Psychiatric morbidity and cervical cancer screening: a population-based case-cohort study

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Number of characters in title: 89
Number of words in abstract: 266
Number of words in body of manuscript: 2467
Number of references: 31
Number of figures: 2
Number of tables: 5 (+2 supplementary)

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Funding Statement
This study is funded by the Innovations Strengthening Primary Healthcare Research Program (Applied Health Research Question Funding). Views expressed do not necessarily reflect those of the province.

Declaration of Competing Interest(s)
ML, WS, JCM, MO, and JE report no potential conflicts of interest.

Abstract

Background: Cervical cancer screening reduces disease-specific mortality. This study aimed to estimate whether common and severe psychiatric disorders are associated with disparities in screening rates in the general population.

Methods: This was a retrospective population-based matched case-cohort study using linked provincial administrative databases comparing cervical cancer screening in community-dwelling women in Ontario, Canada, aged 19 to 69, with a diagnosis of bipolar disorder or schizophrenia (n=119,948) to women without a psychiatric history (n=1,125,509) between 2003 and 2015. We used conditional logistic regression to estimate the relative likelihood of undergoing screening over the follow-up period (median follow-up of 12.5 years) and Cox proportional hazards regression to compare time to receive screening. Poisson regression was used to compare the rate ratios of screening between the two groups. Multivariable models were adjusted for relevant clinical comorbidities.

Results: Women with a diagnosis of bipolar disorder or schizophrenia were 36% less likely to be screened (OR=0.64, 95% CI [0.64-0.65], p<0.0001) than those without a psychiatric history in adjusted models over a median follow-up of 12.5 years, and also took longer to receive their first screen after cohort entry (median 18.98 months vs. 16.63 months; χ^2=3718.2, p<.0001). Women with bipolar disorder or schizophrenia were screened less frequently than those without (median 6.16 vs. 4.69 years per screen; RR=0.85, 95% CI [0.84-0.85], p<0.0001).

Interpretation: Women with bipolar disorder or schizophrenia were less likely to undergo cervical cancer screening, their screening was delayed, and they were screened at a lower rate compared to women with no psychiatric history. This practice gap suggests a need to address barriers to cervical cancer screening in women living with bipolar disorder or schizophrenia.

Introduction

In Canadian women, cervical cancer-related mortality has fallen by 60% between 1977 and 2006 – a decline largely attributable to the implementation of provincial screening programs that facilitate the detection and treatment of precancerous lesions in early stages of disease[1,2]. The 2005 Ontario Cancer Screening Program (OCSP) guidelines recommended that cervical cytology screening be initiated within 3 years of first vaginal sexual activity[3]. Following 3 consecutive annual negative Papanicolaou tests, screening was recommended every 3 years[3]. These guidelines were further updated in 2012, specifying that sexually active women >21 should be screened every 3 years, and removing the criteria for 3 consecutive annual tests[4]. Adherence to these guidelines in the general population has been moderate, with 65% of eligible Ontario women receiving a screen between 2009 and 2011[5]. However, numerous studies have suggested that women with common and severe psychiatric disorders, including schizophrenia and bipolar disorder, face significant barriers to general preventative healthcare utilization[6,7] including the uptake of cancer screening services, and therefore that rates of cervical cancer screening may be significantly lower in this subpopulation[1,8].

Previous reports show substantive variability in their estimates of these proposed disparities[1,9-10], and many have been limited by selection bias, misclassification bias, inadequate follow-up duration, or otherwise non-generalizable data[8,10]. Accordingly, tailored cervical cancer screening guidelines for this vulnerable population have not been established. Meanwhile, individuals with severe psychiatric conditions continue to suffer a 30% higher cancer case fatality rate than those without, despite comparable rates of disease incidence[11]. In light of this issue, population-based estimates of cervical cancer screening rates are required to accurately quantify potential disparities in screening practices and to promote the development of targeted interventions for

women with severe psychiatric morbidity[8,10]. The present study aimed to compare the likelihood and frequency of cervical cancer screening in community-dwelling women with and without a history of bipolar disorder or schizophrenia from the general population in Ontario, Canada.

Methods

Study Design and Data Sources

This was a retrospective matched case-cohort study using linked provincial administrative databases from Ontario, Canada, which has a population of approximately 14 million people[12]. All data were obtained from IC/ES and individuals were identified across databases using unique encoded patient identifiers. Data from the Canadian Institute for Health Information Discharge Abstract Database (CIHI-DAD), National Ambulatory Care Reporting System (NACRS), and Ontario Health Insurance Plan (OHIP) database, which capture universally-available government-funded coverage for all hospital and emergency department services, physician visits, and diagnostic tests, combined with the Ontario Mental Health Reporting System Metadata (OMHRS), were used to identify bipolar disorder and schizophrenia diagnoses, using the International Classification of Diseases (ICD), 10th revision (Supplemental Table 1). Demographic information was obtained from the Ontario Registered Persons Database (RPDB), and data on prescription history (for those 65 and older) were obtained from the Ontario Drug Benefit Claims database. Finally, the Ontario Breast Screening Program (OBSP) database was used for outcome assessment to identify all cervical cancer screening procedures conducted during the study period.

The dataset from this study is held securely in coded form at IC/ES. While data sharing agreements prohibit IC/ES from making the dataset publicly available, access may be granted to

those who meet pre-specified 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 programs may rely upon coding templates or macros that are unique to IC/ES. This study was approved by the Research Ethics Board of Sunnybrook Health Sciences Centre. The details of this study are reported in accordance with STROBE and RECORD guidelines[13, 14].

