The effects of tobacco smoking, and prenatal tobacco smoke exposure, on risk of

schizophrenia: a systematic review and meta-analysis

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Abstract

Introduction: The association between cigarette smoking and schizophrenia is well established. However, up to 90% of people with schizophrenia begin smoking before the onset of their illness, thus smoking could be an independent risk factor for schizophrenia. Prenatal exposure to maternal cigarette smoke is also associated with psychiatric problems in adolescence. Therefore, our aim was to undertake a systematic review and meta-analysis to explore the effect of smoking, and prenatal smoke exposure, on risk of schizophrenia.

Method: We systematically searched Medline, Embase, PsychInfo, Maternity and Infant Care, and Web of Science (from inception to February 2018) to identify comparative observational studies of the risk of schizophrenia in relation to smoking status. Measures of Relative Risk (RR) were pooled in a meta-analysis with 95% confidence intervals, using random effects model.

Results: Twelve studies (9 cohort, 3 case-control) were included. Odds ratios (OR) and hazard ratios (HR) were pooled together to estimate pooled RRs and estimates combined in a meta-analysis on an assumption of constant risk over time. Smokers had a significantly increased risk of schizophrenia compared to non-smokers (RR 1.99, 95% CI 1.10-3.61, $I^2 =$ 97%, 5 studies). Exposure to prenatal smoke increased the risk of schizophrenia by 29% (95% CI 1.10-1.51, $I^2 =$ 71%, 7 studies). Sensitivity analyses identified no significant differences between the results from studies reporting OR and HR.

Conclusions: Our findings suggest smoking, and prenatal smoke exposure, may be an independent risk factor for schizophrenia. Care should be taken when inferring causation, given the observational nature of the studies.

Implications

In this meta-analysis of 12 studies smokers had a significantly increased risk of schizophrenia compared to non-smokers. Exposure to prenatal tobacco smoke also increased the risk of schizophrenia by 29% compared to those with no exposure to prenatal tobacco smoke. Our findings suggest that smoking, and prenatal tobacco smoke exposure, may be independent risk factors for schizophrenia. These results may have important public health implications for decreasing the incidence of schizophrenia. The possibility of a causal link between smoking and schizophrenia warrants further investigation.

Introduction

Smoking is associated with an increased risk of many health conditions [1], and is particularly common among people with mental health problems [2], but the causal nature of the association between smoking and mental illness remains uncertain. In particular, it is unclear whether the high prevalence of smoking among people with schizophrenia [3] arises from a direct causal effect of smoking on the disease, or reverse causation from the use of nicotine to self-medicate psychotic symptoms [4]. Since 90% of people with schizophrenia begin smoking before the onset of their illness [5-7] this suggests that smoking may increase the risk of schizophrenia; however, evidence of cognitive improvements in people with schizophrenia following smoking [8 9] supports the self-medication hypothesis. Furthermore it is possible that maternal smoking is associated with an increased risk of schizophrenia in offspring, since prenatal exposure to maternal cigarette smoke has been shown to be associated with psychiatric and behavioural problems in adolescence [10-12] and in adulthood [13-15].

In view of this uncertainty we have carried out a systematic review to search the international literature for comparative observational studies of smoking and incident schizophrenia, including both personal active smoking and passive exposure to the foetus arising from

maternal smoking in pregnancy, and used meta-analysis to estimate contemporary risks of schizophrenia.

Methods

Our methods followed the EQUATOR (Enhancing the quality and transparency of health research) reporting guidelines and included MOOSE (Meta-analysis of Observational Studies in Epidemiology) Guidelines [16] on reporting meta-analyses of observational studies, and the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement [17]. Our review protocol was registered at PROSPERO (http://www.crd.york.ac.uk/PROSPERO), registration number CRD42017064459.

