581
<b>Breast cancer (females only)</b>					
Number/person-years at risk (10,000s)	1103/4.47	340/1.04	60/0.13	112/0.39	168/0.52
Rate <sup>a</sup> (95%CI)	246.53 (232.40–261.51)	326.25 (293.35–362.84)	454.55 (352.94–585.43)	288.13 (239.42–346.75)	322.19 (276.98–374.79)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.43 (1.21–1.70)	2.74 (1.88–4.00)	1.42 (1.11–1.82)	1.16 (0.91–1.47)
p-value		<0.001	<0.001	0.006	0.222
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.41 (1.19–1.68)	2.71 (1.83–4.00)	1.39 (1.08–1.78)	1.16 (0.91–1.46)
p-value		<0.001	<0.001	0.011	0.226
<b>Prostate cancer (males only)</b>					
Number/person-years at risk (10,000s)	547/1.19	120/0.24	17/0.03	39/0.10	64/0.11
Rate <sup>a</sup> (95%CI)	461.39 (424.30–501.73)	494.12 (413.17–590.93)	564.07 (350.66–907.36)	389.10 (284.29–532.55)	568.95 (445.32–726.89)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.32 (0.99–1.77)	3.11 (1.20–8.09)	0.998 (0.59–1.70)	1.33 (0.90–1.97)
p-value		0.063	0.020	0.995	0.150
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.33 (0.99–1.80)	3.00 (1.05–8.62)	1.03 (0.60–1.79)	1.33 (0.89–1.98)
p-value		0.061	0.041	0.911	0.162

<sup>a</sup> Rate per 10,000 PYR (person years at risk).

<sup>b</sup> A Partially adjusted model: Adjusted for calendar year and sociodemographic factors (sex [except for breast and prostate cancer], primary care practice, ethnicity).

<sup>c</sup> B Fully adjusted model: Additionally adjusted for smoking status (ever smoked) and BMI (underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (≥30)).

mortality rates (aHR 1.69; 95%CI 1.18–2.41 and aHR 3.11; 95%CI 1.20–8.09). For all analyses, the addition of smoking and BMI to the model had little effect.

In patients with linked death certificate data, we found no difference in cancer-specific mortality following a diagnosis of any cancer in patients with SMI compared to patients without SMI (bowel cancer: aHR 1.39; 95%CI 0.85–2.28; lung cancer: aHR 0.78; 95%CI 0.49–1.24; breast cancer: aHR 1.08; 95%CI 0.76–1.53; prostate cancer: 1.34; 95%CI 0.74–2.40, Table 4). However, there was an increased cancer-specific mortality following any cancer diagnosis in those with schizophrenia (aHR 1.96; 95%CI 1.57–2.44) compared to those without SMI.

In competing risks analysis of cancer-specific mortality accounting for all other causes of mortality (Fig. 3), incidence of cancer mortality

was greater in patients with schizophrenia compared to patients without SMI at all time points. At one year after cancer diagnosis, there were 6.08 more deaths per hundred patients than those without SMI (schizophrenia cumulative incidence 14.89 %; 95%CI 12.35–17.89 % vs no SMI cumulative incidence 8.81 %; 95%CI 8.29–9.37) when controlling for age, sex, ethnicity, and year of diagnosis. At 5 years after cancer diagnosis, those with schizophrenia had 10.31 excess deaths per 100 patients (schizophrenia cumulative incidence 26.39 %; 95%CI 22.23–31.17 % vs no SMI cumulative incidence 16.08 %; 95%CI 15.34–16.86 %) and increasing to a 16.54 per 100 patients at 20 years (schizophrenia cumulative incidence 47.01 %; 95%CI 40.62–53.86 % vs no SMI cumulative incidence 30.47 %; 95%CI 29.19–31.79 %). There was no difference in cancer mortality over time between patients with

**Table 4**  
Cancer-specific mortality in patients with a diagnosis of cancer and linked death certificate data (n = 11,120).

