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Cancer Incidence and Stage at Diagnosis among People with Psychotic Disorders: Systematic Review and Meta-Analysis.

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Abstract

Research regarding the incidence of cancer among people with psychotic disorders relative to the general population is equivocal, although the evidence suggests that they have more advanced stage cancer at diagnosis. We conducted a systematic review and meta-analysis to examine the incidence and stage at diagnosis of cancer among people with, relative to those without, psychotic disorders. We searched the MEDLINE, EMBASE, PsycINFO, and CINAHL databases. Articles were included if they reported the incidence and/or stage at diagnosis of cancer in people with psychotic disorders. Random effects meta-analyses were used to determine risk of cancer and odds of advanced stage cancer at diagnosis in people with psychosis, relative to those without psychotic disorders. A total of 40 articles were included in the review, of which, 31 were included in the meta-analyses. The pooled age-adjusted risk ratio for all cancers in people with psychotic disorders was 1.08 (95% CI: 1.01 to 1.15), relative to those without psychotic disorders, with significant heterogeneity by cancer site. People with psychotic disorders had a higher incidence of breast, esophageal, colorectal, testicular, uterine, and cervical cancer, and a lower incidence of skin, prostate, and thyroid cancer. People with psychotic disorders also had 22% higher (95% CI: 2% to 46%) odds of metastases at diagnosis, compared to those without psychotic disorders. Our systematic review found a significant difference in overall cancer incidence among people diagnosed with psychotic disorders and people with psychotic disorders were more likely to present with advanced stage cancer at diagnosis. This finding may reflect a need for improved access to and uptake of cancer screening for patients diagnosed with psychotic disorders.

Keywords: cancer, psychosis, schizophrenia, psychotic disorders, stage at diagnosis

1 Background

People with psychotic disorders, including schizophrenia spectrum disorder, have elevated rates of mortality compared to the general population [1,2], and it is estimated that at least half of this excess mortality is attributable to concurrent medical illnesses [3]. The cause of these disparities is thought to be the combination of biological mechanisms (e.g., ongoing antipsychotic medication use), lifestyle factors (e.g., poor diet, lack of exercise, substance use), and differential interactions within the healthcare system [1,4]. There has been extensive research examining concurrent medical illnesses in those with psychotic disorders, which has definitively identified elevated incidence of cardiometabolic and hepatorenal diseases compared to the general population [2]. However, the incidence of cancer in people with psychotic disorders has remained an area of contention since the Report of the Commissioners of Lunacy in 1909 [5–7], which first reported lower rates of cancer in patients with schizophrenia.

Subsequently, studies examining the incidence of cancer in those with psychotic disorders relative to the general population have produced contrasting results; some found a lower incidence of cancers,[8–10] whereas others found the opposite [11,12]. Several meta-analyses have examined the incidence of cancer at specific sites in people with schizophrenia [13–16]. These meta-analyses have identified an higher risk of breast cancer [14,15], lower risk of liver cancer [13], and no difference in risk of lung cancer for people with schizophrenia, relative to the general population [16]

Two prior meta-analyses have examined cancer at all sites [17,18]. Catts *et al*. found no difference in the overall incidence of cancer between people with schizophrenia and the general population [17]. While the authors found an elevated incidence of lung and breast cancer was found, the difference was attenuated after controlling for smoking prevalence [17]. These results conflict with the results of Li *et al.*, which found a slightly lower risk of cancer overall among people with schizophrenia, as well as lower risk of colorectal, prostate, and lung cancers in particular [18]. The findings of each review are likely

impacted by which studies are included/excluded due to wide variation in direction and magnitude across cancer sites. Thus, it is important to be as inclusive as possible when summarizing the evidence, as it will impact conclusions about overall cancer incidence.

There is also evidence that people with psychotic disorders are more likely to present with a more advanced stage of cancer at diagnosis. A meta-analysis of stage at cancer diagnosis and cancer-specific mortality found that people with pre-existing mental illnesses, including psychotic disorders, had 19% greater odds (OR: 1.19, 95%CI: 1.06, 1.33) of advanced stage cancer at diagnosis, whereas people with psychotic disorders had 30% greater odds (OR: 1.30, 95%CI: 1.01, 1.68), relative to those without mental illnesses [19].

Previous meta-analyses of site-specific cancer incidence among people with psychotic disorders have focused on a limited number of cancer sites (n=6) and restricted inclusion criteria to specific measures of incidence. In addition, several large-scale, population-based cohort studies have been conducted since the publication of the most recent review [20,21]. Furthermore, best practice for systematic reviews includes risk of bias assessment [22], which was not done in previous meta-analyses [17] or was done using reporting guidelines to assess study quality [18]. These reporting guidelines were designed for improving transparency and reporting in observational studies, not to assess study quality [23,24]. The objective of this study was to perform a systematic review and meta-analysis of literature comparing the incidence and stage at diagnosis of any and all cancers among people with psychotic disorders relative to the general population.

2 Methods

The protocol for this systematic review and meta-analysis was registered with PROSPERO (CRD42020179833). We followed the Preferred Reporting Items for Systematic Reviews and Meta-

Analysis (PRISMA) guidelines in the writing of this manuscript; details can be found in Appendix A1 [22].

2.1 Search Strategy and Study Selection

We conducted electronic literature searches of the MEDLINE (1966-2020), PsycINFO (1880-2020), and EMBASE (1947-2020) databases via Ovid, as well as the CINAHL (1937-2020) database via EBSCOhost, in June 2022. The search terms were developed following examination of subject headings and related terms pertaining to cancer incidence, stage of cancer, and psychotic disorders in each database. A research librarian at Western University was consulted regarding the selection of databases and develop of search terms. The final search strategy for each database and respective number of results can be found Appendix A2. As well, we conducted forward and backward citation tracing of included articles to identify any other articles that may have been missed in the database searches.

The articles underwent title and abstract screening by a single reviewer (JW), and full-text screening in duplicate by two reviewers (JW, JCW). Conflicts between reviewers were resolved by consensus, or by a third reviewer (KKA) when consensus could not be reached. Articles were included in the review if they met the following criteria: examined cancer incidence or stage at diagnosis in a sample of people with a diagnosis of any psychotic disorder (schizophrenia, schizoaffective disorder, delusional disorder, affective psychoses, psychosis not otherwise specified (NOS)) using standardized diagnostic criteria, such as DSM or ICD, as well as a non-psychotic or general population comparison group. Furthermore, studies which used a cohort, case-control, or cross-sectional study design were included; those which used other study designs, including randomized control trials and descriptive studies, were excluded. Studies which included people with other non-psychotic mental disorders, without providing

stratum specific estimates for psychotic disorders, were excluded. Non-peer reviewed studies were excluded.

