Curtin School of Population Health

The Influence of Prenatal Alcohol and Tobacco Exposures on Offspring Mental Health and Substance Use Outcomes

Bereket Duko Adema

This thesis is presented for the Degree of
Doctor of Philosophy
of
Curtin University

May, 2022

Declaration by Author

To the best of my knowledge and belief this thesis contains no material previously published by any other person except where due acknowledgment has been made. The content of this thesis is the result of work I have carried out since the commencement of my higher degree by research candidature and includes no material which has been accepted for the award of any other degree or diploma in any university.

I have clearly explained the contribution made by others to co-authored research works that I have incorporated into my thesis. I have also clearly stated the contribution of others to my thesis as a whole, including study design, statistical analysis, technical procedures, funding, and any other original studies included in this thesis.

Abstract

Epidemiological studies suggest that offspring exposed to maternal prenatal alcohol and tobacco use are at increased risk of developing a wide range of mental health and substance use problems. However, previous epidemiological studies examining such associations have several limitations and have produced conflicting results. The purpose of the current work is to examine the prospective associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. The overall scope of this PhD project is to provide up to date epidemiological evidence necessary for strengthening preventive and intervention strategies aimed at reducing the burden of mental health and substance use problems in adolescents and young adults. The specific aims of this thesis were to:

1. Systematically review previous epidemiological studies on the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes.

2. Examine the associations between prenatal alcohol and tobacco exposures and the risks of mental health problems in their offspring.

3. Investigate the risk of subsequent substance use in offspring exposed to maternal prenatal alcohol and tobacco use.

To address the specific aims of this thesis, various data sources and statistical modelling approaches were followed. Data sources included several electronic databases and the use of birth cohort data extracted from the Raine Study;

a multi-generational birth cohort study based in Western Australia. Statistical modelling used included meta-analysis, log-binomial regression, negative-binomial regression, multinomial logistic regression, negative control analysis and also computing E-values. The findings from a systematic review suggested that maternal prenatal alcohol exposure was associated with offspring subsequent alcohol use. Similarly, the findings from the two meta-analyses suggested that offspring exposed to maternal prenatal tobacco smoking are at increased risk of depressive and bipolar disorders, tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence and independently of maternal postnatal tobacco smoking, sociodemographic and other potential confounders. After adjusting for a wide range of confounders, findings from the Raine Study show that elevated risks of depressive symptoms in offspring exposed to prenatal alcohol and tobacco use compared to those non-exposed by age 17 years. Similarly, the risks of conduct disorder and anxiety symptoms were 50% higher for offspring exposed to prenatal tobacco use compared to those non-exposed by age 14 and 20 years, respectively. However, there was insufficient statistical evidence to establish associations between prenatal alcohol exposure and the risk of anxiety symptoms in young adulthood; and paternal prenatal tobacco smoking and offspring conduct disorder symptoms. Adolescents exposed to maternal prenatal alcohol and tobacco use were at increased risks for harmful alcohol use and tobacco smoking during late adolescence, respectively. Similarly, offspring exposed to prenatal alcohol and tobacco use were at increased risk for cannabis use during late adolescence by age 17 years. Moreover, there were suggestions of dose-response associations. The work presented in this thesis contributes a number of substantive findings to the existing body of evidence associated to early life determinants of mental health and substance use outcomes for adolescents and young adults. Taken together with the current body of knowledge, it is clear that there is sufficient evidence of harm observed in this thesis to warrant the precautionary principle, that there is no known safe level of exposure to alcohol and tobacco

during pregnancy and that such exposure should be minimized, if not avoided. Future studies need to consider control for genetic predisposition and shared unmeasured factors, which may be achieved via Mendellian Randomization or via the use of sibling comparisons as such designs may potentially elucidate pathways that are independent of genetic, environmental and social determinants.

Acknowledgements

First and foremost, I thank the Almighty God for his unlimited and inexpressible gift of strength and support to work and protection. I would like to express my sincerest gratitude and special thanks to my supervisors-Professor Rosa Alati, Professor Gavin Pereira and Dr Kim Betts – for providing invaluable advice, continuous support, encouragement, understanding throughout the candidature and patience during my PhD study. I was very fortunate to get your unlimited support, guidance, and mentorship in this PhD journey. I would like to extend my deepest gratitude to- Professor John Newnham and Dr Robert who have contributed to the work presented in this thesis. My special thanks also go to Professor Gavin Pereira and Dr Robert Tait who were very keen to provide infinite support when asked. I sincerely thank you for the time you dedicated and the advice you imparted to me to improve my research writing. You (all mentioned above) have equipped me with fundamental research skills and advanced my critical thinking capacities, which are imperative for the success of my PhD and future endeavours. Your careful revisions of my manuscript have improved my research and organizational skills and made my writing more professional. I would like to thank Curtin University for providing the Curtin University International Postgraduate Research Scholarship (CIPRS), that made my PhD work possible. I gratefully acknowledge the Raine Study for providing the Raine Study PhD top-up scholarship. The National Health and Medical Research Council for long term contribution to funding the Raine Study since initiation, the Raine Medical Research Foundation, The University of Western Australia (UWA), Curtin Uni-

versity, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University, The University of Notre Dame Australia and the Raine Medical Research Foundation are acknowledged for providing funding for core management of the Raine Study. I would like to express my sincerest gratitude to the Raine Study participants, their family, the Raine Study team for data collection and cohort coordination. I extend my heartfelt gratitude to Professor Jonine Jancey for writing a letter in support of my application for the Raine Study Top-up scholarship award. I very much appreciated your time, support, and leadership when you were working as a Director of Graduate Research for the School of Population Health the then School of Public Health. A very special thanks go to my lovely wife Tesfanesh Meskele for unconditional love, care, support, prayers and understanding. Your encouragement and follow-up of my progress was really remarkable. You have been in every step of my PhD study. I would like to deeply express my gratitude to my daughter, Yoadan Bereket. You have joined our family in the middle of my PhD Journey and make me happier. I love you both. Finally, I would like to express my sincerest gratitude to my parents aboard and close friends who have provided me with boundless support and encouragement throughout this PhD project.

Financial Support

This PhD project was funded by Curtin University via Curtin University International Postgraduate Research Scholarship (CIPRS). This scholarship covered full tuition fee and living stipend as a form of salary. Additional merit-based PhD top-up scholarship was also obtained from the Raine Study, the University of Western Australia.