Inclusion criteria and search strategy

We included all cohort (retrospective and prospective) and case-control epidemiologic studies assessing the association between tobacco smoking, or maternal prenatal tobacco smoke exposure and risk of schizophrenia. We included studies that used ICD, DSM or other standardised diagnostic criteria for schizophrenia. We included studies that used any self-reported or biochemically validated measure of smoking, and we included any schizophrenia spectrum disorders (schizophrenia, schizoaffective disorder and schizotypal disorder). Studies in which tobacco use could not be distinguished from use of other substances e.g. cannabis, were excluded, as were studies in which schizophrenia could not be distinguished from bipolar disorder or other diagnosis. The databases Medline (accessed via Ovid), EMBASE (accessed via Ovid), PsychInfo, Maternity and Infant Care Database, and Web of Science, were searched between database inception and February 2018. Search keywords were determined from the Cochrane review group terms for tobacco [18] and schizophrenia [19], and the BMJ Clinical Evidence study design search filters [20]. The search strategy was specified to

capture all potentially eligible records relating to smoking and schizophrenia. The lead author developed the search strategy, with input from The University of Nottingham library support team. A combination of Medical Subject Headings (MeSH) and relevant text words were used wherever possible. An example of the search criteria used for Ovid Medline can be found in Supplementary Table 1. We also searched the reference lists of included studies, and review articles that had been identified in the search. No language restrictions were applied in the search, and where possible, studies were translated.

Screening of the studies

We used *Covidence* software [21] to manage the data screening process. Two authors (AH and RM) independently reviewed the titles and abstracts, and then full text to identify potentially eligible articles. Full text copies of papers were then obtained for all those considered potentially relevant or for which there was insufficient information in the title and abstract to make a firm decision. Any discrepancies at each step were resolved by discussion.

Data extraction

Data extraction was carried out independently by two authors (AH and RM) using a previously piloted form. Key data extracted included details of the study design, methods, diagnostic criteria for schizophrenia, measurement of smoking status, geographic location, reference population, number of people recruited, participant characteristics (age, gender), length of follow up, and results.

Quality assessment

Included articles were independently scored by two authors (AH and RM) for methodological quality using the Newcastle-Ottawa Quality Assessment Scale (NOS) [22]. This scale awards

points for representativeness of the cohort, selection of the non-exposed cohort, ascertainment of exposure/ outcome, adjustment for confounders in the analyses (e.g. age, gender, substance abuse) and follow-up (length and completeness). A separate scale specific for case-control studies was used which awards points for representativeness of the cases, definition of case and controls, selection of controls, comparability of cases and controls, ascertainment of exposure, and non-response rate. Both scales have a maximum score of nine points; a high quality study was deemed to be identified by a score of at least seven. Any disagreement between the reviewers was resolved through discussion.

Statistical analysis

Crude measures of effect or adjusted measures of effect were extracted from the individual studies. Where adjusted measures were available, these were used in preference. Effect measures were extracted as odds ratios (OR), or hazard ratios (HR), with 95% confidence intervals (CI). Where more than two categories of level of cigarette consumption were reported in a study, we extracted adjusted effect measures relating to a comparison of the highest to the lowest exposure group.

Pooled measures of effect across studies were estimated using random effects meta-analysis using the generic inverse variance method to weight the studies. Due to inherent biases in observational study designs, it was deemed appropriate to use a random effects model. We pooled odds ratios and hazard ratios together to estimate pooled Relative Risks (RRs). We combined these estimates in a meta-analysis on an assumption of constant risk over time, and acknowledge that, despite schizophrenia being a rare disease, the odds ratios will slightly overestimate the true relative risk. Additionally, the event rate in the exposed and unexposed groups was low (<10%), also justifying our decision to pool hazard ratios with odds ratios.

Heterogeneity between the studies was quantified using I^2 [23]. Heterogeneity was anticipated due to the diverse methodological and clinical nature of the studies [23]. We performed a sensitivity analysis excluding studies which reported hazard ratios from the meta-analysis to assess the magnitude of the pooled results. Sensitivity analyses were also conducted to assess the robustness of the results based on study design. Due to the small number of studies, only a limited number of sub-group analysis could be performed (study quality and schizophrenia diagnostic criteria). We were unable to perform subgroup analysis based on country (high vs low/middle income) as all studies were from high income countries. As we had fewer than 10 studies for each meta-analysis, it was not possible to visually assess evidence of publication bias using funnel plots, as the test power would be too low to distinguish chance from real asymmetry [24]. Descriptive analysis was undertaken to explore the dose response relationship between cigarette consumption and schizophrenia in those studies that reported different levels of cigarette consumption. Review Manager (version 5.3) was used to perform analyses. P values < 0.05 were taken to represent statistical significance.

