Association of antipsychotic use with breast cancer: a systematic review and meta-analysis of observational studies with over 2 million individuals

Janice Ching Nam Leung1,2,* , Dora Wai Yee Ng1,*, Rachel Yui Ki Chu1,*, Edward Wai Wa Chan1,2, Lei Huang1,2, Dawn Hei Lum1, Esther Wai Yin Chan1,2, Daniel J. Smith3, Ian Chi Kei Wong1,2,4,5 and Francisco Tsz Tsun Lai1,2

1Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong SAR, People’s Republic of China; 2Laboratory of Data Discovery for Health (D24H), Hong Kong Science Park, Hong Kong Science and Technology Park, Hong Kong SAR, People’s Republic of China; 3Centre for Clinical Brain Sciences, Division of Psychiatry, College of Medicine & Veterinary Medicine, The University of Edinburgh, Edinburgh, Scotland, UK; 4Research Department of Practice and Policy, School of Pharmacy, University College London, London, UK and 5Aston School of Pharmacy, Aston University, Birmingham, UK.

Abstract

Aims. Despite reports of an elevated risk of breast cancer associated with antipsychotic use in women, existing evidence remains inconclusive. We aimed to examine existing observational data in the literature and determine this hypothesised association.

Methods. We searched Embase, PubMed and Web of Science™ databases on 27 January 2022 for articles reporting relevant cohort or case-control studies published since inception, supplemented with hand searches of the reference lists of the included articles. Quality of studies was assessed using the Newcastle-Ottawa Scale. We generated the pooled odds ratio (OR) and pooled hazard ratio (HR) using a random-effects model to quantify the association. This study was registered with PROSPERO (CRD42022307913).

Results. Nine observational studies, including five cohort and four case-control studies, were eventually included for review (N = 2 031 380) and seven for meta-analysis (N = 1 557 013). All included studies were rated as high-quality (seven to nine stars). Six studies reported a significant association of antipsychotic use with breast cancer, and a stronger association was reported when a greater extent of antipsychotic use, e.g. longer duration, was operationalised as the exposure. Pooled estimates of HRs extracted from cohort studies and ORs from case-control studies were 1.39 [95% confidence interval (CI) 1.11–1.73] and 1.37 (95% CI 0.90–2.09), suggesting a moderate association of antipsychotic use with breast cancer.

Conclusions. Antipsychotic use is moderately associated with breast cancer, possibly mediated by prolactin-elevating properties of certain medications. This risk should be weighed against the potential treatment effects for a balanced prescription decision.

Introduction

Antipsychotic medications are widely prescribed for people living with mental disorders such as schizophrenia, bipolar disorder, major depressive disorder and dementia, with an increasing trend of off-label use also observed worldwide in recent decades (Häfndarsson et al., 2017; Ng et al., 2021). Despite a more tolerable safety profile of second-generation antipsychotic medications (Herrmann et al., 2004), metabolic and endocrinologic abnormalities associated with antipsychotic use have been observed (De Hert et al., 2012). These abnormalities may represent pathomechanisms underlying the known association of antipsychotic use with a range of relatively rare adverse events such as stroke and myocardial infarction (Douglas and Smeth, 2008; Lai et al., 2020).

Some studies have also reported an elevated cancer incidence related to the use of antipsychotics (Dalton et al., 2006; Nielsen et al., 2017). It has been shown women living with schizophrenia and bipolar disorder have a higher risk of developing breast cancer compared with the general population (Chou et al., 2017; Annella et al., 2021) and antipsychotic use may potentially explain at least part of this increased risk. This is supported by a widely adopted working hypothesis of the hyperprolactinaemia-inducing property of certain antipsychotics such as pimozide, risperidone and clozapramine (De Hert et al., 2016b; Johnston et al., 2018). Other possible mechanisms may include poorer lifestyles regarding self-care and health consciousness among antipsychotic users (Bly et al., 2014), as well as the commonly reported
antipsychotic-mediated weight gain (Balt et al., 2011). With complex mechanisms and likely multiple interacting risk factors, existing evidence remains inconclusive, and no definitive conclusion could be drawn regarding this association. Furthermore, although safety monitoring is an integral component of randomised controlled trials, the study design’s inherent weaknesses such as insufficient sample size for rare outcomes, discrepancies in adverse event reporting and inadequate follow-up period to capture can- ficient sample size for rare outcomes, discrepancies in adverse event monitoring is an integral component of randomised con- could be drawn regarding this association. Furthermore, although antipsychotic-mediated weight gain (Balt et al., 2011) exist- antipsychotic-mediated weight gain (Balt et al., 2011) antipsychotic medications in consideration of the potentially elevated risk of breast cancer. This synthesis will inform the risk–benefit assessment of antipsychotic use in facilitation of an optimal pre- scription decision and treatment outcome. In this study, we aim to systematically review and conduct a meta-analysis on the existing evidence to determine the association of antipsychotic use with breast cancer.

Methods

Search strategy and eligibility

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist in conducting this review (Page et al., 2021). As this meta-analysis was based on published data, ethics approval was not required. In accordance with a protocol registered with PROSPERO (Ref: CRD42022307913), we performed preliminary scoping searches to identify databases with substantial pharmacoepidemiologic evidence on the topic. Based on the results of our preliminary searches, we conducted a systematic search of articles published in English in peer-reviewed scholarly journals in respective electronic databases, namely PubMed, Embase and Web of Science™ from inception. The last search was conducted on 27 January 2022. The search strategy was developed based on two subjects: antipsychotics and breast cancer. Search terms and combinations of Medical Subject Headings (MeSH), keywords and text words were derived from previously published systematic reviews (Moja et al., 2012; Indave et al., 2016; Krause et al., 2018) on the two subjects and were selected for each database to optimise sensitivity and specificity of the search. Hand searches through the reference lists of included articles were conducted to avoid the omission of relevant research. For details of specific search keywords and strategies, refer to online Supplementary eTable 1.