Australian and New Zealand Standard Research Classifications (ANZSRC)

ANZSRC code: 111706, Epidemiology, 70%

ANZSRC code: 11714, Mental Health, 30%

Fields of Research Classification

Field of Research code: 1117, Public Health and Health Services, 70%

Field of Research code: 1114, Paediatrics and Reproductive Medicine, 30%

List of Abbreviations

ADHD: Attention Deficit Hyperactivity Disorders

AIHW: Australian Institute of Health and Welfare

ALSPAC: Avon Longitudinal Study of Parents and Children

ASSAD: Australian Secondary School Students Alcohol and Drug

BDI: Beck Depression Inventory

CBCL: Child Behaviour Checklist

CD: Conduct Disorder

CIDI: Composite International Diagnostic Interview

DALYs: Disability-adjusted life years

DSM: Diagnostic and Statistical Manuel of Mental Disorders

GBD: Global Burden of Diseases

HDP: Hypertensive Disorders of Pregnancy

MUSP: Mater-University of Queensland Study of Pregnancy

NHMRC: National Health and Medical Research Council

NOS: Newcastle Ottawa Scale

SRMA: Systematic Review and Meta-Analysis

TRIALS: Tracking Adolescents' Individual Lives Survey

WHO: World Health Organization

Authorship Attribution Statements

Authorship Attribution Statements

Contributor	Statement of contribution	Signature/date
Bereket Duko Adema (Candidate)	Conceptualization and design methods (100%) Data cleaning and management (100%) Designed the analysis (80%) Performed data analysis (100%) Interpreted results (80%) Wrote papers (100%)	
Professor Rosa Alati (Supervisor)	Critically edited papers (40%) Interpreted results (10%) Statistical analysis advice (5%)	
Professor Gavin Pereira (Co-supervisor)	Critically edited papers (40%) Interpreted results (10%) Statistical analysis advice (20%	
Dr Kim Betts (Associate supervisor)	Critically edited papers (5%) Interpreted results (5% Statistical analysis advice (5%)	
Dr Robert Tait (collaborator from the National Drug and Research Institute, Curtin University)	Critically edited papers (20%) Interpreted results (5%) Statistical analysis advice (5%)	
Professor John Newnham (External collaborator from the University of Western Australia, Division of Obstetrics and Gynaecology)	Critically edited papers (15%) Interpreted results (5%) Statistical analysis advice (5%)	
Getinet Ayano, Asres Bedaso and Sylvester Nyadanu D (PhD students)	Assisted data extraction for systematic review and meta-analysis (5%)	15/02/2022

Note: Each contributor provided similar roles in each paper they were involved. Therefore, the contribution presented above stands for each paper the contributor was included in.

Publications included in this thesis

This thesis included nine papers published in the international peer-reviewed journals. Permission to use these papers as a part of this thesis has been obtained from the respective publishers.

Paper 1: Duko B, Ayano G, Pereira G, Betts K, Alati R. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. *Social Psychiatry and Psychiatric Epidemiology* 2020;55(12):1549-62.

Paper 2: Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study. Journal of Affect Disorders. 2021; 279:426-33.

Paper 3: Duko B, Pereira G, Tait RJ, Newnham J, Betts K, Alati R**.** Prenatal Tobacco and Alcohol Exposures and the Risk of Anxiety Symptoms in Young Adulthood: a Population-Based Cohort Study. Psychiatry Research 2022; 310:11

Paper 4: Duko B, Pereira G, Tait RJ, Newnham J, Betts K, Alati R. Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: Findings from the Raine Study. Journal of Psychiatric Research. 2021; 142:

Paper 5: Duko B, Pereira G, Tait RJ, Bedaso A, Betts K, Alati R. Prenatal alcohol exposure and offspring subsequent alcohol use: a systematic review. Drug and Alcohol Dependence. 2022; 232:109

Paper 6: Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study. Drug and Alcohol Dependence. 2020; 217:108305.

Paper 7: Duko B, Pereira G, Tait RJ, Nyadanu SD, Betts K, Alati R. Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-Analysis. Drug and Alcohol Dependence. 2021; 227:1

Paper 8: Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence. Addictive Behaviours. 2021; 117:106871.

Paper 9: Duko B, Pereira G, Tait RJ, Newnham J, Betts K, Alati R. Prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring: Findings from a population-based cohort study. Neurotoxicology and Teratology:2022; 90:10

Conference presentations arising from this thesis

1. **Duko B**., Pereira G, Tait R, Newnham J, Betts K, Alati R. The risk of depressive symptoms in offspring exposed to prenatal alcohol and tobacco use: evidence from a population-based longitudinal study, European Congress of Psychiatry 2022, Budapest, Hungary.
2. **Duko B**., Pereira G, Tait R, Newnham J, Betts K, Alati R. Prenatal Tobacco Smoking and the Risk of Conduct Disorder Symptoms in offspring: Evidence from the Raine Study, The Raine Study's 2021 Annual Scientific Meeting, Perth, WA.
3. **Duko B**., Pereira G, Tait R, Newnham J, Betts K, Alati R. Maternal and Paternal Smoking During Pregnancy and Risk of Tobacco Smoking in Adolescence: Findings from a Population-Based Prospective Cohort Study, 26th WONCA Europe Conference, Geneva, 2021.
4. **Duko B**., Pereira G, Tait R, Newnham J, Betts K, Alati R. Maternal Alcohol Use During Pregnancy and the Risk of Depression in Offspring, Australian Public Health Conference 2021, Canberra, Australia.
5. **Duko B**., Pereira G, Tait R, Newnham J, Betts K, Alati R. Maternal Prenatal Alcohol Exposure and the Risk of Harmful Alcohol Use in Offspring: Findings from a Population-Based Prospective Cohort Study, 2021 Mark Liveris Seminar, Curtin University, Australia

Contents

Chapter 1: Thesis roadmap

Chapter 1: Thesis roadmap

1.1 Aim and scope

The overall aim of this PhD project was to examine the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. Offspring mental health adverse outcomes of interest were mood disorders, depressive, anxiety and conduct disorder symptoms during adolescence and young adulthood. Offspring substance use related outcomes of interest were alcohol, tobacco, and cannabis use during late adolescence.

1.2 Approach to address the aim

This thesis comprises a series of interlinked studies (Figure 1) that address each research question and are presented as separate chapters based on their theme. A number of mental health and substance use outcomes was incorporated into the literature review (Chapter 2), of which mood disorders, depression, anxiety and conduct disorder symptoms, alcohol, tobacco and cannabis use emerged as outcomes of primary interest for this project. Following the literature review (Chapter 2), this thesis provides an overview of the study designs, measures, data sources and statistical analysis employed (Chapter 3). In subsequent sections, comprehensive systematic reviews and meta-analyses as well as primary studies on the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes are presented. All primary studies were conducted in Western Australia (WA) using a large prospective population-based cohort of pregnancy and childbirth (the Raine Study) (Chapter 4-8), following various analytic approaches. Finally, the findings from this thesis are compared with the existing epidemiological evidence of associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes (Chapter 9). Chapter 9 also includes conclusions, the strengths and limitations of this project, public health implications and proposed directions for future studies.

1.3 Structure of the thesis

This thesis has been divided into nine chapters, including this introduction. Each chapter contains one or more studies detailing the literature review, methods, results and discussion and conclusion. A brief overview of each chapter is provided below:

Chapter 2: Literature review

This chapter reviews rates of maternal alcohol and tobacco consumption during pregnancy, burden of mental health and substance use problems among adolescents and young adults, and provides a comprehensive overview on the associations between prenatal alcohol and tobacco

exposures and mental health and substance use outcomes in their offspring. A brief of methodological limitations and gaps identified in the existing evidence is also presented in this chapter.

