ARTICLE

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Schizophrenia pregnancies should be given greater health priority in the global health agenda: results from a large-scale meta-analysis of 43,611 deliveries of women with schizophrenia and 40,948,272 controls

Damien Etchecopar-Etchart[1,2], Roxane Mignon[1], Laurent Boyer[1,2] and Guillaume Fond[1,2]✉

Women with schizophrenia and their newborns are at risk of adverse pregnancy, delivery, neonatal and child outcomes. However, robust and informative epidemiological estimates are lacking to guide health policies to prioritise and organise perinatal services. For the first time, we carried out a systematic review and meta-analysis to synthesise the accumulating evidence on pregnancy, delivery, neonatal complications, and infant mortality among women with schizophrenia and their newborns ($N = 43,611$) vs. controls ($N = 40,948,272$) between 1999 and 2021 (26 population-based studies from 11 high-income countries) using random effects. Women with schizophrenia had higher odds (OR) of gestational diabetes (2.35, 95% CI: [1.57–3.52]), gestational hypertension, pre-eclampsia/eclampsia (OR 1.55, 95% CI: [1.02–2.36]; 1.85, 95% CI: [1.52–2.25]), antepartum and postpartum haemorrhage (OR 2.28, 95% CI: [1.58–3.29]; 1.14, 95% CI: [1.04–1.24]), placenta abruption, threatened preterm labour, and premature rupture of membrane (OR 2.20, 95% CI: [2.02–2.39]; 2.91, 95% CI: [1.57–5.40]; 1.29, 95% CI: [1.06–1.58]), c-section (OR 1.33, 95% CI: [1.22–1.45]), foetal distress (OR 1.80, 95% CI: [1.43–2.26]), preterm and very preterm delivery (OR 1.79, 95% CI: [1.62–1.98]; 2.31, 95% CI: [1.78–2.98]), small for gestational age and low birth weight (OR 1.63, 95% CI: [1.48–1.80]; 1.75, 95% CI: [1.46–2.11]), congenital malformations (OR 1.86, 95% CI: [1.71–2.03]), and stillbirths (OR 2.06, 95% CI: [1.83–2.31]). Their newborns had higher odds of neonatal death (OR 1.41, 95% CI: [1.03–1.94]), post-neonatal death (OR 2.87, 95% CI: [2.11–3.89]) and infant mortality (OR 2.33, 95% CI: [1.81–3.01]). This large-scale meta-analysis confirms that schizophrenia is associated with a substantially increased risk of very preterm delivery, stillbirth, and infant mortality, and metabolic risk in mothers. No population-based study has been carried out in low- and middle-income countries in which health problems of women with schizophrenia are probably more pronounced. More research is needed to better understand the complex needs of women with schizophrenia and their newborns, determine how care delivery could be optimised, and define best practices. Study registration: PROSPERO CRD42020197446.

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INTRODUCTION

Perinatal mental disorders are frequent and are associated with substantial pregnancy, delivery, neonatal and child morbidity, and mortality [1–3]. The World Health Organisation (WHO) has highlighted the urgent need for 'evidence-based and human rights-oriented mental health care services for early identification and management of maternal mental disorders' [4]. Women with schizophrenia represent an extremely vulnerable and underserved population [5, 6] who have been neglected in perinatal health services research [5]. Schizophrenia is a chronic and severe mental disorder affecting 20 million people worldwide [7], slightly less than half of whom are women [8], and a high proportion of them already have or will have children [9]. Indeed, the incidence peak of the illness occurs twice in women aged 20–29 and 30–39 years [10] covering the childbearing period. In 1999, Denmark was the first country to publish population-based data on the outcomes of women with schizophrenia giving birth [11]. During the last two decades, Australia, Canada, Finland, France, Israel, Japan, Sweden, Taiwan, the UK, and the US have also published their national data, showing poor pregnancy and delivery outcomes for women with schizophrenia and increased neonatal complications and infant mortality for their newborns [11–37]. However, a comprehensive meta-analysis is lacking to produce robust and informative epidemiological estimates necessary to guide health policies to prioritise and organise perinatal services for women with schizophrenia.

Because new knowledge and empirical outcomes are needed to help perinatal care systems achieve high-quality care and decreased infant mortality and severe morbidity in women with schizophrenia [38], we carried out a systematic review and

[1]AP-HM, CEReSS—Health Service Research and Quality of Life Center, Aix-Marseille Univ., Marseille, France. [2]FondaMental Foundation, Creteil, France.
✉email: guillaume.fond@ap-hm.fr

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meta-analysis to synthesise the accumulating evidence on pregnancy, delivery, neonatal complications, and infant mortality among women with schizophrenia and their newborns.

METHODS

Literature search strategy

This meta-analysis was conducted following the Preferred Reporting Items for Systematic reviews and Meta-Analysis guidelines [39]. Systematic bibliographic searches were carried out according to the Cochrane methodology. This project was registered in PROSPERO (reference number CRD42020197446).

The search paradigm was based on the Mesh terms of the Medline® database and adapted for Google Scholar® and Web of Science®: ('schizophrenia' or 'psychotic disorders') AND ('pregnancy' OR 'delivery' OR 'obstetrical' OR 'neonatal'). The last search was carried out on September 30th, 2021. The reference lists of relevant reviews and articles were manually searched for additional eligible articles. If needed, the corresponding authors were asked to provide additional data that were not included in the original publications, and they were asked to provide any unpublished results.

Eligibility

The inclusion criteria were as follows: 1. Any language and date of publication; 2. Original research papers; 3. Population-based Studies 4. Case group: pregnant women diagnosed with schizophrenia-spectrum disorder based on an International Classification of Diseases (ICD) or Diagnostic and Statistical Manual (DSM) code. The schizophrenia-spectrum diagnosis was not necessarily reported before delivery. 5. Control group: women without schizophrenia-spectrum disorder or psychiatric disorder; 6. At least one quantitative pregnancy, delivery, neonatal or infant mortality outcome was reported in the case and control groups.

The exclusion criteria were: non-population-based studies (i.e. cohort or case–control studies based on a single department or hospital except if this hospital covered the whole geographical population area).

RM and DEE carried out the inclusion of studies. In the case of a non-consensus for the inclusion of a study, the last author (GF) made the final decision.