	No SMI	SMI	schizophrenia	Bipolar disorder	Other psychoses
Cancer cases with linked death records, n	9036	2084	297	804	983
<b>All-cause cancer deaths</b>					
Number/person-years at risk (10,000s)	2248/8.17	513/1.77	100/0.19	169/0.68	244/0.90
Rate <sup>a</sup> (95%CI)	275.60 (264.44–287.23)	289.69 (265.68–315.87)	522.76 (429.72–635.95)	250.12 (215.12–290.82)	269.94 (238.11–306.03)
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.10 (0.996–1.21)	1.96 (1.57–2.44)	1.00 (0.86–1.17)	0.98 (0.86–1.12)
p-value		0.059	<0.001	0.957	0.782
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.09 (0.99–1.20)	1.91 (1.54–2.38)	1.00 (0.85–1.16)	0.99 (0.86–1.13)
p-value		0.069	<0.001	0.970	0.845
<b>Bowel cancer deaths</b>					
Number/person-years at risk (10,000s)	228/0.49	60/0.11			
Rate <sup>a</sup> (95%CI)	468.60 (411.56–533.55)	554.57 (430.59–714.24)			
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.39 (0.85–2.28)			
p-value		0.188			
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.42 (0.84–2.39)			
p-value		0.182			
<b>Lung cancer deaths</b>					
Number/person-years at risk (10,000s)	334/0.07	55/0.02			
Rate <sup>a</sup> (95%CI)	4900.6 (4402.2–5455.4)	3240.1 (2487.6–4220.2)			
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	0.78 (0.49–1.24)			
p-value		0.296			
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	0.80 (0.50–1.28)			
p-value		0.348			
<b>Breast cancer deaths</b>					
Number/person-years at risk (10,000s)	301/1.49	76/0.33			
Rate <sup>a</sup> (95%CI)	202.00 (180.42–226.16)	231.53 (184.91–289.90)			
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.08 (0.76–1.53)			
p-value		0.681			
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.12 (0.78–1.60)			
p-value		0.542			
<b>Prostate cancer deaths</b>					
Number/person-years at risk (10,000s)	167/0.38	35/0.07			
Rate <sup>a</sup> (95%CI)	437.88 (375.88–509.08)	472.37(339.16–657.90)			
Hazard ratio (95 % CI) A <sup>b</sup>	1 [reference]	1.34 (0.74–2.40)			
p-value		0.334			
Hazard ratio (95 % CI) B <sup>c</sup>	1 [reference]	1.44 (0.76–2.75)			
p-value		0.265			

<sup>a</sup> Rate per 10,000 PYR (person years at risk).

<sup>b</sup> A Partially adjusted model: Adjusted for calendar year and sociodemographic factors (sex [except for breast and prostate cancer], primary care practice, ethnicity).

<sup>c</sup> B Fully adjusted model: Additionally adjusted for smoking status (ever smoked) and BMI (underweight (<18.5), normal (18.5–24.9), overweight (25–29.9), obese (≥30)).

bipolar disorder or other psychoses and patients without SMI.

#### 4. Discussion

##### 4.1. Main findings

In this large, nation-wide, cohort study people with schizophrenia had almost 20 % lower incidence of cancer diagnoses but 64 % higher all-cause mortality following cancer diagnosis compared to matched comparators without SMI. Where linked death certificate records were available (34 %) cancer-specific mortality was also increased in those with schizophrenia. Patients with schizophrenia had reduced rates of all-cancer diagnosis and of prostate and bowel cancer diagnoses, but not breast cancer. Those with schizophrenia only had an increased incidence of lung cancer prior to adjusting for smoking. Conversely, an increase in all-cause mortality after cancer diagnosis was observed in those with

schizophrenia for the four cancer types. The pattern of decreased incidence but increased cancer-specific mortality remained after accounting for premature death in the competing risks model, suggesting that premature death in people with schizophrenia is not the driver of lower cancer incidence in this group.

In contrast, while patients with bipolar disorder had a decreased cumulative incidence of all-cancer diagnoses, this was not seen in the specific cancer types, nor in the competing risks analysis. Those with bipolar disorder also had an increased all-cause mortality rate following cancer diagnosis, though not for cancer-specific deaths. Results for the group with other non-affective psychotic illnesses are more difficult to interpret. Those with other psychoses had decreased cancer incidence compared to those without SMI, even after accounting for death from other causes, however mortality after cancer diagnosis was similar to those without SMI.

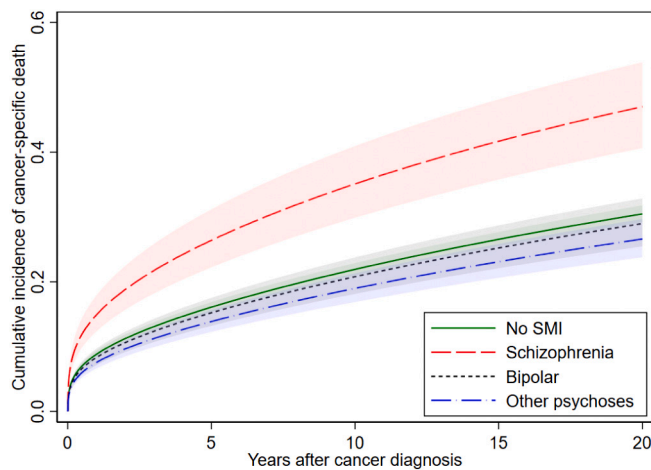


Fig. 3. Cumulative incidence of cancer-specific death accounting for non-cancer deaths.

#### 4.2. Strengths and limitations

This cohort study combines two large primary care databases (CPRD Aurum and GOLD) to create the largest single population sample of people with SMI to date ( $n=69,632$ ) in the study of cancer diagnosis and mortality. The long follow-up period gives the potential to capture the significant changes in cancer incidence and mortality that have occurred over the past decade (Caul and Broggio, 2019).