2.2 Data Extraction

Data were extracted independently by two reviewers (JW, JCW), in duplicate, using a pilot-tested data extraction tool. We collected data pertaining to the following items: author, year of publication, country, study design, study objectives, sample size, sample source, eligibility criteria, psychiatric diagnoses of participants, age of participants, and sex breakdown. We extracted available raw data, crude, and adjusted estimates of the cumulative incidence of overall and site-specific cancers, as well as estimates stratified by psychiatric diagnosis and sex. In addition, the number of people diagnosed at each stage were extracted, where available, for people with psychotic disorders and those without. The risk of bias for each study was assessed independently by two reviewers (JW, JCW) using the Tool to Assess Risk of Bias in Cohort and Case-Control Studies by CLARITY [25].

2.3 Data Synthesis

Data collected from included articles were summarized both qualitatively and quantitatively. Study characteristics and findings of all included articles were displayed in a summary table. Articles were included in a random effects meta-analysis if they reported an age-adjusted effect measure of incidence with confidence intervals and/or count data for stage at diagnoses. All meta-analyses were conducted in Rstudio v1.2.5033 [26] using the *metafor* package [27].

In terms of cancer incidence, we performed two meta-analyses on the age-adjusted effect measures, which were assumed to approximate an age-adjusted risk ratio [15]. The first meta-analysis examined the risk of all cancers in people with psychotic disorders, relative to those without psychotic

disorders; incidence estimates of site-specific cancers were excluded from this analysis. The second meta-analysis examined the incidence of site-specific cancers among people with psychotic disorders, relative to those without psychotic disorders. To explore whether the use of varying effect measures influenced the pooled effect estimate, sensitivity analyses were performed using subgroup analyses with consistent measures. To examine potential outlier influence on pooled estimates, sensitivity analyses were conducted by identifying outliers with the *'find.outliers'* function in the *dmetar* package, and excluding those studies from the meta-analysis. These data were used to calculate the odds of advanced stage at diagnosis among people with psychotic disorders, relative to those without psychotic disorders.

Pooled estimates were presented as risk ratios (RR) and odds ratios (OR) with corresponding 95% confidence intervals (CI). Results of meta-analyses were displayed in forest plots stratified by psychotic disorder diagnosis, as previous studies have identified differences in incidence by psychiatric diagnoses [28,29]. Subgroup differences by psychotic disorder diagnosis were examined using a Q-test [30]. Heterogeneity in each meta-analysis was assessed using an I^2 statistic; 25%, 50%, and 75% indicate low, moderate, and high levels of heterogeneity, respectively [31]. Publication bias was assessed by visual assessment of funnel plots, in addition to an Egger's test of asymmetry [32].

3 Results

3.1 Search results

An outline of the screening process can be found in Figure 1. The electronic literature search initially returned 944 unique citations, and an additional five articles were identified from forwards and backwards citation tracing. Of these, 819 were deemed ineligible upon review of title and abstract.

We screened the full-text of 125 articles, and 85 were excluded for the following reasons: study did not report data on incidence or stage at diagnosis (n=46); not a case-control, cross-sectional, or cohort

study (n=17); sample did not include people with psychotic disorders, or did not differentiate people with psychotic disorders from other mental illnesses (n=17); study did not have a comparison group or the comparison group included people with other mental illnesses (n=2); or no full-text version was published or available (n=3). Forty articles were deemed eligible for inclusion in the review.

There were a number of studies which met a majority of the inclusion criteria, but were excluded due to the absense of a single criterion. A Danish cohort study examining colon cancer in patients with serious mental illnesses was excluded because the authors did not distinguish between those with psychotic disorders and those with other psychiatric illnesses [33]. Similarly, a study examining antipsychotic use on gastric cancer risk was excluded on the basis that the provided odds ratios of developing cancer were not, in fact, measures of cancer incidence as stated in the inclusion criteria [34].

3.2 Study Characteristics

The characteristics of included studies can be found in Table 1, and a comprehensive summary of findings can be found in Appendix B1. Thirty studies examined incidence of cancer, eight examined stage at diagnosis, and two study included information on both incidence and stage at diagnosis. Thirty-nine of the included studies were retrospective cohort studies of health administrative data, and one was a case-control study using a clinical sample. The majority of studies ascertained the outcome of cancer via linkage to a cancer registry, with a median follow-up period of 18 years (IQR: 10 to 27).

Sample sizes ranged from 2011 to 4,040,494 with a mean and median of 350,279 and 33,372, respectively. People with schizophrenia were included in the sample of 36 studies, 12 included people with schizoaffective disorders, 13 included people with affective psychoses, and 5 included people with psychosis NOS; 2 studies did not specify the psychotic disorders included. In terms of the comparison group, 24 studies used a general population comparison group, whereas 16 used a sample of people

without psychotic disorders selected from a list of patients or people eligible for a benefits program, of which 4 were matched on age, sex, and other covariates. All studies that reported measures of incidence adjusted for confounding factors in their estimates, with seven additionally reporting crude measures; the covariates for each adjusted estimate can be found in Appendix B2.

3.3 Risk of Bias

A summary of findings from the risk of bias assessment of included studies is displayed in Figure 2, and the complete findings can be found in Appendix A3. The most common issues identified across included studies were the inability to ensure that the outcome of interest was not present at the beginning of each study, assessment of exposure, inclusion of important confounding factors, and missing data. An intermediate risk of bias for assessment of exposure was present in 75% of studies, with a considerable portion of studies missing information on this item (12.5%). Regarding the inclusion of important confounding factors, 67.5% of studies had intermediate risk of bias and 28% had high risk of bias. Only 53% of studies had low risk of bias for ensuring that cancer was absent at the start of the study, and 48% did not report the extent of missing data. As most studies used health administrative data, the assessment of outcome and measurement of confounding factors were found to have low risk of bias in most of the studies.

3.4 Meta-Analyses

A total of eight studies were excluded from the quantitative synthesis for the following reasons: articles did not report sufficient data (n = 6) or reported sources of data that were duplicate of another study included in the review (n = 2). Of the 31 studies with suitable data for meta-analysis, 24 studies reported incidence estimates, 6 reported stage at diagnosis, and 1 reported both measures. In particular,

13 reported standardized incidence ratios (SIR), 5 reported incidence rate ratios (IRR), 3 reported hazards ratios (HR), and 3 reported standardized RRs. For studies included in the meta-analysis that reported data on stage at diagnosis (n = 7), five included those diagnosed at stages I through IV, while the remainder only reported the proportion of patients with local versus metastasized cancers. Two studies produced adjusted OR using logistic regression: one adjusting for age, gender, income, comorbidities, and type of cancer, and the other adjusting for only age and gender.