All published cohort and case-control observational studies that investigated and quantified the association of antipsychotic use (v. non-use) with breast cancer in individuals aged 16 or above were considered for inclusion in the review. Studies were excluded if they were not published in English, had a study design that was neither cohort nor case-control, included participants who developed breast cancer prior to antipsychotic exposure or did not compare antipsychotic use to non-use, such as comparing between different classes of antipsychotics.

Extraction

Study eligibility was independently determined by JCNL and DWYN. Cohen’s kappa was computed to indicate interrater reliability. Data extraction was completed simultaneously using a standardised data extraction form. Data regarding the context, population, intervention, outcome and measures of association of each study were extracted and recorded in the form. Discrepancies were reconciled through discussion and consultation with a senior author (FTTL).

Quality assessment of included studies

The methodological quality of each included study was assessed using the Newcastle-Ottawa Scale (NOS). Like the data extraction procedure, the quality assessment was conducted independently by JCNL and DWYN. Study quality was indicated by numbers of stars, with nine representing the highest possible methodo- logical rigour. See online Supplementary eTable 3 for details of the quality assessment procedures. Cohen’s kappa was not calculated for the quality assessment decisions, as nine studies were included and there were only a few discrepancies, which were resolved through in-depth discussions.

Pooled estimates

Upon satisfactory assessment result with regards to multivariable adjustment according to the NOS, meta-analyses of the estimates of the association, i.e. odds ratios (ORs) and hazard ratios (HRs), were conducted. Stratified by study design, i.e. cohort and case-control studies, the estimates of the association of antipsychotic use and breast cancer were pooled using a random effects model. The exposure was binarily operationalised as any anti- psychotic use compared with non-use. In cases where this opera- tionalisation was not possible, the longest-term exposure category, or the category representing the farthest extent of antipsychotic use, were used in comparison with non-use in the pooled esti- mates. The inverse variance weighting method was used to deter- mine the relative importance between studies while the I² statistic was used to examine the heterogeneity of the estimates across studies. Upon a sufficient number of included studies, the Egger’s regression test was conducted to detect any publication bias in the pooled estimates. The pooled estimates and test for heterogeneity were implemented using Cochrane Collaboration Review Manager (Version 5.4.1).

Results

As shown in Fig. 1, upon initial search, we retrieved a total of 2549 articles from electronic databases, of which 441 were removed as duplicates. The title and abstract screening process further excluded 2036 articles published in non-English languages, using a study design other than cohort or case-control, not adopting breast cancer as the outcome or not using anti- psychotic use as the exposure. After carefully examining the eligi- bility of the remaining 72 articles full-text, nine studies (N = 2 031 380) were included for a qualitative synthesis and quality assessment. Cohen’s kappa for title and abstract screening [0.496, 95% confidence interval (CI) 0.404–0.588] and full-text selection [0.742, 95% CI 0.567–0.917] suggest moderate and sub- stantial agreement respectively. Two studies were excluded from the meta-analysis (Mortensen, 1987; Dalton et al., 2006), as the effect measures summarising the association were incomparable to that of the other studies and the use of incompatible statistical methods. Seven included studies (N = 1 557 013) provided adequate data for a pooled estimate of the hypothesised
association. Study characteristics and results, as well as quality assessment scores are tabulated in Tables 1 and 2.

Study characteristics
The included studies have been conducted in five countries/jurisdictions: three studies in the United States (Wang et al., 2002; George et al., 2020; Rahman et al., 2022), three studies in Denmark (Mortensen, 1987; Dalton et al., 2006; Pottegård et al., 2018) and one study each in Finland (Taipale et al., 2021), Taiwan (Chou et al., 2017) and the United Kingdom (Hippisley-Cox et al., 2007). Of the nine studies, five were cohort studies (Wang et al., 2002; Dalton et al., 2006; Chou et al., 2017; George et al., 2020; Rahman et al., 2022) and four were case-control studies (Mortensen, 1987; Hippisley-Cox et al., 2007; Pottegård et al., 2018; Taipale et al., 2021). The study sample sizes range from 120 (Mortensen, 1987) to over 0.6 million (Pottegård et al., 2018) individuals. All studies received a moderate to high score in the quality assessment ranging from seven to nine stars based on the criteria of NOS. Six studies (Wang et al., 2002; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) reported a significant association between antipsychotic use (various operationalisations) and breast cancer development.

Outcome – breast cancer
All nine studies defined the outcome of interest as the first-time diagnosis of breast cancer, with five studies specifying the adopted diagnosis explicitly based on International Classification of Diseases (ICD) (Wang et al., 2002; Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022), one of which also identified first claims of breast cancer surgeries without an ICD code diagnosis as cases (Wang et al., 2002). Either surgery, chemotherapy or hospitalisation for breast cancer in addition to the diagnosis with ICD code was adopted for one study (Rahman et al., 2022). Three studies (Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) used a histological or
Table 1. Characteristics and results of the critical appraisal of included studies (N = 9)