The use of competing risks analysis is a key strength. Patients with SMI are known to die early compared to the general population, primarily from suicide or cardiovascular disease (Hayes et al., 2017), and it has been suggested that this may interfere with the development of cancer, a disease of older age. We demonstrated that cancer incidence in the group with schizophrenia remains low compared to the group without SMI even after accounting for all-cause mortality, so the lower cancer diagnosis rate is not explained by earlier deaths. We have also been able to demonstrate that while those with bipolar disorder had an increased incidence of cancer, when taking competing risks into account the incidence was similar to those without SMI.

Using primary care records captures those who may not have attended hospital during the study period, thus generating a patient group more reflective of the general population with SMI, than studies using hospital records alone. Furthermore, many previous studies have used the general population as a reference group (Li et al., 2018; Ni et al., 2019; Xiping et al., 2019; Zhou and Triplett, 2018; Zhou et al., 2019; Zhuo et al., 2017), whereas we used a matched comparison population and were able to adjust for smoking status and BMI, a limiting factor in other cohort studies (Li et al., 2018).

Although the use of primary care records offers numerous advantages, it does have limitations. CPRD records do not include cancer-specific information, such as stage of cancer diagnosis or details of cancer treatment. Only 34 % of patients had linked hospital records and death certificate records, making it difficult to interpret trends in cancer-specific mortality in specific cancers or SMI subgroups.

There may be effects of missing information, in particular with regards to BMI and smoking status. However, as we coded those missing as “normal range BMI” or “never smoker”, the effect of this would be to make the SMI and non-SMI groups more similar. There may be residual or unmeasured confounding, but we aimed to describe the cancer incidence and mortality at a population level, rather than explain between group differences. As such, we were able to observe general trends in incidence and mortality, but not to explore the effect of specific factors, such as use of psychotropic medication or adherence to cancer screening programmes. Such factors introduce complexity beyond the scope of this study and should be explored in depth in separate studies.

#### 4.3. Clinical and research implications

Our findings re-iterate the paradox that people with schizophrenia are less likely to be diagnosed with cancer, despite having increased exposure to cancer risk factors. Importantly, our study suggests this issue is likely limited to those with schizophrenia and possibly other psychotic disorders, at least in the context of healthcare in the United Kingdom in recent decades. The phenomenon of decreased cancer risk and increased cancer mortality in those with schizophrenia has been reported repeatedly, though inconsistently, since the 1990s. Our study suggests the lower incidence of cancer in those with schizophrenia is not simply explained by patients dying before developing cancer. The low incidence of cancer even after accounting for premature death and the elevated all-cause and cancer-specific mortality rates following diagnosis suggests cancer diagnoses are missed, or are made later, in people with schizophrenia. Other studies support this hypothesis. A cohort study of cancer in psychiatric patients found lower cancer incidence but a greater proportion of metastases at first presentation (Kisely et al., 2013), and a 2019 systematic review of all-cause mortality in psychiatric patients found that men with any mental illness lost fewer years to cancer-related deaths but had higher cancer mortality rates than the general population (Plana-Ripoll et al., 2019). Furthermore, a recent meta-analysis found significantly decreased cancer screening rates in people with mental illness world-wide, across a range of cancers (Solmi et al., 2020). Therefore, decreased incidence of recorded cancer in patients with schizophrenia may represent missed cancer diagnoses, associated with later stage of cancer at presentation and poorer prognosis.

An alternative explanation has been postulated: that schizophrenia and psychotic illness (or potentially psychotropic medication) provide protection against tumorigenesis. A cohort study (Lichtermann et al., 2001) found decreased incidence of cancer in relatives of patients with schizophrenia, suggesting that genetic risk factors for schizophrenia may be protective against cancer. A 2019 systematic review of genome wide association studies in patients with schizophrenia or bipolar disorder highlights genes that were found to be overexpressed in schizophrenia (Prata et al., 2019), several of which have been shown to play a role in tumorigenesis (Cianfanelli et al., 2015). However, if schizophrenia offers a selective advantage against cancer, it is concerning that people with schizophrenia and a diagnosis of cancer have a 60 % higher mortality rate than people with cancer without SMI. To clarify whether decreased cancer incidence in SMI truly reflects missed diagnoses, a further study is required using primary care and linked hospital records, to obtain information on cancer screening, mode of cancer presentation, cancer stage at presentation, time from diagnosis to first treatment and treatment modalities received.

If cancer diagnoses are being missed in the population of individuals with schizophrenia diagnoses, we need strategies to improve cancer detection rates in this group. Patients with SMI in the UK are offered an annual review in primary care, making this an ideal setting to introduce simple interventions such as screening for red-flag symptoms or encouraging adherence to cancer screening programmes.

#### Data statement

CPRD data were analysed under license and are not available for public sharing.

#### Role of the funding source

The study sponsors played no role in the study design, collection, analysis and interpretation of data, the writing of the report, or the decision to submit the paper for publication.

## Declaration of competing interest

None.

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