Chapter 3: Methodology

This chapter presents a detailed description of the study design, methods, measures, datasets, and statistical approaches employed to address the specific aims of this project. Further, this chapter also provides brief summary of statistical approaches followed to achieve the aims of the primary studies of this PhD project.

Chapter 4: Prenatal alcohol and tobacco exposures and offspring depressive and anxiety outcomes

This chapter contains one systematic review and meta-analysis, and two primary studies that have been published in: Social Psychiatry and Psychiatric Epidemiology; Journal of Affective Disorders; and Psychiatry Research (3 papers), respectively. Offspring exposed to maternal prenatal tobacco use may have increased risk of mood disorders, however, mixed results have been reported. Therefore, we designed a systematic review and meta-analysis to examine the magnitude and consistency of associations reported between prenatal tobacco exposure and the risk of mood disorders in offspring. Further, in previous epidemiological studies, conventional statistical approaches have been used to examine the association between prenatal alcohol and tobacco exposures and the risk of depressive and anxiety symptoms in offspring. Such methods can be highly affected by confounding bias and do not allow identification of which risk factors contributed to the effects reported by previous studies. To deal with these issues, sequential models were used to estimate the association between prenatal alcohol and tobacco exposures and the risk of depressive and anxiety symptoms in offspring.

Chapter 5: Prenatal tobacco exposure and offspring conduct disorder symptoms

This chapter contains a primary study published in the Journal of Psychiatric Research. Existing epidemiological studies examining the association between prenatal tobacco exposure and risk of conduct disorder symptoms in offspring have been inconclusive. Therefore, further investigations of maternal and paternal tobacco smoking during pregnancy may give vital clues to the etiological basis for conduct disorder symptoms. I hypothesise that if maternal tobacco smoking during pregnancy, but not paternal tobacco smoking, is linked to an increased risk of conduct disorder symptoms in offspring, this may provide support for a prenatal pathway. Conversely, if maternal and paternal tobacco smoking during pregnancy are both associated with an increased risk of this disorder, this would suggest the influence of environmental and/or lifestyle factors or unmeasured confounding. Therefore, sequential statistical models along

with a negative control analysis were used to examine the association between prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring.

Chapter 6: Prenatal alcohol exposure and offspring subsequent alcohol use

Similar to chapter four, this chapter also contains one systematic review and one primary study (2 papers), both published in the Drug and Alcohol Dependence journal. The first study of this chapter systematically reviews the literature on the association between prenatal alcohol exposure and offspring subsequent alcohol use. Based on the findings from that systematic review, the second study of this chapter has compared the effects of pre-pregnancy and post-pregnancy maternal alcohol exposures on offspring subsequent alcohol use with prenatal alcohol exposure.

Chapter 7: Prenatal tobacco exposure and offspring subsequent tobacco use

This chapter presents one systematic review and one primary study (2 papers) that have been published in Drug and Alcohol Dependence and Addictive Behaviours journals, respectively. The first section of this chapter provides a comprehensive systematic review and meta-analysis on the association between prenatal tobacco exposure and offspring subsequent tobacco smoking initiation, lifetime, and current tobacco smoking, as well as tobacco dependence in adolescence and young adulthood. Following on from this study, the second section of chapter 7 comprises a study that compares the effects of paternal and maternal prenatal tobacco exposures on adolescents' subsequent tobacco smoking using a negative control analysis. A practicable statistical approach to reporting results in the presence of unmeasured and residual confounding, such as computing E-values, was used in this study to strengthen the robustness of the findings.

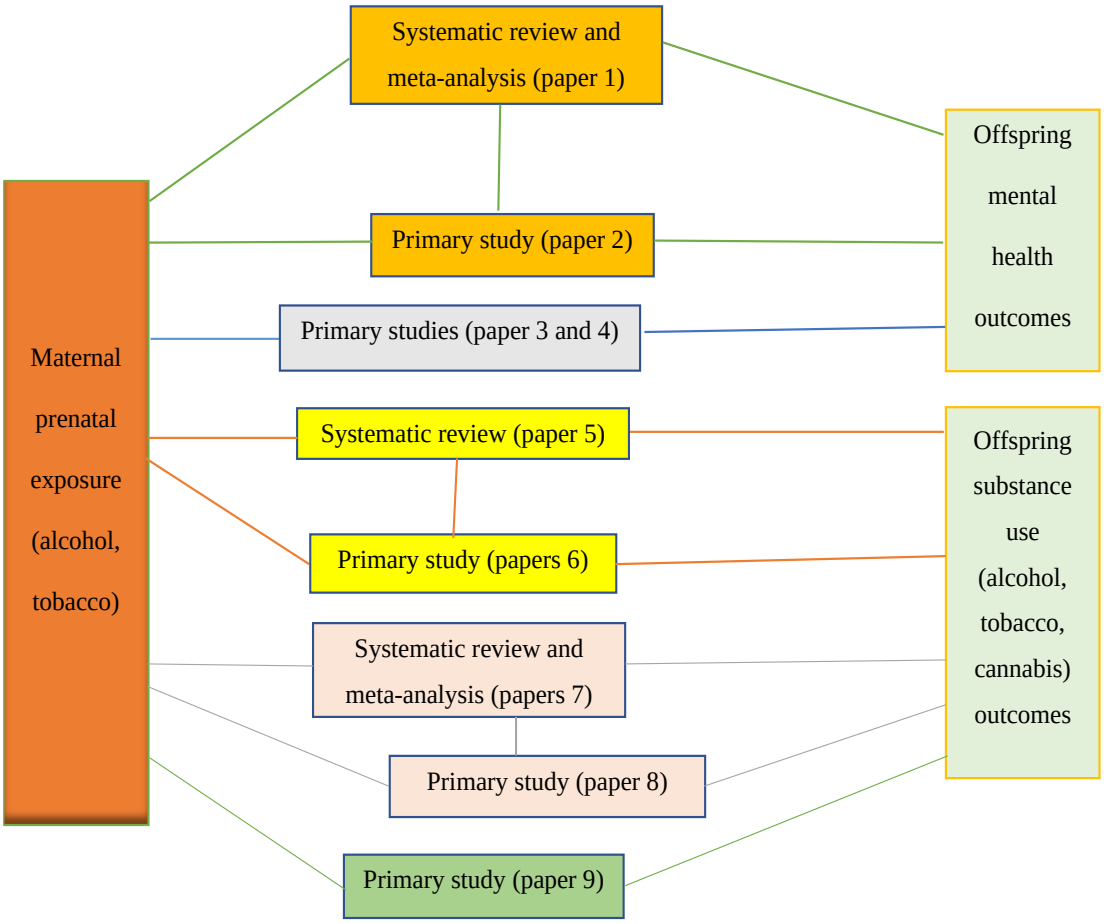
Chapter 8: Prenatal alcohol and tobacco exposures and Offspring cannabis use.