Results

Overview of the included studies

The systematic search of electronic databases identified 7,919 articles (Figure 1). After duplicates were removed, 5,742 articles were screened by title and abstract, and 107 full texts were retrieved to assess eligibility. Of these, 95 were ineligible on the grounds of outcome (n=55), study design (n=15), exposure definitions (n=11), opinion piece (n=10) or because we were unable to locate the full text in any language (n=2), or were unable to translate the text into English (n=2). One article was translated from French [25] and subsequently excluded based on study design. A number of review articles ([26-38]) were identified in the search, and

the reference lists of these, along with the included studies, were hand searched. An additional four articles were identified but after full text screening these were ineligible (included in Figure 1). Twelve articles were eligible for inclusion in the systematic review (five were concerned with personal active smoking; seven were concerned with maternal prenatal tobacco smoke exposure). Supplementary Table 2 summarises the study characteristics of the included studies.

INSERT FIGURE 1

Methodological quality of the studies

The methodological quality of the twelve included studies are presented in Supplementary Table 2. The quality assessment scores ranged from 4 to 9. The median quality score was 7.5, indicating that the overall methodological quality was good, with 67% of the studies scoring 7 or more. The main reason for lower quality scores was lack of information on confounding variables adjusted for, and the use of self-reported rather than objectively validated smoking status (only one study provided objective data in the form of cotinine levels [39]). All studies scored high on outcome, as schizophrenia was clinically diagnosed and linked to medical records. The majority of the studies diagnosed schizophrenia according to ICD criteria, three used DSM diagnostic criteria [40-42], and one used the Present State Examination [43].

Personal active smoking

Five cohort studies reported data on the association between schizophrenia and smoking, published between 2003 and 2015. Two studies each were from Denmark [44 45] and Sweden [4 46], and one study from Israel [47]. Two studies included males only [4 47], one included females only [44], one included males and females [46], and one did not report gender [45] but was assumed

to include males and females as they recruited from both the Copenhagen General Population Study and the Copenhagen City Heart Study. The total number of participants in each study ranged from 7,926 [44] to 1,647,728 [46], and in total the five studies included 1,783,251 participants and 2,028 people with schizophrenia (although Kendler, et al. [46] only reported the number of females with schizophrenia, and not males). The follow up period ranged from 4 years [47] to 40 years [44]. Table 1 presents the odds ratios and 95% confidence intervals for unadjusted and adjusted estimates where available, for all studies.

INSERT TABLE 1

A pooled analysis of the five studies found the combined estimate of effect was a relative risk of 1.99 (95% CI 1.10 to 3.61; I^2=97%, 5 studies; Figure 2). Results from a sensitivity analysis restricted to studies reporting odds ratios were similar (Relative Risk = 2.81, 95% CI 0.67-11.84; I^2=92%, 2 studies), suggesting the findings were robust. Subgroup analysis within the five studies reporting the association between smoking and schizophrenia found that study quality (high versus low-medium; p=0.14) did not explain high level of heterogeneity (Supplementary Figure 1). There was insufficient data to perform further subgroup analysis.

Descriptive analysis was undertaken to explore the dose response relationship between cigarette consumption and schizophrenia. All five studies looking at the effect of personal active smoking on the risk of schizophrenia reported different levels of smoking (see Supplementary Table 3). There was evidence from four studies to suggest that heavier smoking was associated with greater risk for schizophrenia. Weiser and colleagues [47] found a significant linear association between the number of cigarettes smoked and the risk of schizophrenia, with those who smoked 10 cigarettes a day or more, 2.28 times (95%

CI=1.19-4.34; Wald χ^2=6.22, d.f=1, p=0.02) more likely to be hospitalised later for schizophrenia. Sorenson and colleagues [44] also found a significant linear effect of smoking (OR=1.18 (1.07-1.30)). Wium-Anderson and colleagues [45] found that increasing number of pack years was associated with schizophrenia (OR=4.13 (1.61-10.60) for participants with >40 pack-years vs never smokers. Kendler and colleagues [46] also found a clear dose-response relationship between number of cigarettes smoked and risk of schizophrenia, and that the risk for schizophrenia was more strongly associated with heavy than with light smoking in both males (OR=2.21 (1.11-4.42)) and females (OR=2.77 (2.34-3.43)). One further study found that cigarette smoking at age 18 was associated with a lower risk of developing schizophrenia in both medium and heavy smokers compared to non-smokers, with an adjusted hazard ratio for linear trend across the four smoking categories of 0.8 (95% CI=0.7-0.9, p=0.002)[4].