Pregnancy, delivery, neonatal, and infant mortality outcomes

The following pregnancy outcomes (15) were extracted: gestational diabetes; gestational hypertension; thromboembolism; urinary infection; anaemia; pre-eclampsia or eclampsia; placental abruption; antepartum haemorrhage; chorioamnionitis; threatened preterm labour; premature rupture of membrane; placental complication; oligohydramnios; polyhydramnios; and general infection during pregnancy.

The following delivery outcomes (7) were extracted: C-section; labour induction; instrumental delivery, postpartum haemorrhage; foetal distress; breech presentation, maternal death.

The following neonatal outcomes (11) were extracted: congenital malformations; asphyxia; Apgar score at 5 min <7; intensive care; small for gestational age (<10th percentile); large for gestational age (>90th percentile); low birth weight (<2500 g at birth or <10th percentile); high birth weight (>4000 g at birth or >90th percentile); preterm delivery (gestational age between 32 and 37 weeks); very preterm delivery (gestational age <32 weeks); and stillbirths.

The following infant mortality outcomes (3) were extracted: neonatal mortality (between 0 and 28 days of life); post-neonatal mortality (between 29 and 365 days of life); and infant death during the first year of life (0–365 days of life).

Other collected data

The following study characteristics were extracted: author; year of publication; year of first birth inclusion; year of last birth inclusion; country; database used; case definition (time for psychiatric diagnosis; diagnosis period covering the period before pregnancy; inclusion of post-delivery schizophrenia diagnoses; ICD or DSM codes); and control definition (women without schizophrenia; women without the psychiatric disorder).

Sociodemographic variables, comorbidities, treatments, and follow-up variables that could potentially affect pregnancy, delivery, neonatal, and child outcomes were also extracted: age; parity; absence of a partner in supportive environment (single; divorced or widowed); low socioeconomic level; ethnicity; primiparous pregnancy; child sex; smoking; alcohol; illicit drug; obesity; hypertension before pregnancy; diabetes before pregnancy; dysthyroid disorder; epilepsy; infection by human immunodeficiency virus; antipsychotic treatments, and the number of prenatal visits.

Three researchers (RM, DEE, and GF) extracted data from the included studies in a systematic manner using a predesigned extraction form, which was based on the Joanna Briggs Institute Data Extraction Form for Prevalence and Incidence Studies [40]. Additional items relevant to the current study were also added. The first and last authors (DEE and GF) examine each discrepancy in data extraction to reach consensus.

Quality assessment

Study quality analysis was performed using the NIH Study Quality Assessment Tools of case–control studies [41]. This tool was chosen to address the limits of the Newcastle-Ottawa scale [42].

Statistical analyses

Studies included in the present meta-analysis provided comparative data on pregnancy, delivery, neonatal and child outcomes for unmatched, and matched samples. Unmatched studies and matched studies were analysed separately. Using the inverse-variance weighting method, a random effects model was used to calculate the odds ratio (OR) of each outcome and its 95% confidence interval (95% CI) [43, 44]. When available, we used the numbers of events and the sample sizes instead of the OR [45]. Heterogeneity between studies was quantified with the I^2 statistic [46]. Q and I^2 were calculated to assess heterogeneity across all studies and within subgroups, with $I^2 \geq 50\%$ indicating significant heterogeneity [47]. Publication bias was assessed graphically with a funnel plot and statistically with Egger's test when at least ten studies were included in the meta-analysis [48]. Sensitivity analyses were conducted using the leave-one-out method [49].

Subgroup analyses for six binary variables (year of last inclusion < or ≥2009 (median year), high-quality studies or not, studies including only one birth per mother or not, studies including stillbirths or not, schizophrenia diagnosis before pregnancy vs. before and after pregnancy, and studies restricted to singleton births or not) were used to evaluate factors that moderated the individual study estimates of the OR of each outcome.

All analyses and graphs were carried out using R software with the meta and forest plot packages, respectively.

RESULTS

Study and patient characteristics

Twenty-six studies from 11 high-income countries (43,611 deliveries of women with schizophrenia and 40,948,272 deliveries of control women) were included (Flow-chart Fig. 1, excluded studies Supplementary Table 1) [11–37]. No study has been carried out in low- or middle-income countries. The following cohort and countries were included (in order of year of last patient included): Denmark (1973–1993), UK (1996–1998), Sweden (1983–2002), Taiwan (1999–2003), Israel (1998–2008), Japan (2005–2009), Canada ((Ontario)2002–2011), Finland (1991–2013), US (2002–2014, (California) 2005–2011), Australia (1980–1992, (Melbourne) 2008–2012, (Western Australia) 1980–2001, 2007–2017), and France (2015–2019). Their characteristics are presented in Table 1 and Supplementary Table 2 for unmatched studies ($N = 21$) and Table 2 and Supplementary Table 3 for matched studies ($N = 6$) (one study [12] was included in both unmatched and matched studies). Study quality is presented in Supplementary Table 4.

Unmatched studies

Twenty-one eligible studies, 38,680 deliveries of women with schizophrenia and 40,926,243 deliveries of control women, were included [11–32]. Compared to controls, women with schizophrenia were found to be older (mean difference +1.74 years, 95% CI [0.47; 3.01], $p = 0.007$; $I^2 = 96.2\%$, 95% CI [93.5–97.8]), more often without a partner (OR 3.78, 95% CI [3.08–4.65], $p < 0.0001$; $I^2 = 84.6\%$, 95% CI [68.2–92.5]) and with a lower socioeconomic level (OR 1.77, 95% CI [1.30–2.42], $p = 0.0003$; $I^2 = 98.8\%$, 95% CI [98.4–99.1]). They were more frequently smokers (OR 4.87, 95% CI