| Study Data source | Study period | Region | Study design | Inclusion criteria | Exclusion criteria (no need diagnosis codes) | Outcome definition | Scores from Newcastle Ottawa Scale |
|-------------------|--------------|--------|--------------|-------------------|---------------------------------------------|-------------------|------------------------------------|
| Chou et al. (2017) | LHID2000; RCIPD | 1998–2011 | Taiwan | C | Exposed: female schizophrenia patients with AP prescription between 1998 and 2008; non-exposed: females without mental illness and no AP prescription | Diagnosed with BC before or within 1 year after the schizophrenia diagnosis | BC diagnosis (ICD-9-CM) | **** ** ** |
| Dalton et al. (2006) | CPR; Danish Cancer Registry; North Jutland Prescription Database | 01/01/1989–31/12/2002 | Denmark | C | Danish women aged 16–85 years of age | History of cancer diagnosis before 1989 or age of 16 years | First primary diagnosis of cancer | **** ** *** |
| George et al. (2020) | WHI | 1993–31/03/2018 | United States | C | Postmenopausal women aged 50–79 years | History of BC; <1 day follow-up time | BC diagnosis | *** ** ** |
| Hippisley-Cox et al. (2007) | QRESEARCH | 01/01/1995–01/07/2005 | United Kingdom | CC | Patients aged 25–100 years; had ≥12 months computerised medical record data before index date | History of cancer diagnosis before index date; BC cases or controls with mastectomy/tamoxifen use record ≥12 months before first record of BC | First-ever record of index cancer including post-mortem diagnosis | **** ** ** |
| Mortensen (1987) | Census population; Danish Cancer Registry | 1957–1980 | Denmark | CC | Schizophrenia inpatients in Danish psychiatric hospitals on 26/09/1957 | – | BC diagnosis | ** ** *** |
| Pottegård et al. (2018) | Danish Cancer Registry; Danish National Prescription registry; Danish National Patient Register; Danish Pathology Registry; Danish Psychiatric Central Register; Statistics Denmark; Danish Civil Registration System | 1995–2015 | Denmark | CC | Women with first-time diagnosis of invasive breast cancer during study period; had ≥5 years of prescription data | Women outside age range of 18–85 years at index date; resided outside of Denmark within 10 years prior to index date; history of cancer or mastectomy | Histologically verified BC diagnosis (ICD-10) | **** ** ** |
| Rahman et al. (2022) | IBM Marketscan Commercial; Multi-State Medicaid Databases | 01/01/2007–30/06/2016 | United States | C | Women aged 18–64; patients with records of claims from insurance programme for at least 12 months of before prescription of antipsychotic, anticonvulsant or lithium | Women with exposure to prochlorperazine only; patients with prescription drug claim for tamoxifen, a diagnosis of BC without treatment or any history of BC before index date; the first fill of antipsychotics did not fall within a continuous enrolment period | BC diagnosis (ICD-9/10 with pathologic verification, or BC diagnosis with evidence of surgical treatment or chemotherapy | **** ** ** |
| Study          | Country                                | Population                                                                 | Exclusion Criteria                                                                 | Endpoints                                                                 |
|---------------|----------------------------------------|----------------------------------------------------------------------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Taipale et al. (2021) | Finland                                | Women aged ≥16 years; had diagnosis of schizophrenia between 1972 and 2014 | History of cancer diagnosis (except for non-melanoma skin cancer), receipt of organ transplant, mastectomy or diagnosis of HIV | First invasive BC diagnosis (ICD-10) between 2000 and 2017, with histological verification at age between 18 and 85 years |
| Wang et al. (2002) | New Jersey, United States             | Women aged ≥20 years; had ≥1 medical service/prescription in each of 2 consecutive 6-month periods | Non-exposed subject with previously/subsequently filled AP prescription; BC diagnosis, BC surgical procedure or related hospitalisation or tamoxifen citrate prescription on or 3 months after 1 year of enrolment in a benefits programme (Medicaid/PAAD) | First BC diagnosis (ICD-Oncology V2) at least 3 months after index date or had first claim for BC surgery or hospitalisation for BC surgery |

C, cohort; CC, case-control; GPRD, General Practice Research Database; LHID2000, Longitudinal Health Insurance Database 2000; RCIPD, Registry for Catastrophic Illness Patient Database; CPR, Central Population Register; WHI, Women’s Health Initiative cohort; NJ Medicaid, New Jersey Medicaid; PAAD, New Jersey Pharmaceutical Assistance to the Aged and Disabled; NJ Medicare, New Jersey Medicare; NJ Cancer Registry, New Jersey Cancer Registry; AP, antipsychotics; BC, breast cancer; ICD, International Classification of Diseases.
Table 2. Results of included studies (N = 9)