INSERT FIGURE 2

Prenatal tobacco smoke exposure

Seven studies reported data on the association between schizophrenia and prenatal tobacco smoke exposure [39-43 48 49], published between 1995 and 2017. Two studies were from Finland [39 42], and one study each from Great Britain [43], France [40], Greece [41], Denmark [48] and Sweden [49]. Four were cohort studies, and three were case-control studies. Five studies included males and females [39-42 49]. Two studies did not explicitly report gender [43 48]. The total number of participants in each study ranged from 200 [40] to 1,680,219 [49], and in total the seven studies included 2,444,910 participants and 10,278 people with schizophrenia. The follow up period ranged from 11 years [39] to 31 years [49].

A pooled analysis of the seven studies found that those who had been exposed to maternal prenatal smoke had a 29% increased risk of developing schizophrenia (RR= 1.29, 95% CI 1.10 to 1.51; I^2=71%, 7 studies; Figure 3). Results from a sensitivity analysis restricted to studies reporting odds ratios were similar (Relative Risk = 1.34, 95% CI 0.90-1.98; I^2=59%, 5 studies), suggesting the findings are robust.

INSERT FIGURE 3

Subgroup analysis of the studies reporting the association between maternal prenatal smoke exposure and schizophrenia found that study quality (high versus low-medium; p=0.53; Supplementary Figure 2), and schizophrenia diagnostic criteria (International Classification of Diseases (ICD) vs Diagnostic Statistical Manual (DSM)/Present State Examination; p=0.99; Supplementary Figure 3) did not explain the high level of heterogeneity. There was insufficient data to perform further subgroup analysis.

Descriptive analysis was undertaken to explore the dose response relationship between maternal cigarette consumption and schizophrenia. Two studies reported different levels of exposure to prenatal maternal smoke [39] [49] (see Supplementary Table 3), however, no dose-response relationship was observed.

Discussion

This systematic review and meta-analysis of observational studies reporting the risk of schizophrenia in smokers has indicated an approximated doubling of the risk of schizophrenia among smokers relative to non-smokers. We also found evidence of a statistically significant increase in risk of schizophrenia among offspring of those whose mothers smoked during

pregnancy compared to those whose mothers who did not smoke during pregnancy. Although a previous meta-analysis pooled prevalence data and demonstrated a higher likelihood of smoking among people with schizophrenia [3], to our knowledge this is the first attempt to provide summary estimates of incident risk.

Our finding in relation to schizophrenia in personal active smokers is consistent with previous findings that daily tobacco use is associated with an increased risk of a wider group of psychotic disorders and an earlier age at onset [33]. Incident schizophrenia may represent a transition from an earlier at risk state or prodromal period, during which individuals may smoke in order to relieve attenuated psychotic symptoms [50], and it is not possible to exclude reverse causality from the available data. Nevertheless, as the prevalence of smoking in people with schizophrenia is higher compared to other psychiatric disorders [3 51 52], it is possible that smoking could be an independent risk factor for schizophrenia, as our results would suggest.

The dopamine hypothesis remains an important theory in the pathology of schizophrenia [53]; nicotine exposure has been proposed as a plausible risk factor for schizophrenia by directly or indirectly increasing dopamine release [33]. When considering the dose response relationship, there was evidence to suggest an increase in risk of schizophrenia as the number of cigarettes smoked increased, with heavier smoking associated with greater risk for schizophrenia. However, it is worth noting that one study [4] found a reverse effect, in that, at the very least, each incremental increase in smoking was associated with a 10% reduction in the risk of schizophrenia, and therefore the results should be interpreted with caution.

Our finding of a significant association between maternal smoking and risk of schizophrenia in offspring is in line with recently reported research. Despite an early meta-analysis [54] of two cohort studies [42 43] on maternal smoking and schizophrenia in offspring which found no evidence of an association, subsequent studies have suggested there may be an association between maternal smoking and psychiatric disorders, including schizophrenia. Benros, et al. [55] found that the offspring of mothers with lung cancer had an increased risk of child psychiatric disorders and schizophrenia. A recent study with animals suggests that it is plausible to consider prenatal tobacco smoke exposure as a risk factor for schizophrenia in later life. Zugno, et al. [56] found an increased risk of developing schizophrenia (as measured by changes in behaviour and changes in the cholinergic system) in rats exposed to cigarette smoke during the gestational period. Furthermore, our findings are consistent with initial indications that a range of perinatal factors, such as obstetric complications, may increase the risk of psychosis [57].