3.4.1 Overall Cancer Incidence

The results of the meta-analysis of overall cancer incidence are displayed in Figure 3. The pooled estimate of age-adjusted RR of all cancers in people diagnosed with psychotic disorders, relative to people without psychotic disorders, was 1.08 (95% CI: 1.01, 1.15). A very high level of heterogeneity was found across the age-adjusted measures of cancer risk (I^2 = 95.6%, tau^2 = 0.05). Eight estimates were considered outliers, and their removal produced a pooled estimate of 1.06 (95% CI: 1.03 to 1.10), as well as substantially reduced statistical heterogeneity (I^2 = 70.7%; tau^2 = 0.005). Subgroup analyses were conducted according to psychotic disorder diagnosis, and a Q-test revealed no statistically significant difference in cancer incidence between psychotic disorders (Q_M = 4.99, d.f. = 2, p = 0.08). Evaluation of the funnel plot did not suggest publication bias (Appendix A4), and Egger's test of asymmetry indicated that there was insufficient evidence to suggest asymmetry in the funnel plot (z = 0.4769, p = 0.6334).

3.4.2 Site-Specific Cancer Incidence

The results of the meta-analysis of cancer incidence for 26 types of cancer are displayed in Figure 4. Elevated RRs were found for breast (RR: 1.22, 95% CI: 1.02, 1.43), esophageal (RR: 1.36, 95% CI: 1.06, 1.66), testicular (RR: 1.27, 95% CI: 1.03, 1.50), cervical (RR: 1.35, 95% CI: 1.20, 1.50), and

endometrial (RR: 1.62, 95% CI: 1.15, 2.09) cancers. Lower RRs were found for colorectal (RR: 0.91, 95% CI: 0.83, 0.99), prostate (RR: 0.57, 95% CI: 0.51, 0.63), skin (RR: 0.71, 95% CI: 0.62, 0.79), and thyroid (RR: 0.76, 95% CI: 0.65, 0.87) cancers.

3.4.3 Stage at Diagnosis

The results of the meta-analysis of stage at diagnosis are displayed in Figure 5. The pooled OR of advanced stage at diagnosis for people with psychotic disorders, relative to people without psychotic disorders, was 1.23 (95% CI: 1.05 to 1.44); a very high level of heterogeneity was found (I^2 = 95%, tau^2 = 0.04). Three estimates were considered outliers, and their removal of these produced a pooled OR of 1.16 (95% CI: 1.06 to 1.29), as well as reduced statistical heterogeneity (I^2 = 84%; tau^2 = 0.009).

Evaluation of the funnel plot displayed in Appendix 2G did not show evidence of publication bias. Egger's test of asymmetry indicated that there was insufficient evidence to suggest asymmetry in the funnel plot (z = 1.4290, p = 0.1530). However, the power of the egger's test to detect publication bias may have been limited by the number of studies.[32]

4 Discussion

This meta-analysis found a higher overall cancer risk for people with psychotic disorders, relative to the general population. The contributions of the present review are fourfold. First, the current systematic review and meta-analysis builds on this prior evidence by including several recent cohort studies which use population-based health administrative data. Second, the present review provides an assessment of the risk of bias and methodological limitations of the current literature, which had not been done previously. Third, the present review examines cancer incidence among people with both affective and non-affective

psychotic disorders and includes a broader range of estimates of incidence than have been previously included in meta-analyses. Fourth, the present review includes estimates of the incidence of several site-specific cancers which haven't been included in previous reviews, including uterine and cervical cancer. Ultimately, the present review included several additional articles since the publication of the most recent review [10,20,21,35,36], and represents the most comprehensive summary of the evidence to date on the risk of cancer among people with psychotic disorders.

Two prior meta-analyses of overall cancer incidence in people with psychotic disorders have focused on people with schizophrenia – one found a lower risk of cancer (SIR = 0.90, 95% CI: 0.81 to 0.99) [18], whereas the other found no difference (SIR = 1.05, CI 0.95 to 1.15), relative to people without schizophrenia [17]. The difference in the pooled estimate produced in the present review is likely a reflection of the inclusion of more recently published cohort studies using population-based health administrative data.

It was first hypothesized that people with psychotic disorders had a lower incidence of cancer, relative to those without psychotic disorder [7], and since that time a wide range of theories to explain this phenomenon have been proposed. Three studies compared cancer incidence among people with schizophrenia to both relatives without schizophrenia and to the general population [8,11,37]. Relatives of people with schizophrenia were found to have a lower incidence of cancer, relative to the general population. The authors of these studies hypothesized that there may be shared genetic factors that are associated with schizophrenia and a lower risk for developing cancer.

Other studies have examined dopamine, and its role in the regulation of cell proliferation, as an important factor affecting cancer risk in people with psychotic disorders [38,39]. Indeed, the effects of dopamine antagonists, including antipsychotics and anti-emetics, have been explored through several models, with effects on cancer risk largely heterogeneous by cancer site. Both in vitro and rodent models

have demonstrated largely anti-cancer effects via a number of pathways, with the exception of breast and liver cancer in females, where dopamine antagonists were found to increase risk [40]. However, the evidence for a causal relationship between antipsychotic exposure and cancer is not proven [41].

Additionally, people with schizophrenia have been found to smoke at much higher rates compared to the general population [64]. Although the association between smoking and both lung and bladder cancer is well established and thoroughly documented [65,66], this meta-analysis did not find a significantly elevated risk of lung or bladder cancer among people with psychotic disorders, which is similar to previous meta-analyses [16–18]. However, one prior meta-analysis found an elevated risk of lung cancer among people with schizophrenia, which was attenuated when estimates were adjusted for smoking behaviour [17].

A number of included studies identified an elevated risk of sex-specific cancers among females with schizophrenia, namely cancer of the breast, uterus, and cervix [8,21,29,36,46–48]. One such study found the risk of all cancers to be higher among females with schizophrenia, relative to the general population, but not among males with schizophrenia [49]. This difference was eliminated when female-specific cancers were excluded from the analysis [49]. Our meta-analysis found the risk of breast, cervical, and uterine cancer to be significantly elevated among females with psychotic disorders, which is consistent with the findings of prior meta-analyses of breast cancer in people with schizophrenia [14,15,17]. To our knowledge, there are no prior meta-analyses of the risk of cervical and uterine cancer among women with psychotic disorders.

The effect of dopamine antagonists on breast cancer has been examined in epidemiological studies, wherein exposure to dopamine antagonists is significantly associated with an increased risk of breast and endometrial cancer [42–44]. Although the mechanism of action is unclear, it is also thought that

antipsychotic medication may increase levels of prolactin, which is associated with breast carcinogenesis [41,45].

