Infertility treatment and new-onset maternal mental illness: population-based cohort study

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Abstract

Background: Subfertility and infertility treatment can be stressful to a woman trying to conceive. It is not clear whether each predisposes to postpartum mental illness.

Our objective was to quantify the association between subfertility, with or without infertility treatment, and newly diagnosed mental illness after birth.

Methods: This was a population-based cohort study of women without known preexisting mental illness, and who gave birth in Ontario, Canada, 2006-2014. Exposures were: (i) *Subfertility without infertility treatment* (N = 78,283); (ii) *Non-invasive infertility treatment*, namely, ovulation induction +/- intrauterine insemination (N = 9178); (iii) *Invasive infertility treatment,* namely, *in vitro* fertilization (N = 9633). Each was compared to (iv) women who gave birth following spontaneous conception (N = 688,970).

The primary outcome was new-onset postpartum mental illness ≤ 365 days after birth, defined as either ≥ 2 outpatient visits, any ED visit or a hospitalization, with a diagnosis of a mood or anxiety disorder, psychotic disorder, substance use disorder, self-harm event, or other mental illness.

Results: Women who conceived spontaneously had a rate of postpartum mental illness of 60.8 per 1000 births. Relative to these women, those with subfertility not receiving infertility treatment had a higher aRR of the composite outcome of 1.14 (95% CI 1.10-1.17), as did those who received non-invasive (1.12, 95% CI 1.04-1.21) or invasive (1.14, 95% CI 1.05 to 1.24) infertility treatment.

Interpretation: Women with a history of subfertility or infertility treatment show a somewhat higher risk of mental illness after birth and may benefit from increased monitoring.

Introduction

Pregnancy and childbirth are vulnerable periods for the development of mental illness. Peripartum depression affects 1 in 10 women,[1] with adverse sequelae for mother and child.[2] The US Preventive Services Task Force emphasizes the importance of identifying women at risk for peripartum depression,[2] since appropriate treatment can improve their mental health trajectory.[3] A significant proportion of postpartum emergency department (ED) visits within Canada are due to maternal mental health concerns, while 5% of maternal deaths in the first year postpartum, and a majority of direct, late maternal deaths are attributed to suicide.[4-6]

Infertility treatments are increasingly used worldwide. Up to 4% of births in Canada are conceived using some form of infertility treatment.[7,8] Women with a history of infertility, i.e., those who do not conceive after 12 months of unprotected intercourse, may be at higher risk of mental illness, whether or not they use infertility treatment. Potential mechanisms include psychological distress from infertility,[9-12] adverse effects from hormonal therapy, a higher rate of perinatal loss, and a greater predisposition to medical complications arising in pregnancy or at birth.[11] Prior studies, hampered by cross-sectional designs, have not evaluated more specific psychiatric endpoints, such as emergency department (ED) visits, hospitalization for severe mental illness, or suicidality. Furthermore, previous studies included women with prevalent mental illness and did not assess whether having conceived with or without treatment influenced the outcome.[13-15] We therefore assessed the incidence of new-onset mental illness within 1 year postpartum in relation to subfertility and type of infertility treatment.

Methods

Study cohort and data sources

This population-based cohort study considered hospital births in Ontario, Canada, 2006 to 2014. During this period, consulting with a physician about infertility issues and monitoring of non-invasive infertility treatment were covered under the province's universal health insurance plan; however, use of *in vitro* fertilization (IVF) was largely self-paid.[16,17]

Data were analyzed at ICES - an independent, not-for-profit research institute that securely houses an accessible array of Ontario's health-related data (http://www.ices.on.ca). ICES is a prescribed entity under Section 45 of Ontario's Personal Health Information Privacy Act, in which consent is not required for use of personal data. We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guideline. [18] The study had research ethics approval by Queen's University, the Children's Hospital of Eastern Ontario, and McGill University Health Centre.

At ICES, patient-level records from several databases are linked using unique encoded identifiers. These databases include administrative and health information on care received under the publicly-funded Ontario Health Insurance Program (OHIP). Births and infertility treatments were identified using the Better Outcomes Registry & Network (BORN) Ontario database, which captures 99% of maternal and newborn health records for in-hospital births.[19] Other data sources are listed in eTable 1.

This study considered all women in Ontario who had a livebirth or stillbirth at ≥ 20 weeks' gestation, between April 1, 2006 and March 31, 2014. We restricted the study to women aged 18 to 55 years who had a valid OHIP number, and also excluded women with pregnancies that ended as induced abortions, surrogate carrier births, as well as women with any diagnosis of mental illness within the 2 years before the estimated date of conception (calculated from the

index birth date minus gestational age in weeks). Each woman was followed for 365 days following delivery hospitalization discharge date, or, very rarely, if her OHIP eligibility ended or she died (<0.5% of the cohort).

Exposures

We categorised the type of conception among the women in the study population as follows: i) *spontaneous conception* (the referent), which was contrasted with ii) conception following *subfertility without infertility treatment* (i.e., women who had an infertility consult with a physician within 2 years before the estimated date of conception, based on ICD-9 diagnostic code 628, and who did not receive any infertility treatment); iii) conception following *non-invasive infertility treatment* (i.e., ovulation induction or intrauterine insemination [IUI] only); and iv) conception following *invasive infertility treatment* (i.e., IVF or intracytoplasmic sperm injection [ICSI]) (eTable 2).

Outcomes

The primary composite mental illness outcome included a diagnosis of a mood or anxiety disorder, psychotic disorder, substance use disorder, self-harm event, or other conditions, such as an eating disorders or an obsessive-compulsive disorder – identified based on a single ED visit or hospitalization, or ≥ 2 outpatient visits, within 365 days following maternal discharge date from hospital following the index delivery (eTable 3). These algorithms for identifying mental health conditions have been previously used, and their results align with worldwide estimates of postpartum mental illness.[20-23] As a proxy for more severe mental illness, we

restricted the analysis to diagnoses based on ED visits and hospitalizations, and excluded women identified only in outpatient settings.

Covariates

Among available potential confounders, we considered those that may have, directly or indirectly, influenced infertility and access/use of infertility treatment, as well as mental health. These included maternal age at index delivery, parity, a diagnostic code for chronic hypertension, diabetes, or obesity in the 2 years prior to estimated date of conception, income quintile, urban vs. rural residence, and immigrant status (immigrant vs. Canadian-born) (eTable 4).

The following covariates were not adjusted for in our main models due to the fact that they were factors in the causal pathway: multiple gestation (vs. singleton), very pre-term delivery (< 34 weeks vs. ≥ 34 weeks), stillbirth vs. livebirth, the presence of an indicator of severe maternal morbidity (SMM) composite arising in the pregnancy or ≤ 42 days postpartum[24] (vs. none). We considered these covariates primarily as effect modifiers. We further stratified results based on eligibility for Ontario Drug Benefit Plan (ODB - a public drug funding system available to persons above age 65 years or those requiring social assistance).

Data analyses

Descriptive statistics included proportions for categorical variables and means (SD) or medians (interquartile range [IQR]) for continuous variables. Starting from their date of discharge for the index hospital delivery, and with a follow up for 365 days thereafter,

cumulative incidence rates of maternal mental illness were calculated per 1000 deliveries. Unadjusted and adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) were calculated using modified Poisson regression, with robust error variance, which can account for more than one delivery per woman in the study period (n=196,466 repeat deliveries to 172,633 women). We used a change-in-estimate (CIE) approach to determine inclusion of variables in the final model. We further examined whether the association changed when stratifying by effect modifiers as listed above. We performed a complete case analysis. An additional analysis was done, including women with a diagnosis of mental illness in the 2 years preceding the date of conception, in order to assess mental health exacerbations as well as de novo mental illness.

Analyses were carried out using SAS Enterprise Guide, version 7.1 (Cary, NC, USA).

