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Colorectal cancer treatment in people with severe mental illness: a systematic review and meta-analysis

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Original Article

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Abstract

Aims. People with severe mental illness (SMI) have a greater risk of dying from colorectal cancer (CRC), even though the incidence is lower or similar to that of the general population This pattern is unlikely to be solely explained by lifestyle factors, while the role of differences in cancer healthcare access or treatment is uncertain

Methods. We undertook a systematic review and meta-analysis on access to guideline-appropriate care following CRC diagnosis in people with SMI including the receipt of surgery, chemo- or radiotherapy. We searched for full-text articles indexed by PubMed, EMBASE, PsychInfo and CINAHL that compared CRC treatment in those with and without pre-existing SMI (schizophrenia, schizoaffective, bipolar and major affective disorders). Designs included cohort or population-based case–control designs.

Results. There were ten studies (sample size = 3501–591 561). People with SMI had a reduced likelihood of surgery (RR = 0.90, 95% CI 0.92–0.97; $p = 0.005$; $k = 4$). Meta-analyses were not possible for the other outcomes but in results from individual studies, people with SMI were less likely to receive radiotherapy, chemotherapy or sphincter-sparing procedures. The disparity in care was greatest for those who had been psychiatric inpatients.

Conclusions. People with SMI, including both psychotic and affective disorders, receive less CRC care than the general population. This might contribute to higher case-fatality rates for an illness where the incidence is no higher than that of the general population. The reasons for this require further investigation, as does the extent to which differences in treatment access or quality contribute to excess CRC mortality in people with SMI.

Introduction

Cancer is a leading cause of mortality in people with a range of mental illnesses including severe mental illness (SMI) (Lawrence *et al*., 2000; Kisely *et al*., 2008, 2013*a*, 2016; Lawrence *et al*., 2013). For instance, they are 60% more likely to die from colorectal cancer (CRC) than the general population with CRC being second only to lung cancer as a cause of cancer death in this group (Kisely *et al*., 2008). The disparity is greater for people with SMI such as schizophrenia, major depressive disorder and bipolar disorder (Kisely *et al*., 2008, 2013*a*). This is despite the incidence of CRC in people with mental illness being the same or even lower than that of the general population (Lawrence *et al*., 2000; Kisely *et al*., 2008, 2013*a*, 2016). It is unlikely that this pattern can solely be explained by lifestyle factors following diagnosis such as diet or alcohol use.

Differences in cancer healthcare access and treatment may be another factor mediating the relationship between SMI and the increased risk of CRC mortality (Grassi and Riba, 2021). A recent systematic review found that women with SMI were less likely to be screened for breast and cervical cancer, although data on CRC were more limited (Solmi *et al*., 2020). An Australian study found that people with SMI had lower rates of screening in primary care for colorectal, prostate and cervical cancer after adjustment for age, gender and clinic visits (Tuesley *et al*., 2019). Australia has a National Bowel Cancer Screening Programme and there is ongoing research into whether there are similar disparities in participation for people with SMI (Protani *et al*., 2021). Reduced access to screening may therefore be one explanation

for the finding that people with pre-existing mental illness are more likely to have advanced cancer stage at diagnosis, particularly those with SMI (Davis *et al.*, 2020).

There is less information on care following diagnosis and it is possible that another contributor to higher mortality is differential access to guideline appropriate treatment such as resection and adjuvant radio- or chemotherapy (Brown *et al.*, 2019; Grassi and Riba, 2021). We therefore undertook a systematic review of CRC treatment rates and modalities in those with and without SMI. A further aim was to assess if any differences in treatment between those with and without SMI were reflected in differences in subsequent mortality between the two groups.

Methods

Search strategy

This systematic review was registered with PROSPERO (ID CRD42021224360) and conducted according to PRISMA guidelines (Page *et al.*, 2021) and recommendations for the reporting of meta-analyses of observational studies in epidemiology (Stroup *et al.*, 2000). PubMed, EMBASE, PsychInfo and CINAHL were searched from inception to December 2021 to identify studies comparing CRC treatment in groups with and without pre-existing SMI. The search strategy included key terms for CRC, SMI and cancer treatments (surgical, systemic and radiation therapies) (see online Supplementary Table 1 for full list of search terms). There were no language restrictions. The reference lists of all eligible papers and related reviews were also scanned to identify any additional relevant studies.

Study selection

Studies were eligible for inclusion if they were cohort or population-based case–control studies of adults that reported original data on cancer treatment, stratified by pre-existing SMI status, in those with CRC. Studies that did not establish that the SMI diagnosis preceded the cancer diagnosis were excluded, as were those that did not include a representative comparison group of CRC patients without mental illness. Search results were imported into EndNote software, which was then used to eliminate duplicates. Articles were initially screened by title and abstract and then full text for their eligibility for inclusion in the review by pairs of reviewers working independently.

Data extraction and quality assessment

Data were extracted into an Excel spreadsheet and included study characteristics (country, sample size, age at diagnosis, years of cancer diagnosis, cancer type and staging), type and definition of psychiatric disorders, the cancer treatment of interest, effect estimates of the relationship between SMI and cancer treatment, and confounders adjusted for. Although some studies looked at predictors of subsequent mortality, none directly compared mortality in those with and without SMI as a result of any differences in treatment between the two groups. Study quality was assessed using the Newcastle–Ottawa Scale for cohort studies (Wells *et al.*, 2011). Study selection, data extraction and quality assessment were independently conducted by three co-authors working in pairs with disagreements settled by consensus with or without the assistance of a fourth reviewer. Consensus was achieved in all cases.