Study Population and Exposure

Community-dwelling women aged 19 to 69 with a prior diagnosis of bipolar disorder or schizophrenia between 2003 and 2012 were identified from the Ontario population and followed for the primary outcome of cervical cancer screening until the age of 70 (when screening is no longer recommended), death, loss of OHIP eligibility, or termination of follow-up on December 31st, 2015. Exclusions included an invalid OHIP number, a history of cervical cancer, or hysterectomy prior to July 1st of the year of cohort entry.

The exposure was a prior diagnosis of bipolar disorder or schizophrenia, defined using the following algorithm: 1) a discharge diagnosis of bipolar disorder or schizophrenia from DAD/OMHRS using ICD10 diagnostic codes (Supplemental Table 1) within a 10-year period prior to entry into the study cohort, or 2) an OHIP diagnostic billing code of bipolar disorder or schizophrenia, with accompanying specialty code for psychiatry (19) within a 12 month period within 10 years prior to cohort entry, or 3) two OHIP diagnostic billing codes of bipolar disorder or two OHIP billing codes for schizophrenia within a 12 month period within 10 years prior to cohort entry. The number of individuals with the exposure was 119,948.

Women with bipolar disorder or schizophrenia were matched at a ratio of up to 10:1 to community-dwelling women from the general Ontario population on age, geographic Local Health Integration Network (LHIN) region, Charlson Comorbidity Index (CCI) score, income quintile, urban or rural residence, and Adjusted Diagnostic Group classification using nearest-neighbour matching[15]. The number of individuals without the exposure was 1,125,509.

Outcome

The outcome was a documented screen for cervical cancer defined using OHIP procedure codes (Supplemental Table 1)

Statistical Analysis

Descriptive statistics were generated to characterize the study cohort with respect to all demographic and clinical variables. Baseline characteristics between women with and without the exposure were compared using t-tests and Chi-square tests. Incidence rates of cervical cancer screening per 3 person-years were determined to assess adherence to Ontario cervical cancer screening interval guidelines.

Conditional logistic regression was used to estimate adjusted odds ratios (OR [95% CI]) of cervical cancer screening likelihood in women with a history of bipolar disorder or schizophrenia to those without. Poisson regression was used to compare adjusted rate ratios (RR [95% CI]) of screening between these groups, and Cox proportional hazards regression was used to estimate adjusted hazard ratios (HR [95% CI]) of time to screening associated with major psychiatric history. These parameters were calculated using data within 3 years of cohort entry, and for all available follow-up, with a maximum interval of 12 years. Finally, a log-rank test was used to compare time to first screen. All multivariable models were adjusted for potential clinical

confounders including vascular disease, hypertension, diabetes, dyslipidemia, respiratory diseases, arthritis, Crohn's disease/ulcerative colitis, osteoporosis, obesity, pelvic inflammatory diseases, and polycystic ovarian syndrome (PCOS), each of which may be specifically more likely to occur in women with psychiatric morbidity than in those without, and may affect overall medical burden and/or propensity to receive cervical screening.

Depressive disorders are common psychiatric comorbidities[16, 17], and they have been independently associated with reduced healthcare utilization [18-21]; however, inconsistent usage of diagnostic codes for MDD can result in misclassification bias[22]; therefore, suspected major depressive disorder (MDD; ICD10 code F33.x) were not included in the psychiatric disorders group. Further, they were excluded in a sensitivity analysis to determine if suspected MDD affected observed screening rates and associations. All statistical analyses were performed using SAS, Version 14.2.

Results

Baseline Characteristics

The cohort was comprised of 1,245,457 Ontario women aged 19 to 69 upon cohort entry. Table 1 shows baseline characteristics for the 119,948 women in the exposed group with bipolar disorder or schizophrenia and the 1,125,509 matched women in the unexposed group. The proportion of women in the exposed group who were matched at a 10:1 ratio was 87.4%; the remaining 12.6% were matched at an intermediate ratio ranging between 1:1 and 9:1. The distribution of age in the exposed group (median 42 years, IQR 30-52) and the unexposed group (median 42 years, IQR 29-52) was very similar. Women with bipolar disorder or schizophrenia had a similar income and geographic distribution compared to women without these diagnoses across Ontario. The

prevalence of vascular diseases, hypertension, diabetes, dyslipidemia, respiratory diseases, arthritis, osteoporosis, obesity, pelvic inflammatory diseases, and PCOS differed significantly between these groups (p<0.0003).

Likelihood of screening

Overall, within the first 3 years of cohort entry, 57.7% of women underwent cervical cancer screening (50.4% in the schizophrenia or bipolar disorder group, and 58.5% in the unexposed group). The adjusted OR for having received one screen within the first 3 years was 0.71 [0.70-0.72], p<0.0001 (Table 2). Throughout the entire follow-up period (median 12.5 years), 76.9% of women received at least one screen (70.2% in the exposure group and 77.7% in the unexposed group), and the adjusted OR for having received at least one screen was 0.64 [0.64-0.65], p<0.0001 (Table 2).

Screening rates

The rate of screening within the first 3 years was 0.27 [0.27-0.28] screens per 3 person-years in women with bipolar disorder or schizophrenia and 0.36 [0.36-0.37] in those without (RR=0.80, [0.80-0.81]) (Table 3, 4).

Over the entire follow-up period, the rate of screening in women with bipolar disorder or schizophrenia was 0.49 [0.48-0.49] screens per 3 person-years (i.e. on average, screening occurred every 6.16 years), and 0.64 [0.64-0.64] in those without (i.e. screening every 4.69 years) (RR=0.85, [0.84-0.85]) Table 3, 4).