Results

Of the 1,080,726 deliveries in the study period, 786,064 deliveries to 589,598 women were eligible for the study. These included 78,823 deliveries to women with *subfertility without infertility treatment*, 9178 deliveries following *non-invasive infertility treatment*, 9633 deliveries receiving *invasive infertility treatment*, and 688,970 deliveries with no indication of subfertility or infertility treatment (i.e., deliveries following spontaneous conception; Figure 1).

Women who conceived spontaneously tended to be younger, and were more likely to have resided in a rural area, been eligible for the ODB program, and less likely to be primiparous, have SMM or a stillbirth (Table 1). In contrast, a greater proportion of women who conceived by invasive infertility treatment resided in a high-income quintile area. Complications during pregnancy, and multiple gestation were more common among women who conceived following

invasive infertility treatment, as was the proportion of primiparas. Women who received a non-invasive infertility treatment had a higher prevalence of obesity (Table 1).

The overall incidence of any mental illness within 1 year postpartum was 61 per 1000 deliveries, corresponding to 47493 women with outpatient and/or severe events captured within an ED visit or hospitalization. The majority of events (89.6%) were diagnosed in an outpatient setting. Events occurred a median (IQR) of 5.2 (2.3 to 8.4) months after discharge from hospital for delivery, but occurred on average earlier among those with subfertility or infertility treatment than among those who conceived spontaneously (Table 2). Non-psychotic disorders were most frequently observed in the outpatient setting, with the highest cumulative incidence (63.0 per 1000 deliveries, 95% CI 57.8 to 68.1) seen among those who received non-invasive infertility treatment. Severe mental illness requiring mental health hospitalization or ED visit was much less common, occurring more frequently among those who conceived spontaneously (7.0 per 1000 deliveries, 95% CI 6.8 to 7.2) than in other groups. The most common diagnosis requiring hospitalization or ED visit was a mood or anxiety disorder (4260 women [80.1%]). Deliberate self-harm was rare (Table 2).

Main outcomes

The cumulative incidence of the mental illness composite outcome among women who conceived spontaneously was 60.8 per 1000 births (Figure 2 top). Relative to these women, those with subfertility but no infertility treatment had a higher risk of the composite outcome (62.1 per 1000, aRR 1.14, 95% CI 1.10 to 1.17), with a similar aRR for those with non-invasive infertility treatment (65.8 per 1000, aRR 1.12, 95% CI 1.04 to 1.21). Women who conceived by

invasive infertility treatment had a lower crude absolute risk, but higher adjusted relative risk of the mental illness composite outcome relative to those conceiving spontaneously (60.4 per 1000, aRR 1.14, 95% CI 1.05 to 1.24).

While no associations were seen between mode of conception and the severe mental health outcome (Figure 2, middle), the pattern seen for mental illness diagnosed as an outpatient paralleled that for the composite (Figure 2, lower).

Stratified and additional analyses

Although the absolute rates of the composite mental illness outcome were mostly higher in women who experienced SMM, gave birth before 34 weeks, had a multifetal pregnancy, or who were eligible for ODB, the aRRs were similar across the three different fertility groups, compared with those who conceived spontaneously. Results were unchanged when restricted to women with a live birth. Due to small numbers, data cannot be presented for women who experienced a stillbirth.

When we included 137,611 women with a diagnosis of mental illness in the 2 years preceding the index date of conception, the rate of the composite outcome was substantially higher in all exposure groups (eFigure 1). Women with subfertility but no infertility treatment had an aRR of the composite outcome of 1.10 (95% CI 1.08 to 1.13), an aRR of outpatient mental illness of 1.11 (1.08-1.13) and an aRR of severe mental illness of 0.91 (95% CI 0.83-0.99) (eFigure 1).

Interpretation

In this cohort of 786,064 births in Ontario, Canada, the risk of new-onset mental illness was slightly higher in women who experienced subfertility, including among those who did and did not receive infertility treatment to conceive. Most mental health outcomes were mood or anxiety disorders, diagnosed in outpatient settings approximately 4 to 5 months after giving birth.

IVF, typically characterized by repeated rounds of high dose ovarian stimulation and intense hormonal fluctuations, has been postulated to contribute to increased peripartum mood disorders,[25] although not consistently so.[26] IVF-treated women in our cohort experienced a low absolute rate of postpartum mental illness, but a higher relative risk of postpartum mental illness when compared with spontaneous births after adjustment for confounders. A prior systematic review found that women who use IVF are not at higher risk of postpartum mental illness.[26] In our cohort, IVF-treated women were socially advantaged, resided in higher income neighborhoods, and thus able to afford the cost of IVF therapy.[16,17] Second, IVF necessitates closer medical follow-up, and in some cases, more intense screening for "readiness" for pregnancy, including both physical and mental health fitness.[27] However, the slightly higher relative risk that we found indicates "reverse confounding", in that after adjustment for maternal age and social determinants of health, there exists an underlying predisposition towards adverse postpartum mental health.

Our findings suggest that women with subfertility, independent of treatment, may experience new-onset mental illness. Previous studies have documented high rates of depressive and anxiety symptoms among individuals seeking assistance for infertility.[28,29] In our cohort, women with subfertility were more likely to be smokers, and to have antecedent cardiovascular disease

risk factors, suggesting that pre-existing poor physical health could contribute to both reduced fertility and onset of mental illness postpartum.[30,31]Women using non-invasive infertility treatment also experienced a higher risk of the composite of postpartum mental illness. IUI-assisted conception is often required among women with polycystic ovarian syndrome,[32] and 15% of women in the non-invasive infertility group were obese. Both obesity and polycystic ovarian syndrome are independent risk factors for mood and anxiety disorders.[33]

Our findings align with existing estimates of the rate of postpartum mental illness in approximately 6% of women following delivery.[21-23] In keeping with the work of others,[34] our stratified analyses suggest that obstetric factors, especially preterm birth < 34 weeks' gestation, some of which are a consequence of the exposure, are significant determinants of postpartum mental illness.

Strengths and limitations

This study has a number of strengths, such as its large sample size, accrued from a multi-ethnic population in the setting of universal provincial health coverage. The ability to categorize women according to the type of infertility treatment, and the possibility of capturing objective psychiatric outcomes were additional strengths. We were also able to evaluate subfertility without treatment, which studies have not done.

This study has several limitations related to the use of administrative health data; namely, misclassification and residual confounding. Exposure to treatment was captured by chart review by trained abstractors at the time of birth, and is therefore likely to be highly reliable, as

are other data elements in our data source[35]. However, it is possible that some women who conceived by IVF or IUI were not captured with this approach, resulting in non-differential misclassification and a possible underestimate of the effect on mental health. We examined those with *subfertility*, rather than with *infertility*, as we lacked information on time to pregnancy. While we could only capture a subset of women who experienced problems conceiving, we believe nevertheless that our definition is likely a specific indicator of infertility.[36-38] A further study limitation was the absence of information on cause of infertility, clinical parameters such as body mass index and blood pressure, specific fertility medications, partner experience, and patient-reported outcomes. Finally, we did not have data beyond 2014, thereby limiting our ability to examine the associated effect of the Ontario IVF program[17] -- launched in 2015 and provided specified IVF services at no costs to all infertile couples -- on mental illness.

Conclusion

Women who give birth following a history of subfertility may be more vulnerable to mental illness after birth. It remains to be determined whether these women should receive enhanced resources to optimize peripartum mental health. Future studies should also examine access to infertility treatments among women with mental illness.