| Study                          | Sample size | Exposed group definition                                      | Number of cases in 'exposed group' | Association of antipsychotic use with breast cancer (BC) | Adjusted covariates                                                                 |
|-------------------------------|-------------|----------------------------------------------------------------|-----------------------------------|--------------------------------------------------------|----------------------------------------------------------------------------------|
| **Chou et al. (2017)**        | Exposed: 10 727 Non-exposed: 10 727 | Had FGA, SGA or both FGA and SGA prescription | 119                          | HR: 1.94 (1.43–2.63)                                | Age, occupation, monthly income, comorbidities, medication (lithium, valproate sodium, antidepressants, anxiolytics and hypnotics) |
| **Dalton et al. (2006)**      | Exposed: 25 264 Non-exposed: 448 983 | ≥2 neuroleptic medication prescription (ATC: N05A)      | 258                          | IRR: 1.06 (0.93–1.21)                               | Age, hospitalisations for COPD, liver cirrhosis/alcoholism, ever use of NSAID/HT, number of children, age at first birth |
| **George et al. (2020)**      | Exposed: 642 Non-exposed: 155 095 | Self-reported AP medication (UpToDate)                  | Invasive BC: Typical AP: 10  Atypical AP: 4 In situ BC: Typical AP: 7 | Invasive BC: Typical AP HR: 0.67 (0.36–1.25) Atypical AP HR: 1.45 (0.54–3.87)  In situ BC: Typical AP HR: 2.05 (0.97–4.30) | Age, WHI participation, HT trial arm |
| **Hippisley-Cox et al. (2007)** | BC cases: 10 535 BC controls: 50 074 | ≥1 prescription of AP (conventional, atypical, lithium) | 40                          | OR: 1.55 (1.08–2.23)                                | Age, obesity, use of oral contraceptives/HT, smoking, BMI, Townsend score, comorbidities, medications, other serious mental health conditions |
| **Mortensen (1987)**          | BC cases: 40 BC controls: 80 | Exposure expressed as mean yearly number of defined daily doses (1 DDD = 300 mg chlorpromazine) | 40                          | Haloperidol user cancer incidence ratio: 0.3 (p = 0.03) Neuroleptics (excluding reserpine and haloperidol) cancer incidence ratio: 0.4 (p = 0.09) | Age at first admission, length of stay in psychiatric hospital, ECT, other shock treatment, lobotomy, neuroleptic treatment, no. chest X-rays, social group, marital status, residence, occupation, childbirths, alcohol/drug abuse |
| **Pottegård et al. (2018)**   | Cases: 60 360 Controls: 603 600 | Cumulative exposure since 1995 until 1 year prior index date | Ever use: 4798 Long-term use: 693 | AP ever use OR: 1.00 (0.97–1.04) Pro lactin-inducing AP long-term use OR: 1.18 (1.06–1.32) | Age, use of drugs known/suspected to modify BC risk, prior diagnoses of diabetes, COPD and alcohol-related disease, prior psychiatric diagnoses, Charlson comorbidity index scores, highest achieved education |
| **Rahman et al. (2022)**      | Exposed: 312 702 Non-exposed: 228 035 | Had outpatient prescription drug claim with at least 1 day’s supply for antipsychotics | 914                          | HR: 1.35 (1.14–1.61)                               | Age, HT, diabetes, obesity, alcohol abuse, pre-existing benign breast disease, Medicaid enrolment, mental health diagnoses |
| **Taipale et al. (2021)**     | Cases: 1069 Controls: 5339 | Had antipsychotic prescription until 1 year before cancer diagnosis | Exposed 1–4 years: 108 Exposed ≥5 years: 830 | Exposed 1–4 years OR 1.18 (0.86–1.62) Exposed ≥5 years: OR 1.74 (1.38–2.21) | Age, diagnoses of CVD/diabetes/asthma/COPD, substance misuse, suicide attempt, number of children, use and duration of use of drugs potentially modifying risk of BC |
| **Wang et al. (2002)**        | Exposed: 52 819 Non-exposed: 55 289 | AP prescription 1 year before index date; had 2 other AP prescriptions not used for psychiatric indications | 1239                          | HR: 1.16 (1.07–1.26)                               | Age, race, socioeconomic status, benign breast disorders, obesity, non-breast malignancies, Charlson comorbidity score, no. medical outpatient visits, nursing home use |

FGA, first-generation antipsychotics; SGA, second-generation antipsychotics; ATC N05A, Anatomical Therapeutic Chemical Classification System (Antipsychotics); AP, antipsychotics; BC, breast cancer; HT, hormone replacement therapy; NSAID, nonsteroidal anti-inflammatory drugs; COPD, chronic obstructive pulmonary disease; WHI, Women’s Health Initiative cohort; ECT, electroconvulsive therapy.
postmortem verification for the breast cancer diagnosis. Post-mortal diagnosis of breast cancer in cases who died was also used to define cases in a case-control study (Hippisley-Cox et al., 2007).

Three studies (Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) that included additional verification like histology received at least eight out of nine stars in the quality assessment. All three studies (Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) reported a significant association. All five studies (Wang et al., 2002; Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) that specified the diagnosis based on ICD codes supported the association. From the remaining studies that received quality assessment scores ranging from seven to nine stars (Mortensen, 1987; Dalton et al., 2006; Hippisley-Cox et al., 2007; Chou et al., 2017; George et al., 2020), both association and non-association were observed.

**Confounder adjustment**

Confounder adjustment applied in nine studies can be summarised into three main categories, namely clinical history; lifestyle and socioeconomic factors. All nine studies adjusted for covariates related to age and clinical history. In particular, the use of drugs known or suspected to modify breast cancer risk such as lithium, oral contraceptives or hormone replacement therapy were adjusted in seven out of nine studies (Dalton et al., 2006; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; George et al., 2020; Taipale et al., 2021; Rahman et al., 2022).

Adjusted lifestyle factors include obesity, smoking, body mass index (BMI) and substance misuse. Five of the nine studies had made such adjustments (Mortensen, 1987; Wang et al., 2002; Hippisley-Cox et al., 2007; Taipale et al., 2021; Rahman et al., 2022), of which three (Wang et al., 2002; Hippisley-Cox et al., 2007; Rahman et al., 2022) had adjusted for obesity – suggested to be associated with an increased risk of breast cancer (Iyengar et al., 2019), whilst substance misuse or smoking have been adjusted in four studies (Mortensen, 1987; Hippisley-Cox et al., 2007; Taipale et al., 2021; Rahman et al., 2022). Of the five studies with adjustment for lifestyle factors, four studies reported a significant association between antipsychotic use and breast cancer risk.

Socioeconomic factors were mostly represented by occupation, income, education status or a summarised Townsend score. Six studies (Mortensen, 1987; Wang et al., 2002; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; Rahman et al., 2022) adjusted for socioeconomic status, of which five (Wang et al., 2002; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; Rahman et al., 2022) reported a significant association between antipsychotic use and breast cancer risk.

**Exposure – antipsychotic use**

Antipsychotic use was defined with electronic records in eight out of the nine studies (Mortensen, 1987; Wang et al., 2002; Dalton et al., 2006; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022), the remaining study (George et al., 2020) used self-reported antipsychotic use to determine the exposure group. All studies took any antipsychotic use into account. Exposure durations were specified in three studies, Wang et al. included participants with at least 3 months’ exposure to antipsychotics prior to the index date from which the follow-up started (Wang et al., 2002); Dalton et al. only included participants who had received at least two prescriptions (Dalton et al., 2006); and Taipale et al. considered participants with prior antipsychotic exposure until 1 year before breast cancer diagnosis, with a case control design (Taipale et al., 2021).