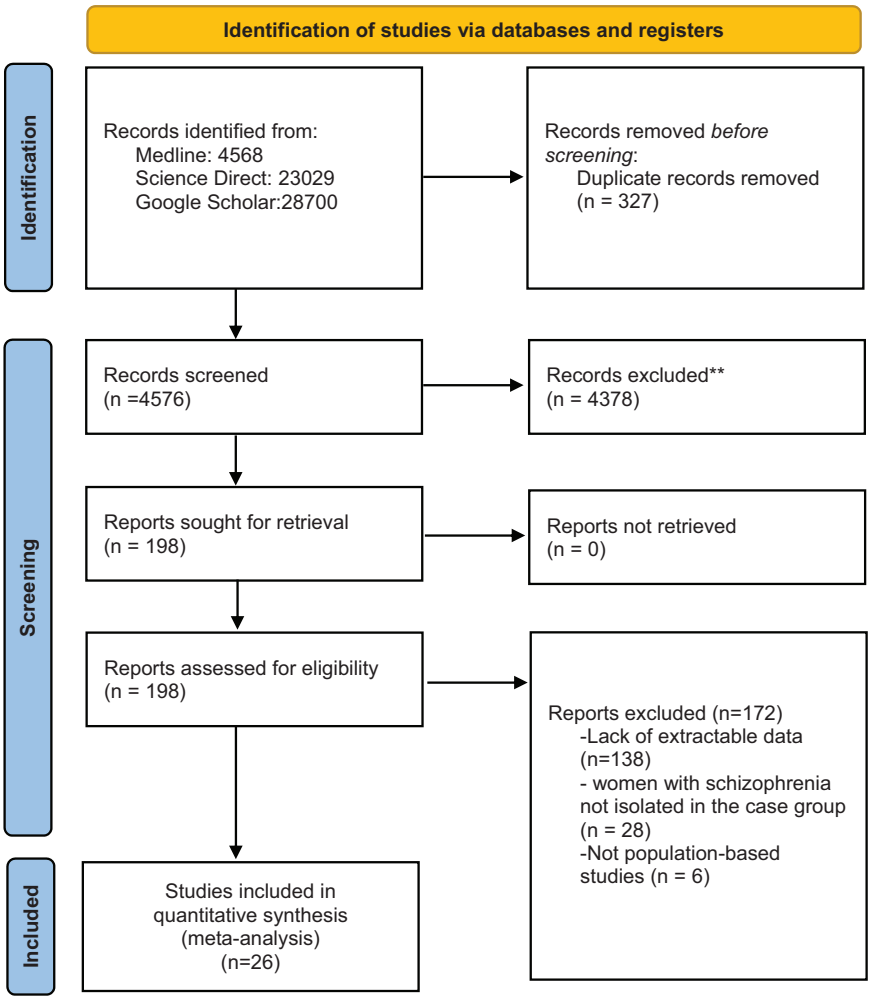


Fig. 1 Flow-chart selection for the included studies. Flow diagram.

[3.65–6.50], $p < 0.0001$; $I^2 = 98\%$, 95% CI [97.3–98.5]) and illicit drug consumers (OR 13.33, 95% CI [8.65–20.54], $p < 0.0001$; $I^2 = 93.2\%$, 95% CI [85.8–96.7]). They had more obesity (OR 2.38, 95% CI [1.78–3.19], $p < 0.0001$; $I^2 = 84.4\%$, 95% CI [61.0–93.8]), hypertension before pregnancy (OR 1.77, 95% CI [1.51–2.07], $p < 0.0001$; $I^2 = 11.2\%$, 95% CI [0.0–86.4]) and diabetes before pregnancy (OR 3.09, 95% CI [1.73–5.50], $p < 0.0001$; $I^2 = 93.5\%$, 95% CI [86.5–96.8]). No significant difference was found for primiparous pregnancy (OR 1.07, 95% CI [0.94–1.21], $p = 0.34$; $I^2 = 93.2\%$, 95% CI [89.3–95.7]) or child sex (OR 1.03, 95% CI [0.99–1.08], $p = 0.16$; $I^2 = 0\%$, 95% CI [0.0–79.2]). Ethnicity, alcohol consumption, dysthyroid disorder, epilepsy, infection by human immunodeficiency virus, antipsychotic treatments and number of antenatal visits were not systematically collected and could not be analysed.

Of the 36 pregnancy, delivery, neonatal and child complications that were extracted, 20 were measured in 4 studies or more and were included in the quantitative analyses. The ORs for each outcome were compiled in a forest plot (Fig. 2).

Pregnancy outcomes. Compared to controls, women with schizophrenia had increased risk of gestational diabetes (OR 2.35, 95% CI [1.57–3.52], $p < 0.001$; $I^2 = 80.4\%$, 95% CI [60.1–90.3]), gestational hypertension (OR 1.55, 95% CI [1.02–2.36], $p = 0.041$; $I^2 = 85.5\%$, 95% CI [72.1–92.5]), pre-eclampsia or eclampsia (OR 1.85, 95% CI [1.52–2.25], $p < 0.001$; $I^2 = 57.7\%$, 95% CI [2.0–81.7]), antepartum haemorrhage (OR 2.28, 95% CI [1.58–3.29], $p < 0.001$; $I^2 = 54.9\%$, 95% CI [0.0–83.4]), placenta abruption (OR 2.20, 95% CI [2.02–2.39], $p < 0.001$; $I^2 = 47.7\%$, 95% CI [0.0–77.9]), threatened preterm labour (OR 2.91, 95% CI [1.57–5.40], $p < 0.001$; $I^2 = 88.8\%$, 95% CI [73.8–95.2]), and premature rupture of membrane (OR 1.29, 95% CI [1.06–1.58], $p = 0.012$; $I^2 = 76.1\%$, 95% CI [46.4–89.4]).

Delivery outcomes. Compared to controls, women with schizophrenia had an increased risk of c-section (OR 1.33, 95% CI [1.22–1.45], $p < 0.001$; $I^2 = 77.8\%$, 95% CI [56.1–88.7]), postpartum haemorrhage (OR 1.14, 95% CI [1.04–1.24], $p = 0.003$; $I^2 = 0\%$, 95% CI [0.0–84.7]) and foetal distress (OR 1.80, 95% CI [1.43–2.26], $p < 0.001$; $I^2 = 71.4\%$, 95% CI [87.5–96.1]). Women with schizophrenia had no statistically significant increased risk for breech presentation, labour induction or instrumental delivery (all $p > 0.05$).