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Authorship: ND conceived the study, obtained access to the data, interpreted the analyses, and wrote the first draft of the manuscript. MV conceived the study, obtained access to the data, interpreted the analyses, and revised the manuscript for important intellectual content. JGR conceived the study, contributed to study design, interpretation of results and revised the manuscript for important intellectual content. SV contributed to study design, interpretation of results and revised the manuscript for important intellectual content. JP contributed to study design, interpretation of results, formatting of tables and figures, and revised the manuscript for important intellectual content. MD performed the analyses and contributed to writing of the manuscript. IJG assisted with interpretation of results and writing of the manuscript. DBF

assisted with data access and approval, interpreted results and revised the manuscript for important intellectual content. KSJ, OB, DBF and VN contributed to study design and revised the manuscript for important intellectual content.

Data sharing

The data from this study are held securely in coded form at ICES. While data-sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at www.ices.on.ca/DAS. The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programmes may rely upon coding templates or macros that are unique to ICES and therefore either inaccessible or requiring modification.

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Table 1. Characteristics of the included 786,064 livebirths and stillbirths in Ontario, 2006-2014, according to mode of conception. All data are presented as a number (%) unless otherwise indicated.

Patient characteristics	Spontaneous conception (N=688,970)	Subfertility without infertility treatment (N=78,283)	Non-invasive infertility treatment (N=9178)	Invasive infertility treatment (N=9633)
Mean ± SD maternal age, y	30.0 ± 5.3	33.1 ± 4.7	32.8 ± 4.4	35.4 ± 4.9
<25	108,511 (15.75)	2,589 (3.31)	230 (2.51)	56 (0.58)
25-29	200,202 (29.06)	14,768 (18.86)	1,847 (20.12)	907 (9.42)
30-34	242,387 (35.18)	30,741 (39.27)	3,906 (42.56)	3,313 (34.39)
35-39	116,043 (16.84)	23,340 (29.81)	2,538 (27.65)	3,542 (36.77)
40-44	20,964 (3.04)	6,465 (8.26)	636 (6.93)	1,389 (14.42)
≥45	863 (0.13)	380 (0.49)	21 (0.23)	426 (4.42)
Income quintile (Q)				
1 (lowest)	152,848 (22.2)	12,959 (16.6)	1235 (13.5)	948 (9.8)
2	139,654 (20.3)	14,300 (18.3)	1603 (17.5)	1528 (15.9)
3	141,676 (20.6)	16,509 (21.1)	1922 (20.9)	2070 (21.5)
4	144,089 (20.9)	18,818 (24.0)	2484 (27.1)	2619 (27.2)
5 (highest)	110,703 (16.1)	15,697 (20.1)	1934 (21.1)	2468 (25.6)
Rural residence	53,421 (7.8)	3381 (4.3)	553 (6.0)	376 (3.9)
Immigrant	168,131 (24.4)	23,972 (30.6)	1853 (20.2)	2522 (26.2)
Ontario Drug Benefit (ODB) eligible	76,433 (11.1)	5379 (6.9)	629 (6.9)	683 (7.1)
Primiparity	283,389 (41.1)	39,638 (50.6)	5901 (64.3)	6711 (69.7)
Multi-fetal pregnancy	8381 (1.2)	2723 (3.5)	1084 (11.8)	2502 (26.0)
Median [IQR], gestational age at birth, weeks	39 [38-40]	39 [38-40]	39 [38-40]	38 [37-40]
<34	11,027 (1.6)	2303 (2.9)	445 (4.9)	765 (7.9)
34+0 - 36+6	33,349 (4.8)	5272 (6.7)	839 (9.1)	1442 (15.0)
≥37	644,594 (93.6)	70,708 (90.3)	7894 (86.0)	7426 (77.1)
Caesarean birth	217,000 (26.8)	33,480 (36.2)	4133 (38.7)	5682 (50.6)
Stillbirth	986 (0.1)	164 (0.2)	29 (0.3)	41 (0.4)
Severe maternal morbidity composite[a]	12,724 (1.9)	1927 (2.5)	250 (2.7)	509 (5.3)
Comorbidities[b]				
Obese[c]	59,807 (8.7)	7530 (9.6)	1406 (15.3)	867 (9.0)
Smoking	61,804 (9.0)	2449 (3.1)	252 (2.8)	142 (1.5)
Substance use[d]	6167 (0.9)	137 (0.2)	21 (0.2)	23 (0.2)
Alcohol use	816 (0.1)	41 (0.1)	9 (0.1)	6 (0.1)
Chronic hypertension	15,734 (2.3)	2800 (3.6)	367 (4.0)	379 (3.9)
Diabetes mellitus	9770 (1.4)	2133 (2.7)	263 (2.9)	227 (2.4)

[a]From 20 weeks' gestation up to 42 days postpartum (eTable 4 contains the respective diagnostic codes).

[b] Based upon hospitalizations, emergency room visits or outpatient physician visits from within 2 years before conception, up to 19 weeks' gestation.

[c]Diagnosis of obesity if maternal body mass index > 30 at time of birth or OHIP billing code for obesity (dxcode=278) in 2-yeaar lookback period prior to estimated date of conception

[d]Includes any marijuana, cocaine, gas/glue, hallucinogens, methadone, narcotics, opioids and other substance use.

Table 2. Rate of maternal mental illness health outcome within 365 days after the index birth, in relation to type of pregnancy conception. Shown is the severe mental illness outcome and the outpatient mental illness composite outcome, as well as the time to diagnosis of each after the index obstetric birth hospital discharge. All data presented as a rate per 1000 births, unless otherwise indicated. Fewer than 6 outcome events are suppressed.