The following variables were used to represent the extent of exposure for further stratification of the exposed group: cumulative doses (Wang et al., 2002; Pottegård et al., 2018), average yearly dosage (Mortensen, 1987; Chou et al., 2017), prescription count (Dalton et al., 2006), duration (Taipale et al., 2021) and prolactin-elevating propensity (Rahman et al., 2022). Two remaining studies (Hippisley-Cox et al., 2007; George et al., 2020) included participants with any use of antipsychotics without further stratifying by the extent of exposure in their exposed groups. Of the two studies that did not stratify participants by the extent of exposure, one reported a significant association (OR 1.55, 95% CI 1.08–2.23) (Hippisley-Cox et al., 2007). Five out of the seven studies (Wang et al., 2002; Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022) that stratified participants by the extent of exposure reported significant associations of antipsychotic use with breast cancer.

Despite a null association with the exposure defined as any antipsychotic use, long-term use (defined as having a cumulative dose of over 10,000 mg of olanzapine equivalents) was found to have a small association with breast cancer development in Pottegård et al. (2018). An increased risk with prolonged exposure was also suggested in two other studies (Wang et al., 2002; Taipale et al., 2021). Taipale et al. reported ORs 1.18 (95% CI 0.86–1.62) for 1–4 years of antipsychotic use and 1.74 (95% CI 1.38–2.21) for at least 5 years of antipsychotic use (Taipale et al., 2021), and Wang et al. showed an increased risk with at least 6 years of antipsychotic exposure (HR 2.37, 95% CI 1.25–4.47), whereas breast cancer risk amongst antipsychotic users of less than 6 years were reported to be non-significant. In contrast, the dose–response relationship was not observed in the atypical antipsychotic subgroup of Chou et al., where an apparent association was observed with lower exposure instead of increased exposure. They reported HRs 2.49 (95% CI 1.69–3.66) and 1.05 (95% CI 0.58–1.87) for mean antipsychotic exposure of less than 28 and greater than 245 g/year, respectively.

Some studies have also investigated the prolactin-elevating properties of antipsychotics and its association with breast cancer development (Chou et al., 2017; Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022). Exposure to antipsychotics with prolactin-elevating properties were included in Pottegård et al. (2018), to which long-term exposure showed an increased risk of breast cancer. Rahman et al. grouped exposure according to prolactin-elevating propensity into three categories of low, medium and high propensity. They reported that users of antipsychotics with medium and high prolactin-elevating properties were significantly associated with breast cancer development (Rahman et al., 2022). Taipale et al. (2021) compared prolonged periods of prolactin-increasing antipsychotic use to those exposed for less than a year. The results showed an increased risk amongst those exposed for at least 5 years (OR 1.56, 95% CI 1.27–1.92), corresponding to the results seen in Pottegård et al. Prolactin-elevating antipsychotics reported in Chou et al. were defined as risperidone, paliperidone or amisulpride, the study compared schizophrenia patients exposed to said antipsychotics to a non-schizophrenia cohort as the non-exposed comparator, the results indicate a significant association in the use of the three prolactin-elevating antipsychotics with breast cancer development (HR 1.96, 95% CI 1.36–2.82) (Chou et al., 2017).
Quality assessment scores

All nine studies received a satisfactory quality assessment score of seven to nine stars (Wang et al., 2002; Dalton et al., 2006; Hippisley-Cox et al., 2007; Chou et al., 2017; Pottegård et al., 2018; George et al., 2020; Rahman et al., 2022). One case-control study (Mortensen, 1987) received a lower score of two out of four stars in regards to the selection of cases and controls and the limited representativeness of the cases due to its small sample size. All studies had adjusted for both age and other covariates associated with the risk of breast cancer such as comorbidity or concurrent medication.

Pooled estimates of the association

Using a random effects model, we pooled the HRs and ORs of breast cancer between antipsychotic users and non-users from four cohort studies (Wang et al., 2002; Chou et al., 2017; George et al., 2020; Rahman et al., 2022) and three case-control studies (Hippisley-Cox et al., 2007; Pottegård et al., 2018; Taipale et al., 2021) respectively, with the I² estimated at 75 and 93%. Figures 2 and 3 show the forest plots for the pooled estimate as well as the estimated ratios reported by individual studies. Results suggest a moderate association of antipsychotic use (v. non-use) with breast cancer with a >30% increased risk observed, although the pooled OR did not reach statistical significance (HR 1.39, 95% CI 1.11–1.73; OR 1.37, 95% CI 0.90–2.09). As only three and four studies were included in the pooled estimates of the OR and HR, we did not conduct the Egger’s regression test for publication bias.

As one of the cohort studies (George et al., 2020) stratified the analysis by typical/atypical antipsychotics and invasive/in-situ breast cancer, we included the HR for atypical antipsychotics and invasive breast cancer in that study for the pooled estimate and replicated the analysis with all three other HRs separately as a sensitivity analysis to test for the robustness of the results. No substantial difference was observed as shown in online Supplementary eTable 2.