Antipsychotic medication has also been associated with a lower risk of prostate and colorectal cancer [50]. A cohort study published in 1992 identified a significantly lower incidence of prostate cancer among males with schizophrenia who were prescribed large doses of phenothiazines [51]. It is hypothesized that elevated prolactin levels suppress testosterone levels, an important factor in prostatic tumour growth [52]. Regarding colorectal cancer, antipsychotic medication has been found to exert anti-oncogenic effects in vitro via downregulation of fibroblast growth factor receptors in colorectal cancer cells [53]. In the current review, people with psychotic disorders were found to have a significantly lower risk of both prostate and colorectal cancers.

Other health and behavioral factors, such as cardiometabolic disorders and smoking, might have a bigger influence on cancer risk [41]. People with psychotic disorders have a higher risk of developing cardiometabolic disorders such as cardiovascular disease, diabetes, and obesity. This is the result of exposure to antipsychotic medication and exacerbation by sedentary lifestyle and poor eating habits [4,57–61]. Diabetes and obesity are established risk factors for a variety of cancers, including breast and colorectal cancer [59,60]. However, diabetes is negatively associated with prostate cancer risk and PSA score as a result of reduced insulin response and lower levels of testosterone [61–63].

Screening uptake represents another factor which may influence both observed cancer incidence as well as stage at diagnosis among people with psychotic disorders. Women with psychotic disorders have significantly lower odds of receiving cervical and breast cancer screening, compared to women without psychotic disorders [67–70]. As such, people with psychotic disorders are less likely to benefit from the screening programs for cervical cancer and human papillomavirus (HPV) which have reduced the incidence of cervical cancer in the general population [48,71]. This can be contrasted with breast and

prostate cancer screening, whereby increased screening in the general population has resulted in overdiagnosis. Low uptake of breast and prostate cancer could have resulted in underestimation of breast and prostate cancer among people with psychotic disorders, relative to the general population [20,72].

Prior meta-analyses have challenged the hypothesis that the lower incidence of particular cancers in people with psychotic disorders are the result of delayed detection, citing post-mortem data which found that undiagnosed cancer was a rare event [17]. Catts *et al.* further suggested that the aggressive nature of lung and bladder cancer, along with the rapid course of these cancers, makes it very unlikely that there would be diagnostic delay for people with psychotic disorders [17]. Although it may be unlikely that cancer would go entirely undetected, this does not preclude the existence of a diagnostic delay. Furthermore, the more advanced stage at diagnosis in this population is in and of itself indicative of this delay, and this diagnostic delay has been shown to account for a portion of the difference in cancer mortality between people with psychotic disorders and those without [10]. Our review identified a significantly elevated odds of metastases at diagnosis for people with psychotic disorders. Although we do not have data on stage at diagnosis for site-specific cancers, this does suggest a more advanced cancer at diagnosis, possibly indicative of delays in detection and diagnosis.

4.1 Limitations of Included Studies

The risk of bias assessment identified several limitations to the studies included in this review. For many included studies, there was no clear lookback window to exclude prevalent cases of cancer prior to the start of the study, and so it cannot be ensured that the studies only included incident cases of cancer. Moreover, most of the included studies had intermediate risk of bias regarding assessment of the exposure.

Most studies did not adequately control for important confounding factors, either through matching or multivariable regression, and many studies relied on indirect standardization to control for age and sex.

Additionally, a large proportion of studies did not report the extent of missing data, and thus we are unable to account for how it may have influenced the results of individual studies [10].

Many of the included studies used population-based health administrative data. Some databases only included people eligible for a public health insurance program that often represented a particular subset of the population, such as those with lower income or receiving benefits for disability/unemployment. Conversely, other studies included data from private health insurance programs, which would likely include people who are employed and of higher socioeconomic status. Therefore, the sampled populations are substantially heterogenous across the included studies.

In addition, the follow-up periods varied significantly across studies. A large proportion of studies used incidence measures which cannot account for differences in follow-up time among participants, e.g. SIR or SRR. Among these studies, variation in follow-up time was inconsistently reported.

Furthermore, included studies variably reported case definitions, limiting the ability to assess the validity of these case definitions. Finally, our meta-analysis found evidence of a lower risk of skin cancer among people with psychotic disorders. However, it should be noted that included studies had varying definitions of skin cancer, with one study excluding non-melanoma skin cancer [71]. Therefore, pooled estimates of skin cancer risk may be unreliable. Additionally, some studies reported estimates of site-specific cancers with a small number of outcome events, thereby creating extremely wide confidence intervals, often extending down to zero.

4.2 Limitations of the Review

The findings of this review must be considered in light of its limitations. First, the literature search did not include grey literature or other unpublished studies, thereby potentially excluding a body of relevant research and introducing publication bias. Second, a high degree of statistical heterogeneity was

found in each of our meta-analyses. All effect measures of cancer risk that adjusted for age were assumed to approximate an age-adjusted RR, to analyze a broader range of studies with varying methodology, this likely contributed to the observed heterogeneity. Third, a majority of the studies adjusted for age and sex, however a smaller number of studies accounted for other confounding variables, so the estimates included in the meta-analysis have varying amounts of residual confounding. Fourth, the confidence limits of the estimates of all cancer incidence among people with affective psychoses were very wide, as a result of the limited numbers of people included in these sub-samples. Fifth, our meta-analysis of stage at diagnosis used unadjusted odds ratios calculated using raw count data extracted from articles; therefore, these estimates may be subject to confounding by several factors. Lastly, the power of the Egger's test to detect publication bias across studies reporting stage at diagnosis was limited by the smaller number of studies available for meta-analysis [32], and thus it is unclear whether publication bias was present in our examination of stage at diagnosis.

4.3 Conclusions

This systematic review and meta-analysis identified a greater overall cancer risk among people with psychotic disorders, with differences by specific cancer sites. These differences are likely the product of biological, behavioural, and environmental factors—the effects of which need to be further investigated. People with psychotic disorders have higher odds of metastases at diagnosis compared to people without psychotic disorders, suggesting delayed detection and diagnosis. These disparities in either access or uptake may be contributing to higher mortality among patients with psychotic disorders [67,70,72–74]. Programs that target education, screening, and early diagnosis of cancer among individuals with psychotic disorders may translate into better health outcomes.

As informed by the findings of this review, we have many suggestions for future research conducted on this topic. First, researchers should consider additional confounding factors in the relationship between psychotic disorder and cancer risk, particularly cardiometabolic comorbidities. Second, researchers should explore age- and sex-related differences in cancer incidence among people with psychotic disorders, to clarify how these variables may modify this relationship. Finally, researchers should explore the interrelationships between incidence, stage at diagnosis, and treatment on mortality among people with psychotic disorders.

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6 Competing Interests

Declarations of interest: none

7 Supplementary material

Additional information and data can be found in the appendices.