Time to screen

In women who were screened at least once throughout the follow-up period, those with bipolar disorder or schizophrenia were less likely to be screened first after cohort entry than those without (HR=0.80, [0.80-0.81], p<0.0001; Table 5; Fig. 1A). Specifically, women with the exposure were screened a median of 18.98 months after cohort entry, whereas those without the exposure were screened after a median of 16.63 months (log-rank test χ^2=3718.22, p<0.0001). Since a greater proportion of women with the exposure did not undergo screening at any point during the study period, the median length of time to either first screening after cohort entry or termination of follow-up was significantly longer in women with a psychiatric history (30.70 months) relative to those without (23.40 months).

Finally, in those who were screened prior to cohort entry (exposed n=54,180; unexposed n=489,142), the average time since last screen prior to cohort entry was significantly longer in women with schizophrenia or bipolar disorder than those without (median 4.49 years vs. 4.11 years, p<0.0001).

Sensitivity analysis of women without MDD comorbidity

Among all women in the overall cohort, 6.94% (n=86,475) had a history of comorbid depressive illness (7.10% of exposed, and 6.95% of unexposed; Supplemental Table 2). After excluding these women, the likelihood of screening remained lower in women with a psychiatric history both in the first 3 years (OR=0.72, [0.71-0.73], p<.0001) and over all available follow-up (OR=0.65, [0.64-0.66], p<0.0001). Similarly, the adjusted HR for time to screening remained significantly lower 0.81 [0.80-0.82], p<0.0001; (Table 5, Fig. 1B).

Interpretation

In women with bipolar disorder or schizophrenia, we report a 36% reduced likelihood of receiving at least one cervical cancer screen, and a 15% lower rate ratio of screening over the 12-year follow-up period, translating into an overall adherence to triannual screening recommendations that was roughly 24% lower. The time to first screen after cohort entry was greater in women with these psychiatric conditions compared to matched unexposed cases, further confirming a reduced propensity for cervical cancer screening. The groups were matched for important demographics, and the models were adjusted for vascular and other clinical comorbidities that may affect complexity of care or screening rates directly. While other chronic conditions, notably vascular and metabolic, were more prevalent in the women with bipolar disorder or schizophrenia, their presence did not account for the disparity in screening. In adjusted models, the independent effect of bipolar disorder or schizophrenia was similar to those of respiratory diseases, arthritis, osteoporosis and obesity, smaller than that of vascular diseases, and larger than the effects of hypertension, diabetes, or dyslipidemia.

The findings confirm and quantify a preventative health service utilization gap between Ontario women with and without severe psychiatric disorders, and contribute to a growing body of literature that identifies mental health conditions as barriers to the uptake of cervical cancer screening[1, 8, 10, 23-25]. Notably, one study of women with and without schizophrenia in Manitoba, identified a comparable magnitude of disparity (30%) in the likelihood of receiving cervical screening[1]. A recent investigation by Abrams et al.[9] reported a higher frequency of cervical cancer screening in women with psychosis, bipolar disorder, or mania. In contrast to the present study, those cross-sectional data were drawn from an independent insurer-paid model with

exclusively low-income subjects, suggesting that demographics and care model may affect screening rates.

Further research might focus on identifying specific actionable barriers that could be targeted to diminish the observed disparity. Prior studies have suggested that both patient and physician efforts to address acute psychiatric symptoms may supersede indications for preventative procedures[26,27]. For women with psychosis-related delusions and hallucinations, the purpose of screening or treatment may be unclear, and fear or distrust towards primary care physicians and invasive procedures may result in avoidance of care[6-7, 25]. The values and attitudes of physicians can also play a role, and stigma can translate into disparities in screening and other services[24,28]. Evidence suggests that distributing targeted letters of invitation, offering telephone counseling, addressing financial barriers, and focusing on continuity of care might improve uptake[25,29], but effectiveness of these methods has yet to be investigated specifically in women with severe psychiatric disorders[30].

Limitations

Although the population-based nature, utilization of public health records, and relatively long follow-up are notable strengths of the present work, we also acknowledge several limitations. Ontario residents have access to universal health care services under OHIP, limiting the generalizability of our findings to populations under other models of care; however, the results provide estimates that are less likely to reflect differences in insurance availability, unemployment and socioeconomic status. The current analysis matched on LHN, to further account for geographical and to some extent socioeconomic barriers, but we were unable to control for several individual sociodemographic factors that have been linked to underutilization

of healthcare services, including household income, cultural differences and comorbid substance use disorders[31]. As a further limitation, estimates for MDD alone were not ascertained; however, the observed differences associated with bipolar disorder or schizophrenia remained consistent in sensitivity analyses excluding women with a diagnostic code for MDD.

Conclusion

The likelihood of cervical cancer screening was 36% lower in women who suffered from schizophrenia or bipolar disorder compared to carefully matched women without these conditions. Because screening is critical for the early detection and treatment of cervical cancer, this disparity is likely to result in increased morbidity and mortality, warranting the attention of patients, their care providers, and health professionals. Family physicians may want to audit their practices to identify their rate of cervical cancer screening in this defined population and adopt quality improvement plans to target this screening disparity. Psychiatrists, social workers, and mental health outreach professionals should advocate for these patients to have primary care access and encourage them to visit family physicians for preventative care screening. Future studies might stratify analyses based on sociodemographic factors to identify subgroups that may be at the highest risk, and to identify specific barriers to address in order to mitigate underutilization.

Acknowledgements

WS gratefully acknowledges support from the Department of Psychiatry, Sunnybrook Health Sciences Centre, and from the Department of Pharmacology & Toxicology, University of Toronto.