Neonatal outcomes. Compared to controls, newborns of women with schizophrenia had increased risk of congenital malformations (OR 1.86, 95% CI [1.71–2.03], $p < 0.001$; $I^2 = 39.2\%$, 95% CI [0.0–77.5]), Apgar score <7 at 5 min (OR 1.93, 95% CI [1.25–2.96], $p = 0.003$; $I^2 = 56.7\%$, 95% CI [0.0–85.6]), small for gestational age (OR 1.63, 95% CI [1.48–1.80], $p < 0.001$; $I^2 = 65\%$, 95% CI [28.5–82.8]), low birth weight (OR 1.75, 95% CI [1.46–2.11], $p < 0.001$; $I^2 = 75.8\%$, 95% CI [53.5–87.4]), preterm delivery (OR 1.79, 95% CI [1.62–1.98], $p < 0.001$; $I^2 = 76\%$, 95% CI [60.5–85.4]), very preterm delivery (OR 2.31, 95% CI [1.78–2.98], $p < 0.001$; $I^2 = 47.6\%$, 95% CI [0.0–82.6]) and stillbirth (OR 2.06, 95% CI [1.83–2.31], $p < 0.001$; $I^2 = 0\%$, 95% CI [0.0–67.6]). Stillbirth affected 0.96% of births (95% CI [0.74–1.25]; $I^2 = 58.9\%$, 95% CI [10.3–81.2%]) in women

Table 1. Characteristics of the included unmatched studies.

Author, ref. (year of first/ last inclusion)	Country	Database	Inclusion of post-delivery schizophrenia diagnoses	Cases-ICD codes or DSM	Controls definition	Number of deliveries in the schizophrenia group	Number of deliveries in the control group
Jablensky et al. [22] (1980–1992)	Australia	Mental Health Information System/Maternal and Child Health Research Database	Yes	Schizophrenic disorders (ICD-9: 295)	Women without psychiatric disorder	618	3129
Bennedsen et al. [11, 23] (1973–1993)	Denmark	Danish Psychiatric Case/The Medical Birth Registers/The National Registry of Congenital Malformations	Yes	Schizophrenic disorders (ICD-8: 295)	Women without schizophrenia	2230	123,544
Ellman et al. [13] (1991–2000)	Finland	Finnish Perinatal Register (from the National Research and Development Centre for Welfare and Health)/Hospital discharge, Pension register and Free medicine register (for psychiatric database)	No	Schizophrenic disorders (ICD-9: 295) at risk of obstetrical complications	Women without personal and familial psychiatric disorder	53	36,895
Di Prinzio et al. [24] (1980–2001)	Western Australia	Midwives' Notification System linked to Hospital Morbidity Data Collection/Mental Health Information System	Yes	Schizophrenic disorders (ICD-9: 295)	Women without psychiatric disorder	1653	449,329
Liu et al. [25] (1999–2001)	Taiwan	National Health Insurance Research/Birth and Death certificate databases	Yes	Schizophrenic disorders (ICD-9: 295)	Women and fathers without schizophrenia or affective disorder	592	605,107
Nilsson et al. [14] (1983–1997)	Sweden	National Board of Health and Welfare: Medical Birth Register/Hospital Discharge Register	Yes	Schizophrenic disorders (ICD-8 and ICD-9: 295 and ICD-10: F20, F21, F23.1, F23.2 and F25)	Women without schizophrenia or schizoaffective disorder	2096	1,555,975
Nilsson et al. [15] (1983–2002)	Sweden	National Board of Health and Welfare: Medical Birth Register/Hospital Discharge Register	Yes	Schizophrenic disorders (ICD-8 and ICD-9: 295 and ICD-10: F20, F21, F23.1, F23.2 and F25)	Women without schizophrenia or schizoaffective disorder	3119	1,880,976
Lee et al. [26] (2001–2003)	Taiwan	National Health Insurance Research/Birth and Death certificate databases	No	Schizophrenic disorders (ICD-9: 295)	Women and fathers without psychiatric disorder	493	528,061
Hizkiyahu et al. [27] (1998–2008)	Israel	Soroka University Medical Centre, Be'er-Sheva, Israel	No	Schizophrenia and schizoaffective disorder (ICD codes not reported)	Women without schizophrenia or schizoaffective disorder	97	186,457
Mannisto et al. [16] (2002–2008)	USA	Consortium on Safe Labour: Electronic medical records/ Maternal discharge summaries of 19 hospitals	No	Schizophrenic disorders (ICD-9: 295) without other psychiatric diagnoses	Women without psychiatric disorder	134	206,996
Nguyen et al. [28] (2005–2008)	USA (California)	MD	MD	Schizophrenia (ICD codes not reported)	Women without schizophrenia	587	2,039,283