Statistical analysis

Outcomes were the receipt of surgery, radio- or chemotherapy. Where data were available for three or more studies, they were combined in a meta-analysis using RevMan and Win-Pepi (Abramson, 2011). Odds ratios were converted to risk ratios (Zhang and Yu, 1998; Schünemann *et al.*, 2019; ClinCalc.com). Where studies reported both crude and adjusted risk ratios, adjusted ratios were included in analysis. If there were at least 10 studies in a meta-analysis, we planned to assess for publication bias using funnel plots. We used an I^2 statistic value of greater than 50% as an indicator of significant heterogeneity. We explored any heterogeneity further through sensitivity analyses of the effect of omitting each study in turn. A random effects model was used for all analyses because of variation in studies between settings and methods.

Results

The search identified 13 153 citations, of which nine met the criteria for inclusion. We also included re-analysed data from a further published study by two of the present review's authors (SK and DL) (Kisely *et al.*, 2013*a*). Although this had compared rates of colorectal surgery between those with any psychiatric disorder and the general population, separate data for schizophrenia/psychosis were available.

The three main reasons for exclusion were that studies did not examine treatment for CRC in people with SMI, did not evaluate the exposure (SMI) prior to cancer diagnosis, or did not report original outcome data (Fig. 1).

Characteristics of the ten studies are included in Table 1. These were all retrospective cohorts of patients diagnosed with CRC between 1988 and 2013 (colon = 1, rectal = 1; colorectal = 8). Three were conducted in the United States (Baillargeon *et al.*, 2011; Wieghard *et al.*, 2015; Ho *et al.*, 2018), two in Canada (Kisely *et al.*, 2012; Mahar *et al.*, 2020), and one each from Australia (Kisely *et al.*, 2013*a*), Denmark (Kaerlev *et al.*, 2018), Finland (Manderbacka *et al.*, 2018), Taiwan (Huang *et al.*, 2018) and Japan (Ishikawa *et al.*, 2016). The sample size ranged from 3501 to 591 561, with a median of 24 507. The median number of people with SMI was 1106 (range = 136–11 837).

Four studies reported cancer treatment by psychotic disorders and mood disorders separately, three looked at combined SMIs and three studies considered only schizophrenia (Table 1). Pre-existing SMI diagnoses were identified using databases from insurance records, hospital admissions or outpatient/psychiatrist visits. One study also used prescriptions of antipsychotic medication or selective serotonin/norepinephrine reuptake inhibitors (SSRI/SNRIs) as indicators of schizophrenia, schizoaffective, bipolar and major affective disorders (Kisely *et al.*, 2012).

Quality assessment revealed that all studies, except for one (Manderbacka *et al.*, 2018), reported adjusted estimates controlling for at least age and cancer stage (Table 2). Other important confounders adjusted for in most studies included sociodemographic factors (e.g., race/ethnicity, income, rurality), comorbidities and year of diagnosis. In the one study that did not give adjusted estimates for treatment access, largely because this was not the primary outcome, the authors presented raw numbers on the presence of metastases stratified by sex. Using these it was possible to calculate that there were no significant differences for either males or females in the proportion of people presenting with metastases in the psychosis, mood or control groups

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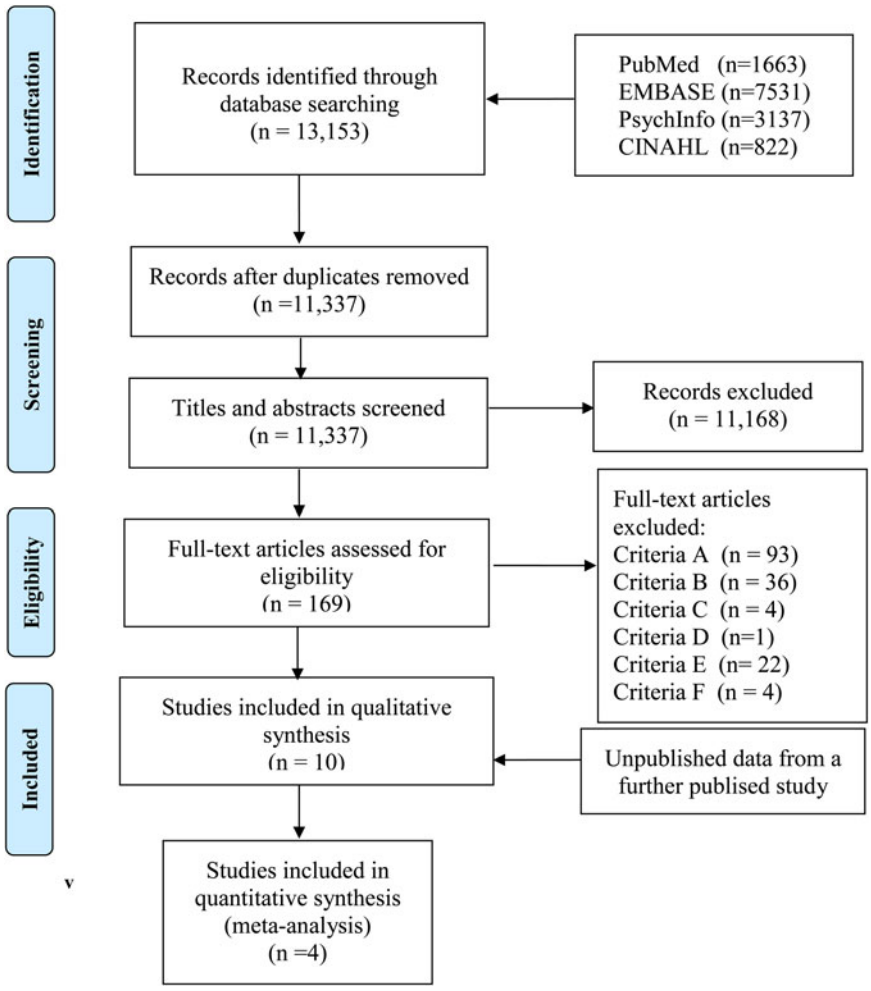