References

1. Martens PJ, Chochinov HM, Prior HJ, Fransoo R, Burland E. Are cervical cancer screening rates different for women with schizophrenia? A Manitoba population-based study. Schizophrenia Research. 2009 May; 113(1):101-106.

2. Kitchener HC, Castle PE, Cox JT. Chapter 7: Achievements and limitations of cervical cytology screening. Vaccine. 2006 Aug; 24(Suppl 3):S3/63-70.

3. McLachlin CM, Mai V, Murphy J, Fung Kee Fung M, Chambers A, and members of the Cervical Screening Guidelines Development Committee of the Ontario Cervical Screening Program and the Gynecology Cancer Disease Site Group of Cancer Care Ontario. Cervical screening: practice guideline report. Program in evidence-based care: a Cancer Care Ontario program. 2005 May.

4. Murphy J, Kennedy EB, Dunn S, McLachlin CM, Kee Fung MF, Gzik D, et al. Cervical screening: a guideline for clinical practice in Ontario. Journal of Obstetrics and Gynaecology Canada. 2012 May; 34(5), 453–458.

5. Cancer Care Ontario [Internet]. Ontario; c2019. Cervical cancer screening rates below provincial target and vary with neighbourhood income; 2014 Feb [cited 2019 Dec 20]. Available from https://www.cancercareontario.ca/en/cancer-facts/cervical-cancer-screening.

6. Owen C, Jessie D, De Vries Robbé M. Barriers to cancer screening amongst women with mental health problems. Health Care Women Int. 2002 Sep-Nov; 23(6–7):561–6.

7. Kahn LS, Fox CH, Krause-Kelly J, Berdine DE, Cadzow RB. Identifying barriers and facilitating factors to improve screening mammography rates in women diagnosed with mental illness and substance use disorders. Women & Health. 2005 Feb; 42(3):111–26.

8. Howard LM, Barley EA, Davies E, Rigg A, Lempp H, Rose D, et al. Cancer diagnosis in people with severe mental illness: practical and ethical issues. The Lancet Oncology. 2010 Aug; 11(8):797-804.

9. Abrams MT, Myers CS, Feldman SM, Boddie-Willis C, Park J, McMahon RP, et al. Cervical cancer screening and acute care visits among Medicaid enrollees with mental and substance use disorders. Psychiatr Serv. 2012 Aug; 63(8):815-822.

10. James M, Thomas M, Frolov L, Riano NS, Vittinghoff E, Schillinger D, et al. Rates of cervical cancer screening among women with severe mental illness in the public health system. Psychiatric Services. 2017 Aug; 68(8), 839–842.

11. Kisely S, Crowe E, Lawrence D. Cancer-related mortality in people with mental illness. JAMA Psychiatry. 2013 Feb; 70(2):209–217.

12. Government of Canada SC [Internet]. Population by year, by province and territory (Number) 2017. [cited 2018 Oct 18]. Available from http://www.statcan.gc.ca/tables-tableaux/sum-som/l01/cst01/demo02a-eng.htm.

13. Von Elm E, Altman DG, Egger M, Pocock SJ, Gøtzsche PC, Vandenbroucke JP, et al. The strengthening the reporting of observational studies in epidemiology (STROBE) statement: guidelines for reporting observational studies. J Clin Epidemiol. 2008 Apr; 61(4):344-9.

14. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. (2015). The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. 2016 Oct. PLOS Medicine 12(10): e1001885.

15. Bergstralh EJ, Kosanke, JL. Computerized matching of cases to controls. Rochester, MN: Mayo Foundation 1995; Technical Report #56.

16. Buckley PF, Miller BJ, Lehrer DS, Castle DJ. Psychiatric comorbidities and schizophrenia. Schizophrenia Bulletin. 2009 Mar; 35(2):383-402.

17. Gozdzik-Zelazny A, Borecki L, Pokorski M. Depressive symptoms in schizophrenic patients. European Journal of Medical Research. 2011 Dec; 16(12):549-552.

18. Lo C, Calzavara A, Kurdyak P, Barbera L, Shepherd F, Zimmermann C, et al. Depression and use of health care services in patients with advanced cancer. Canadian Family Physician. 2013 Mar; 59(3):e168-e174

19. Beaulieu T, Ti L, Milloy M-J, Nosova E, Wood E, Hayashi K. Major depressive disorder and access to health services among people who use illicit drugs in Vancouver, Canada. Substance Abuse Treatment, Prevention, and Policy. 2018 Jan; 13(1):3.

20. Patten SB, Williams JV, Lavorato DH, Eliasziw M. The effect of major depression on participation in preventive health care activities. BMC Public Health. 2009 Mar; 9:87.

21. Price MA, Butow PN, Charles M, Bullen T, Meiser B, McKinley JM, et al. Predictors of breast cancer screening behavior in women with a strong family history of the disease. Breast Cancer Res Treat. 2010 Nov; 124(2):509-19.

22. Zimmermann P, Brückl T, Nocon A, et al. Heterogeneity of DSM-IV major depressive disorder as a consequence of subthreshold bipolarity. Arch Gen Psychiatry. 2009 Dec; 66(12):1341–1352.

23. Woodhead C, Cunningham R, Ashworth M, Barley E, Stewart RJ, Henderson MJ. Cervical and breast cancer screening uptake among women with serious mental illness: a data linkage study. BMC Cancer. 2016 Oct; 16:819.

24. Lofters AK, Mark A, Taljaard M, Green ME, Glazier RH, & Dahrouge S. Cancer screening inequities in a time of primary care reform: A population-based longitudinal study in Ontario, Canada. BMC Family Practice. 2018 Aug; 19(1), 1–14.