This chapter provides a primary study that has been published in the Neurotoxicology and Teratology journal. Examination of the association between prenatal and offspring addictive substances has been limited to alcohol and tobacco although the same biological pathways potentially apply to offspring cannabis use. Further, to my knowledge, there is no previous study that has examined the link between prenatal alcohol exposure and cannabis use in adolescence. The same statistical approach of computing E-values was also adopted in this study to assess the presence of unmeasured and/or potential confounding.

Chapter 9: Overall discussion and conclusion

This chapter provides an overall summary and consolidates the main findings from each study incorporated into this thesis. It also presents the strengths and limitations and compares the findings of this thesis with the existing evidence and recommends possible intervention

strategies. This chapter also provides potential mechanisms, public health implications of the findings and direction for future similar epidemiological studies.



***Note**: paper 1, 2 and 3 are included in chapter four; paper 4 is included in chapter five; paper 5 and 6 are included in chapter six; paper 7 and 8 are included in chapter seven and, paper 9 is included in chapter eight.*

Figure 1. Schematic representation and interconnection of papers (publications) included in the thesis.

Chapter 2: Literature review

Chapter 2: Literature review

This chapter provides a comprehensive literature review on the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. This chapter includes five sections: 1) an overview on maternal alcohol and tobacco use during pregnancy; 2) mental health and substance use problems among adolescents; 3) evidence regarding associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes; 4) gaps identified in the literature; and, 5) the role of potential confounders.

2.1 Overview of maternal alcohol and tobacco use during pregnancy

Consumption of alcohol and tobacco during pregnancy is prevalent (1). A systematic review and meta-analysis conducted in 2017 estimated that the global prevalence of maternal alcohol use during pregnancy to be 9.8%, with the highest reported prevalence in Ireland, UK, Denmark, Belarus and Russia, ranging from 36.5% to 60.4% (2). Similarly, reports from the Australian Institute of Health and Welfare (AIHW) in 2017 showed that 35% of women aged 14-49 years drank alcohol during pregnancy in 2016, although 49% of these women reported they were unaware of being pregnant for a part of their pregnancy (3). Of these women, approximately 16% drank alcohol at least 2-4 times a month during pregnancy, 97% consumed one to two standard drinks and 1.4% had consumed six or more standard drinks on a single occasion during prenatal period (3). According to the National Health and Medical Research Council (NHMRC) guidelines of 2009 (4), one standard drink in Australia contains 10 grams of alcohol.

The global prevalence of maternal tobacco smoking during pregnancy was found to be 1.7% (5), with an estimated prevalence of 8.1% in Europe, 5.9% in the Americas and 1.2% in Southeast Asia and 1.2% in the Western Pacific region (5). Evidence from that global study also suggested that approximately 52·9% of women who smoked daily also continued to smoke daily during pregnancy. In Australia, estimates from the AIHW in 2017 revealed that approximately 11% of women who gave birth in 2014 smoked tobacco in the first 20 weeks of pregnancy, with 8% smoking after 20 weeks of pregnancy (3).

2.2 The burden of mental health problems in adolescents and young adults

Mental health problems are still included in the top ten causes of disease burden globally with no evidence of reduction in global burden since 1990 (6), and result in significant impact on physical health, social and, economic consequences. Mental health problems comprise a wide spectrum of severe and less severe disorders (7). Although mental health and behavioural

problems are common in all age groups, particular conditions such as conduct disorder, depressive and anxiety symptoms (8) frequently start to appear during adolescence and may proceed to young adulthood and even beyond (9-12). Estimates from the WHO also suggested that mental health problems account for 16% of the global burden of disease and injury in adolescents (13).The pooled prevalence of mental health problems in children and adolescents in 2015 was estimated to be 13.4% globally (8). Similarly, the results of the Australian Child and Adolescent Survey of Mental Health and Wellbeing suggested that approximately 14% children and adolescents had a mental health problem in the previous 12 months of the survey date (14).

Conduct disorder (CD) is one of the most common behavioural problems and is characterized by repetitive and persistent patterns of behaviours whereby affected children and adolescents can manifest aggression against people or animals, destroy properties or commit other serious violations of societal norms (15, 16). A recent systematic review and meta-analysis that synthesized the results of 50 primary studies conducted in 35 countries incorporating 186,056 children and adolescents reported that the global prevalence of conduct disorder was 8% (17). In Australia, approximately 2.5% of children and adolescents reportedly have CD (18). Conduct disorder is an antecedent to a range of social difficulties, poor interpersonal relationships, poor academic attainment, even suicidal ideation and attempt (16, 19-23). Further, evidence from epidemiological studies also suggests that approximately 40% of boys and 25% of girls with CD may eventually develop antisocial personality disorder in adulthood (24).

Children and adolescents with depressive symptoms can experience mood disturbance or irritability, lack of interest or pleasure in nearly all activities, feeling of guilt, excessing crying, rrestlessness, social isolation and low self-esteem (25) and this in turn can lead to impairments in social and academic skills (25), substance use disorders (26) and even suicide (25, 27). Similarly, adolescents and young adults suffering from anxiety symptoms can experience excessive and uncontrollable fear and worry, panic attacks, cold flushes, and restlessness or feeling tense, avoiding perceived threats and obsessive thinking (28). Evidence also suggests that adolescents who experience depression are more likely to develop depressive disorders during adulthood when compared to adolescents without depression (29). A recent systematic review and meta-analysis that included the results of 29 primary studies incorporating 80,879 children and adolescents showed that the pooled global prevalence of depression and anxiety were 25.2% and 20.5%, respectively (30). Further, reports from the Global Burden of Diseases

2019 study indicated that anxiety disorder is responsible for about 28.68 million disability-adjusted life years (DALYs) in adolescents and young adults (31).

2.3 The burden of substance use problems in adolescents

Substance use problems contribute to several adverse outcomes for the health, social and economic productivity of the young populations (32). Alcohol, tobacco, and cannabis (marijuana) are the most common substances often initiated during adolescence. They are closely linked to increased morbidity and mortality and represent a significant public health concern. Estimates from the recent Global Burden of Disease study showed that alcohol use contributes 5.1% to the global burden of disease and contributes to approximately 1 in 10 deaths of people aged 15-49 years (33). The AIHW in 2016 reported that 42% of youths exceeded the alcohol single occasion risk guidelines and 15.3% of youths consumed greater than 11 standard drinks on one occasion, and 28.2% have experimented with illicit drugs in Australia (34).

The global prevalence of tobacco smoking during adolescence was reported to be 19.3% (35). Reports from the AIHW showed that in 2015 tobacco smoking contributed 13.3% to deaths and illnesses in Australia (34), suggesting more than one in every seven deaths is due to tobacco use. Recent estimates from the Australian Secondary Students' Alcohol and Drug (ASSAD) survey of 2017 (36) also indicated that from 33% of adolescents who reported current tobacco smoking approximately 22% smoked tobacco daily.