Fig. 1. Study selection process.
Notes: Exclusion criteria A: studies that did not examine treatment in SMI patients with colorectal/colon/rectal cancer. Exclusion criteria B: studies that did not examine SMI (schizophrenia/psychotic disorders/bipolar/major depression) that occurred prior to cancer diagnosis. Exclusion criteria C: studies which did not contain a comparison population (i.e. CRC patients without history of SMI). Exclusion criteria D: studies which contained a repeated analysis for the same outcome in a single population. Exclusion criteria E: Studies not reporting original data (e.g. reviews/text book chapters). Exclusion criteria F: Full text could not be retrieved/conference abstract contained insufficient information.

(Table 3). Two studies did not explicitly demonstrate that cancer treatment outcomes occurred after, rather than before, the psychiatric diagnosis (Wieghard *et al.*, 2015; Ho *et al.*, 2018).

Receipt of surgery

Table 4 presents results for the seven studies that examined surgical outcomes by SMI status. Outcomes including any operation, sphincter preserving or emergency surgery. Four studies compared the likelihood of any surgery in people with schizophrenia/psychosis to controls (Kisely *et al.*, 2012, 2013*a*; Ishikawa *et al.*, 2016; Manderbacka *et al.*, 2018), although in one study this was combined with endoscopy (Ishikawa *et al.*, 2016). Two studies presented results for mood disorders (Kisely *et al.*, 2012; Manderbacka *et al.*, 2018). In almost all comparisons, people in either diagnostic group were significantly less likely to receive surgery (Table 4). The one exception was the study by Manderbacka *et al.* (2018) that found non-significant results for females although they were still significant for males (Table 4). However, in the other study that also presented results by sex, there were no differences between males and females (Table 4) (Kisely *et al.*, 2013*a*). There was little difference between the two diagnostic groups given overlapping 95% confidence intervals (Table 4).

We were only able to meta-analyse results for schizophrenia/psychotic disorders and this confirmed the findings from the majority of individual studies that people with SMI were less likely to receive any surgery (RR = 0.90; 95% CI 0.84–0.98; $I^2 = 76\%$; $p = 0.003$) (Fig. 2). Omitting the study that combined colorectal surgery with endoscopy did not alter the findings (RR = 0.85; 95% CI 0.74–0.97; $I^2 = 81\%$; $p = 0.02$).

In terms of other surgical outcomes that could not be meta-analysed, people with either schizophrenia/psychotic or mood disorders were significantly less likely than people without SMI to receive sphincter preserving as opposed to non-sphincter preserving rectal surgery on adjusted analyses in one study (Table 4) (Wieghard *et al.*, 2015). In another study, people with all forms of SMI were also significantly more likely to require emergency colorectal surgery, even after adjustment for important confounders (RR = 1.25; 95% CI 1.04–1.50) (Ho *et al.*, 2018).

A final study reported on the likelihood of not receiving CRC surgery in people with SMI who had an inpatient psychiatric history and those who had only been outpatients (Table 4). Only those with an inpatient history were less likely than non-psychiatric controls to have had surgery on adjusted analyses (RR = 2.15; 95% CI 1.07–4.33).

Receipt of adjuvant therapy

Four studies examined the receipt of adjuvant therapy such as chemo- and radiotherapy therapy, all but one presenting adjusted results (Table 5). However, in the latter case, there were no

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Table 1. Characteristics of studies included in the systematic review ($n = 10$)