25. Tilbrook D, Polsky J, Lofters A. Are women with psychosis receiving adequate cervical cancer screening? Canadian Family Physician. 2010 Apr; 56(4):358-363.

26. Choconta-Piraquive LA, Alvis-Guzman N, De la Hoz-Restrepo F. How protective is cervical cancer screening against cervical cancer mortality in developing countries? The Colombian case. BMC health services research. 2010 Sept; 10:270.

27. Ross LE, Vigod S, Wishart J, Waese M, Spence JD, Oliver J et al. Barriers and facilitators to primary care for people with mental health and/or substance use issues: a qualitative study. BMC Family Practice, 2015 Oct; 16(1), 1–13.

28. Clifton A, Burgess C, Clement S, Ohlsen R, Ramluggin P, Sturt J, et al. Influences on uptake of cancer screening in mental health service users: a qualitative study. BMC Health Services Research, 2016 Jul; 16(1), 1–13.

29. Black ME, Yamada J, Mann V. A systematic literature review of the effectiveness of community-based strategies to increase cervical cancer screening. Canadian Journal of Public Health. 2002 Sep-Oct; 93(5), 386–93.

30. Barley EA, Borschmann RD, Walters P, Tylee A. Interventions to encourage uptake of cancer screening for people with severe mental illness. Cochrane Database of Systematic Reviews. 2016 Sep; 9.

31. Kelly DL, Myers CS, Abrams MT, Feldman S, Park J, McMahon RP, et al. The Impact of Substance Abuse on Osteoporosis Screening and Risk of Osteoporosis in Women with Psychotic Disorders. Osteoporosis International, 2011 Apr; 22(4):1133-1143.

Appendix

Table 1. Baseline demographics and health characteristics for females in the general Ontario population aged 19-69 between July 2003 and July 2012, comparing those with bipolar disorder or schizophrenia to those without.

Characteristic	Overall	Exposure	Matched	SD	p-value
	N=1,245,457	N=119,948	N=1,125,509		
Demographics					
Age (Median, IQR)	42 (29-52)	42 (30-52)	42 (29-52)	0.02	<.0001
Income quintile, n (%)					
1 - Lowest	298,115 (23.9%)	29,896 (24.9%)	268,219 (23.8%)	0.03	<.0001
2	265,181 (21.3%)	25,548 (21.3%)	239,633 (21.3%)	<.001	
3	236,935 (19.0%)	22,443 (18.7%)	214,492 (19.1%)	0.01	
4	224,190 (18.0%)	21,186 (17.7%)	203,004 (18.0%)	0.01	
5 - Highest	219,010 (17.6%)	20,601 (17.2%)	198,409 (17.6%)	0.01	
Geographic Data					
Urban Residence, n (%)	1,131,150 (90.9%)	108,389 (90.3%)	1,022,761 (90.9%)	0.01	<.0001
Rural Residence, n (%)	113,879 (9.1%)	11,496 (9.6%)	102,383 (9.1%)	0.02	
Charlson Comorbidity Index n(%)					
Missing	1,029,649 (82.7%)	89,235 (74.4%)	940,414 (83.6%)	0.23	<.0001
0	178,386 (14.3%)	24,961 (20.8%)	153,425 (13.6%)	0.19	
1	18,447 (1.5%)	3,451 (2.9%)	14,996 (1.3%)	0.11	
2	10,749 (0.9%)	1,299 (1.1%)	9,450 (0.8%)	0.02	
3+	8,226 (0.7%)	1,002 (0.8%)	7,224 (0.6%)	0.02	
Adjusted Diagnostic Group, n (%)					
0	32,505 (2.6%)	3,011 (2.5%)	29,494 (2.6%)	0.01	<.0001
1-3	137,524 (11.0%)	12,762 (10.6%)	124,762 (11.1%)	0.01	

4-6	318,091 (25.5%)	29,369 (24.5%)	288,722 (25.7%)	0.03	
7-9	371,691 (29.8%)	34,265 (28.6%)	337,426 (30.0%)	0.03	
10+	385,646 (31.0%)	40,541 (33.8%)	345,105 (30.7%)	0.07	
Comorbidities, n (%)				χ^2	
Vascular Diseases	15,082 (1.21)	1,898 (1.58)	13,184 (1.17)	153.04	<.0001
Hypertension	44,240 (3.55)	3,720 (3.10)	40,520 (3.60)	78.72	<.0001
Diabetes	18,251 (1.47)	2,173 (1.81)	16,078 (1.43)	110.18	<.0001
Dyslipidemia	4,504 (0.36)	618 (0.52)	3,886 (0.35)	86.90	<.0001
Respiratory Diseases	8,390 (0.67)	1,740 (1.45)	6,650 (0.59)	1197.55	<.0001
Arthritis	2,547 (0.20)	302 (0.25)	2,245 (0.20)	14.53	.0001
Crohn's/Ulcerative Colitis	2,135 (0.17)	198 (0.17)	1,937 (0.17)	0.31	.5759
Osteoporosis	724 (0.06)	138 (0.12)	586 (0.05)	74.02	<.0001
Obesity	4,646 (0.37)	942 (0.79)	3,704 (0.33)	607.13	<.0001
Pelvic Inflammatory Diseases	870 (0.07)	115 (0.10)	755 (0.07)	12.87	.0003
Polycystic Ovarian Syndrome	126 (0.01)	27 (0.02)	99 (0.01)	20.15	<.0001

Table 2. Odds ratios from conditional logistic regression of screening likelihood within the first 3 years and over all available follow-up (2003-2015) in psychiatric subgroup relative to non-psychiatric subgroup, adjusted for comorbidities