Table 1. continued

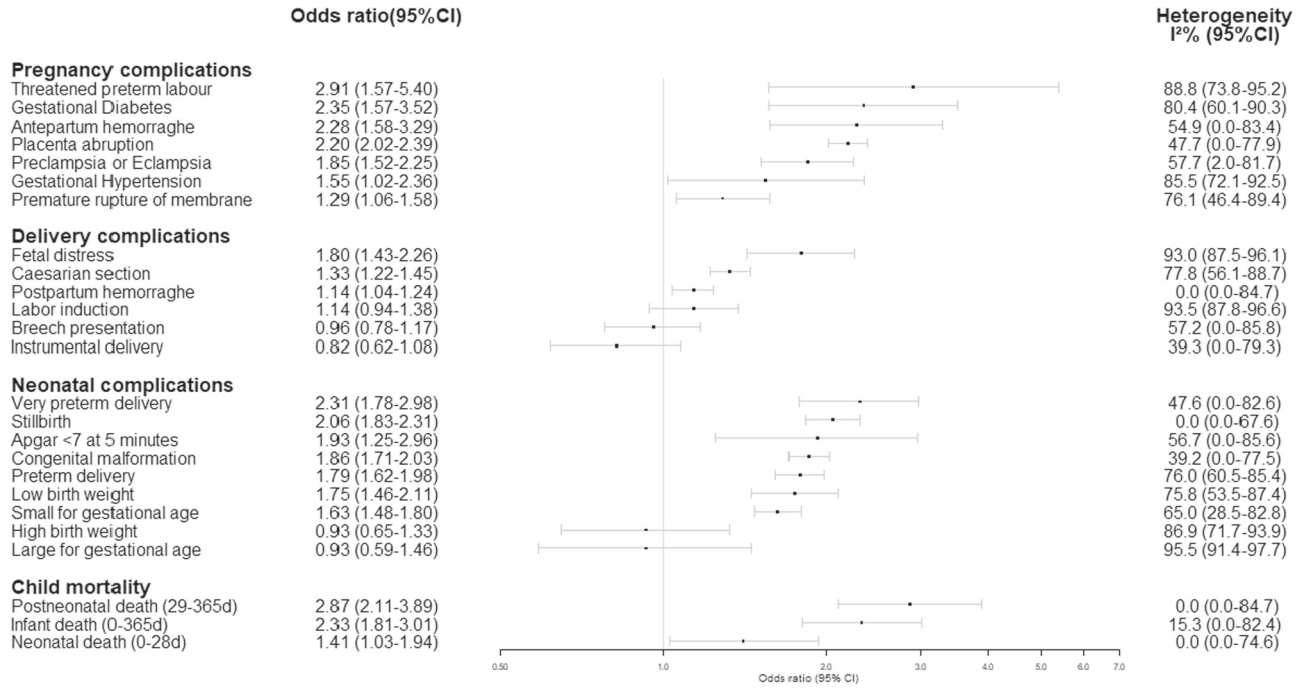
Author, ref. (year of first/ last inclusion)	Country	Database	Inclusion of post-delivery schizophrenia diagnoses	Cases-ICD codes or DSM	Controls definition	Number of deliveries in the schizophrenia group	Number of deliveries in the control group
Hironaka et al. [29] (2005–2009)	Japan	Nagoya University Hospital database	No	Schizophrenic disorders (ICD-10: F20-F29)	Women without psychiatric disorder	15	278
Baer et al. [17] (2007–2011)	USA (California)	Hospital discharge database of the California Office of Statewide Health Planning and Development	No	Schizophrenic disorders (ICD-9: 295) with California Medicaid Programme	Women with California Medicaid without psychiatric disorder	196	24,792
Vigod et al. [18] (2002–2011)	Canada (Ontario)	Health administrative data linked to clinical birth-registry data	No	Schizophrenic disorders (ICD-9: 295 and ICD-10: F20, F25)	Women without psychiatric disorder	1391	432,358
Vigod et al. [19] (2006–2011)	Canada (Ontario)	Health administrative data linked to clinical birth-registry data	No	Schizophrenic disorders (ICD-9: 295 and ICD-10: F20, F22–25,F28–29)	Women without psychiatric disorder in the 5 years preceding conception	4279	286,147
Zhong et al. [20] (2007–2012)	USA	Health care Cost and Utilisation Project—Nationwide/National Inpatient Sample	No	Schizophrenic disorders (ICD-9: 295)	Women without psychosis (including bipolar disorder)	14125	23,343,336
Nguyen et al. [30] (2007–2011)	Western Australia	Childbirth and mental illness database/2008 Western Australian Midwives' Notification System	No	Schizophrenic disorders (ICD-10 codes not reported)	2008 Western Australia singleton population	44	29,805
Frayne et al. [31] (2007–2017)	Western Australia	Childbirth and mental illness database/2013 Western Australian Midwives' Notification System	No	Schizophrenic disorders (ICD-10: F20, F25 and F29)	2013 Western Australia population	90	33,928
Judd et al. [32] (2008–2012)	Australia (Melbourne)	Centricity Perinatal Data of Royal Women's Hospital	No	Schizophrenia (DSM IV)	Women without schizophrenia or bipolar disorder	63	19,755
Heun-Jonhson et al. [21] (2008–2014)	USA	Health care Cost and Utilisation Project—Nationwide/National Inpatient Sample	No	Schizophrenic disorders (ICD-9: 295)	Women without severe mental disorder	3697	5,475,739
Fabre et al. [12] (2015–2019)	France	French national hospital database	No	Schizophrenic disorders (ICD-10: F20, F22 and F25)	Women without severe mental disorder	3108	3,664,353

ICD International Classification of Diseases, *DSM* Diagnostic and Statistical Manual, *MD* Missing Data.

Table 2. Characteristics of the included matched studies.

Author, ref.	Country	Database	Inclusion of post-delivery schizophrenic diagnoses	Cases-ICD codes	Controls definition	Number of deliveries in the schizophrenia group	Number of deliveries in the control group
Suvisaari et al. [33] (1960–1964)	Finland	Central archives of psychiatric hospital care in Helsinki/Helsinki High-Risk Study	No	Schizophrenia, schizoaffective disorders, schizophreniform disorders (DSM IV)	No psychiatric disorder	59	242
Howard et al. [34] (1996–1998)	UK	General Practice Research Database	MD	Schizophrenic disorders (ICD-9 or 10, not reported)	Women without schizophrenic disorder	199	787
Lin et al. [35] (2001–2003)	Taiwan	National Health Insurance Research/Birth and Death certificate databases	No	Schizophrenic disorders (ICD-9: 295 codes other than schizoaffective disorder 295.7)	Women without schizophrenic disorder	607	1821
Simoila et al. [36] (1991–2013)	Finland	Finnish Central Population Register/Care Register for Health Care from the National Institute of Health and Welfare/Medical Birth Register/Finnish Register of Congenital Malformation	No	Schizophrenic disorders (ICD-9: 295 and ICD-10: F20, F25)	Women without psychotic disorder	1162	4683
Simoila et al. [37] (1991–2013)	Finland	Finnish Central Population Register/Care Register for Health Care from the National Institute of Health and Welfare/Medical Birth Register/Finnish Register of Congenital Malformation/ Finnish Child welfare	MD	Schizophrenic disorders (ICD-9: 295 and ICD-10: F20, F25)	Women without psychotic disorder	2904	14,496
Fabre et al. [12] (2015–2019)	France	French national hospital database	No	Schizophrenic disorders (ICD-10: F20, F22 and F25)	Women without severe mental disorder	2659	10,243

ICD International Classification of Diseases, *DSM* Diagnostic and Statistical Manual, *MD* Missing Data.



95% CI: 95% confidence interval.

Fig. 2 Forest plots of unmatched studies. The segments to the right of the vertical line refer to more frequent outcomes in pregnant women with schizophrenia.

with schizophrenia vs. 0.40% (95% CI [0.31–0.51]; $I^2 = 99.9\%$) in controls. Women with schizophrenia had no statistically significant increased risk for large for gestational age and high birth weight (all $p > 0.05$).