It has been estimated that approximately 35% of adolescents aged 14 years and over have used cannabis during their lifetime in Australia (3), with the mean age for first-time cannabis use being 17 years. Reports from the ASSAD in 2017 showed that 8% of adolescents aged 12-17 years reported current cannabis use, making cannabis the most commonly consumed illicit drug in this age group (36). Substance use problems are considered as one of the most common determinants of morbidity among adolescents and young adults and demonstrated in one of the following ways: suicide; accidental injury; and violence (37).

2.4 Prenatal alcohol exposure and offspring mental health and substance use outcomes

It remains unclear whether maternal prenatal alcohol exposure could result in offspring mental health problems. A few existing epidemiological studies have linked prenatal alcohol exposure to offspring mental health problems, with conflicting results including detrimental, protective, and null effects (38-40). A population-based retrospective cohort study using the data from the Avon Longitudinal Study of Parents and Children (ALSPAC) in the UK (n=14,062) found a 17% greater likelihood of depression in offspring exposed to any prenatal alcohol use at the

age of 18 years (Adjusted odds ratio (AOR) =1.17, 95% CI:1.02-1.34) (38). An additional study conducted using the same cohort (ALSPAC) with participants aged 4 and 8 years observed gender-specific associations, such that maternal alcohol consumption during pregnancy was associated with internalizing behaviors such as depression and anxiety in girls only (40). The authors acknowledged the lack of statistical evidence for dose-response associations and call for additional investigations to confirm their observations. A retrospective population-based cohort study by Robinson et al, showed that offspring born to mothers who reported alcohol consumption during pregnancy were less likely to develop internalizing behaviors when compared to those exposed to occasional prenatal alcohol use and non-exposed (39). However, that study combined 'abstainers' with 'occasional prenatal alcohol use' as a reference control group as well as using parent report from the Child Behavior Checklist (CBCL) to measure outcomes in offspring. Nonetheless, multi-informant approaches have been recommended in the assessment of young children's CBCL syndromes (41).

Prenatal alcohol exposure has also been associated with offspring conduct disorder (42). This observation is strongly supported by a Mendelian Randomization (MR) study (43). Mendelian Randomization is a powerful study design that uses genetic variation as a natural experiment to assess the link between modifiable health risks and offspring outcomes (43). In that study, offspring (n=3544) exposed to moderate amounts of alcohol consumption during the prenatal period was associated with persistent conduct disorder in offspring (AOR = 1.29, 95%CI: 1.04-1.60). Moreover, a study that synthesized the results of nine observational studies reported an increased odds of developing conduct disorder in offspring exposed to prenatal alcohol use (AOR=2.11, 95%CI: 1.42-3.15) (44). That study also indicated the necessity of additional epidemiological studies to address important unresolved issues such as confounding by socio-environmental factors, postnatal parental substance use and maternal mental health and behavioural problems.

Whether or not prenatal alcohol exposure influence offspring future substance use is unclear. Longitudinal studies examining the associations between prenatal alcohol exposure and offspring alcohol and cannabis use during adolescence are scarce. Evidence from those few and geographically limited epidemiological studies suggests that offspring exposed to prenatal alcohol use are at increased risk of alcohol use when compared to non-exposed (45-47). For instance, a longitudinal prospective cohort study conducted among 2,555 offspring exposed to prenatal alcohol use in Queensland, Australia found a greater likelihood of alcohol use disorder in offspring exposed to early pregnancy alcohol exposure (AOR = 2.95, 95% CI: 1.62-5.36) (47). In that study, 25% of offspring fulfilled the clinical criteria for a diagnosis of alcohol use

disorder. However, a study based on the ALSPAC observed insufficient statistical evidence for associations between prenatal alcohol exposure and offspring alcohol initiation after controlling for parental demographic covariates and confounders (48). A prospective cohort study from the US suggested a 2.56-fold increased risk of drug use disorders in offspring exposed to prenatal alcohol use (49). Further, a retrospective cohort study (n=5922) from the German Health Interview and Examination Survey for Children and Adolescents (the KiGGS study) observed gender-specific associations, such that low to moderate maternal prenatal alcohol use was linked with illicit drug use in adolescent females only (50). However, these two studies have reported illicit drug use as a single outcome (combining all illicit drug use) in offspring exposed to maternal prenatal alcohol use.

2.5 Prenatal tobacco exposure and offspring mental health and substance use outcomes

The immediate adverse effects of prenatal tobacco exposure on offspring such as preterm birth (51), small for gestational age (52) and low birth weight (53, 54) are well documented. However, epidemiological evidence regarding adverse mental health and substance use outcomes in offspring exposed to prenatal tobacco use is less clear. It has been proposed that direct and indirect effects of tobacco on the developing brain may result in unfavourable consequences in offspring (55, 56), while others suggest the detrimental effect might be due to maternal mental illness, use of other substances, adverse pregnancy outcomes and other socio-economic confounders (57, 58). However, findings from *in vivo* studies suggest that deficits in synaptic neurochemistry resulting from prenatal nicotine exposure may prompt alterations in neural cell replication (59), which in turn may lead to shortfalls in behavioural self-regulation (57). Therefore, prenatal tobacco exposure could result in irreversible modifications to synaptic capacity of fetal brain and sensitized fetus to subsequent impacts of tobacco (56).

Epidemiological studies on humans have reported mixed results. A longitudinal study that combined data from the ALSPAC cohort in the UK, Pelotas birth cohort in Brazil and the HUNT study in Norway with study participants aged 18, 30 and 32 years, respectively, observed a 20% increased likelihood of depression in offspring exposed to prenatal tobacco use (AOR = 1.20, 95% CI:1.08-1.34) (60). Similarly, a population-based retrospective cohort study from Brazil reported a 48% greater risk of depression in offspring exposed to parental tobacco use at the age of 18 years (61). Additional longitudinal studies conducted in Denmark (62) and the Netherlands (63) reported that offspring exposed to prenatal tobacco exposure are at increased risk of experiencing symptoms of anxiety in childhood and young adulthood, respectively. Some epidemiological studies observed conflicting results. A study examining

internalising behaviours, such as depression and anxiety among younger (N= 3,714) and older (N= 3,841) children that were exposed to prenatal tobacco use has observed virtually similar rates of internalising behaviours in both exposed and non-exposed offspring (64). Similarly, a study from the Netherlands (N=2230) has reported null association between maternal smoking in pregnancy and offspring internalising behaviours (AOR=1.33, 95% CI:0.70–2.55) (65). In contrast, an additional study from the Netherlands has reported gender specific associations (66). In that study, boys exposed to maternal prenatal tobacco exposure have scored higher on anxiety-depression sub scales of CBCL compared to exposed girls. Nonetheless, in a retrospective cohort study conducted in the US prenatal tobacco exposure was associated with lower risk of mood disorder in boys (AOR=0.42, 95% CI: 0.17, 0.98) (54).