Study author (year), Country	*N*	Age at Dx	Years of cancer Dx	Cancer type; staging	Psychiatric Disorder/s Examined (n)	Psychiatric disorders definition/ measure	Cancer treatments examined
Baillargeon *et al.* (2011), USA (SEER)	80 670	⩾67 years	1993–2005	Colon; I-IV & unknown	Psychotic disorders (3576); Mood disorders (8261)	Pre-existing diagnosis; Dx codes from Medicare claims data during 2 years pre-cancer diagnosis	Non-receipt of treatment; Non-receipt of chemotherapy (restricted to stage 3 cancers)
Ho *et al.* (2018), USA (NIS)	591 561	⩾18 years; 60% >65 years	2007–2011	Colorectal; Not advanced & advanced disease	Schizophrenia (5443)	Coexisting mental disorder; ICD-9 dx codes from NIS comorbidity data at time of cancer surgery	Receipt of emergency colorectal surgery
Huang *et al.* (2018), Taiwan	9555	⩾20 years	2000–2012	Colorectal; (inc. only those who had died)	Schizophrenia (1911)	Coexisting diagnosis; Dx from Catastrophic Illness Patient Database or previous hospitalisation and dx of schizophrenia or previous diagnosis 2 + times within 1 year in outpatient clinics.	Utilisation of palliative care treatments (ICU; hospice ward admission; palliative care consultation; hospice home care; chemotherapy) in the month prior to death.
Ishikawa *et al.* (2016), Japan	12 475	⩾40 years	2010–2013	Colorectal (n = 6011) and Gastric (n = 6464); I-IV & unknown	Schizophrenia (2495)	Coexisting diagnosis; ICD-10 dx codes recorded in Japanese Diagnosis Procedure Combination in-patient database	Receipt of surgical (or endoscopic) treatment (all stages)
Kaerlev *et al.* (2018), Denmark	25 194	All ages; Mean ∼68 years	2007–2013	Colorectal; I-IV & unknown (inc. only those who received surgery)	'Serious' psychiatric disorders (422) Comprised of: affective disorders (77.8%) and psychotic disorders (22.2%)	Pre-existing 'serious' psychiatric diagnosis based on ICD-10 codes of history of hospital contact from 10 years −120 days prior to cancer surgery	Receipt of at least one oncological treatment (chemotherapy or radiotherapy)
Kisely *et al.* (2012), Canada	3501	All ages (>67 years for models psychiatric disorders based on prescription history)	2001–2005	Colorectal; I-IV	SSRI/SNRI prescription (194); Antipsychotic prescription (28)	Pre-existing psychiatric contact with primary or specialist services between 1–2 years prior to cancer dx (based on medical insurance claims); OR prescription of at least 1 SSRI/ SNRI or antipsychotic in the 2 years prior to CRC diagnosis	Receipt of surgery (stages I-III) within 1 year of diagnosis
Kisely *et al.* (2013*a*) Australia	14 278	⩾50 years; median 70.0	1988–2007	Any stage CRC.	SMI (136); Comprised of schizophrenia (9), affective psychosis (75), other psychoses (52).	Pre-existing diagnosis; Inpatient record for the treatment of schizophrenia, affective psychosis, or other psychoses.	Receipt of surgery.
Mahar *et al.* (2020), Canada	24 507	⩾18 years	2007–2012	Colorectal; I-IV & unknown	Any SMI (740); Comprised of major depression, bipolar disorder, schizophrenia, non-organic psychotic illness	Pre-existing diagnosis (6 months to 5 years prior to cancer dx) based on administration records. Stratified by inpatient (1 + hospitalisations) and outpatient (2 + visits to a psychiatrist or emergency department)	Non-receipt of surgical resection; Non-receipt of adjuvant treatment
Manderbacka *et al.* (2018), Finland	40 799[a]	NS	1990–2013	Colorectal; Localised, regional, distant & unknown	Psychotic disorders (751); Mood disorders (722)	Pre-existing diagnosis requiring hospital treatment 1 + years prior to cancer dx based on the Hospital Discharge Register	Non-receipt of treatment; Receipt of surgery; Receipt of chemotherapy; Receipt of radiation
Wieghard *et al.* (2015), USA	23 890	NS	2004–2011	Rectal	Mood disorder (1367); Schizophrenia/psychotic disorder (190); Multiple psychiatric diagnoses (535)	Coexisting mental disorder in NIS dataset (identified based on ICD codes)	Receipt of sphincter preserving rectal surgery

CRC, colorectal cancer; dx, diagnosis; NS, not stated; SMI, severe mental illness.
[a]Excludes substance use disorder.

Table 2. Quality assessment of studies included in the systematic review using the Newcastle–Ottawa Scale

	Selection				Comparability		Outcome		
Study	(1) Representative-ness of exposed cohort	(2) Selection of non-exposed cohort	(3) Ascertainment of exposure	(4) Demonstration of outcome of interest not present at start of study	(1) Study adjusted/ controlled for at least stage	(2) Study also controlled for age	(1) Assessment of outcome	(2) Was follow up long enough for outcomes to occur?	(3) Adequacy of f-u of cohorts
Baillargeon *et al.* (2011)	*	*	*	*	*	*	*	*	*
Ho *et al.* (2018)	*	*	*	N/S	*	*	*	*	*
Huang *et al.* (2018)	*	*	*	*	*	*	*	*	*
Ishikawa *et al.* (2016)	*	*	*	*	*	*	*	*	*
Kaerlev *et al.* (2018)	*	*	*	*	*	*	*	*	*
Kisely *et al.* (2012)	*	*	*	*	*	*	*	*	*
Kisely *et al.* (2013*a*)	*	*	*	See	*	*	*	*	*
Mahar *et al.* (2020)	*	*	*	*	*	*	*	*	*
Manderbacka *et al.* (2018)	*	*	*	*	See below†		*	*	*
Wieghard *et al.* (2015)	*	*	*	N/S	*	*	*	*	*

Notes: * indicates that the study met the criterion; N/S: not stated; †There were no significant differences between cases and controls in the presence of metastases at presentation.