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9 Tables and Figures

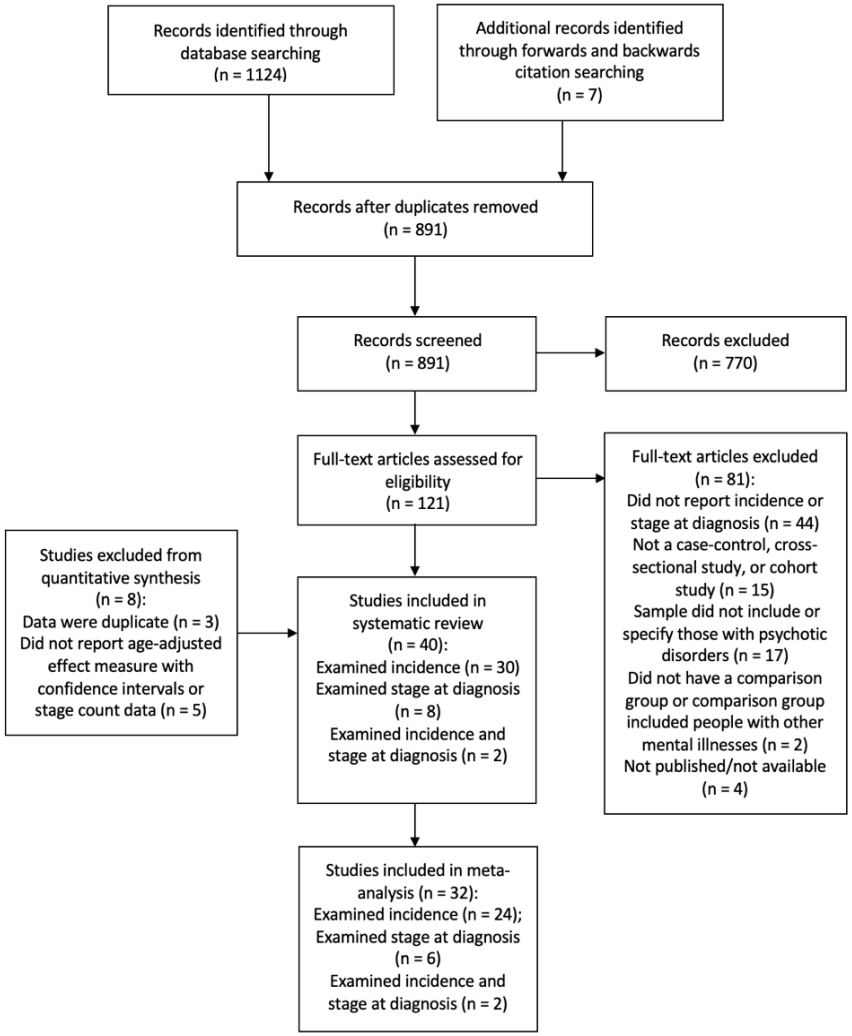

Figure 1: PRISMA flowchart

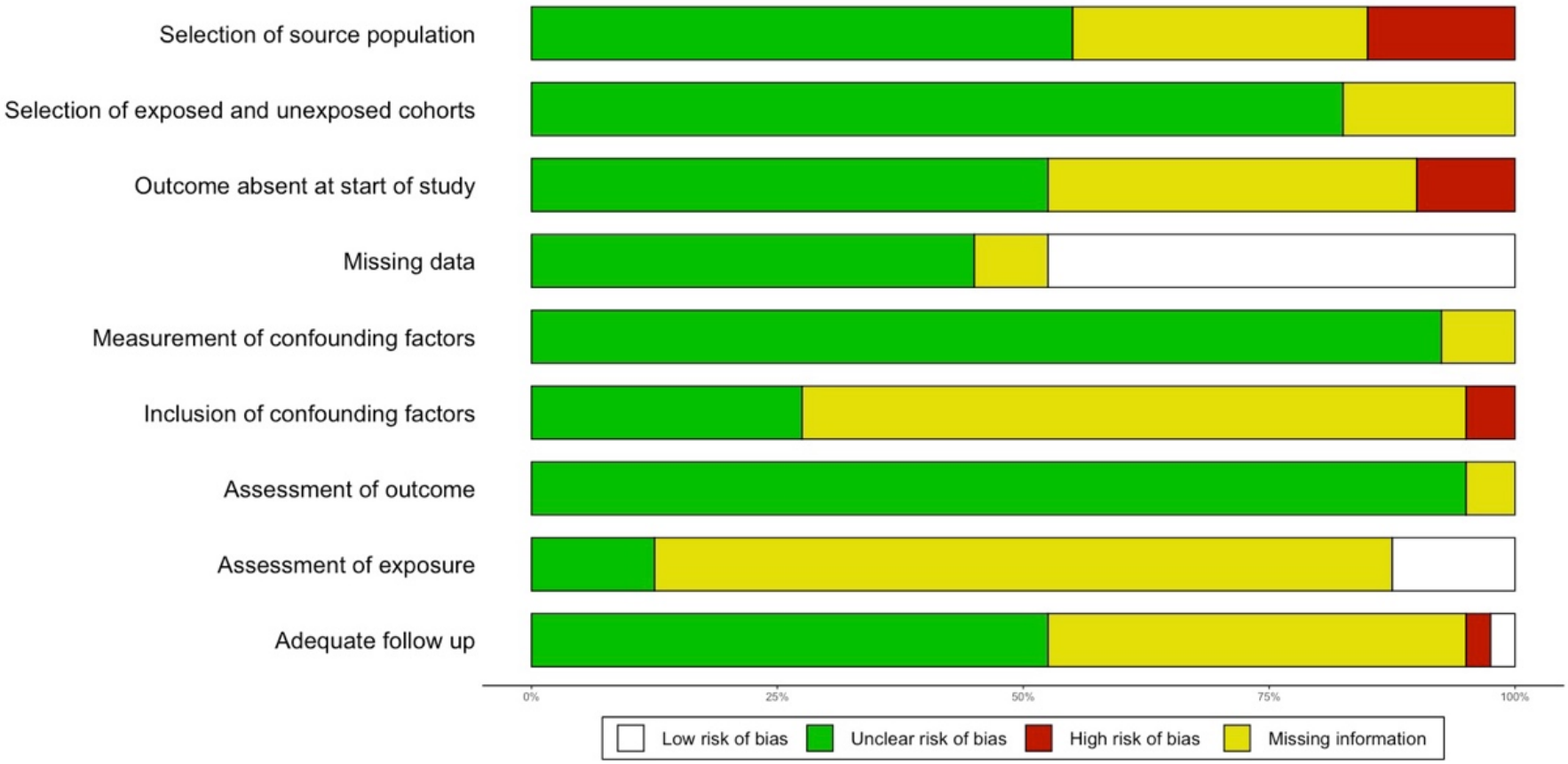

Figure 2: Summary of risk of bias assessment

Table 1: Characteristics of studies included in qualitative synthesis

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Ahlgrén-Rimpiläinen et al., 2020 [75]	Finland	Admin.	non-affective psychotic disorders	Stage	breast	Retrospective cohort	1969 - 2013	78,079	Finnish Cancer Registry	without psychotic disorders
Arffman et al., 2019 [76]	Finland	Admin.	non-affective psychotic disorders	Stage	lung	Retrospective cohort	1990 - 2013	34,572	Finnish Cancer Registry	without psychotic disorders
Baillargeon et al., 2011 [77]	USA	Admin.	unspecified	Stage	colon	Retrospective cohort	1993 - 2005	63,547	Surveillance, Epidemiology, and End Results Program	without psychotic disorders
Barak et al., 2005 [9]	Israel	Admin.	schizophrenia, bipolar	Incidence	all cancer	Retrospective cohort	1993 - 2003	3,226	Inpatients at Abarbanel Mental Health Center	general population
Barak et al., 2008 [48]	Israel	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1960 - 2005	2,011	Inpatients at Abarbanel	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
									Mental Health Center	
Bergamo et al., 2014 [78]	USA	Admin.	schizophrenia	Stage	all cancer	Retrospective cohort	1992 - 2009	96,702	Surveillance, Epidemiology, and End Results Program	without psychotic disorders
Brink et al., 2019 [35]	Denmark	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1980 - 2012	27,141	Danish National Patient Register	without psychotic disorders
Chang et al., 2013 [79]	UK	Admin.	schizophrenia, bipolar disorder, schizoaffective disorder	Stage	all cancer	Retrospective cohort	1999 - 2008	28,477	Clinical Record Interactive System (CRS) at South London and Maudsley (SLAM) and Biomedical Research Centre (BRC)	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Chen et al., 2018 [36]	Taiwan	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	2000 - 2010	32,731	Psychiatric Inpatient Medical Claims Database	general population
Chou et al., 2011 [80]	Taiwan	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	2000 - 2008	237,413	National Health Insurance Research Database	general population
Chou et al., 2017 [81]	Taiwan	Admin.	schizophrenia	Incidence	breast	Retrospective cohort	1998 - 2008	21,454	National Health Insurance Research Database (NHIRD)	without psychotic disorders
Cunningham et al., 2015 [82]	New Zealand	Admin.	schizophrenia, bipolar disorder, schizoaffective disorder	Stage	all cancer	Retrospective cohort	2006 - 2010	8,434	New Zealand Ministry of Health	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Dalton et al., 2005 [47]	Denmark	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1969 - 1995	22,766	Danish Psychiatric Central Register	general population
Dalton et al., 2008 [83]	Denmark	Admin.	schizophrenia and other psychoses	Incidence	lung	Retrospective cohort	1994 - 2003	3,218,440	Danish Civil Registration System	general population
Dalton et al., 2008 [84]	Denmark	Admin.	schizophrenia and other psychoses	Incidence	all cancer	Retrospective cohort	1994 - 2003	3,218,440	Danish Civil Registration System	general population
Goldacre et al., 2005 [85]	UK	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1963 - 1999	9,649	National Health Service Hospitals Database	general population