Discussion

Results of this review support the association between the use of antipsychotic medications and an increased risk of breast cancer. Six out of nine included studies of a good quality reported a significant association. Evidence shows a further extent of exposure to antipsychotics, such as a longer duration of use, is associated with a significant association. Exposure to antipsychotics, such as stroke and myocardial infarction, were investigated previously (Douglas and Smeeth, 2008; Sørensen et al., 2013; Lai et al., 2020), and use of prolactin-inducing antipsychotics was also reported to be associated with hip fractures (De Hert et al., 2016a). Given the potentially multifold underlying physiological mechanisms underlying the side effects, a comprehensive holistic assessment of the clinical profile of the patients should be made along with the safety profile of specific antipsychotics to optimise the treatment outcome (Huhn et al., 2013). Atypical antipsychotics have a higher risk of inducing metabolic syndrome, including central obesity and hyperlipidaemia, than typical antipsychotics (De Hert et al., 2012; Wei Xin Chong et al., 2016), both of which have been investigated to have a potentially increased risk of breast cancer (Iyengar et al., 2019; Chowdhury et al., 2021). Moreover, studies on schizophrenia patients showed that the risk of developing cardiovascular disease as well as type-2 diabetes mellitus of individuals was higher in atypical antipsychotic drugs (Drici and Priori, 2007; De Hert et al., 2012), with recent literature suggesting an association between diabetes and breast cancer risk (Liao et al., 2011). Hence, the association between antipsychotic use and breast cancer may possibly be explained by more than one physiological mechanism. With a majority of the included studies in this review having made reasonable adjustments for potential confounders such as clinical history, lifestyle factors and socioeconomic background, with several studies reporting increased breast cancer risk in prolactin-elevating antipsychotics (Pottegård et al., 2018; Taipale et al., 2021; Rahman et al., 2022), the observed association may likely be attributed to these biological mechanisms as described.

With an increasingly prevalent use of antipsychotic medications worldwide, the risk of adverse events associated with it should be investigated in more breadth and depth to inform clinical practice. This study on the potentially elevated risk of breast cancer adds to the current knowledge of adverse events associated with antipsychotic use, such as stroke and myocardial infarction, were investigated previously (Douglas and Smeeth, 2008; Sorensen et al., 2013; Lai et al., 2020), and use of prolactin-inducing antipsychotics was also reported to be associated with hip fractures (De Hert et al., 2016a). Given the potentially multifold underlying physiological mechanisms underlying the side effects, a comprehensive holistic assessment of the clinical profile of the patients should be made along with the safety profile of specific antipsychotics to optimise the treatment outcome (Huhn et al., 2013).
Interestingly, the elevated breast cancer risk observed in this study may not be applicable to other cancer types. In fact, a lower risk of lung and other cancers have been found associated with the use of antipsychotics and there are ongoing efforts in drug repurposing to experiment the cancer prevention properties of antipsychotic medications (Li et al., 2022). The exact mechanism of this inverse relationship is largely unclear.

The increased use of routine electronic health records in pharmacovigilance studies has contributed to the existing literature significantly, as shown in the included studies in this review. While providing a typically large sample size with realistic real-world clinical data, there are intrinsic limitations to these records. Specifically, the lack of lifestyle and other important factors might introduce bias to the estimated association. Primary data collection may provide much more detailed information but with a much-limited sample size. Therefore, both types of research are much warranted, and the evidence needs to be considered in the context of a variety of study designs with various strengths and weaknesses for a balanced overall assessment. With the benefits of record-linkage techniques with prescription registries, antipsychotic prescription practices such as antipsychotic polypharmacy in comparison with monotherapy can be addressed in future studies. One review suggested that aripiprazole use in combination with another antipsychotic was associated with better lipid profile outcomes than the use of other antipsychotic polypharmacy or monotherapy, although the quality of evidence was lacking (Ijaz et al., 2018). Further investigation in this area could possibly provide a more substantiated association.

**Limitations**

In spite of the important clinical implications, there are several limitations. First, the reviewed evidence is all generated from observational research without randomisation. There is likely unmeasured confounding effects and causal inferences need to be made with great caution. Specifically, the comparators selected for some included studies may not be entirely suitable and could be subject to potential selection bias. One example of mitigating this bias is demonstrated in Rahman et al. through the use of anticonvulsants and lithium as comparator drugs, which are also prescribed to patients with psychiatric disorders such as anxiety, depression and bipolar disorder, but with no known risk of hyperprolactinaemia (Ajmal et al., 2014). Second, the rare incidence of male breast cancer cases, even in very large electronic health record databases, poses as a challenge to derive a meaningful statistical analysis. Despite having included studies with male breast cancer cases in this review, the association of antipsychotic use with breast cancer amongst the male population would be difficult to conclude.

There are also limitations specific to this review as well. First, although the meta-analysis generated consistent results across study designs, i.e. cohort and case-control, the association could not be appropriately pooled across designs to increase the precision of the estimate. Second, the number of studies is too small to provide a more precise estimate of the hypothesised association and the presence of publication bias could not be tested as a result. Third, significant heterogeneity was observed between studies even within the same design, probably due to different populations, research practice and availability of data, further studies with more accrued data should investigate factors that contribute to this heterogeneity. Recent studies reported higher basal epigenetic changes in African American women (Joshi et al., 2022), a population found to have the highest rates of BRCA genetic mutations (Fackenthal and Olopade, 2007), which could increase the risk of breast cancer development. Varying degrees of risk in certain breast cancer subtypes between women of Hispanic, Asian, Black and White descent were also reported (Kurian et al., 2010). The variation in breast cancer risk between ethnicities is suggestive of biological heterogeneities; further exploration may be warranted for clarification on the potential differences with regards to the observed association. Fourth, we only examined studies written in English language. Further reviews including other languages may be warranted.

**Conclusion**

In conclusion, we found a moderate association between the use of antipsychotics and breast cancer with a more evident association observed with prolactin-elevating medications and greater extent of antipsychotic exposure. This risk, together with other known associated adverse events, should be weighed against the anticipated treatment outcomes for a balanced clinical management decision.

**Supplementary material.** The supplementary material for this article can be found at https://doi.org/10.1017/S2045796022000476.