Child outcomes. The following variables were significantly increased in children of women with schizophrenia compared to controls: neonatal death (OR 1.41, 95% CI [1.03–1.94], $p = 0.033$; $I^2 = 0\%$, 95% CI [0.0–74.6]), post-neonatal death (OR 2.87, 95% CI [2.11–3.89], $p < 0.001$; $I^2 = 0\%$, 95% CI [0.0–84.7]) and infant death (OR 2.33, 95% CI [1.81–3.01], $p < 0.001$; $I^2 = 15.3\%$, 95% CI [0.0–82.4]). Infant death affected 1.05% of births (95% CI [0.83–1.33]; $I^2 = 9.5\%$, 95% CI [0.0–81.2]) in women with schizophrenia vs. 0.44% of births (95% CI [0.38–0.51]; $I^2 = 98.9\%$, 95% CI [98.4–99.2]) in controls.

Publication bias. Funnel plots and Egger's test were performed only for preterm delivery measured in more than ten studies. This difference was not statistically significant ($p > 0.05$) (Supplementary Fig. 1).

Sensitivity analysis. Sensitivity analyses using the leave-one-out method found that these results were maintained after removing each of the included studies except for gestational hypertension, which became nonsignificant after removing the Frayne et al. study [31]. When omitting the study by Vigod et al. [18] the negative association between schizophrenia in mothers and high birth weight became significant (OR = 0.77 [0.60–0.99], $p = 0.041$; $I^2 = 42.5\%$, 95% CI [0.0–80.7]).

Subgroup analyses (Table 2). All results found in the global analyses were maintained in the subgroup analyses except for 6. First, the associations between tobacco smoking and preterm delivery with schizophrenia were stronger in studies with last inclusion in 2009 or after than in studies with last inclusions before 2009 (OR = 6.60 [4.90–8.89] vs. 3.61 [2.80–4.65], $p = 0.003$ and OR = 1.94 [1.74–2.16] vs. 1.62 [1.41–1.85], $p = 0.041$). In contrast, the association between low birth weight and schizophrenia was lower in studies with last inclusion in 2009 or after than in studies with last inclusions before 2009 (1.38 [1.20–1.59] vs. OR = 1.86 [1.52–2.28], $p = 0.018$). No significant difference between associations between schizophrenia and the following outcomes was found between studies with the year of last inclusion in 2009 or after vs. before 2009: low socioeconomic level, primiparous pregnancy, gestational diabetes, placental abruption, small for gestational age, and stillbirth. The other outcomes could not be analysed due to a lack of data.

Second, the association between schizophrenia in the mother and foetal distress was higher in studies including single pregnancy per mother than those including multiple pregnancies (OR = 3.55 [2.50–5.03] vs. OR = 1.35 [1.30–1.40], $p < 0.001$). A negative association between schizophrenia in mothers and large for gestational age was found in studies including single pregnancy per mother but not in those including multiple pregnancies (OR = 0.63 [0.56–0.71] vs. OR = 1.38 [0.93–2.05], $p = <0.001$).

Third, another negative association between schizophrenia in mother and instrumental delivery was found in studies including stillbirths but not in those excluding stillbirths (OR = 0.73 [0.62–0.86] vs. 1.21 [0.77–1.89], $p = 0.040$) and in high-quality studies but not in low- to moderate-quality studies (OR = 0.73 [0.62–0.86] vs. 1.21 [0.77–1.89], $p = 0.040$).

Matched studies

Six matched studies were included (7590 deliveries of women with schizophrenia and 32,272 deliveries of control women) [12, 33–37]. Five studies were matched for age [12, 34–37], and 3 were matched for age and geographical location [12, 36, 37]. The following associations found in unmatched studies were replicated in matched studies: schizophrenia in the mother was associated with increased gestational hypertension (OR 1.32, 95% CI [1.07–1.61], $I^2 = 0\%$, 95% CI [0.0–79.2]) and congenital malformations (OR 1.33, 95% CI [1.15–1.53], $I^2 = 0\%$, 95% CI [0.0–79.2]). The other variables could not be analysed due to a lack of data.

Table 3. Subgroup analyses of unmatched studies.