Grinshpoon et al., 2005 [46]	Israel	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1962 - 2001	33,372	Israeli Psychiatric Case Register	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Hippisley-Cox et al., 2007 [86]	UK	Admin.	schizophrenia, bipolar	Incidence	breast, colon, rectal, gastroesophageal, prostate, and respiratory	Retrospective cohort	1995 - 2005	4,040,494	QRESEARCH database	without psychotic disorders
Ishikawa et al., 2016 [87]	Japan	Admin.	schizophrenia	Stage	gastric, colorectal	Retrospective cohort	2010 - 2013	12,475	Japanese Diagnosis Procedure Combination database	without psychotic disorders
Ji et al., 2013 [8]	Sweden	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1965 - 2008	59,233	Swedish Hospital Discharge Register	general population
Kisley et al., 2013 [88]	Australia	Admin.	schizophrenia, affective psychosis,	Incidence	all cancer	Retrospective cohort	1988 - 2007	135,451	Western Australia Data Linkage System	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
			other psychoses							
Kisley et al., 2016 [28]	Australia	Admin.	schizophrenia, affective psychosis, other psychoses	Incidence	all cancer	Retrospective cohort	2002 - 2007	93,271	Queensland Hospital Admitted Patients' Data Collection	general population
Lawrence et al., 2000 [89]	Australia	Admin.	schizophrenia, affective psychosis, other psychoses	Incidence	all cancer	Retrospective cohort	1982 - 1995	172,932	Western Australia Data Linkage System	general population
Levav et al., 2007 [37]	Israel	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1960 - 2003	6,132	Israeli Psychiatric Case Register	general population
Levav et al., 2009 [90]	Israel	Admin.	schizoaffective	Incidence	all cancer	Retrospective cohort	1980 - 2005	2,400	Israeli Psychiatric Case Register	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Liao et al., 2015 [91]	Taiwan	Admin.	schizophrenia	Incidence	liver	Retrospective cohort	1998 - 2010	11,965	National Health Insurance Research Database	without psychotic disorders
Lichtermann et al., 2001 [11]	Finland	Admin.	schizophrenia, schizoaffective disorder	Incidence	all cancer	Retrospective cohort	1969 - 1996	26,996	National Hospital Discharge Register, National Disability Pension Register	general population
Lin et al., 2013 [49]	Taiwan	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1995 - 2007	102,202	National Health Insurance Research Database	general population
Lin et al., 2013 [29]	Taiwan	Admin.	schizophrenia, bipolar	Incidence	all cancer	Retrospective cohort	1995 - 2009	91,884	National Health Insurance	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
									Research Database	
Manderbacka et al., 2017 [92]	Finland	Admin.	unspecified	Stage	all cancer	Retrospective cohort	1990 - 2013	600,052	Finnish Cancer Registry	without psychotic disorders
McGinty et al., 2012 [71]	USA	Admin.	schizophrenia, bipolar	Incidence	all except non-melanoma skin cancer	Retrospective cohort	1996 - 2004	3,317	Maryland Medicaid Program	general population
Mortensen et al., 1989 [93]	Denmark	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1957 - 1984	6,152	Inpatients at Danish psychiatric hospitals	general population
Mortensen, 1994 [94]	Denmark	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1970 - 1988	9,156	Danish Psychiatric Case Register	general population
Osborn et al., 2013 [95]	UK	Admin.	schizophrenia, schizoaffective, bipolar,	Incidence	all cancer	Retrospective cohort	1990 - 2008	136,784	The Health Improvement	without psychotic disorders