Variables	Adjusted OR (95% CI) Within the first 3 years	Adjusted OR (95% CI) All follow-up
Exposure	0.71 (0.70-0.72) (p<0.0001)	0.64 (0.64-0.65) (p<0.0001)
Vascular Diseases	0.47 (0.45-0.49) (p<0.0001)	0.45 (0.43-0.46) (p<0.0001)
Hypertension	0.92 (0.90-0.94) (p<0.0001)	0.92 (0.90-0.95) (p<0.0001)
Diabetes	0.73 (0.71-0.76) (p<0.0001)	0.73 (0.70-0.76) (p<0.0001)
Dyslipidemia	0.86 (0.80-0.93) (p<0.0001)	0.91 (0.84-0.98) (p=0.0101)
Respiratory Diseases	0.59 (0.56-0.62) (p<0.0001)	0.52 (0.49-0.55) (p<0.0001)
Arthritis	0.76 (0.70-0.84) (p<0.0001)	0.86 (0.78-0.95) (p=0.0020)
Crohn's/Colitis	0.75 (0.68-0.83) (p<0.0001)	0.77 (0.68-0.86) (p<0.0001)
Osteoporosis	0.52 (0.43-0.63) (p<0.0001)	0.43 (0.35-0.51) (p<0.0001)
Obesity	0.57 (0.53-0.61) (p<0.0001)	0.54 (0.50-0.58) (p<0.0001)
Pelvic Inflammatory Diseases	0.66 (0.56-0.77) (p<0.0001)	0.58 (0.49-0.69) (p<0.0001)
Polycystic Ovarian Syndrome	0.93 (0.63-1.38) (p=0.7221)	1.04 (0.60-1.80) (p=0.9043)

Table 3. Incidence of screening and average screening frequency over the first 3 years of cohort entry and the entire follow-up period (2003-2015) for the overall cohort and by subgroup

Group	Analytical Period	Number of Screens	Person-years	Incidence (95% CI) per 3 person-years	Average Years per Screen
Overall	3 years	719,240	6,071,289	0.355 (0.355-0.356)	8.45
	All follow-up	958,249	4,615,795	0.623 (0.622-0.624)	4.82
Women with a history of psychiatric disorder	3 years	60,436	661,669	0.274 (0.272-0.276)	10.95
	All follow-up	84,288	519,348	0.487 (0.483-0.490)	6.16
Women without history of psychiatric disorder	3 years	658,804	5,409,619	0.365 (0.364-0.366)	8.22
	All follow-up	874,021	4,096,447	0.640 (0.639-0.641)	4.69

Table 4. Rate ratios from Poisson regression of cervical cancer screening rates over 3 years and over all available follow-up (2003-2015) in psychiatric subgroup relative to non-psychiatric subgroup, adjusted for comorbidities

Variables	Adjusted RR (95% CI) 3 years	Adjusted RR (95% CI) All follow-up
Schizophrenia or bipolar disorder	0.80 (0.80-0.81) (p<0.0001)	0.85 (0.84, 0.85) (p< 0.0001)
Vascular Diseases	0.66 (0.65-0.67) (p<0.0001)	0.75 (0.74, 0.76) (p< 0.0001)
Hypertension	0.95 (0.94-0.95) (p<0.0001)	0.96 (0.96, 0.97) (p< 0.0001)
Diabetes	0.87 (0.86-0.88) (p<0.0001)	0.91 (0.90, 0.92) (p< 0.0001)
Dyslipidemia	0.89 (0.86-0.92) (p<0.0001)	0.91 (0.89, 0.93) (p< 0.0001)
Respiratory Diseases	0.81 (0.80-0.83) (p<0.0001)	0.86 (0.85, 0.87) (p< 0.0001)
Arthritis	0.82 (0.79-0.84) (p<0.0001)	0.87 (0.85, 0.89) (p< 0.0001)
Crohn's/Colitis	0.94 (0.91-0.97) (p=0.0001)	0.96 (0.94, 0.98) (p< 0.0001)
Osteoporosis	0.76 (0.70-0.82) (p<0.0001)	0.82 (0.78, 0.87) (p< 0.0001)
Obesity	0.79 (0.77-0.81) (p<0.0001)	0.85 (0.83, 0.86) (p< 0.0001)
Pelvic Inflammatory Diseases	0.91 (0.86-0.97) (p=0.0031)	0.96 (0.92, 0.99) (p=0.0151)
Polycystic Ovarian Syndrome	1.03 (0.91-1.16) (p=0.6613)	1.03 (0.97, 1.10) (p=0.3239)

Table 5. Hazard ratios from Cox proportional hazards regression for time to first cervical cancer screen in the complete cohort, and in the subgroup with depressive disorders excluded, adjusted for comorbidities

Variables	Hazard Ratio	
	Complete Cohort	MDD-Excluded Subgroup
Schizophrenia or bipolar disorder	0.80 (0.80, 0.81) (p<0.0001)	0.81 (0.80, 0.82) (p<0.0001)
Vascular Diseases	0.61 (0.60, 0.63) (p<0.0001)	0.62 (0.60, 0.64) (p<0.0001)
Hypertension	0.94 (0.93, 0.96) (p<0.0001)	0.94 (0.93, 0.95) (p<0.0001)
Diabetes	0.82 (0.80, 0.84) (p<0.0001)	0.82 (0.81, 0.84) (p<0.0001)
Dyslipidemia	0.88 (0.84, 0.92) (p<0.0001)	0.87 (0.83, 0.92) (p<0.0001)
Respiratory Diseases	0.73 (0.70, 0.75) (p<0.0001)	0.72 (0.70, 0.75) (p<0.0001)
Arthritis	0.85 (0.80, 0.90) (p<0.0001)	0.84 (0.79, 0.90) (p<0.0001)
Crohn's/Ulcerative Colitis	0.85 (0.80, 0.90) (p<0.0001)	0.85 (0.80, 0.90) (p<0.0001)
Osteoporosis	0.63 (0.55, 0.72) (p<0.0001)	0.63 (0.55, 0.72) (p<0.0001)
Obesity	0.68 (0.65, 0.71) (p<0.0001)	0.69 (0.66, 0.72) (p<0.0001)
Pelvic Inflammatory Diseases	0.81 (0.73, 0.89) (p<0.0001)	0.81 (0.73, 0.89) (p<0.0001)
Polycystic Ovarian Syndrome	0.95 (0.76, 1.18) (p= 0.6826)	0.93 (0.73, 1.16) (p=0.5206)