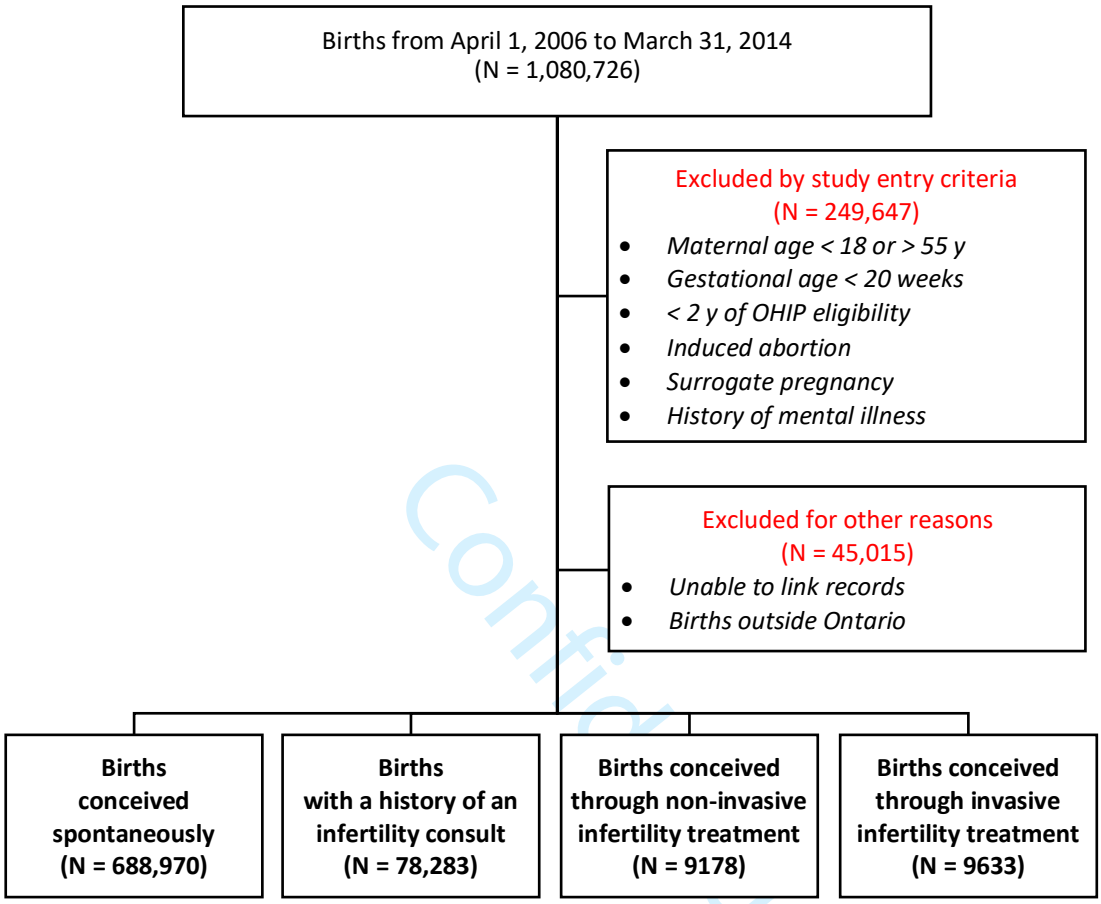
Outcome	Spontaneous conception (N = 688,970)		Subfertility without infertility treatment (N = 78,283)		Non-invasive infertility treatment (N = 9178)		Invasive infertility treatment (N = 9633)	
	N	Rate per 1000 (95 CI)	N	Rate per 1000 (95 CI)	N	Rate per 1000 (95 CI)	N	Rate per 1000 (95 CI)
Overall Composite Outcome	**41894**	**60.8 (60.2, 61.4)**	**4863**	**62.1 (60.4, 63.9)**	**604**	**65.8 (60.6, 71.1)**	**582**	**60.4 (55.5, 65.3)**
Diagnosed outpatient mental illness[b]	39473	57.3 (56.7, 57.9)	4713	60.2 (58.5, 61.9)	589	64.2 (59.0, 69.4)	565	58.7 (53.8, 63.5)
Substance use disorder	1074	1.6 (1.5, 1.7)	20	0.6 (0.1, 0.4)	< 6	-	< 6	-
Psychotic disorder	1274	1.9 (1.8, 2.0)	174	2.2 (1.9, 2.6)	23	2.5 (1.5, 3.5)	22	2.3 (1.3, 3.2)
Non-psychotic disorder	37913	55.0 (54.5, 55.6)	4613	58.9 (57.2, 60.6)	578	63.0 (57.8, 68.1)	552	57.3 (52.5, 62.1)
Median (IQR) time to composite outcome, months	5.3 (2.4-8.5)		5.0 (2.1-8.2)		4.5 (1.8-8.3)		4.0 (1.8-7.7)	
Diagnosed severe mental illness[a]	4832	7.0 (6.8, 7.2)	349	4.5 (4.0, 4.9)	53	5.8 (4.2, 7.3)	36	3.7 (2.5, 5.0)
Substance use disorder	634	0.9 (0.9, 1.0)	15	0.2 (0.1, 0.3)	< 6	-	< 6	-
Psychotic disorder	164	0.2 (0.2, 0.3)	19	0.2 (0.1, 0.4)	< 6	-	< 6	-
Mood and anxiety disorder	3878	5.6 (5.5, 5.8)	301	3.9 (3.4, 4.3)	47	5.1 (3.7, 6.6)	34	3.5 (2.3, 4.7)
Deliberate self-harm	292	0.4 (0.4, 0.5)	14	0.2 (0.1, 0.3)	< 6	-	< 6	-
Other	94	0.1 (0.1, 0.2)	8 (0.1)	0.1 (0.03, 0.2)	< 6	-	< 6	-
Median (IQR) time to composite outcome, months	5.3 (2.3-8.4)		4.5 (1.6-8.1)		5.4 (1.2-8.0)		3.0 (1.2-7.4)	

CI confident interval; IQR interquartile range

[a]Defined by the presence of 1 or more inpatient hospitalizations or emergency department visits for a substance-related and addictive disorder, schizophrenia spectrum and other psychotic disorder, mood disorder and anxiety disorder, deliberate self harm event, or other mental illness (eTable 3 contains the respective diagnostic codes).

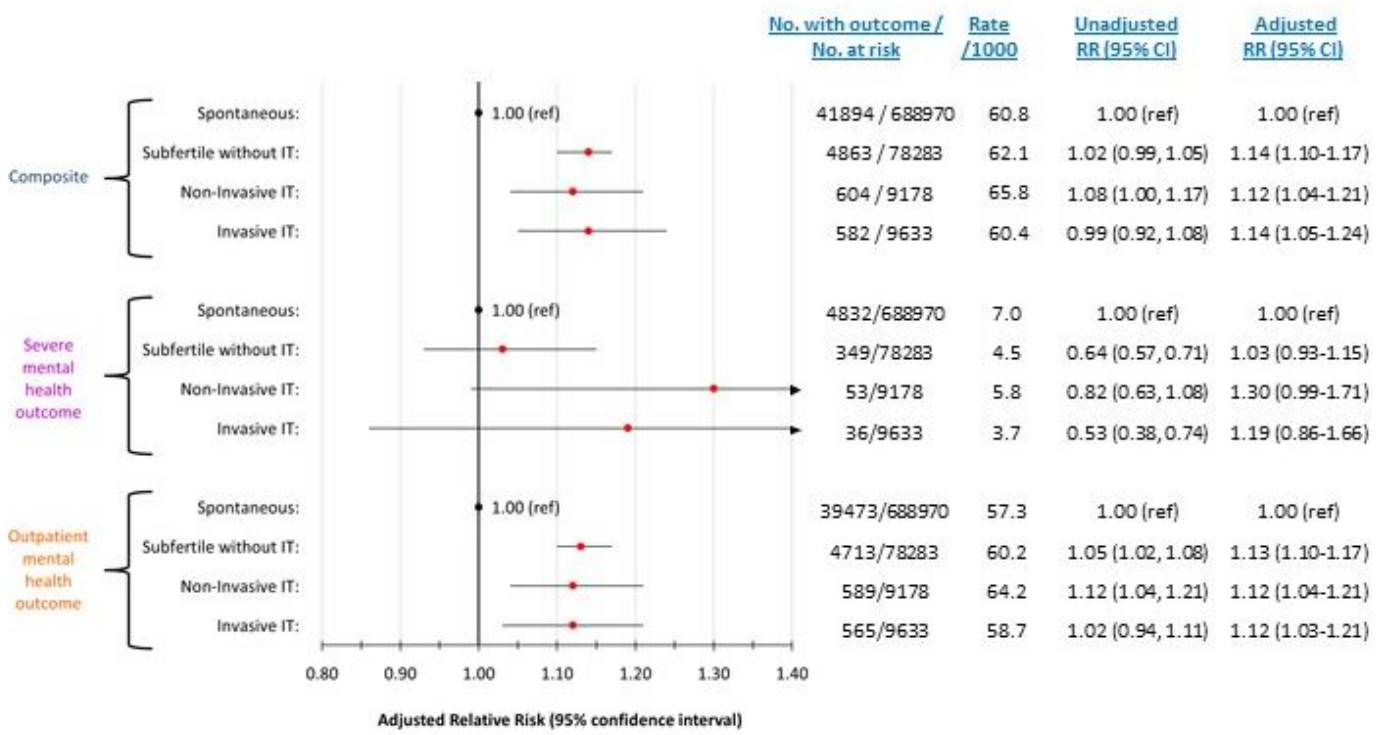
[b]Defined by the presence of 2 or more outpatient visits for a substance use disorder, psychotic disorder, or a non-psychotic disorder (eTable 3 contains the respective diagnostic codes).

Figure 1. Study flow chart.



OHIP Ontario Health Insurance Plan; EDC estimated date of conception.