In our review, two studies [39 49] reported different levels of exposure to prenatal maternal smoke and both found that those who had been exposed to heavy prenatal tobacco smoke had a significantly increased risk of having schizophrenia compared to those not exposed to prenatal tobacco smoke, though there was no evidence of a dose-response relationship. However, previous studies have found a dose response relationship between smoking during pregnancy and adult intelligence [58] risk of childhood cancer [59], childhood obesity [60] suggesting that heavy smoking has the greatest risk on the health of the offspring.

The main strength of this systematic review and meta-analysis is the broad and inclusive search strategy designed to be as extensive as possible to maximise sensitivity and ensure that as many as possible relevant studies were included. However, despite the fact we developed a

comprehensive and robust search strategy, there is always the possibility that inappropriate indexing may result in a publication being missed. A limitation of this meta-analysis was the fact that we combined odds ratios and hazard ratios due to the small number of studies included. The presenting risk estimates for odds ratios and hazard ratios were combined in the meta-analysis on an assumption of constant risk over time, and acknowledging that, despite schizophrenia being a rare disease, the odds ratios will slightly overestimate the true relative risk. It is also possible that there is some publication bias, but due to the small number of studies, we did not perform tests of funnel plot asymmetry. All but one of the studies we assessed relied on self-reported smoking status which has been shown to be a good indicator of true smoking status in general [61], but nevertheless may underestimate the true extent of smoking particularly in retrospective accounts where women are asked to think back to how much they smoked during pregnancy.

The mixed findings could partly be explained by confounding factors. There are likely to be risk factors that we were unable to adjust for such as personality, as the personality trait neuroticism has been found to show a strong association with both schizophrenia [62] and smoking [63]. Ethnicity may also be a confounding factor, as one birth cohort study found that African Americans had substantially elevated rates of schizophrenia in comparison with Caucasians [64]. Furthermore, in the UK, there is a substantial body of research showing higher incidence of schizophrenia in Black Caribbean and African populations [65]. However, no studies in our meta-analysis reported, or controlled for ethnicity, so it is unclear whether any studies involved African Americans. Another potential confounder is substance abuse, which is also a recognised risk factor for schizophrenia [66]. Less than half of the studies reported controlling for either substance abuse or cannabis use. There are indications of a genetic relationship between nicotine dependence and schizophrenia [67] and these shared risk genes

may explain the observed association between smoking and schizophrenia. Equally, familial confounding may explain some of the observed association between prenatal tobacco exposure and schizophrenia risk [48]. Maternal adverse life events are proposed to increase the risk of psychosis, and may be a confounder [68] [69]. Additionally, the association may be because mothers who smoke are more likely to have children who smoke[70] and it is the active smoking that causes schizophrenia.

It is also worth noting that, although our study search was not restricted by geographical location, all studies were from the European Region (according to the World Health Organisation (WHO) regions [71]. There were no studies from any of the other five regions (African Region, Region of the Americas, South-East Asia Region, Eastern Mediterranean Region, Western Pacific Region).

Conclusions

Although observational studies have their limitations, i.e. we cannot be certain about the causal pathways, the results here suggest that it is plausible to consider that tobacco smoking is a causal risk factor for schizophrenia, and that there is a dose-response relationship in that the risk of schizophrenia increases with the number of cigarettes smoked. We also found evidence that heavy maternal smoking is a risk factor for schizophrenia in offspring. Identifying smoking as a potential modifiable risk factor is an important development for the field, however due to the small number of studies and the conflicting individual results, further longitudinal studies, particularly from regions outside of Europe, are required to determine the extent of the risk.

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References

1. US Department of Health Human Services. The health consequences of smoking—50 years of progress: a report of the Surgeon General. *Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health* 2014;**17**

2. Lasser K, Boyd JW, Woolhandler S, Himmelstein DU, McCormick D, Bor DH. Smoking and mental illness: a population-based prevalence study. *Jama* 2000;**284**(20):2606-10

3. de Leon J, Diaz FJ. A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 2005;**76**(2):135-57

4. Zammit S, Allebeck P, Dalman C, Lundberg I, Hemmingsson T, Lewis G. Investigating the association between cigarette smoking and schizophrenia in a cohort study. *Am J Psychiatry* 2003;**160**(12):2216-21

5. Beratis S, Katrivanou A, Gourzis P. Factors affecting smoking in schizophrenia. *Compr Psychiatry* 2001;**42**(5):393-402