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
			affective psychosis, brief psychoses, psychoses NOS						Network Database	
Pettersson et al., 2020 [21]	Sweden	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1990 - 2013	111,306	National Patient Register	general population
Raviv et al., 2014 [96]	Israel	Admin.	schizophrenia	Incidence	all cancer	Retrospective cohort	1990 - 2011	4,326	Inpatients at Abarbanel Mental Health Center	general population
Scheflen, 1951 [97]	USA	Clinical	schizophrenia, bipolar, affective psychosis, non-organic psychosis	Incidence	lung	Case-control	1928 - 1942	NR	Inpatients at Worcester State Hospital	general population

Citation	Country	Data	Psychotic disorder(s)	Outcomes	Cancer sites	Study Design	Study Period	Sample Size (n)	Sample	Comparison group
Toender et al., 2018 [10]	Denmark	Admin.	schizophrenia, bipolar disorder, schizoaffective disorder	Incidence, Stage	all cancer	Retrospective cohort	1978 - 2012	579,039	Danish Civil Registration System	without psychotic disorders
Truyers et al., 2011 [98]	Belgium	Admin.	schizophrenia, affective psychosis, other psychoses	Incidence	all cancer	Retrospective cohort	1997 - 2007	4,904	Integro (general practice registration network)	without psychotic disorders
Wootten et al., 2022 [20]	Canada	Admin.	Schizophrenia, psychosis NOS	Incidence, Stage	all cancer	Retrospective cohort	1995 – 2019	313949	Ontario Health Insurance Program, Discharge Abstract Database	without psychotic disorders

Admin.= Administrative, NOS = not otherwise specified

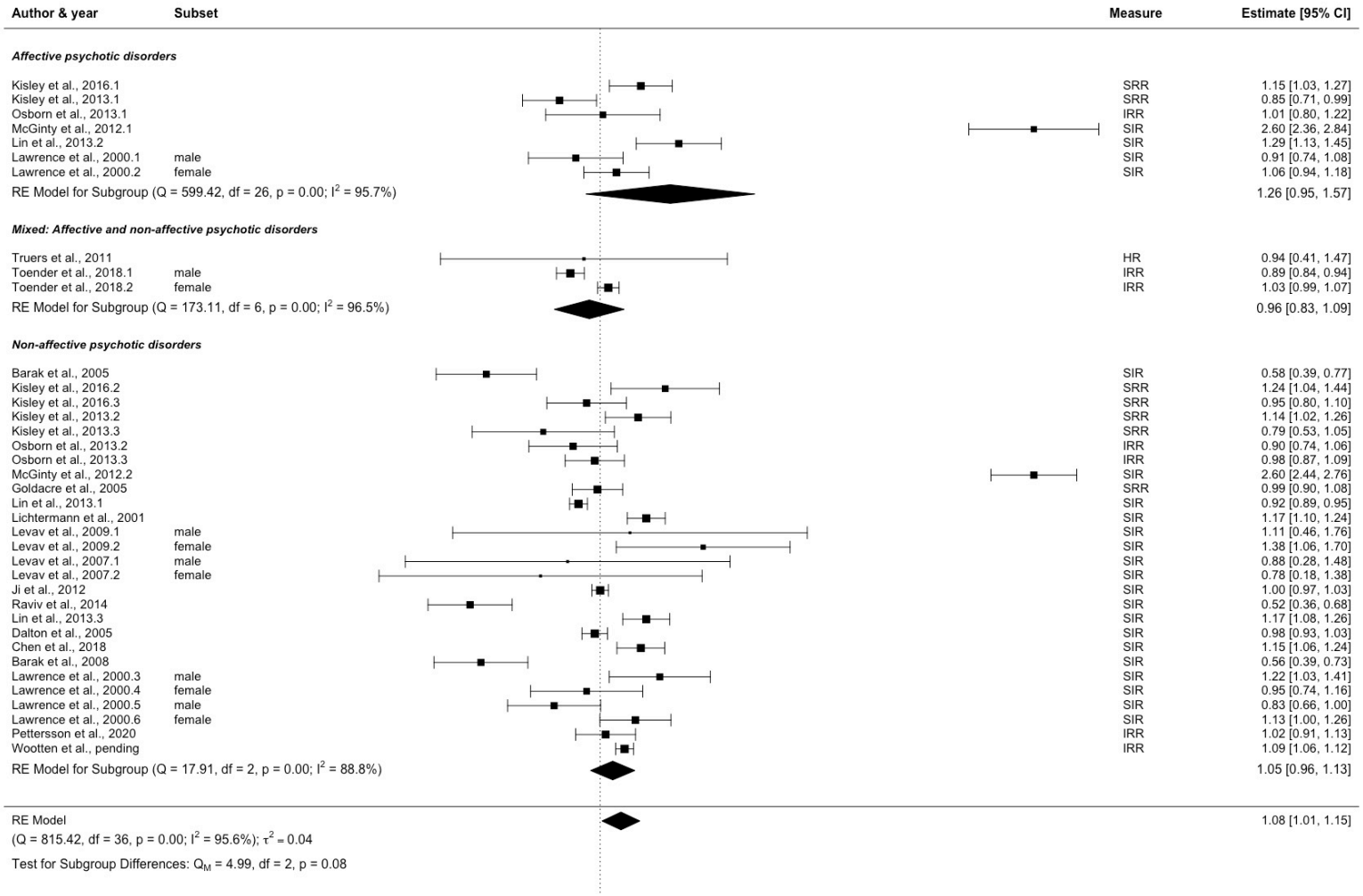

Figure 3: Forest plot of meta-analysis of age-adjusted incidence of cancer in people with psychotic disorders, relative to the general population, sub-grouped by psychiatric diagnosis