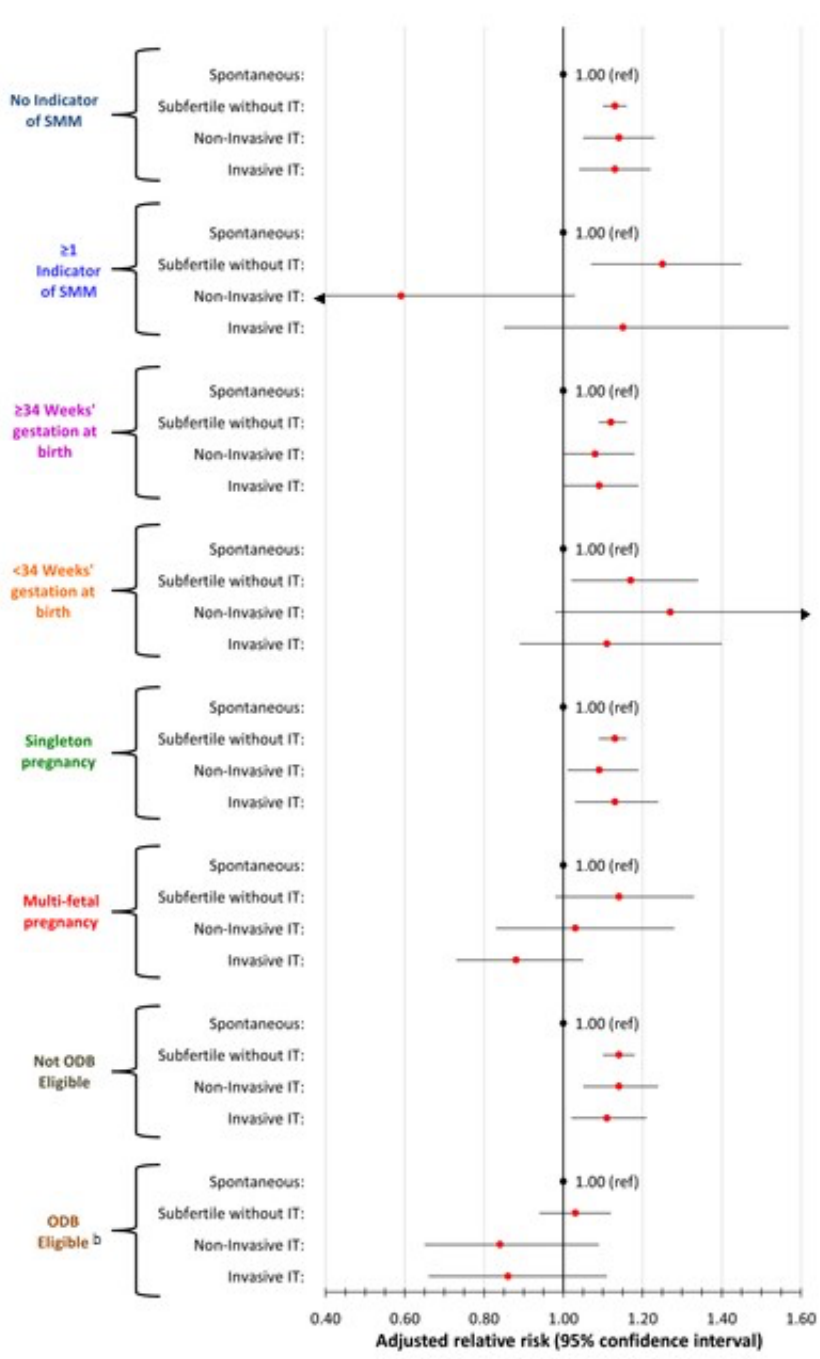
Figure 2: Risk of a maternal mental illness outcome within 1 year after birth in relation to type of pregnancy conception. Shown is the composite mental health outcome of any severe mental health or outpatient mental health encounter (upper); the severe mental health outcome (middle); and the outpatient mental health outcome (lower), as described in eTable 3.[a]



[a]Relative risks are adjusted for maternal age, income quintile, rurality, immigrant status, parity, chronic hypertension, diabetes mellitus, and obesity.

RR relative risk; CI confidence interval; IT infertility treatment.

Figure 3: Risk of the composite maternal mental health outcome of any severe mental illness or outpatient mental health encounter within 1 year after birth in relation to type of pregnancy conception, further stratified by patient and pregnancy characteristics.[a]



	No. with outcome / No. at risk	Rate /1000	Adjusted RR (95% CI)
No Indicator of SMM			
Spontaneous:	40809 / 676246	60.4	1.00 (ref)
Subfertile without IT:	4682 / 76356	61.3	1.13 (1.10-1.16)
Non-Invasive IT:	592 / 8928	66.3	1.14 (1.05-1.23)
Invasive IT:	540 / 9124	59.2	1.13 (1.04-1.22)
≥1 Indicator of SMM			
Spontaneous:	1085 / 12724	85.3	1.00 (ref)
Subfertile without IT:	181 / 1927	93.9	1.25 (1.07-1.45)
Non-Invasive IT:	12 / 250	48.0	0.59 (0.34-1.03)
Invasive IT:	42 / 509	82.5	1.15 (0.85-1.57)
≥34 Weeks' gestation at birth			
Spontaneous:	40770 / 677943	60.1	1.00 (ref)
Subfertile without IT:	4616 / 75980	60.8	1.12 (1.09-1.16)
Non-Invasive IT:	549 / 8733	62.9	1.08 (1.00-1.18)
Invasive IT:	506 / 8868	57.1	1.09 (1.00-1.19)
<34 Weeks' gestation at birth			
Spontaneous:	1124 / 11027	101.9	1.00 (ref)
Subfertile without IT:	247 / 2303	107.3	1.17 (1.02-1.34)
Non-Invasive IT:	55 / 445	123.6	1.27 (0.98-1.64)
Invasive IT:	76 / 765	99.4	1.11 (0.89-1.40)
Singleton pregnancy			
Spontaneous:	41274 / 680589	60.6	1.00 (ref)
Subfertile without IT:	4640 / 75560	61.4	1.13 (1.09-1.16)
Non-Invasive IT:	518 / 8094	64.0	1.09 (1.01-1.19)
Invasive IT:	426 / 7131	59.7	1.13 (1.03-1.24)
Multi-fetal pregnancy			
Spontaneous:	620 / 8381	74.0	1.00 (ref)
Subfertile without IT:	223 / 2723	81.9	1.14 (0.98-1.33)
Non-Invasive IT:	86 / 1084	79.3	1.03 (0.83-1.28)
Invasive IT:	156 / 2502	62.4	0.88 (0.73-1.05)
Not ODB Eligible			
Spontaneous:	33179 / 612537	54.2	1.00 (ref)
Subfertile without IT:	4344 / 72904	59.6	1.14 (1.10-1.18)
Non-Invasive IT:	551 / 8549	64.5	1.14 (1.05-1.24)
Invasive IT:	529 / 8950	59.1	1.11 (1.02-1.21)
ODB Eligible [b]			
Spontaneous:	8715 / 76433	114.0	1.00 (ref)
Subfertile without IT:	519 / 5379	96.5	1.03 (0.94-1.12)
Non-Invasive IT:	53 / 629	84.3	0.84 (0.65-1.09)
Invasive IT:	53 / 683	77.6	0.86 (0.66-1.11)

[a]Relative risks are adjusted for maternal age, income quintile, rurality, immigrant status, parity, chronic hypertension, diabetes mellitus, and obesity.

[b]Ontario Drug Benefit Programme (ODB) eligibility was based on a woman having ≥ 1 ODB-insured medication claim between the estimated date of conception and 1 year after the index birth.

RR relative risk; CI confidence interval; IT infertility treatment; SMM severe maternal morbidity, ODB Ontario Drug Benefit Programme.

Supplement eTable 1: Data Sources accessed at ICES.