**Data.** All data used in the systematic review and meta-analyses can be found in the included studies.

**Acknowledgements.** FTTL and ICKW are partially supported by the Laboratory of Data Discovery for Health (D^4^H) funded by the by AIR@InnoHK administered by Innovation and Technology Commission. We thank Miss Kaitlyn Zhang for her assistance in the earlier stages of the study.

**Financial support.** No specific funding for this research was received by the authors.

**Conflict of interest.** FTTL has been supported by the RGC Postdoctoral Fellowship under the Hong Kong Research Grants Council and has received research grants from the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, outside the submitted work.
EWYC reports grants from Research Grants Council (RGC, Hong Kong), Research Fund Secretariat of the Food and Health Bureau, National Natural Science Fund of China, Wellcome Trust, Bayer, Bristol-Myers Squibb, Pfizer, Janssen, Amgen, Takeda and Narcotics Division of the Security Bureau of the Hong Kong Special Administrative Region, outside the submitted work. ICKW receives research funding outside the submitted work from Amgen, Bristol-Myers Squibb, Pfizer, Janssen, Bayer, GSK, Novartis, the Hong Kong Research Grants Council, the Food and Health Bureau of the Government of the Hong Kong Special Administrative Region, National Institute for Health Research in England, European Commission and the National Health and Medical Research Council in Australia; has received speaker fees from Janssen and Medice in the previous 3 years; and is an independent non-executive director of Jacobson Medical in Hong Kong. The remaining authors have nothing to disclose.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

References

Ajmal A, Joffe H and Nachtigall LB (2014) Psychotropic-induced hyperprolactinemia: a clinical review. Psychosomatics 55, 29–36.
Anmella G, Fico G, Lotfaliany M, Hidalgo-Mazzei D, Soto-Angona O, Giménez-Palomo A, Amoretti S, Murru A, Radua J, Solanes A, Pacchiarotti I, Verdolini N, Cowdery S, Dodd S, Williams LJ, Mohebbi M, Carvalho AF, Kessing LV, Vieta E and Berk M (2021) Risk of cancer in bipolar disorder and the potential role of lithium: international collaborative systematic review and meta-analyses. Neuroscience & Biobehavioral Reviews 126, 529–541.

Balt SL, Galloway GP, Baggott MJ, Schwartz Z and Mendelson J (2021) Mechanisms and genetics of antipsychotic-associated weight gain. Clinical Pharmacology & Therapeutics 90, 179–183.

Bargiota S, Bonotis K, Messinis I and Angelopoulos N (2013) The effects of antipsychotics on prolactin levels and women's menstruation. Schizophrenia Research and Treatment 2013, 502697.

Besnard I, Aucelay V, Callery G, Gabriel-Bordenave C and Roberge C (2013) Antipsychotic-drug induced hyperprolactinemia: physiopathology, clinical features and guidance. L'Encephale 40, 86–94.

Bly MJ, Taylor SF, Dalack G, Pop-Busui R, Burghardt KJ, Lipton RB, Melani JP, Olopade OU, Stewart PM, Varghese C and Dardamanis P (2016) Risk factors of osteoporosis in patients with schizophrenia: a cross-sectional study. Acta Psychiatrica Scandinavica 133, 5–22.

Douglas IJ and Smeeth L (2008) Exposure to antipsychotics and risk of stroke: self-controlled case series study. BMJ 337, a1227.

Drir MD and Priori S (2007) Cardiovascular risks of atypical antipsychotic drug treatment. Pharmacopoeiologia and Drug Safety 16, 882–890.

Fackenthal JD and Olopade OI (2007) Breast cancer risk associated with BRCA1 and BRCA2 in diverse populations. Nature Reviews Cancer 7, 937–948.

George A, Sturgeon SR, Hankinson SE, Shadyb AH, Wallace RB and Reeves KW (2020) Psychotropic medication use and postmenopausal breast cancer risk. Cancer Epidemiology, Biomarkers and Prevention 29, 254–256.

Hålánarson Ò, Zöega H, Aagaard I, Bernardo M, Fredt AC, Furu K, Garuoliené K, Hoffmann F, Huybrechts KF, Kalverdijk LJ, Kawakami K, Kieler H, Kinoshta T, Litchfield M, López SC, Machado-Alba JE, Machado-Duque ME, Mahesri M, Nishlata P, Pearson S-A, Reutfors J, Saastamoinen L, Sato I, Schirling-Veninga CCM, Shyu Y-C, Skurtveit S, Verdoux H, Wang J-I, Yahni CZ and Bachmann C (2017) International trends in antipsychotic use: a study in 16 countries, 2005–2014. European Neuropsychopharmacology 27, 1064–1076.

Herrmann N, Mamedani M and Lantiot KL (2004) Atypical antipsychotics and risk of cerebrovascular accidents. American Journal of Psychiatry 161, 1113–1115.

Hippius-Cox J, Vinogradova Y, Coupland C and Parker C (2007) Risk of malignancy in patients with schizophrenia or bipolar disorder: nested case-control study. Archives of General Psychiatry 64, 1368–1376.

Hughes S, Cohen D and Jagger R (2014) Differences in reporting serious adverse events in industry sponsored clinical trial registries and journal articles on antidepressant and antipsychotic drugs: a cross-sectional study. BMJ Open 4, e005535.

Huhn M, Nikolakopoulou A, Schneider-Thoma J, Krause M, Samara M, Peter N, Arndt T, Bäckers L, Rothe P and Cipriani A (2019) Comparative efficacy and tolerability of 32 oral antipsychotics for the acute treatment of adults with multi-episode schizophrenia: a systematic review and network meta-analysis. The Lancet 394, 939–951.

Ijaz S, Bolea D, Davies S, Savovic J, Richards A, Sullivan S and Moran P (2018) Antipsychotic polypharmacy and metabolic syndrome in schizophrenia: a review of systematic reviews. BMC Psychiatry 18, 275.