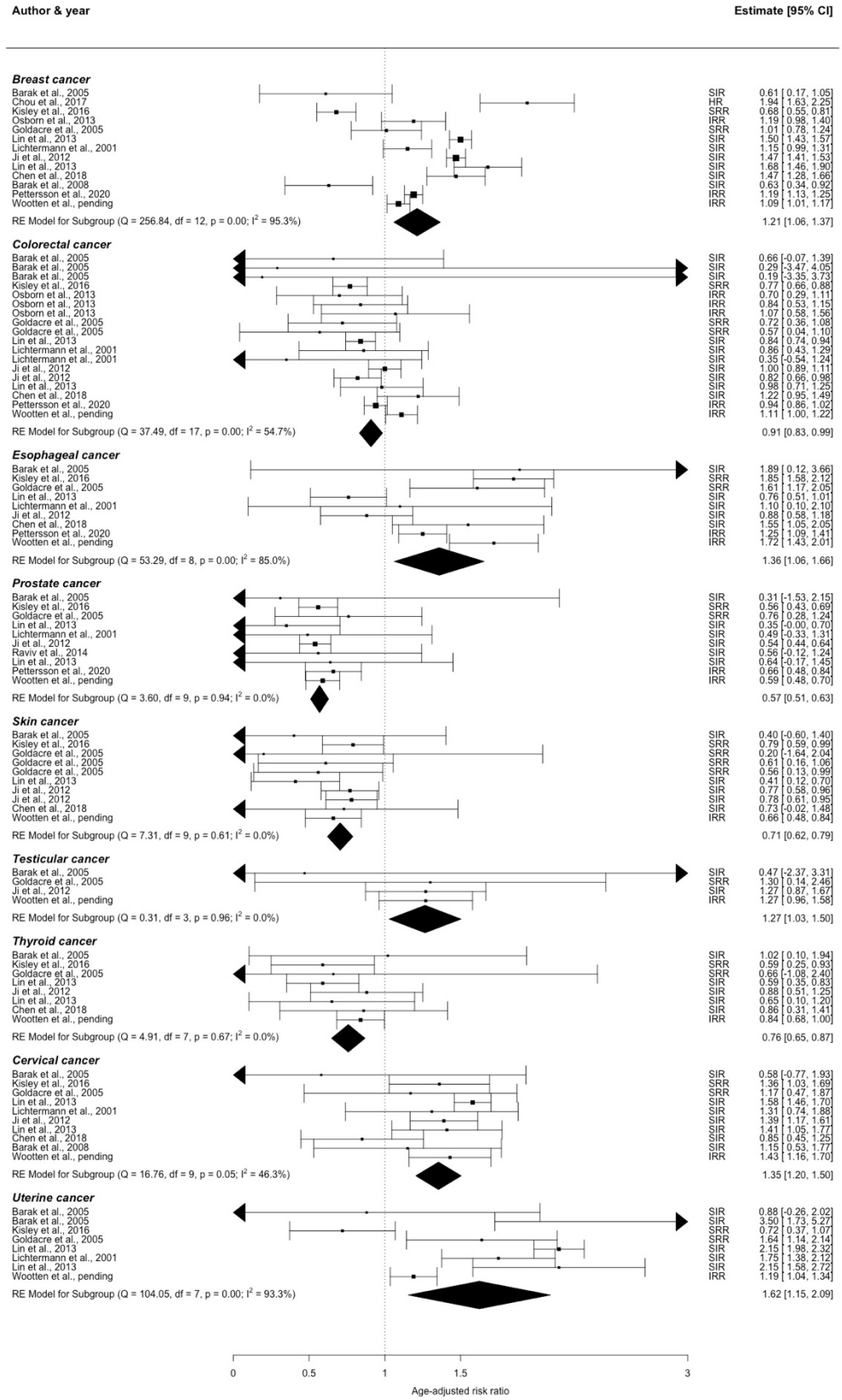

Figure 4: Forest plot of site-specific cancer incidence in people with PD, relative to the general population

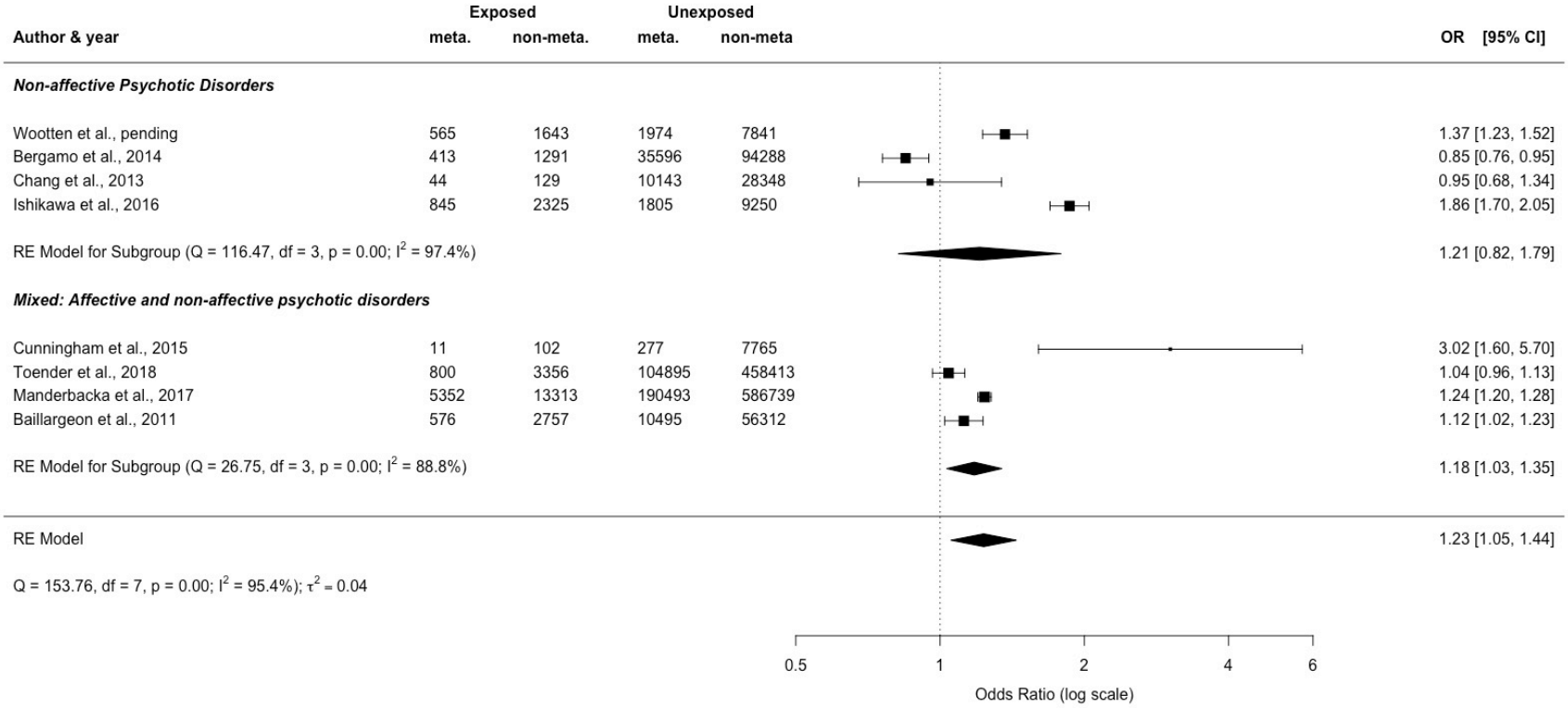

Figure 5: Forest plot of meta-analysis of odds of metastases in people with psychotic disorders, relative to the general population.