Dataset	Description
Health Services	
Canadian Institute for Health Information Discharge Abstract Database (CIHI DAD)	A dataset that captures administrative, clinical, and demographic information on hospital discharges, including deaths, sign-outs, and transfers.
National Ambulatory Care Reporting System (NACRS)	A dataset that contains data on hospital-based and community-based ambulatory care: day surgery, outpatient and community-based clinics, and emergency departments.
Ontario Health Insurance Plan Claims Database (OHIP)	A dataset that records all claims for reimbursement by Ontario physicians for inpatient and ambulatory visits, consultations and procedures. The data also include claims from optometrists for publicly funded reimbursement and from laboratories for all diagnostic tests performed.
Ontario Drug Benefit Claims (ODB)	The Ontario Drug Benefit (ODB) database contains claims for prescription drugs received under the Ontario Drug Benefit program. The Ontario Drug Benefit is a public drug funding system that is only available to persons under the age of 65 who are in special access drug programs or who receive social assistance through the provincial government.
Ontario Mental Health Reporting System (OMHRS)	The Ontario Mental Health Reporting System (OMHRS) in Ontario officially collects data on patients in adult designated inpatient mental health beds. This includes beds in General, Provincial Psychiatric, and Specialty Psychiatric facilities.
Population and Demographics	
Registered Persons Database (RPDB)	A dataset that provides demographic information about all individuals who have received an Ontario health card number, including their date of birth, sex, and home address.
Vital Statistics – Office of the Registrar General – Deaths (ORGD)	ORGD is an annual dataset containing information on all deaths registered in Ontario starting on January 1 1990. Information on cause of death is included.
Postal Code Conversion File (PCCF)	A digital file which provides a correspondence between the Canada Post Corporation (CPC) six-character postal code and Statistics Canada's standard geographic areas for which census data and other statistics are produced.
Immigration, Refugees and Citizenship Canada Dataset (IRCC)	A dataset that provides information on permanent and temporary residents of Canada, in addition to immigration and citizenship programs.
Patient Contact and Eligibility Yearly Files (CONTACT)	Once a person becomes eligible for OHIP an initial record is created with a start date and an infinite end date. When eligibility ends a second record is created with the same start date but a finite end date.
ICES Derived Cohorts	
Ontario Asthma dataset (ASTHMA)	The Ontario Asthma Database contains all Ontario asthma patients identified since 1991. A patient is said to be asthmatic if s/he had one hospital admission with an asthma diagnosis or two OHIP claims with asthma diagnosis within two years.
Congestive Heart Failure (CHF)	The Ontario Congestive Heart Failure Database contains all Ontario individuals identified as having CHF since 1991. A patient is said to have CHF if s/he had one hospital admission (either from the DAD or from OMHRS) with a CHF diagnosis or an OHIP claim/NACRS ED record with a CHF diagnosis followed within one year by either a second record with a CHF diagnosis from any source.
Chronic Obstructive Pulmonary Disease (COPD)	The database was created using hospital discharge abstracts from the CIHI database (including same day surgery), physician service claims from the OHIP database and information regarding the demographics of persons eligible for health care coverage in Ontario from the Registered Persons Database (RPDB). A patient is said to have COPD if s/he had

Dataset	Description
	one COPD diagnosis in OHIP or CIHI-SDS or CIHI-DAD and is age 35 years or older.
Ontario HIV Database (HIV)	The database was created using physician claims in the OHIP database. Persons enter the HIV database as incident cases when they have 3 physician claims in 3 years with a diagnosis code of “042”, “043”, or “044”.
Ontario Hypertension Dataset (HYPER)	A dataset of all of the people in Ontario identified as having hypertension.
Linked Delivering Mothers and Newborns (MOMBABY)	A dataset that is derived within ICES to link the inpatient admission records of delivering mothers and their newborns.
Ontario Diabetes Dataset (ODD)	A dataset of all of the people in Ontario diagnosed with diabetes.
Acquired Cohorts	
Better Outcomes Registry & Network (BORN) Ontario	A longitudinal administrative data source that collects information related to maternal, perinatal, and newborn health in Ontario. Includes a six-year dataset (2006-2011) of legacy birth record data (formerly collected in the Niday Perinatal Database).

Supplement eTable 2: Variables used to define cohort entry, exclusion criteria and study exposures.

Assessment	Timing	Disease or procedure or condition	Applicable codes	Data Sources
Cohort entry criterion	April 1st, 2006 to March 31st, 2014.	All livebirths and stillbirths at ≥20^0 weeks gestation among women aged 18-55 years.	--	BORN
Exclusion Criteria	At the time of hospitalization for delivery	Inductions for the purposes of termination.	BORN Field= IND_FOR_LBR_INDUCT_PRIM_ID=1014250 OR ALL_IND_FOR_LBR_INDUCT_ID=1014250	BORN
	Same	Surrogate pregnancy.	BORN Field= CONCEPTION_TYPE_ID=1013170	BORN
	Same	Less than 2 years of OHIP eligibility prior to the estimated date of conception.	Calculations for estimated date of conception: NIDAY = date of delivery – (gestational age in weeks*7) BORN = estimated_bdate – (40*7)	RPDB
	Same	Birth outside of Ontario.	--	BORN
	Same	No infant record in BORN.	--	BORN
	Same	No IKN or inability to link to ICES datasets.	--	RPDB
	Same	Warning in Niday dataset.	--	BORN
	Same	History of mental health outcome	History of a mental health outcome as defined by one of our study outcomes within the 2 years prior to the estimated date of conception.	OMHRS, DAD, NACRS, OHIP, BORN
Main Study Exposures	At the index pregnancy	Mode of conception	BORN Field= CONCEPTION_TYPE_ID Niday Field= REPASS **Invasive IT (IVF or IVF-ICSI):** BORN=1013130, 1013140 Niday=3,4 **Non-Invasive IT (OI, IUI):** BORN=1013110, 1013120, 1013150, 3000006 Niday=2,5 **Subfertile:** • Conception type = Spontaneous or Unknown (1013160, 1013180 [BORN] or 1,9,0 [Niday]) AND • History of infertility=YES **Spontaneous:** • Conception type = Spontaneous or Unknown (1013160, 1013180 [BORN] or 1,9,0 [Niday]) AND • History of infertility=NO	BORN
	Same	History of Infertility	Determined based on OHIP billing codes in the look-back window of 2 years prior to the estimated date of conception. Infertility is to be defined as any occurrence of billing code 628 (all feecodes, include lab, feesuff=A).	OHIP

Supplement eTable 3: Variables used to define study outcome up to 365 days after the maternal date of discharge for the index birth. If date of discharge is missing, assume date of delivery is date of discharge.