	High-quality studies	Not high-quality studies	*P* value	Last inclusion before 2009	Last inclusion in 2009 or after	*P* value	Only one birth per mother	Not restricted to one birth per mother	*P* value	Stillbirths	Not including stillbirths	*P* value	Diagnosis before pregnancy	Post-delivery SZ diagnoses	*P* value	Restricted to singleton births	Not restricted to singleton births	*P* value
Gestational hypertension	1.12 (0.85–1.47)	3.18 (0.83–12.25)	0.136	–	–	–	1.12 (0.43–2.91)	1.67 (0.76–3.65)	0.527	–	–	–	2.10 (0.82–5.39)	0.94 (0.79–1.13)	0.1	–	–	–
Gestational diabetes	1.61 (0.68–3.81)	2.70 (1.81–4.01)	0.285	1.94 (1.53–2.45)	2.66 (1.23–5.74)	0.441	2.51 (1.12–5.62)	2.76 (1.55–4.92)	0.85	1.68 (1.19–2.36)	4.12 (2.73–6.22)	**0.001**	–	–	—	2.80 (1.20–6.52)	2.18 (1.35–3.52)	0.61
Pre-eclampsia or Eclampsia	1.76 (1.46–2.12)	2.49 (1.13–5.48)	0.402	–	–	–	–	–	–	–	–	–	–	–	–	1.71 (1.34–2.18)	2.63 (1.02–6.83)	0.389
Antepartum haemorrhage	1.96 (1.79–2.16)	4.14 (2.41–7.11)	**0.008**	–	–	–	–	–	–	1.96 (1.79–2.16)	4.14 (2.41–7.11)	**0.008**	–	–	–	–	–	–
Placenta abruption	2.06 (1.70–2.48)	2.62 (1.54–4.45)	0.399	2.67 (1.78–4.02)	2.00 (1.64–2.46)	0.215	1.87 (1.45–2.40)	2.14 (1.66–2.75)	0.189	–	–	–	–	–	–	2.18 (1.80–2.63)	1.75 (1.45–2.10)	0.105
Threatened preterm labour	1.81 (1.27–2.57)	6.43 (3.25–12.72)	**0.001**	–	–	–	–	–	–	1.81 (1.27–2.57)	6.43 (3.25–12.72)	**0.001**	–	–	–	–	–	–
Premature rupture of membrane	1.28 (1.03–1.58)	1.43 (0.58–3.57)	0.806	–	–	–	–	–	–	1.24 (1.00–1.53)	2.29 (1.12–4.72)	0.109	–	–	–	1.37 (0.97–1.93)	1.29 (1.12–1.49)	0.774
Caesarean section	1.29 (1.18–1.40)	1.79 (1.34–2.41)	**0.035**	–	–	–	1.30 (1.06–1.59)	1.35 (1.24–1.47)	0.735	1.26 (1.17–1.36)	2.08 (1.60–2.70)	**<0.001**	–	–	–	1.37 (1.21–1.55)	1.30 (1.22–1.39)	0.471
Postpartum haemorrhage	–	–	–	–	–	–	1.07 (0.84–1.35)	1.25 (0.92–1.69)	0.425	–	–	–	–	–	–	–	–	–
Foetal distress	1.65 (1.32–2.05)	2.35 (0.46–11.96)	0.673	–	–	–	3.55 (2.50–5.03)	1.35 (1.30–1.40)	**<0.001**	–	–	–	–	–	–	2.64 (1.24–5.62)	1.37 (1.27–1.48)	0.091
Labour induction	–	–	–	–	–	–	1.21 (0.94–1.54)	1.12 (0.63–2.00)	0.813	–	–	–	–	–	–	–	–	–
Instrumental delivery	0.73 (0.62–0.86)	1.21 (0.77–1.89)	**0.04**	–	–	–	0.79 (0.59–1.07)	0.85 (0.43–1.67)	0.867	0.73 (0.62–0.86)	1.21 (0.77–1.89)	**0.04**	–	–	–	–	–	–
Congenital malformation	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–	1.86 (1.70–2.04)	2.15 (1.72–2.68)	0.244
Apgar <7 at 5 min	1.56 (0.99–2.54)	4.00 (1.74–9.17)	0.058	–	–	–	2.26 (1.26–4.04)	1.86 (0.56–6.15)	0.774	–	–	–	–	–	–	–	–	–
Small for gestational age	1.64 (1.47–1.83)	1.54 (1.29–1.84)	0.548	1.52 (1.40–1.66)	1.72 (1.48–2.00)	0.168	1.51 (1.35–1.69)	1.68 (1.48–1.91)	0.216	–	–	–	1.72 (1.52–1.94)	1.50 (1.36–1.64)	0.081	1.59 (1.43–2.77)	2.04 (1.76–2.37)	**0.007**
Low birth weight	1.56 (1.34–1.83)	2.02 (1.36–3.01)	0.241	1.86 (1.52–2.28)	1.38 (1.20–1.59)	**0.017**	1.54 (1.18–2.00)	1.68 (1.52–1.86)	0.549	–	–	–	1.47 (1.30–1.66)	1.68 (1.51–1.86)	0.104	–	–	–
Preterm delivery	1.82 (1.63–2.05)	1.66 (1.48–1.86)	0.254	1.62 (1.41–1.85)	1.94 (1.74–2.16)	**0.041**	1.75 (1.62–1.90)	1.79 (1.55–2.06)	0.819	1.76 (1.58–1.97)	2.20 (1.63–2.98)	0.174	1.92 (1.73–2.14)	1.50 (1.28–1.75)	**0.008**	1.83 (1.62–2.07)	1.83 (1.68–2.00)	0.986
Very preterm delivery	–	–	–	–	–	–	–	–	–	2.01 (1.52–2.68)	4.28 (2.33–7.86)	**0.028**	–	–	–	–	–	–
Stillbirth	2.05 (1.82–2.32)	1.87 (0.74–4.74)	0.847	1.71 (1.26–2.34)	2.12 (1.87–2.40)	0.215	–	–	–	–	–	–	2.12 (1.87–2.40)	1.68 (1.21–2.32)	0.19	2.03 (1.78–2.30)	2.37 (1.76–3.18)	0.345
Large for gestational age	–	–	–	–	–	–	1.38 (0.93–2.05)	0.63 (0.56–0.71)	**<0.001**	–	–	–	–	–	–	–	–	–
High birth weight	0.93 (0.52–1.64)	0.92 (0.57–1.49)	0.996	–	–	–	–	–	–	–	–	–	–	–	–	–	–	–
Neonatal death (0–28 d)	1.23 (0.75–2.03)	1.60 (1.02–2.50)	0.449				–	–	–	–	–	–	–	–	–	–	–	–
Post neonatal death (29–365 d)	2.20 (1.04–4.66)	3.21 (2.15–4.80)	0.384				–	–	–	–	–	–	–	–	–	–	–	–
Infant death (0–365 d)	1.89 (1.22–2.92)	2.75 (2.02–3.74)	0.17				–	–	–	–	–	–	–	–	–	–	–	–

In bold: *p* value < 0.05. Missing values: the outcome was not reported in the studies included in the subgroup analysis.

Publication bias. Funnel plots and Egger's tests were not performed because the number of studies was <10.

Sensitivity analysis. Sensitivity analyses using the leave-one-out method found that these results were maintained after removing each of the included studies except for the association between schizophrenia and gestational hypertension, which became nonsignificant ($p > 0.05$) after removing Fabre et al. [12] matched study (Table 3).

Subgroup analysis. Due to the small number of matched studies, no subgroup analyses were performed.

DISCUSSION

This large-scale meta-analysis is the first to synthesise the accumulating evidence on pregnancy, delivery, neonatal complications, and infant mortality among women with schizophrenia and their newborns. A recent review highlighted the opportunity for real-world data from medico-administrative and electronic medical records databases to obtain for the first time a large sample of pregnant women with schizophrenia, longitudinal follow-up, and findings on rare outcomes [50]. Our meta-analysis included data from over 40 million people in 11 high-income countries published during the last two decades. Given the importance of health disparities between women with and without schizophrenia, further investment, and research into preventing preterm delivery, stillbirth, and infant mortality are needed.

These health disparities have appeared relatively stable since 1999 despite important investments in maternal and infant health care systems. In Australia, a universal psychosocial assessment was developed in maternal and infant health care systems in the 2000s [51]. The enactment of the Affordable Care Act in 2010 has been associated with great improvements in women's perinatal mental health care in the US [52]. Since 2016, the UK has invested >£400 million into new specialist perinatal mental health to ensure that women in all parts of the UK have access to specialist community services and psychiatric inpatient mother and baby units and extending service provision up to 2 years postpartum [53–56]. In France, three perinatal plans were implemented in 1970, 1995, and 2005. These programmes have targeted care access for all women with a special focus on depression and postpartum psychosis but nothing dedicated to women with schizophrenia. Our findings suggest that these programmes are insufficient to address the complex needs of women with schizophrenia and that programmes based on tailor-made and intensive care could be the key.