Table 3. Presence of metastases on presentation from Manderbacka *et al*

	Males	Psychosis	Mood disorder	No SMI	χ^2 statistic	*p*-value
Males	Metastases recorded	149	126	9941	2.107	0.349
	No metastases recorded	148	137	9177		
Females	Metastases recorded	250	232	10 104	4.592	0.101
	No metastases recorded	204	227	10 104		

significant differences between cases and controls in the presence of metastases (Table 5). In two studies, the outcome was any adjuvant therapy (Kaerlev *et al*., 2018; Mahar *et al*., 2020), in another, the non-receipt of chemotherapy (Baillargeon *et al*., 2011), and in the fourth, the receipt of chemotherapy and radiation therapy separately (Manderbacka *et al*., 2018).

Three studies found that those with SMI were less likely to receive adjuvant therapies (Baillargeon *et al*., 2011; Kaerlev *et al*., 2018; Mahar *et al*., 2020). One of the three studies stratified by SMI severity and reported that participants who had previously received inpatient psychiatric care were significantly less likely to receive adjuvant therapy (RR = 2.07; 95% CI 1.72–2.50) than those with SMI only receiving outpatient care (RR = 1.22; 95% CI 1.00–1.49) (Mahar *et al*., 2020). However, in another that presented results separately by diagnostic group, the likelihood of not receiving chemotherapy was similar for people with psychotic illness (RR = 1.56; 95% CI 1.21–2.03) and mood disorders (RR = 1.27; 95% CI 1.10–1.46) as shown by overlapping 95% confidence intervals (Baillargeon *et al*., 2011).

There were mixed findings in the fourth study which presented separate results for males and females. In the case of radiotherapy, both males and females with either psychotic illnesses or mood disorders had the same likelihood of treatment as the controls (Manderbacka *et al*., 2018). This was also true for the receipt of chemotherapy in females. However, males were significantly less likely to receive this treatment irrespective of diagnostic group.

Other outcomes

A study from Taiwan examined CRC palliative care outcomes in patients with and without schizophrenia between 2000 and 2012 (Huang *et al*., 2018). This included palliative care consultation services (OR = 0.59; 95% CI 0.43–0.82) and chemotherapy (OR = 0.60, 95% CI 0.55–0.66). By contrast, they were more likely to receive intensive care treatment (OR = 1.21, 95% CI 1.07–1.36) or invasive interventions, such as cardiopulmonary resuscitation (OR = 1.34, 95% CI 1.15–1.57) (Huang *et al*., 2018). There were no significant differences in the use of hospice ward or home care (Huang *et al*., 2018). As noted previously, there were no studies that assessed if any differences in treatment between those with and without SMI were reflected in differences in subsequent mortality between the two groups.

Non-receipt of any treatment

Two studies reported on the non-receipt of any CRC treatment in people with psychotic disorders or mood disorders (Baillargeon *et al*., 2011; Manderbacka *et al*., 2018). The first study reported an increased risk of non-receipt of treatment in people with psychotic illness (RR = 1.42; 95% CI 1.13–1.78) and mood disorders (RR = 1.28; 95% CI 1.08–1.52) compared to those without mental illness (Baillargeon *et al*., 2011). This study adjusted for age, stage, race, ethnicity, sex, marital status, region, income, comorbidity, and year of diagnosis. The second study also observed an increased risk of non-receipt of treatment in those with psychotic illness, but inconsistent results for severe mood disorders (Manderbacka *et al*., 2018). Although unadjusted, these results were stratified by sex and there were no significant differences between cases and controls in the presence of metastases at presentation.

Heterogeneity and publication bias

The results for the receipt of surgery in SMI showed significant heterogeneity (Fig. 2). We therefore explored this by excluding each study in turn in every analysis. The omission of the unpublished re-analysed data that came from one of the studies (Kisely *et al*., 2013*a*) resulted in an I^2 of less than 50% (RR = 0.93; 95%CI 0.89–0.97; $p = 0.0008$; $I^2 = 46\%$). We were unable to analyse for the effects of publication bias as none of the analyses had 10 or more studies.

Discussion

This systematic review identified a small number of studies ($n = 10$) examining CRC treatment in those with and without SMI. Despite significant inter-study heterogeneity, those with SMI appeared to be generally less likely to receive CRC treatment (any treatment, surgery or adjuvant therapy) compared to those without SMI. These differences persisted after adjustment for socio-demographic variables and cancer stage at presentation. The latter is an important potential covariate given that people with pre-existing mental illness are more likely to have advanced cancer stage at diagnosis.

These overall findings are consistent with studies examining treatment for other cancer sites such as breast and cervix. For instance, people with SMI were less likely to receive guideline recommended treatment for breast cancer (Mahabaleshwarkar *et al*., 2015) (Dalton *et al*., 2018) and encountered greater delays before initiation of therapy than those without SMI (Iglay *et al*., 2017; Haskins *et al*., 2019).