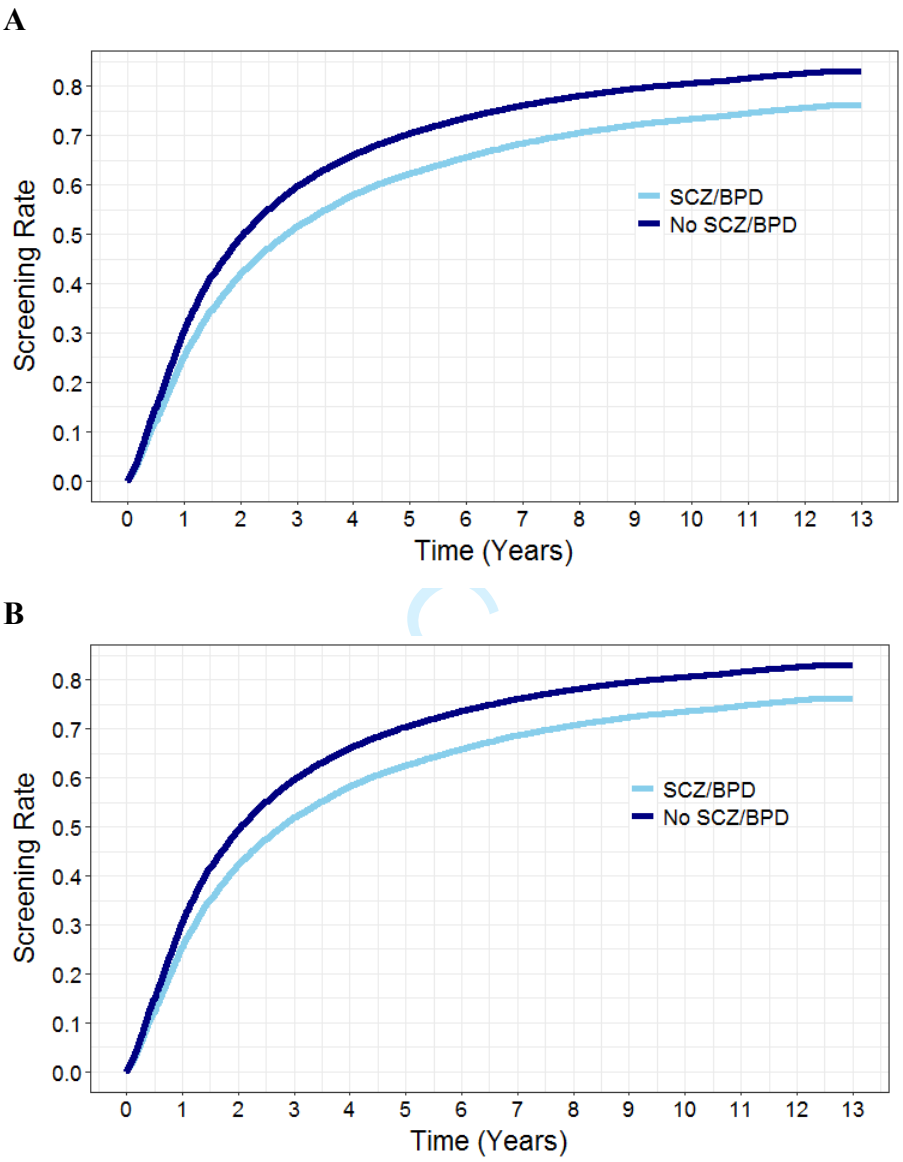

Figure 1. Cumulative incidence curve for screening over the follow-up period (2003-2015) for A) all matched women, and B) matched women with MDD excluded. Women without bipolar disorder or schizophrenia (light blue), women with bipolar disorder or schizophrenia (dark blue), log-rank test $p<0.001$.

Supplemental Data

Supplemental Table 1. 10th Edition International Classification of Diseases (ICD) and OHIP billing codes used for psychiatric exposure and cervical procedure identification.

	Code	Interpretation
ICD10	F20.x	Schizophrenia
	F25.x	Schizoaffective Disorder
	F31.x	Bipolar Disorder
	F33.x	Major Depressive Disorder
	C53.9	Cervical Cancer
OHIP	G365	Papanicolaou Smear
	E430	Papanicolaou Smear Outside of Hospital Environment
	G394	Additional or Follow-up Papanicolaou Smear

Supplemental Table 2. Baseline demographics and health characteristics for all matched women without a diagnosis of MDD in the general Ontario population aged 19-69 between July 2003 and July 2012, comparing those with bipolar disorder or schizophrenia to those without.