Offspring exposed to maternal prenatal tobacco use may have an increased risk of CD compared to non-exposed offspring (67-69). An epidemiological study that combined the data of two birth cohorts, the Brazilian Pelotas and the ALSPAC, found an increased risk of CD in offspring exposed to maternal prenatal tobacco use after adjusting for socioeconomic positions, parental psychopathology and paternal smoking during pregnancy (69). However, there is also evidence of null associations between prenatal tobacco exposure and an increased risk of CD in offspring (53, 70-72).

Epidemiological evidence also suggests a prospective association between maternal prenatal tobacco exposure and subsequent offspring tobacco and cannabis smoking (73-76). For instance, a prospective cohort study from Sweden observed a 2-fold-increased risk of tobacco smoking in offspring exposed to prenatal tobacco use when compared to non-exposed (AOR=2.04, 95%CI:1.32-3.16) (77). Nonetheless, some epidemiological studies found null associations (65, 75, 78-81). A retrospective cohort study from the US observed an increased risk of tobacco dependence in offspring exposed to maternal prenatal tobacco use but found insufficient statistical evidence for current and lifetime tobacco smoking in offspring (79). Additional studies also observed similar outcomes (80, 81).

2.6 The role of confounders

Confounders may explain an observed relationship between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes (82). Specific potential confounders are discussed below. The association between maternal prenatal alcohol and tobacco exposures and offspring mental health outcomes may be confounded by genetic or biological factors, adverse pregnancy outcomes, socio-demographic and economic and other

factors. Figure 2 sets out the conceptual framework of the association between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes.

2.6.1 Parental mental health problems (genetic predisposition)

Several studies have found an elevated risk of depression, anxiety and conduct disorder symptoms in offspring of mothers with mental health problems. A systematic review and meta-analysis that synthesized the results of 191 primary studies found that maternal perinatal depression and anxiety were associated with a wide range of mental health and behavioral problems (83). This is also supported by findings of a meta-analysis that suggested a 32% increased likelihood of developing mental health problems in offspring of parents with mental health problems (84). Evidence has also shown that maternal history of depression and maternal anxiety symptoms might be related with offspring behavioral and anxiety symptoms, respectively (85-87).

2.6.2 Adverse pregnancy and birth outcomes (mediators)

Numerous epidemiological studies examined the association between adverse pregnancy and birth outcomes such as preeclampsia, preterm birth and low birthweight, and risk of mental health and substance use outcomes in offspring. A population-based study of 5231 mother-offspring pairs from ALSPAC study observed a 2.43-fold increased risk of anxiety disorders (88) and a 2.3-fold increased risk of depression (89) in adolescents of mothers with hypertensive disorders of pregnancy (HDP). Further, according to findings from the recent systematic review and meta-analysis, any form of HDP such as preeclampsia or gestational hypertension predicts approximately 1.5-fold increased risk of behavioural and severe mental illness in offspring (90). Furthermore, an additional systematic review and meta-analysis has estimated the risk of psychiatric diagnoses among preterm born and low birthweight adolescents and young adults (91). In that study, the odds of being diagnosed with any psychiatric illness increased approximately by 4-fold (AOR=3.66, 95% CI:2.57-5.21) and anxiety or depressive disorder increased by approximately 3-fold (AOR=2.86, 95% CI:1.73-4.73) in persons born preterm or with low birthweight.

2.6.3 Socio-demographic factors

Parental socio-demographic and economic factors may influence the link between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes included maternal educational status, age, family income, marital status, ethnicity, and others. Findings from epidemiological studies suggested that lower educational attainment and socioeconomic status including family income have been often reported by pregnant women who smoke tobacco during pregnancy compared to non-smoking pregnant women (66, 92-96).

These in turn have been associated with mental health and substance use problems in offspring (97, 98). Further, epidemiological studies also indicated that there is an association between advanced parental age and mental health problems in offspring. A systematic review and meta-analysis that synthesised the results of twenty-seven primary studies have reported an association between advanced parental age and behavioural problems in offspring (99).

2.6.4 Parental postnatal substance use and other factors

Postnatal environmental risk factors might play a significant role in the occurrence of mental health and substance use problems in adolescents. Evidence from longitudinal studies suggested that adolescents exposed to postnatal parental tobacco smoking may develop adverse mental health outcomes (97, 100). Similarly, substance use during adolescence may be largely affected by parental substance use (101). For instance, finding from a population-based cohort study suggested that offspring exposed to prenatal tobacco use are more likely to be exposed to maternal postnatal tobacco smoking in childhood if their mothers continued to smoke after the pregnancy (102) and may initiate tobacco smoking later in life by emulating their parents' smoking behaviour. Similarly, adolescents living with mothers drinking alcohol are at increased risks of developing problematic alcohol use in adolescence (103). Moreover, parity, familial alcohol dependence and prenatal stressful life events have also been associated with an increased risk of mental health problems in offspring (104-106).

2.7 Gaps identified in the existing literature

There are a few studies on prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes and as discussed in the preceding sections, the findings of these studies are conflicting. Further, there are also methodological differences in assessing mental health outcomes. Notably, prospective cohort studies examined the association between prenatal alcohol (39), and tobacco exposures (107) and the risk of behavioural problems in offspring reported only externalising and internalising behaviours total scores while not showing subscale scores of individual mental health problems such as conduct disorders, depression and anxiety, making replications of results more problematic. There are also disparities in study designs. Some previous studies may have over-estimated the risk due to selection bias as introduced by selection of clinical participants (54, 108, 109), suggesting the necessity of additional population-based studies that allow examinations of mental health and substance use problems in adolescents and young adults who represent a wide range of prenatal alcohol and tobacco exposures (110). Furthermore, the exposure status may be underestimated because of recall bias, measured several years after pregnancy and hinder the identification of

risks in terms of gestation as the assessment is done retrospectively. Most of existing studies focused exclusively on first trimester prenatal alcohol and tobacco exposures. Nonetheless, it has been believed that the timing of such exposures are critically important to identify risks in terms of gestational age at exposure (111). Furthermore, there was incomplete adjustment for immediate pregnancy outcomes such as preeclampsia, preterm birth and low birthweight, mental health status of parents, parental postnatal substance use and child previous mental health problems. Moreover, some of existing epidemiological studies used relatively small sample sizes. Small sample size could reduce the power of the study and result in less precise estimate.