Indave BI, Minozzi S, Panu PP and Amato L (2016) Antipsychotic medications for cocaine dependence. Cochrane Database of Systematic Reviews 3, CD006306.

Iyengar NM, Arthur R, Manson JE, Chlebowski RT, Kroenke CH, Peterson L, Cheng TD, Feliciano EC, Lane D, Luo J, Nassir R, Pan K, Wasserteil-Smoller S, Kamensky V, Rohan TE and Dannenberg AJ (2013) Association of body fat and risk of breast cancer in postmenopausal women with normal body mass index: a secondary analysis of a randomized clinical trial and observational study. JAMA Oncology 5, 155–163.

Johnston AN, Bu W, Hein S, Garcia S, Camacho L, Xue L, Qin L, Naci G, Hilsenbeck SG, Kapali J, Podyspanka N, Nangia J and Li Y (2018) Hyperprolactinemia-inducing antipsychotics increase breast cancer risk by activating JAK-STAT5 in precancerous lesions. Breast Cancer Research 20, 42.

Joshi S, Garlapati C and Aneja R (2022) Epigenetic determinants of racial disparity in breast cancer: looking beyond genetic alterations. Cancers 14, 1903.

Krause M, Zhu Y, Huhn M, Schneider-Thoma J, Bighelli I, Nikolakopoulou A and Leucht S (2018) Antipsychotic drugs for patients with schizophrenia and predominant or prominent negative symptoms: a systematic review and meta-analysis. European Archives of Psychiatry and Clinical Neuroscience 268, 625–639.

Kurian AW, Fish K, Shema SJ and Clarke CA (2010) Lifetime risks of specific breast cancer subtypes among women in four racial/ethnic groups. Breast Cancer Research 12, R99.

Lai FTT, Guthrie B, Mercer SW, Smith DJ, Yip BHK, Chung GKK, Lee K-P, Chung RY, Chau PYK, Wong ELY, Yeoh E-K and Wong SYS (2019) Association between antipsychotic use and acute ischemic heart disease in women but not in men: a retrospective cohort study of over one million primary care patients. BMC Medicine 18, 289.

Li J, Tang F, Si S and Xue F (2022) Association between antipsychotic agents and risk of lung cancer: a nested case-control study. Cancer Communications 42, 175–178.
Liao S, Li J, Wei W, Wang L, Zhang Y, Li J, Wang C and Sun S (2011) Association between diabetes mellitus and breast cancer risk: a meta-analysis of the literature. Asian Pacific Journal of Cancer Prevention 12, 1061–1065.

Madhusoodanan S, Parida S and Jimenez C (2010) Hyperprolactinemia associated with psychotropics – a review. Human Psychopharmacology: Clinical and Experimental 25, 281–297.

Manu P (2012) Medical Consultation in Psychiatry. Goldman’s Cecil Medicine. Amsterdam: Elsevier.

Moja L, Tagliabue L, Balduzzi S, Parmelli E, Pistotti V, Guarneri V and D’Amico R (2012) Trastuzumab containing regimens for early breast cancer. Cochrane Database of Systematic Reviews 4, CD006243.

Mortensen PB (1987) Neuroleptic treatment and other factors modifying cancer risk in schizophrenic patients. Acta Psychiatrica Scandinavica 75, 585–590.

Ng VWS, Man KKC, Gao L, Chan EW, Lee EHM, Hayes JF and Wong ICK (2021) Bipolar disorder prevalence and psychotropic medication utilisation in Hong Kong and the United Kingdom. Pharmacoepidemiology and Drug Safety 30, 1588–1600.

Nielsen RE, Lolk A, Rodrigo-Domingo M, Valentín JB and Andersen K (2017) Antipsychotic treatment effects on cardiovascular, cancer, infection, and intentional self-harm as cause of death in patients with Alzheimer’s dementia. European Psychiatry 42, 14–23.

Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P and Moher D (2021) The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 372, n71.

Phillips R, Hazell L, Sauzet O and Cornelius V (2019) Analysis and reporting of adverse events in randomised controlled trials: a review. BMJ Open 9, e024537.

Pottégaard A, Lash TL, Cronin-Fenton D, Ahern TP and Damkier P (2018) Use of antipsychotics and risk of breast cancer: a Danish nationwide case-control study. British Journal of Clinical Pharmacology 84, 2152–2161.

Rahman T, Sahrmann JM, Olsen MA, Nickel KB, Miller JP, Ma C and Grucza RA (2022) Risk of breast cancer with prolactin elevating antipsychotic drugs an observational study of US women (ages 18–64 years). Journal of Clinical Psychopharmacology 42, 7–16.

Sorensen HJ, Jensen SO and Nielsen J (2013) Schizophrenia, antipsychotics and risk of hip fracture: a population-based analysis. European Neuropsychopharmacology 23, 872–878.

Taipale H, Solmi M, Lähteenvuo M, Tanskanen A, Correll CU and Tiihonen J (2021) Antipsychotic use and risk of breast cancer in women with schizophrenia: a nationwide nested case-control study in Finland. The Lancet Psychiatry 8, 883–891.

Vuk Pisk S, Matić K, Gereš N, Ivezić E, Ruljančić N and Filipčić I (2019) Hyperprolactinemia – side effect or part of the illness. Psychiatria Danubina 31, 148–152.

Wang PS, Walker AM, Tsuang MT, Orav EJ, Glynn RJ, Levin R and Avorn J (2002) Dopamine antagonists and the development of breast cancer. Archives of General Psychiatry 59, 1147–1154.

Wei Xin Chong J, Hsien-Jie Tan E, Chong CE, Ng Y and Wijesinghe R (2016) Atypical antipsychotics: a review on the prevalence, monitoring, and management of their metabolic and cardiovascular side effects. Mental Health Clinician 6, 178–184.