Integrated interventions appear essential for holistic perinatal care, but relatively few have been developed and assessed thus far [5]. To reduce care fragmentation, these integrated interventions should include multiple professionals with a case manager at the same unit of time and place in a patient-centred approach. At the same time, women with schizophrenia are currently referred to separate services [12]. In 2019, a francophone alliance for perinatal health was created to support the development of primary care in perinatal mental health integrated into a graduated care system, implementing systematised psychosocial assessments, building a system that integrates all health disciplines and primary, secondary and tertiary perinatal care, and providing continuous, coordinated and graduated interventions (from preconception to postnatal) [57].

There is evidence that a high proportion of pregnancies are unplanned for schizophrenia, promoting pre-conceptional interventions within usual care for all women with schizophrenia [58]. A preconception conceptual framework may include a biological perspective (the days to weeks before embryo development), an individual perspective (a conscious intention to conceive) and a public health perspective (months or years beforehand) to address preconception risk factors such as diet and obesity [58]. Although not all women want to be mothers, the pregnancy perspective may be a strong motivational factor to prevent risky health behaviours and metabolic comorbidities in some patients [5]. We have identified addictive behaviours (i.e. tobacco smoking and illicit drug consumption) and metabolic comorbidities (i.e. obesity, hypertension, and diabetes) as major issues in women with schizophrenia. The association between tobacco smoking and schizophrenia was stronger in studies with the last year of inclusion in 2009 or after vs. those before 2009, suggesting that women with schizophrenia may not have benefitted from public health interventions or other interventions for tobacco smoking than other women without schizophrenia. Optimising healthy lifestyle interventions is needed, as the Swedish MINT and the UK INTERaCT and STEPWISE interventions delivered to patients with schizophrenia from both sexes reported disappointing results [59, 60]. In addition to reduced care fragmentation, including fathers [61] and family caregivers [62], may improve the effectiveness of these programmes. Other effective interventions (i.e. nicotine substitute and varenicline [63], N-acetylcysteine [64], omega 3 fatty acids [65], metformin and/or topiramate [66], statins, fenofibrate, and adipose tissue surgical reduction [67]) are insufficiently provided in usual care for multiple reasons [68]. While probably frequent, we lack data on alcohol consumption in women with schizophrenia [69]. Alcohol consumption is often associated with other addictions [70] and should also be addressed.

Mother and baby units have improved the clinical and social outcomes of women. However, women with schizophrenia with low social support and low socioeconomic level have lower chances of having improved outcomes after discharge from these units [71]. We confirmed that women with schizophrenia were more frequently socially deprived and without partners than those without schizophrenia. Clinical studies have shown more frequent exposure to domestic violence, childhood adversity, and other stress factors [72–78]. Psychosocial interventions are recommended in adjunction to pharmacological treatments and psychotherapies [79] and could be individual or in groups, including peer support or peer support groups [80, 81]. The development of video sessions has been considerably accelerated with the COVID-19 pandemic and maybe an opportunity to improve coordination and care access [82].

Limitations and perspectives. Our results show that women with schizophrenia have an increased risk of very preterm delivery. We do not know if these very preterm deliveries are spontaneous or induced. The increased c-section rate in schizophrenia is in favour of induced preterm delivery. Increased urogenital infections in women with schizophrenia may also increase spontaneous preterm delivery and could be prevented [12, 36]. Additional data on the causes and interventions to prevent preterm deliveries are needed. Early and frequent antenatal visits are recommended to adapt treatments and prevent pregnancy complications, but we lack data on the care access of women with schizophrenia [12]. We also lack data on antipsychotic exposure, which may increase the risk of gestational diabetes in mothers [83, 84] and congenital malformation in newborns [85–88]. They probably have no role in low birth weight, small for gestational age [89] or stillbirth [90]. We lack data on trimester exposure to antipsychotics, that may also modulate the risk for the new born. Trimesters are rarely reported in the population-based studies as the conception date is missing in the national databases. These risks should be balanced with uncontrolled/untreated schizophrenia that may increase all risky health behaviours, delayed antenatal follow-up and congenital malformations [12, 91]. Some countries have published only matched or unmatched analyses. Matched data are difficult to include in meta-analyses due to multiple matching factors varying across studies. It seems recommended for future studies to

publish both matched and unmatched data, as these analyses yield complementary evidence. Most of national databases have not been designed for clinical studies and use the ICD codes for diagnoses. Tobacco smoking is probably underreported as it is often a secondary diagnosis and as the F17* codes focus on tobacco consumption adverse events (craving, withdrawal symptoms and addictive behaviour). However, all smokers could be considered as having a problematic tobacco use. National databases should address this issue to improve the coding of tobacco consumption and better identify tobacco smokers. However, we may hypothesise that tobacco smoking may be better coded in pregnant women, as tobacco smoking increase the risk of pregnancy, delivery and neonatal complications. The analysis of administrative databases must be complemented by qualitative approaches to identify patients' needs and expectations. Pregnancy denial is a rare and serious event that is also unreported and should be further explored [92]. Unwanted pregnancy is more frequent and may also increase poor pregnancy's outcomes [93]. Our results have raised complex ethical questions for the prevention of poor health outcomes in both mothers with schizophrenia and their children. These ethical issues would benefit from an expert consensus to guide clinical practice. It is necessary to have analyses of the pathways/trajectories of patients before/during/after pregnancy. Longitudinal analyses must now complement these cross-sectional approaches. Network research should be encouraged due to the small number of cases per site. International studies should be carried out on this subject.

CONCLUSION

This large-scale meta-analysis confirms that schizophrenia is associated with a substantially increased risk of very preterm delivery, stillbirth, and infant mortality, and metabolic risk in mothers. Integrated patient-centred care interventions are needed to address the complex social and biological needs of women with schizophrenia and their newborns, and define best practices. On a global health agenda, we lack data on low- and middle-income countries. At the same time, other studies converge to show that the health problems of women with schizophrenia are even more serious in these countries than in high-income countries [5]. Women with schizophrenia should be listed as a priority in the mental health agenda.

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AUTHOR CONTRIBUTIONS

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COMPETING INTERESTS

The authors declare no competing interests.

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Correspondence and requests for materials should be addressed to Guillaume Fond.

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