2.8 Significance of this study

Globally, there are a few studies that have investigated the association between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. Adolescents exposed to prenatal alcohol and tobacco use may have an increased risk of mental health and substance use problems compared to non-exposed. Existing epidemiological studies suggest that the risk of developing mental health and substance use problems in offspring considerably differ by type of prenatal exposure (e.g. alcohol, tobacco, etc). Further, some studies have produced less precise estimates due to lack of statistical power from the small sample size. To address gaps in literature, more longitudinal studies with relatively larger sample sizes, which are warranted to produce more precise estimates and to improve the generalizability of the findings. This project used online available resources and existing data from a population-based prospective cohort study (the Raine Study) which allows comprehensive adjustment for confounders in testing the hypotheses. This project makes an important contribution to the sparse literature on effects of prenatal alcohol and tobacco exposures on offspring mental health and substance use outcomes during adolescence and young adulthood. Moreover, this project examined the association between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes and formulated recommendations and directions for clinical practice and future research.

2.9 Aims and hypothesis

2.9.1 Aim of this thesis

The main aim of this thesis was to examine the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes.

2.9.2 Specific aims of this thesis

The specific aims of this thesis were to:

1. Systematically review previous epidemiological research on the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes.
2. Test associations between maternal prenatal alcohol and tobacco exposures and the risk of depressive symptoms in adolescent offspring.
3. Examine the association between prenatal alcohol and tobacco exposures and the risk of anxiety symptoms in young adulthood.
4. Investigate the association between maternal prenatal tobacco smoking and conduct disorder symptoms in adolescent offspring.
5. Estimate the risk of subsequent substance use in offspring exposed to maternal prenatal alcohol and tobacco use.

2.9.3 Hypothesis

I hypothesized that after controlling for a wide range of confounders, maternal prenatal alcohol and tobacco exposures will still be associated with a greater risk of mental health and substance use outcomes in offspring.

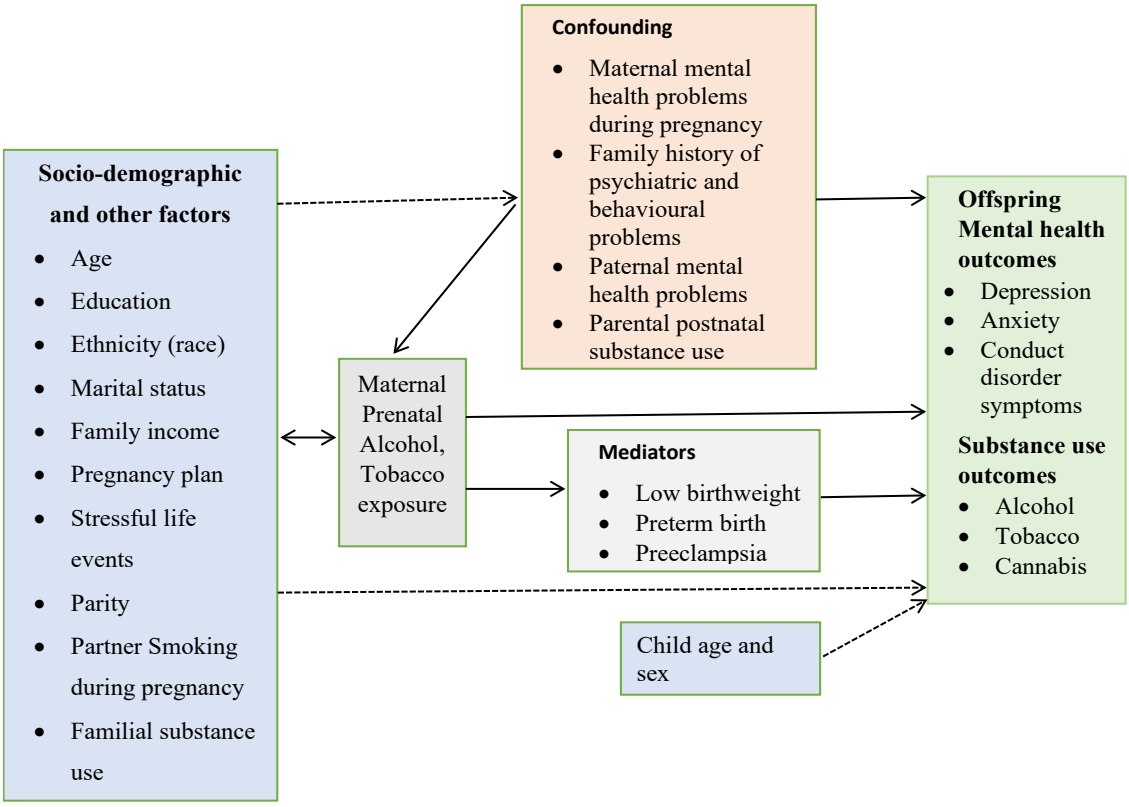


Figure 1. Overview of proposed pathways of prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes

References

1. Winklbaur B, Jung E, Fischer G. Opioid dependence and pregnancy. Current Opinion in Psychiatry. 2008;21(3).
2. Popova S, Lange S, Probst C, Gmel G, Rehm J. Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis. Lancet Glob Health. 2017;5(3):e290-e9.
3. AIHW. National Drug Strategy and Household Survey 2016. key findings online data tables Canberra: AIHW. 2017.
4. NHMRC. Australian guidelines to reduce health risks from drinking alcohol: Commonwealth of Australia. 2009. p. Pages 2, 3.
5. Lange S, Probst C, Rehm J, Popova S. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. The Lancet Global Health. 2018;6(7):e769-e76.
6. GBD. Global, regional, and national burden of 12 mental disorders in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet Psychiatry. 2022;9(2):137-50.
7. Zimmerman M, Morgan TA, Stanton K. The severity of psychiatric disorders. World Psychiatry. 2018;17(3):258-75.
8. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. J Child Psychol Psychiatry. 2015;56(3):345-65.
9. Bosquet M, Egeland B. The development and maintenance of anxiety symptoms from infancy through adolescence in a longitudinal sample. Dev Psychopathol. 2006;18(2):517-50.
10. Onunaku N. Improving Maternal and Infant Mental Health: Focus on Maternal Depression.Los Angeles, CA: National Center for Infantand Early Childhood Health Policy at UCLA. 2005.
11. Sadock BJ, Sadock VA, Ruiz P. Kaplan and Sadock's Synopsis of psychiatry 11th edition : behavioral sciences/clinical psychiatry,. Book chapter 31. 2015.
12. Kessler RC, Angermeyer M, Anthony JC, De Graaf R, Demyttenaere K, Gasquet I, et al. Lifetime prevalence and age-of-onset distributions of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):168-76.
13. WHO. Adolescents mental health report. 2018.
14. Lawrence D, Johnson S, Hafekost J, deHaan K, Sawyer M, Ainley J, et al. Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. 2015;Australian Government Department of Health.
15. Erskine HE, Ferrari AJ, Nelson P, Polanczyk GV, Flaxman AD, Vos T, et al. Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. J Child Psychol Psychiatry. 2013;54(12):1263-74.
16. APA. American Psychiatric Association, Diagnostic and statistical manual of mental disorders (5th ed.). 2013.
17. Mohammadi M-R, Salmanian M, Keshavarzi Z. The Global Prevalence of Conduct Disorder: A Systematic Review and Meta-Analysis. Iran J Psychiatry. 2021;16(2):205-25.
18. Lawrence D, Johnson S, Hafekost J, K Boterhoven De Haan , M Sawyer, J Ainley, et al. The Mental Health of Children and Adolescents. Report on the second Australian Child and Adolescent Survey of Mental Health and Wellbeing. Department of Health, Canberra. 2015.
19. Biederman J, Petty CR, Dolan C, Hughes S, Mick E, Monuteaux MC, et al. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. Psychol Med. 2008;38(7):1027-36.
20. Loeber R, Burke JD, Lahey BB, Winters A, Zera M. Oppositional defiant and conduct disorder: a review of the past 10 years, part I. J Am Acad Child Adolesc Psychiatry. 2000;39(12):1468-84.