6. Kelly C, McCreadie RG. Smoking habits, current symptoms, and premorbid characteristics of schizophrenic patients in Nithsdale, Scotland. *Am J Psychiatry* 1999;**156**(11):1751-57

7. Goff DC, Henderson DC, Amico E. Cigarette smoking in schizophrenia: relationship to psychopathology and medication side effects. *Am J Psychiatry* 1992;**149**(9):1189-94

8. Adler LE, Hoffer LD, Wiser A, Freedman R. Normalization of auditory physiology by cigarette smoking in schizophrenic patients. *Am J Psychiatry* 1993;**150**(12):1856

9. Olincy A, Ross RG, Young DA, Roath M, Freedman R. Improvement in smooth pursuit eye movements after cigarette smoking in schizophrenic patients. *Neuropsychopharmacology* 1998;**18**(3):175

10. Zammit S, Thomas K, Thompson A, et al. Maternal tobacco, cannabis and alcohol use during pregnancy and risk of adolescent psychotic symptoms in offspring. *Br J Psychiatry* 2009;**195**(4):294-300

11. Kotimaa AJ, Moilanen I, Taanila A, et al. Maternal smoking and hyperactivity in 8-year-old children. *J Am Acad Child Adolesc Psychiatry* 2003;**42**(7):826-33

12. Kovess V, Keyes KM, Hamilton A, et al. Maternal smoking and offspring inattention and hyperactivity: results from a cross-national European survey. *Eur Child Adolesc Psychiatry* 2015;**24**(8):919-29

13. Ekblad M, Gissler M, Lehtonen L, Korkeila J. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. *Arc Gen Psychiatry* 2010;**67**(8):841-49

14. Räsänen P, Hakko H, Isohanni M, Hodgins S, Järvelin M-R, Tiihonen J. Maternal smoking during pregnancy and risk of criminal behavior among adult male offspring in the Northern Finland 1966 Birth Cohort. *Am J Psychiatry* 1999;**156**(6):857-62

15. Tiesler CM, Heinrich J. Prenatal nicotine exposure and child behavioural problems. *Eur Child Adolesc Psychiatry* 2014;**23**(10):913-29

16. Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000;**283**(15):2008-12

17. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009;**6**(7):e1000097

18. Lancaster T, Stead LF, Cahill K, et al. Cochrane Tobacco Addiction Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)). Secondary Cochrane

Tobacco Addiction Group. About The Cochrane Collaboration (Cochrane Review Groups (CRGs)) 2017. http://onlinelibrary.wiley.com/o/cochrane/clabout/articles/TOBACCO/sect0-meta.html

19. Collaboration C. List of Searches Resources. Secondary List of Searches Resources 2017. http://schizophrenia.cochrane.org/sites/schizophrenia.cochrane.org/files/public/uploads/List%20of%20Searches%20Resources.pdf.

20. Evidence BC. Study design search filters. Secondary Study design search filters 2017. http://clinicalevidence.bmj.com/x/set/static/ebm/learn/665076.html.

21. Cochrane. Covidence: Cochrane Melbourne, Australia, 2016.

22. Wells G, Shea B, O'connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa (ON): Ottawa Hospital Research Institute; 2009: Oxford, 2011.

23. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557

24. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;**343**:d4002

25. Bouhlel S, Jones Y, Msolly M, Ben SH, El-Hechmi Z. Effects of tobacco on antipsychotic treatments and their symptoms in schizophrenia. *Tunis Med* 2012;**90**(4):311-15

26. Addington J, Case N, Saleem MM, Auther AM, Cornblatt BA, Cadenhead KS. Substance use in clinical high risk for psychosis: a review of the literature. *Early Interv Psychiatry* 2014;**8**(2):104-12

27. Beary M, Hodgson R, Wildgust HJ. A critical review of major mortality risk factors for all-cause mortality in first-episode schizophrenia: clinical and research implications. *J Psychopharmacol* 2012;**26**(5_suppl):52-61

28. Cao X-L, Li Y, Zhong B-L, et al. Current cigarette smoking in Chinese female patients with schizophrenia: A meta-analysis. *Psychiatry Res* 2016;**235**:203-05

29. Carliner H, Collins PY, Cabassa LJ, McNallen A, Joestl SS, Lewis-Fernández R. Prevalence of cardiovascular risk factors among racial and ethnic minorities with schizophrenia spectrum and bipolar disorders: a critical literature review. *Compr Psychiatry* 2014;**55**(2):233-47