This mirrors findings for other chronic physical illness such as cardiovascular disease and diabetes in studies in people with SMI from the United States, Canada, Australia, and Great Britain (Druss *et al*., 2001; Hippisley-Cox *et al*., 2007; Kisely *et al*., 2007, 2009; Kilbourne *et al*., 2008; Mitchell *et al*., 2009; Lawrence and Kisely, 2010). For instance, psychiatric patients are less likely to have their weight or blood pressure measured in primary care or be assessed or treated for hyperlipidaemia despite physician consultation rates being generally high in people with SMI (Jablensky *et al*., 2000; Hippisley-Cox *et al*., 2007; Kilbourne *et al*., 2008). In secondary care, psychiatric patients are less likely to receive specialist procedures such as cardiac catheterisations and coronary artery bypass grafting than the general population, even though their mortality rates for the same

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Table 4. Results of studies examining receipt of surgery for CRCs, by SMI type

Study (year), Country	Mental illness	Outcome	Result (RR, 95% CI)	Covariates that were considered
Psychotic disorders/Schizophrenia				
Kisely *et al.* (2012), Canada	Prescription of at least 1 antipsychotic in 2 years prior to cancer dx (*v.* no antipsychotic prescription)	Receipt of surgery[a] (stage 1–3 cancer) within 1 year of dx	0.27 (0.08–0.92)[b]	Age, sex, residence, social deprivation, comorbidities, history of cancer
Kisely *et al.* (2013*a*), Australia	Inpatient record for the treatment of schizophrenia, affective psychosis, or other psychoses.	Receipt of surgery.	57/ 132 (43.2%) cases *v.* 6562/11 931 (55.0%) controls (no mental health contact) Both sexes 0.50 (0.35–0.73) Males 0.48 (0.33–0.70) Females 0.53 (0.36–0.76)	Sex, age group, grade of tumour at diagnosis, amount of contact with mental health services.
Manderbacka *et al.* (2018), Finland	Psychotic Illness (*v.* no SMI)	Receipt of surgery	Males: 0.91 (0.84–0.97) Females: 0.96 (0.92–1.01)	No significant differences between cases and controls in the presence of metastases
Ishikawa *et al.* (2016), Japan	Schizophrenia (*v.* no mental disorder)	Receipt of surgical or endoscopic[c] treatment	0.77 (0.69–0.85)[b]	Age, stage, sex, comorbidities, income, smoking status, cancer type, reason for admission
Ho *et al.* (2018), USA	Schizophrenia (*v.* no mental disorder)	Receipt of emergency colorectal surgery	1.30 (1.04–1.62)[b]	Age, metastatic disease, sex, race, income, comorbidity, fluid/ electrolyte disorders, blood loss, weight loss
Wieghard *et al.* (2015), USA	Schizophrenia/ psychotic disorders (*v.* no mental disorder)	Receipt of sphincter preserving rectal surgery *v.* non-sphincter preserving surgery (rectal cancer only)	0.64 (0.42–0.98)[b]	Age, sex, race, Charlson comorbidity score, income, insurance status, hospital volume/ location/ teaching status, year of dx
Mood disorders				
Kisely *et al.* (2012), Canada	Prescription of at least 1 SSRI/SNRI in the 2 years prior to cancer dx (*v.* no SSRI/SNRI prescription)	Receipt of surgery[a] within 1 year of dx	0.54 (0.30–0.97)[b]	Age, sex, residence, social deprivation, comorbidities, history of cancer
Manderbacka *et al.* (2018), Finland	Severe Mood disorders (*v.* no SMI)	Receipt of surgery	Male: 0.92 (0.85–0.98) Female: 0.96 (0.92–1.01)	No significant differences between cases and controls in the presence of metastases
Wieghard *et al.* (2015), USA	Mood disorders (*v.* no mental disorder)	Receipt of sphincter preserving rectal surgery *v.* non-sphincter preserving surgery (rectal cancer only)	0.70 (0.60–0.81)[b]	Age, sex, race, Charlson comorbidity score, income, insurance status, hospital volume/ location/ teaching status, year of dx
Any SMI				
Mahar *et al.* (2020), Canada	Any SMI (major depression, bipolar, schizophrenia, non-organic psychotic illness) (*v.* no mental disorder)	Non-Receipt of surgical resection[d]	SMI inpatients: 2.15 (1.07–4.33) SMI outpatients: 1.55 (0.88–2.59)	Age, stage, sex, rurality, year of dx, primary tumour location

dx, diagnosis.
[a]Restricted to stage I-III patients.
[b]Odds ratios were presented, rather than relative risks.
[c]Study included both gastric and CRC included (~50% CRC).
[d]Restricted to stage II/III patients.

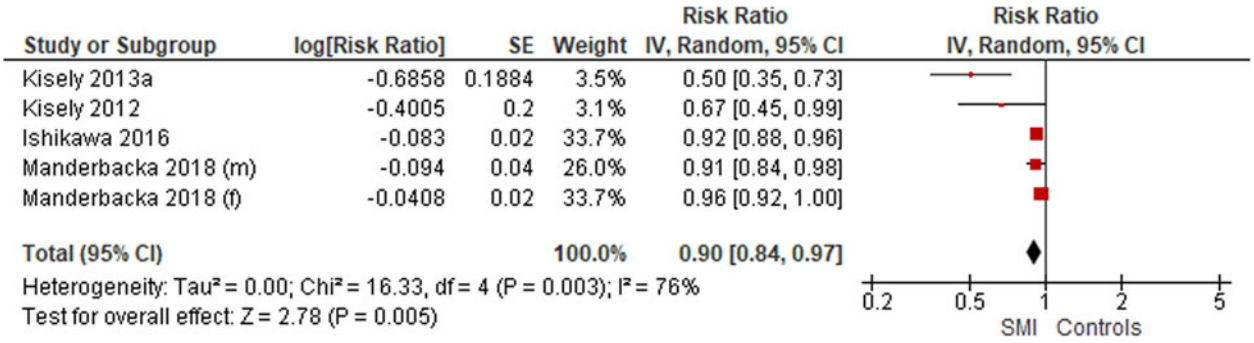

Fig. 2. Receipt of surgery in people with schizophrenia/ psychotic disorders.