Disease or procedure or condition	Applicable codes	Data Sources
Composite: Severe or Outpatient Mental Health Outcome	Any occurrence of the severe or outpatient mental health composite outcomes below.	OMHRS, DAD, NACRS, OHIP
Composite: Severe mental health outcomes. Hospitalizations and emergency room visits.[a]	Any 1 occurrence of the below 5 components.	OMHRS (ICD-9) DAD or NACRS (ICD-10)
Severe Component 1: Substance-Related and Addictive Disorders	ICD-9 • AXIS1_DSM4CODE_DISCH1 = 291.x (all 291 codes, excluding 291.82), 292.x (all 292 codes, excluding 292.85), 303.x (all 303 codes), 304.x (all 304 codes), 305.x (all 305 codes). • PROVDX_DSM4CODE_ADM1 =4 ICD-10 • DX10CODE1 = F55, F10 to F19	Same
Severe Component 2: Schizophrenia Spectrum and Other Psychotic Disorders	ICD-9 • AXIS1_DSM4CODE_DISCH1 = 295.x (all 295 codes), 297.x (all 297 codes), 298.x (all 298 codes), 293.81, 293.82 • PROVDX_DSM4CODE_ADM1 =5 ICD-10 • DX10CODE1 = F06.0, F06.2, F20 (excluding F20.4), F22, F23, F24, F25, F28, F29, F53.1	Same
Severe Component 3: Mood and Anxiety Disorders	*ICD-9* • AXIS1_DSM4CODE_DISCH1 = 296.x (all 296 codes), 300.4x, 301.13, 311.x, 293.83 • PROVDX_DSM4CODE_ADM1 =6 • AXIS1_DSM4CODE_DISCH1 = 300.0x, 300.2x, 300.3x, 308.3x, 309.0x, 309.24, 309.28, 309.3x, 309.4x, 309.8x, 309.9x, 293.84 • PROVDX_DSM4CODE_ADM1 =7, 15 ICD-10 • DX10CODE1 = F06.3, F30, F31, F32, F33, F34, F38, F39, F53.0 • DX10CODE1 = F06.4, F40, F41, F42, F43, F48.8, F48.9; F93.1, F93.2	Same
Severe Component 4: Deliberate Self-Harm	ICD-10 • DX10CODE2-10 = X60-X84, Y10-Y19, Y28 when DX10CODE1 ne F06-F99 (DXTYPE = alldx or DXTYPE = 9)	Same
Severe Component 5: Other	ICD-9 • AXIS1_DSM4CODE_DISCH1 = 293.89, 293.90, 300.6, 300.7, 300.8, 300.9, 301, 301.0, 301.2, 301.4, 301.5, 301.6, 301.7, 301.8, 301.9, 307.1, 307.50, 307.51, 307.52, 307.53 • PROVDX_DSM4CODE_ADM1 = 12, 16 ICD-10 • DX10CODE1 = F06.1, F21, F45, F50, F53.8, F53.9, F60, F61, F69	Same
Composite: Outpatient mental health outcomes.[b]	Any 2 occurrences of the same component is considered an outcome. Outcome date is the day the second code occurs. Psychiatrist [SPEC=19] and outpatient (LOCATION: O, L, H) and non-lab service [substr(FEECODE,1,1) ne 'G'] *OR* FP/GP [SPEC=00] and MHA diagnosis code [DXCODE] and outpatient (LOCATION: O, L, H) and non-lab service [substr(FEECODE,1,1) ne 'G']	OHIP
Outpatient Component 1: Psychotic disorders	295 Schizophrenia 296 Manic-depressive psychoses, involutional melancholia	Same

Disease or procedure or condition	Applicable codes	Data Sources
	297 Other paranoid states 298 Other psychoses	
Outpatient Component 2: Non-Psychotic disorders	300 Anxiety neurosis, hysteria, neurasthenia, obsessive-compulsive neurosis, reactive depression 301 Personality disorders 302 Sexual deviations 306 Psychosomatic illness 309 Adjustment reaction 311 Depressive disorder	Same
Outpatient Component 3: Substance use disorders	303 Alcoholism 304 Drug dependence	Same

[a]ICD-9-CM and ICD-10-CA diagnoses codes associated with mental health and addictions (MHA), by clinical category from ICES Concept Dictionary. For ICD-9 methodology refer to Health Reports, Vol. 20, no. 2, June 2009 • Statistics Canada, Catalogue no. 82-003-XPE Identifying deliberate self-harm in emergency department data • Methodological Insights.

[b]MHA-related services algorithm for adults (ages 16-105) and qualifying diagnoses codes from ICES Concept Dictionary.

Supplement eTable 4: Variables used to define covariates.

Assessment	Timing	Disease or procedure or condition	Applicable codes	Data Sources
Patient Characteristics	At the index pregnancy	Maternal Age	--	RPDB
	Same	Income Quintile	(1) Lowest quintile (2) Second quintile (3) Third quintile (4) Fourth quintile (5) Highest quintle If income quintile is unknown → set to (1) lowest	PCCF and Census
	Same	Rurality Index	(1) Urban (RIO 0-39) (2) Rural (RIO >=40) If rurality is unknown → set to (2) rural	PCCF and Census
	Same	Immigrant Status	(1) Immigrant (2) Canadian Born	IRCC
	Same	ODB Eligibility	--	ODB
	Same	Maternal BMI	--	BORN
	At index pregnancy and in 2 year look back period	Obese	Yes, if maternal BMI ≥ 30 or OHIP billing code for obesity (dxcode=278) in 2-year lookback prior to estimated date of conception.	BORN and OHIP
	At the index pregnancy	Smoking	--	BORN
	Same	Substance Use	--	BORN
	Same	Alcohol Use	--	BORN
Pregnancy Characteristics and Outcomes	At the index pregnancy	Parity	--	BORN
	Same	Number of fetuses	--	BORN
	Same	Gestational age at delivery	--	BORN
	Same	Mode of delivery	--	BORN
	Same	Stillbirth	--	BORN
	Incident from $20^{0/7}$ weeks gestation till 42 days postpartum	Modified SMM Index[a]	- Placenta previa with hemorrhage and red cell transfusion: O44.1 + DAD Red blood cell transfusion indicator = 1 - Placental abruption with coagulation defect: O45.0 - Antepartum hemorrhage with coagulation defect: O46.0 - Intrapartum hemorrhage with coagulation defect: O67.0 - Intrapartum hemorrhage with red cell transfusion: O67 + DAD Red blood cell transfusion indicator = 1	BORN, DAD, NACRS, OHIP

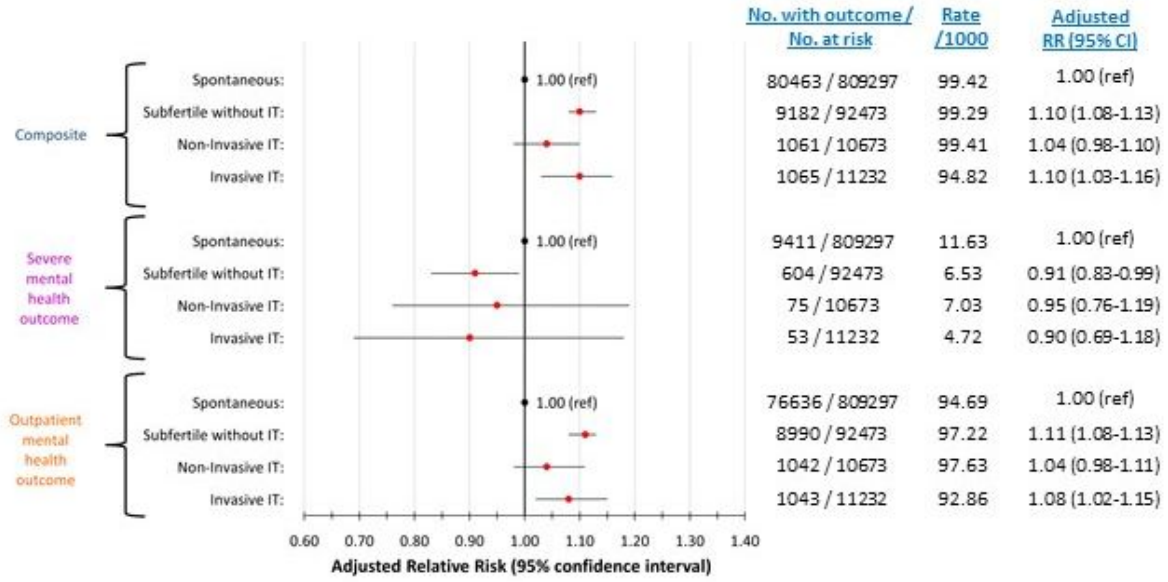
Assessment	Timing	Disease or procedure or condition	Applicable codes	Data Sources
			- Postpartum hemorrhage with red cell transfusion, procedures to the uterus or hysterectomy: O72 + any of the following: • DAD Red blood cell transfusion indicator = 1, or • (1.RM.13*, 1.KT.51*, 5.PC.91.LA* or 5.PC.91.HV*) + DAD Red blood cell transfusion indicator = 1, or • (5.MD.60.RC*, 5.MD.60.RD*, 5.MD.60.KE*, 5.MD.60.CB* or 1.RM.89.LA*), or • 1.RM.87.LA-GX* NOTE: 1.RM.89.LA* is included only if codes 1.PL.74*, 1.RS.74* or 1.RS.80* are NOT also present - Curettage with red cell transfusion: (5.PC.91.GA*, 5.PC.91.GC* or 5.PC.91.GD*) + DAD Red blood cell transfusion indicator = 1 - Complications of obstetric surgery and procedures: O75.4 - Evacuation of incisional hematoma with RBC transfusion: 5.PC.73.JS* + DAD Red blood cell transfusion indicator = 1 - Reclosure of caesarean wound with RBC transfusion: (5.PC.80.JM*, 5.PC.80.JH*) + DAD Red blood cell transfusion indicator = 1 - Procedures to the uterus with RBC transfusion: (1.RM.13*, 1.KT.51*, 5.PC.91.LA*, 5.PC.91.HV*) + DAD Red blood cell transfusion indicator = 1 - Caesarean hysterectomy, hysterectomy using an open approach: 5.MD.60.RC*, 5.MD.60.RD*, 5.MD.60.KE*, 5.MD.60.CB*, 1.RM.89.LA* (exclude if 1.PL.74*, 1.RS.74* or 1.RS.80* code also present), 1.RM.87.LAGX* - Obstetric shock: O75.1, R57, T80.5 or T88.6 - Rupture of the uterus with red cell transfusion, procedures to the uterus or hysterectomy: (O71.0 or O71.1) + any of the following: • DAD Red blood cell transfusion indicator = 1, or • (1.RM.13*, 1.KT.51*, 5.PC.91.LA* or 5.PC.91.HV*) + DAD Red blood cell transfusion indicator = 1, or • (5.MD.60.RC*, 5.MD.60.RD*, 5.MD.60.KE*, 5.MD.60.CB* or 1.RM.89.LA*), or • 1.RM.87.LA-GX* NOTE: 1.RM.89.LA* is included only if codes 1.PL.74*, 1.RS.74* or 1.RS.80* are NOT also present - Acute fatty liver with red cell transfusion or plasma transfusion: O26.6 + (DAD Red blood cell transfusion indicator = 1 or Plasma transfusion indicator = 1) - Sickle-cell anemia with crisis: D57.0 - Severe pre-eclampsia or HELLP syndrome: O14.1 or O14.2 - Eclampsia: O15 - Maternal ICU admission: DAD Special care unit = ‘10’, ’20’, ’25’, ’30’, ’35’, ’40’, ’45’, ’60’ or ’80’ - Repair of bladder, urethra, or intestine: 5.PC.80.JR*, 1.NK.80*, 1.NM.80*	