30. Casey DA, Rodriguez M, Northcott C, Vickar G, Shihabuddin L. Schizophrenia: medical illness, mortality, and aging. *Int J Psychiatry Med* 2011;**41**(3):245-51

31. Cerimele JM, Katon WJ. Associations between health risk behaviors and symptoms of schizophrenia and bipolar disorder: a systematic review. *Ann Gen Psychiatry* 2013;**35**(1):16-22

32. Dervaux A, Laqueille X. Tabac et schizophrénie: aspects épidémiologiques et cliniques. Smoking and schizophrenia: Epidemiological and clinical features. *Encephale* 2008;**34**(3):299-305

33. Gurillo P, Jauhar S, Murray RM, MacCabe JH. Does tobacco use cause psychosis? Systematic review and meta-analysis. *Lancet Psychiatry* 2015;**2**(8):718-25

34. Hausswolff-Juhlin V, Bjartveit M, Lindström E, Jones P. Schizophrenia and physical health problems. *Acta Psychiatr Scand* 2009;**119**(s438):15-21

35. Lyon ER. A review of the effects of nicotine on schizophrenia and antipsychotic medications. *Psychiatric Services* 1999;**50**(10):1346-50

36. MacCabe JH, Murray RM, McGrath JJ. No smoke without fire: Could tobacco smoking have a causal role in psychosis? . *Schizophr Res* 2014;**153**:S7

37. Matevosyan NR. Pregnancy and postpartum specifics in women with schizophrenia: a meta-study. *Arch Gynecol Obstet* 2011;**283**(2):141-47

38. Muñoz PG, Jauhar S, Murray RM, MacCabe JH. Systematic review and meta-analysis on associations between tobacco smoking and both the diagnosis and the clinical symptoms of psychosis? *Schizophr Res* 2014;**153**:S8

39. Niemelä S, Sourander A, Surcel H-M, et al. Prenatal nicotine exposure and risk of schizophrenia among offspring in a national birth cohort. *Am J Psychiatry* 2016;**173**(8):799-806

40. Baguelin-Pinaud A, Robert S, Ménard J-F, Thibaut F. Prenatal exposure to tobacco and risk for schizophrenia: a retrospective epidemiological study. *Compr Psychiatry* 2010;**51**(2):106-09

41. Stathopoulou A, Beratis IN, Beratis S. Prenatal tobacco smoke exposure, risk of schizophrenia, and severity of positive/negative symptoms. *Schizophr Res* 2013;**148**(1):105-10

42. Jones PB, Rantakallio P, Hartikainen A-L, Isohanni M, Sipila P. Schizophrenia as a long-term outcome of pregnancy, delivery, and perinatal complications: a 28-year follow-up of the 1966 north Finland general population birth cohort. *Am J Psychiatry* 1998;**155**(3):355-64

43. Sacker A, Done DJ, Crow TJ, Golding J. Antecedents of schizophrenia and affective illness obstetric complications. *Br J Psychiatry* 1995;**166**(6):734-41

44. Sørensen HJ, Mortensen EL, Reinisch JM, Mednick SA. A prospective study of smoking in young women and risk of later psychiatric hospitalization. *Nord J Psychiatry* 2011;**65**(1):3-8

45. Wium-Andersen MK, Ørsted DD, Nordestgaard BG. Tobacco smoking is causally associated with antipsychotic medication use and schizophrenia, but not with antidepressant medication use or depression. *Int J Epidemiol* 2015;**44**(2):566-77

46. Kendler KS, Lönn SL, Sundquist J, Sundquist K. Smoking and schizophrenia in population cohorts of Swedish women and men: a prospective co-relative control study. *Am J Psychiatry* 2015;**172**(11):1092-100

47. Weiser M, Reichenberg A, Grotto I, et al. Higher rates of cigarette smoking in male adolescents before the onset of schizophrenia: a historical-prospective cohort study. *Am J Psychiatry* 2004;**161**(7):1219-23

48. Meier SM, Mors O, Parner E. Familial confounding of the association between maternal smoking during pregnancy and schizophrenia. *Am J Psychiatry* 2017;**174**(2):187-87

49. Quinn PD, Rickert ME, Weibull CE, et al. Association between maternal smoking during pregnancy and severe mental illness in offspring. *JAMA Psychiatry* 2017;**74**(6):589-96