Table 5. Results of studies examining receipt of adjuvant therapies (chemotherapy and/or radiation therapy), by SMI type

Study (year), Country	Mental Illness	Outcome	Result (RR, 95% CI)	Covariates that were considered
Psychotic Disorders/Schizophrenia				
Baillargeon *et al.* (2011), USA	Psychotic Illness (*v.* no mental disorder)	Non-receipt of chemotherapy[a]	1.56 (1.21–2.03)	Age, stage, race, ethnicity, sex, marital status, SEER region, income, comorbidity, year of dx
Manderbacka *et al.* (2018), Finland	Psychotic Illness (*v.* no SMI)	Receipt of chemotherapy	Male: 0.67 (0.39–0.95) Female: 0.78 (0.55–1.01)	No significant differences between cases and controls in the presence of metastases
Manderbacka *et al.* (2018), Finland	Psychotic Illness (*v.* no SMI)	Receipt of radiation	Male: 0.69 (0.37–1.02) Female: 0.83 (0.55–1.11)	Ditto
Mood disorders				
Baillargeon *et al.* (2011), USA	Any mood disorder (*v.* no mental disorder)	Non-receipt of chemotherapy (in stage 3 pts)	1.27 (1.10–1.46)	Age, stage, race, ethnicity, sex, marital status, SEER region, income, comorbidity, year of dx
Manderbacka *et al.* (2018), Finland	Severe Mood disorders (*v.* no SMI)	Receipt of chemotherapy	Male: 0.67 (0.37–0.97) Female: 0.88 (0.67–1.09)	No significant differences between groups in the presence of metastases
Manderbacka *et al.* (2018), Finland	Severe Mood disorders (*v.* no SMI)	Receipt of radiation	Male: 0.88 (0.58–1.18) Female: 0.74 (0.45–1.04)	Ditto
Any SMI				
Kaerlev *et al.* (2018), Denmark	Any SMI (Schizophrenia; schizotypal; delusional disorder; mood disorder) (*v.* no mental disorder)	Receipt of at least one adjuvant tx (chemotherapy or radiation)	Colon: 0.55 (0.40–0.76)[b] Rectal: 0.72 (0.46–1.11)[b]	Age, stage, sex, comorbidity, education, socioeconomic status
Mahar *et al.* (2020), Canada	Any SMI (major depression, bipolar, schizophrenia, non-organic psychotic illness) (*v.* no mental disorder)	Non-Receipt of adjuvant therapy[c] (chemotherapy or radiation)	SMI inpatients: 2.07 (1.72–2.50) SMI outpatients: 1.22 (1.00–1.49)	Age, stage, sex, rurality, year of dx, primary tumour location

SMI, severe mental illness; RR, relative risk; CI, confidence intervals; dx, diagnosis; SEER, Surveillance; Epidemiology and End Results database.
[a]Restricted to stage III patients.
[b]Odds ratios were presented, rather than relative risks.
[c]Restricted to stage II/III patients.

conditions are significantly higher (Kisely *et al.*, 2007, 2009). On discharge from hospital following myocardial infarction, they are also less likely to be prescribed beta-blockers and statins (Kisely *et al.*, 2009).

In terms of variations within the SMI group, males were significantly less likely to receive chemo- or radiotherapy than the general population while rates for females were no different. Although not the focus of the present study, there were mixed findings on sex as a predictor of CRC treatment in overall study samples. For instance, females were less likely to require emergency resection but more likely to have sphincter-sparing surgery in adjusted analyses from two studies (Wieghard *et al.*, 2015; Ho

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et al., 2018). By contrast, there were no differences between males and females in the overall receipt of surgery ± endoscopy in two further studies (Kisely *et al*., 2013*a*; Ishikawa *et al*., 2016). The reasons for these conflicting results are unclear but are reflected elsewhere. On one hand, a care pathways study in Great Britain found that while CRC incidence was higher in males, subsequent access to services was generally the same for both sexes (White *et al*., 2018). On the other hand, qualitative work found that males and females with CRC had different treatment experiences (Brewer *et al*., 2020). We did not find larger disparities in participants with psychotic illnesses compared with severe mood disorders although those who had previously received inpatient psychiatric care were significantly less likely to receive adjuvant therapy than people with SMI only receiving outpatient care (Mahar *et al*., 2020).

Possible mechanisms

There are several possible explanations as to why people with SMI who are diagnosed with CRC are less likely to receive guideline recommended cancer treatment. Firstly, those with SMI are more likely to have higher comorbidity burdens (e.g., cardiovascular disease, chronic obstructive pulmonary disease, obesity, diabetes) compared to those without SMI (Viron and Stern, 2010; Janssen *et al*., 2015; Onyeka *et al*., 2019). This may influence clinician/patient decision making around the provision of treatment such as chemotherapy (Gross *et al*., 2007; Boakye *et al*., 2021). However, most studies in this review adjusted for differences in comorbidities and still identified treatment disparities, so this is unlikely to be the primary mediating factor. Clinical decisions on chemotherapy may also be influenced by concerns over potential interactions between particular anti-neoplastic agents and some psychotropic medications such as clozapine (Yap *et al*., 2011). Another mechanism for reduced surgery could be the perception of poor post-operative outcomes in those with SMI (Irwin *et al*., 2014; McBride *et al*., 2018). For instance, people with schizophrenia have higher rates of complications and mortality following surgery. These include respiratory failure, sepsis, deep venous thrombosis, pulmonary embolism, paralytic ileus, stroke, and delirium (Irwin *et al*., 2014).