Assessment	Timing	Disease or procedure or condition	Applicable codes	Data Sources
			- Puerperal sepsis: O85 - Septicemia during labour: O75.3 - Obstetric embolism: O88 - Disseminated intravascular coagulation: D65 - Assisted ventilation through endotracheal tube: 1.GZ.31.CA-ND* - Assisted ventilation through tracheostomy: 1.GZ.31.CR-ND* - Cardiomyopathy, cardiac arrest and resuscitation, myocardial infarction, pulmonary edema and heart failure: O74.2, O89.1, O90.3, I21, I22, I42, I43, I46, I49.0, I50, J81, 1.HZ.09 or 1.HZ.30 - Acute renal failure: O90.4, N17, N19 or N99.0 Dialysis: 1.PZ.21* - Subarachnoid and intracranial hemorrhage, cerebral infarction: I60, I61, I62, I63, or I64 - Cerebral venous thrombosis in pregnancy: O22.5 - Cerebral venous thrombosis in the puerperium: O87.3 - Cerebral edema or coma: G93.6 or R40.2 - Pulmonary, cardiac, and CNS complications of anesthesia during pregnancy, labour, delivery or the puerperium: O29.0, O29.1, O29.2, O89.0, O89.1, O89.2, O74.0, O74.1, O74.2 or O74.3 - Status asthmaticus: J45.01, J45.11, J45.81 or J45.91 - Adult respiratory distress syndrome: J80 Hepatic failure: K71 or K72 - Acute abdomen: K35, K37, K65, N73.3 or N73.5 - Surgical or manual correction of inverted uterus for vaginal births only: 5.PC.91.HQ* or 5.PC.91.HP*, restricted to vaginal births (i.e., absence of caesarean 5.MD.60*) - Status epilepticus: G41	
Comorbidities [a]	Consider all hospitalizations, emergency room visits and physician visits that occurred during pregnancy (<$20^{0/7}$ weeks gestational age) and 2 years pre-conception.	Cardiovascular disease	Chronic congestive heart failure: • ICD9-428 • BORN=MAT_PRE_EXIST_HEALTH_COND_ID • 1016610 = Cardiovascular \ Acquired Heart Disease • NIDAY=MATHP16=1 • ICD10-I50 Congenital heart disease: • ICD9-745-747 • ICD10-Q20-Q26 Pulmonary hypertension: • ICD10-I27.0, I27.2 Coronary artery disease: • ICD9-410, 412, 413, 429 • ICD10- I20, I21, I24, I25.0, I25.1, I51.3, 1HZ80, 1IJ50, 1IJ55, 1IJ57, 1IJ76, 1IJ80, 1IK80, 1IK87, 1IL35, 2IL70, 3IP10	BORN, DAD, NACRS, OHIP

Assessment	Timing	Disease or procedure or condition	Applicable codes	Data Sources
			Cardiac dysrhythmia: • ICD9-427 • ICD10- I48, I47.2, I49.0 Chronic rheumatic heart diseases: • ICD9-398 • ICD10- I05-I09 Previous stroke: • ICD9-432, 436, 437 • ICD10-G46, I63.0-I66.9, I67.2, I67.8 Previous myocardial infarction: • ICD9-410 • ICD10-I21	
	Same	Dyslipidemia	• ICD9-272 • ICD10-E78	DAD, NACRS, OHIP
	Same	Sickle cell disease	• ICD10- D57.1, D57.2, D57.3, D57.8	DAD, NACRS, OHIP
	Same	Systemic lupus erythematosus	• BORN=MAT_PRE_EXIST_HEALTH_COND_ID =1016540 • NIDAY=MATHP19=1 • ICD10-M32, M32.0, M32.1 (I39.-, I32.8, N08.5, N16.4, J99.1), M32.8	BORN, DAD, NACRS, OHIP
	Same	HIV	Incident or Prevalent case in HIV database	HIV
	Same	Chronic hypertension	Incident or Prevalent case in HYPER database	HYPER
	Same	Diabetes mellitus	Incident or Prevalent case in ODD database	ODD
	Same	Liver disease	• ICD9-571, 573 • ICD10- K70-K77	DAD, NACRS, OHIP
	Same	Asthma	• BORN=MAT_PRE_EXIST_HEALTH_COND_ID =1017330 • NIDAY=MATHP2=1 • ICD9-493 • ICD10- J45-J46	BORN, DAD, NACRS, OHIP

[a]https://obgyn.onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2F1471-0528.16216&file=bjo16216-sup-0002-TableS1-S3.pdf. Removed the mortality codes: O95, O97, R96, R97, R98 and R99. Removed: Acute psychosis: F53.1 or F23

eFigure 1. Risk of a maternal mental illness outcome within 1 year after birth in relation to type of pregnancy conception, additionally including women with a prior history of mental illness. Shown is the composite mental health outcome of any severe mental health or outpatient mental health encounter (upper); the severe mental health outcome (middle); and the outpatient mental health outcome (lower), as described in eTable 3.[a]



[a]Relative risks are adjusted for maternal age, income quintile, rurality, immigrant status, parity, chronic hypertension, diabetes mellitus, and obesity.

RR relative risk; CI confidence interval; IT infertility treatment.