Characteristic	Overall	Exposure	Matched	SD	p-value
	N=1,158,712	N=111,432	N=1,047,280		
Demographics					
Age (Median, IQR)	41 (29-52)	42 (29-52)	41 (29-52)	0.02	<.0001
Income quintile, n (%)					
1 - Lowest	274,639 (23.7%)	27,448 (24.6%)	247,191 (23.6%)	0.02	
2	274,639 (23.7%)	27,448 (24.6%)	247,191 (23.6%)	0.02	
3	245,544 (21.2%)	23,630 (21.2%)	221,914 (21.2%)	0.00	<.0001
4	221,564 (19.1%)	20,974 (18.8%)	200,590 (19.2%)	0.01	
5 - Highest	209,491 (18.1%)	19,792 (17.8%)	189,699 (18.1%)	0.01	
Geographic Data					
Urban Residence, n (%)	1,052,860 (90.9%)	100,741 (90.4%)	952119 (90.9%)	0.01	<.0001
Rural Residence, n (%)	105,450 (9.1%)	10,633 (9.5%)	94,817 (9.1%)	0.02	
Charlson Comorbidity Index n(%)					
Missing	963,437 (83.1%)	85,508 (76.7%)	877,929 (83.8%)	0.18	
0	161,852 (14.0%)	21,114 (18.9%)	140,738 (13.4%)	0.15	<.0001
1	16,400 (1.4%)	2,853 (2.6%)	13,547 (1.3%)	0.09	
2	9,674 (0.8%)	1,093 (1.0%)	8,581 (0.8%)	0.02	
3+	7,349 (0.6%)	864 (0.8%)	6,485 (0.6%)	0.02	
Adjusted Diagnostic Group, n(%)					
0	30,828 (2.7%)	2,855 (2.6%)	27,973 (2.7%)	0.01	
1-3	131,226 (11.3%)	12,178 (10.9%)	119,048 (11.4%)	0.01	<.0001
4-6	300,764 (26.0%)	27,763 (24.9%)	273,001 (26.1%)	0.03	

7-9	347,287 (30.0%)	32,022 (28.7%)	315,265 (30.1%)	0.03	
10+	348,607 (30.1%)	36,614 (32.9%)	311,993 (29.8%)	0.07	
Comorbidities, n (%)				χ^2	
Vascular Diseases	13,631 (1.18)	1,682 (1.51)	11,949 (1.14)	117.03	<.0001
Hypertension	40,602 (3.50)	3,417 (3.07)	37,185 (3.55)	69.83	<.0001
Diabetes	16,749 (1.45)	1,939 (1.74)	14,810 (1.41)	75.11	<.0001
Dyslipidemia	4,028 (0.35)	523 (0.47)	3,505 (0.33)	52.73	<.0001
Respiratory Diseases	7,373 (0.64)	1,396 (1.25)	5,977 (0.57)	741.06	<.0001
Arthritis	2,308 (0.20)	261 (0.23)	2,047 (0.20)	7.61	.0058
Crohn's/Ulcerative Colitis	1,940 (0.17)	173 (0.16)	1,767 (0.17)	1.09	.2957
Osteoporosis	651 (0.06)	118 (0.11)	533 (0.05)	54.26	<.0001
Obesity	4,050 (0.35)	749 (0.67)	3,301 (0.32)	368.45	<.0001
Pelvic Inflammatory Diseases	798 (0.07)	105 (0.09)	693 (0.07)	11.52	.0007
Polycystic Ovarian Syndrome	113 (0.01)	21 (0.02)	92 (0.01)	10.45	.0012

The RECORD statement – checklist of items, extended from the STROBE statement that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	a) Title b) Abstract	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	1.1) Title, Abstract 1.2) Abstract 1.3) Abstract
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	Introduction		
Objectives	3	State specific objectives, including any prespecified hypotheses	Introduction		
Methods					
Study Design	4	Present key elements of study design early in the paper	Methods: Study Design and Data Sources		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	Methods: Study Population and Exposure		
Participants	6	*(a) Cohort study* - Give the	a) Methods: Study	RECORD 6.1: The methods of study	6.1) Methods:

		eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	Population and Exposure b) Methods: Study Population and Exposure	population selection (such as codes or algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	Study Population and Exposure 6.2) N/A 6.3) No diagram
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	Methods: Study Population and Exposure, Outcome, Statistical Analysis	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	Methods: Study Population and Exposure, Statistical Analysis, Supplemental Table 1
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	Methods: Study Population and Exposure, Supplemental Table 1		
Bias	9	Describe any efforts to address	Methods: Study		

		potential sources of bias	Population and Exposure, Statistical Analysis		
Study size	10	Explain how the study size was arrived at	Methods: Study Population and Exposure		
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	Methods: Statistical Analysis		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	a-c, e) Methods: Statistical Analysis, Appendix: Table 1 and Supplemental Table 1 d) Not applicable		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population.	12.1) Methods: Study Design and Data Sources

				RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	12.2) Methods: Study Design and Data Sources
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	12.3) Methods: Study Design and Data Sources
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	a) Results: Baseline characteristics, Sensitivity analysis of women without MDD comorbidity	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	13.1) Methods: Study Design and Data Sources, Study Population and Exposure,
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	a) Results: Baseline characteristics b) Tables c) Results: Likelihood of screening, Table 3		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures	Results		

		of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures			
Main results	16	(a) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	a) Results b) N/A c) N/A		
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	Results: Sensitivity analysis of women without MDD comorbidity		
Discussion					
Key results	18	Summarise key results with reference to study objectives	Interpretation		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	Interpretation: Limitations	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	Methods: Statistical Analysis Interpretation
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar	Interpretation, Conclusion		

		studies, and other relevant evidence			
Generalisability	21	Discuss the generalisability (external validity) of the study results	Interpretation		
Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	Funding Sources		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	Methods: Study Design and Data Sources

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.