Other explanations for our findings could include health service access and/or patient treatment adherence. For instance, three of the studies were from the United States where people with mental illness may face barriers to private health cover. It is also possible that people with SMI are treated differently by medical professional with negative attitudes or stigma leading to disparities in care (Thornicroft, 2008; Ostrow *et al*., 2014). Finally, 'overshadowing' may contribute to delays in diagnosis or treatment (Jopp and Keys, 2001; Giddings, 2013; Jones et al., 2008). This is the tendency to regard somatic symptoms such as decreases in energy, appetite or weight as being due to an underlying psychiatric disorder (Giddings, 2013), or that the presence of psychiatric co-morbidity adversely affects the quality of care (Jopp and Keys, 2001). This might include an unwillingness to address possible barriers to appropriate treatment.

Limitations

There are several limitations to these findings. Firstly, there was a large variation in the definitions of SMI and the reference categories used. While all studies used medically diagnosed SMI from hospital/insurance records, definitions included any psychotic illness, only schizophrenia, the prescription of anti-psychotic medication, any mood disorder, severe mood disorder and any SMI. In addition, the reference categories ranged from the absence of SMI to that of any mental disorder, making direct comparisons between studies difficult. Most studies also did not incorporate markers of severity within their definition of psychiatric illness. In the one that did, people with SMI who were treated as inpatients were more likely to have greater treatment disparities than those managed as outpatients (Mahar *et al*., 2020).

From an oncology perspective, the majority of studies used simple binary measures of receipt/non-receipt of CRC treatment. However, there are several other indicators of the quality of cancer care that have, thus far, received limited attention in those with SMI and cancer. Outcomes such as lower chemotherapy relative dose intensity (which considers both chemotherapy dose reductions and delays between cycles), early cessation of chemotherapy/radiation and longer time between diagnosis and initiation of cancer treatment have all been shown to be associated with poorer long-term outcomes such as increased recurrence and poorer cancer survival (Lyman, 2009; Cone *et al*., 2020). There was also no standard definition of guideline-appropriate CRC care.

None of the included studies examined the reasons for the differences in treatment rates in those with and without SMI. We are, therefore, presently unable to distinguish whether treatment disparities are due to lack of patient adherence (being offered treatment with subsequent refusal) or inequitable access to treatment (not being offered/having access to relevant treatment options). Identifying the cause of treatment disparities will help to determine the best avenues for intervention, e.g., clinician-based education, enhanced multidisciplinary team meetings or better patient support and education around the processes and benefits of cancer treatment. In addition, more information is required about the effect of treatment disparities on subsequent outcomes such as mortality.

Other limitations to this research are that we only undertook backward citation searching in retrieved articles and did not search forwards. We also did not calculate agreement between reviewers on the inclusion of studies but resolved any disagreements through consensus with the assistance of a third author if required. We were only able to meta-analyse the results for one outcome, the receipt of surgery. Despite being statistically significant, the likelihood of surgery was reduced by less than 10%. The results also showed heterogeneity. Although we used a random effects model to incorporate heterogeneity into our analyses and the I^2 value was no longer significant with the removal of one study, our findings should still be viewed with caution. We were also unable to test for publication bias.

Possible interventions

In terms of possible interventions, a small study from Japan reported that case management including education and patient navigation for CRC screening in people with schizophrenia resulted in greater participation than treatment as usual (Fujiwara *et al*., 2021). This approach might also be applied to CRC treatment following diagnosis, including the use of navigators, possibly in combination with collaborative care between general practitioners, oncology and mental health services (Irwin *et al*., 2014). One particular focus might be people with SMI who have been lost to psychiatric follow-up. As an example, re-engagement in psychiatric care was associated with a six-fold

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reduction in mortality, including that due to cancer (Bowersox *et al.*, 2012; Irwin *et al.*, 2014). In another, improved community or outpatient follow-up by mental health teams led to reductions in all-cause mortality, the vast majority of which was due to medical illness (Kisely *et al.*, 2013*b*). These interventions should be combined with efforts to address stigma, patient factors (e.g., lack of trust), clinician factors (e.g., inadequate training), and healthcare fragmentation (e.g., between psychiatry and oncology) (Grassi and Riba, 2021). Further research is indicated into where along the CRC care pathway, from screening to end of life care, barriers to intervention occur and the reasons for these (Protani *et al.*, 2021). In particular, people with experience of SMI and CRC, or their carers, should be asked about their experience of barriers and enablers to treatment (Protani *et al.*, 2021).

Conclusion

In conclusion, this review identified a small number of studies on the receipt of CRC treatment in those with and without SMI. There was consistent evidence that those with SMI received less CRC treatment than those without SMI, and that the disparity may be greater in those who have required inpatient treatment. Despite this, there is limited understanding as to why those with SMI experience CRC treatment disparities, and to what extent these treatment differences may mediate the excess CRC mortality observed in those with SMI.

Supplementary material. The supplementary material for this article can be found at https://doi.org/10.1017/S2045796022000634.

Data. Data supporting the findings are available from the corresponding author.

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