50. Burrell H, Lawson M, Addington J, et al. Tobacco Use and Psychosis Risk in Persons at Clinical High Risk. *Schizophr Bull* 2017;**43**(suppl_1):S80-S80

51. Dickerson F, Stallings CR, Origoni AE, et al. Cigarette smoking among persons with schizophrenia or bipolar disorder in routine clinical settings, 1999–2011. *Psychiatr Serv* 2013;**64**(1):44-50

52. Pratt LA, Brody DJ. Depression and smoking in the US household population aged 20 and over, 2005-2008. *NCHS data brief* 2010(34):1-8

53. Brisch R, Saniotis A, Wolf R, et al. The role of dopamine in schizophrenia from a neurobiological and evolutionary perspective: old fashioned, but still in vogue. *Front Psychiatry* 2014;**5**:47

54. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry* 2002;**159**(7):1080-92

55. Benros ME, Laursen TM, Dalton SO, Nordentoft M, Mortensen PB. The risk of schizophrenia and child psychiatric disorders in offspring of mothers with lung cancer and other types of cancer: a Danish nationwide register study. *PloS One* 2013;**8**(11):e79031

56. Zugno AI, Oliveira MB, Mastella GA, et al. Increased risk of developing schizophrenia in animals exposed to cigarette smoke during the gestational period. *Prog Neuropsychopharmacol Biol Psychiatry* 2017;**75**:199-206

57. Radua J, Ramella-Cravaro V, Ioannidis J, et al. What causes psychosis? An umbrella review of risk and protective factors. *World Psychiatry* 2018;**17**(1):49-66

58. Mortensen EL, Michaelsen KF, Sanders SA, Reinisch JM. A dose-response relationship between maternal smoking during late pregnancy and adult intelligence in male offspring. *Paediatr Perinat Epidemiol* 2005;**19**(1):4-11

59. Stjernfeldt M, Lindsten J, Berglund K, Ludvigsson J. Maternal smoking during pregnancy and risk of childhood cancer. *Lancet* 1986;**327**(8494):1350-52

60. Sharma AJ, Cogswell ME, Li R. Dose-response associations between maternal smoking during pregnancy and subsequent childhood obesity: effect modification by maternal race/ethnicity in a low-income US cohort. *Am J Epidemiol* 2008;**168**(9):995-1007

61. Newell SA, Girgis A, Sanson-Fisher RW, Savolainen NJ. The accuracy of self-reported health behaviors and risk factors relating to cancer and cardiovascular disease in the general population 1: A critical review. *Am J Prev Med* 1999;**17**(3):211-29

62. Van Os J, Jones PB. Neuroticism as a risk factor for schizophrenia. *Psychol Med* 2001;**31**(6):1129-34

63. Hu S, Brody C, Fisher C, et al. Interaction between the serotonin transporter gene and neuroticism in cigarette smoking behavior. *Mol Psychiatry* 2000;**5**(2):181

64. Bresnahan M, Begg MD, Brown A, et al. Race and risk of schizophrenia in a US birth cohort: another example of health disparity? *Int J Epidemiol* 2007;**36**(4):751-58

65. Kirkbride JB, Errazuriz A, Croudace TJ, et al. Incidence of schizophrenia and other psychoses in England, 1950–2009: a systematic review and meta-analyses. *PloS One* 2012;**7**(3):e31660

66. Breslau N. Psychiatric comorbidity of smoking and nicotine dependence. *Behav Genet* 1995;**25**(2):95-101

67. Chen J, Bacanu S-A, Yu H, et al. Genetic relationship between schizophrenia and nicotine dependence. *Sci Rep* 2016;**6**:25671

68. Dorrington S, Zammit S, Asher L, Evans J, Heron J, Lewis G. Perinatal maternal life events and psychotic experiences in children at twelve years in a birth cohort study. *Schizophr Res* 2014;**152**(1):158-63

69. Hauge LJ, Torgersen L, Vollrath M. Associations between maternal stress and smoking: findings from a population-based prospective cohort study. *Addiction* 2012;**107**(6):1168-73

70. Buka SL, Shenassa ED, Niaura R. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. *Am J Psychiatry* 2003;**160**(11):1978-84

71. Organisation WH. WHO regional offices Secondary WHO regional offices 2017. http://www.who.int/about/regions/en/.