21. Fairchild G. Adult outcomes of conduct problems in childhood or adolescence: further evidence of the societal burden of conduct problems. European Child & Adolescent Psychiatry. 2018;27(10):1235-7.
22. Lin YT, Hsu JW, Huang KL, Tsai SJ, Su TP, Li CT, et al. Sexually transmitted infections among adolescents with conduct disorder: a nationwide longitudinal study. Eur Child Adolesc Psychiatry. 2020.
23. Wei H-T, Lan W-H, Hsu J-W, Bai Y-M, Huang K-L, Su T-P, et al. Risk of Suicide Attempt among Adolescents with Conduct Disorder: A Longitudinal Follow-up Study. The Journal of Pediatrics. 2016;177:292-6.
24. Black DW. The Natural History of Antisocial Personality Disorder. The Canadian Journal of Psychiatry. 2015;60(7):309-14.
25. Sadock BJ, Sadock VA, P. R. Kaplan and Sadock's Synopsis of psychiatry 11th edition : behavioral sciences/clinical psychiatry,. Book chapter 8. 2015.
26. Keenan-Miller D, Hammen CL, Brennan PA. Health outcomes related to early adolescent depression. J Adolesc Health. 2007;41(3):256-62.
27. APA. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR, Washington, DC: American Psychiatric Association. 2000.
28. Craske MG, Rauch SL, Ursano R, Prenoveau J, Pine DS, Zinbarg RE. What is an anxiety disorder? Depress Anxiety. 2009;26(12):1066-85.
29. Johnson D, Dupuis G, Piche J, Clayborne Z, Colman I. Adult mental health outcomes of adolescent depression: A systematic review. Depress Anxiety. 2018;35(8):700-16.
30. Racine N, McArthur BA, Cooke JE, Eirich R, Zhu J, Madigan S. Global Prevalence of Depressive and Anxiety Symptoms in Children and Adolescents During COVID-19: A Meta-analysis. JAMA Pediatrics. 2021;175(11):1142-50.
31. Vos T, Lim SS, Abbafati C, Abbas KM, Abbasi M, Abbasifard M, et al. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. The Lancet. 2020;396(10258):1204-22.
32. Degenhardt L, Charlson F, Ferrari A, Santomauro D, Erskine H, Mantilla-Herrara A, et al. The global burden of disease attributable to alcohol and drug use in 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet Psychiatry. 2018;5(12):987-1012.
33. Griswold MG, Fullman N, Hawley C, Arian N, Zimsen SRM, Tymeson HD, et al. Alcohol use and burden for 195 countries and territories, 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. The Lancet. 2018;392(10152):1015-35.
34. AIHW. Australian institute health and welfare (AIHW), Alcohol, tobacco & other drugs in Australia, accessed March 28, 2019, . 2018.
35. Nazir MA, Al-Ansari A, Abbasi N, Almas K. Global Prevalence of Tobacco Use in Adolescents and Its Adverse Oral Health Consequences. Open Access Maced J Med Sci. 2019;7(21):3659-66.
36. Guerin N, White V. Australian secondary school students' use of tobacco, alcohol, and over-the-counter and illicit substances in 2017. Victoria: Centre for Behavioural Research in Cancer. 2018.
37. Keyes KM, Brady JE, Li G. Effects of minimum legal drinking age on alcohol and marijuana use: evidence from toxicological testing data for fatally injured drivers aged 16 to 25 years. Injury epidemiology. 2015;2(1):1.
38. Easey KE, Timpson NJ, Munafò MR. Association of Prenatal Alcohol Exposure and Offspring Depression: A Negative Control Analysis of Maternal and Partner Consumption. Alcohol Clin Exp Res. 2020;44(5):1132-40.
39. Robinson M, Oddy WH, McLean NJ, Jacoby P, Pennell CE, de Klerk NH, et al. Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. Bjog. 2010;117(9):1139-50.

40. Sayal K, Heron J, Golding J, Emond A. Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. Pediatrics. 2007;119(2):e426-34.
41. Derks EM, Hudziak JJ, van Beijsterveldt CE, Dolan CV, Boomsma DI. A study of genetic and environmental influences on maternal and paternal CBCL syndrome scores in a large sample of 3-year-old Dutch twins. Behav Genet. 2004;34(6):571-83.
42. Larkby CA, Goldschmidt L, Hanusa BH, Day NL. Prenatal alcohol exposure is associated with conduct disorder in adolescence: findings from a birth cohort. J Am Acad Child Adolesc Psychiatry. 2011;50(3):262-71.
43. Murray J, Burgess S, Zuccolo L, Hickman M, Gray R, Lewis SJ. Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a Mendelian randomisation study. J Child Psychol Psychiatry. 2016;57(5):575-84.
44. Ruisch IH, Dietrich A, Glennon JC, Buitelaar JK, Hoekstra PJ. Maternal substance use during pregnancy and offspring conduct problems: A meta-analysis. Neuroscience & Biobehavioral Reviews. 2018;84:325-36.
45. Goldschmidt L, Richardson GA, De Genna NM, Cornelius MD, Day NL. Prenatal alcohol exposure and offspring alcohol use and misuse at 22 years of age: A prospective longitudinal study. Neurotoxicology and teratology. 2019;71:1-5.
46. O'Brien JW, Hill SY. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. Alcohol Clin Exp Res. 2014;38(12):2952-61.
47. Alati R, Al Mamun A, Williams GM, O'Callaghan M, Najman JM, Bor W. In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study. Arch Gen Psychiatry. 2006;63(9):1009-16.
48. Zaso MJ, Youngentob SL, Park A. Characterizing the role of early alcohol reexposure in associations of prenatal alcohol exposure with adolescent alcohol outcomes. Alcohol Clin Exp Res. 2021;45(7):1436-47.
49. Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. Am J Psychiatry. 2006;163(6):1061-5.
50. Pfinder M, Liebig S, Feldmann R. Adolescents' Use of Alcohol, Tobacco and Illicit Drugs in Relation to Prenatal Alcohol Exposure: Modifications by Gender and Ethnicity. Alcohol and Alcoholism. 2014;49(2):143-53.
51. Kyrklund-Blomberg NB, Granath F, Cnattingius S. Maternal smoking and causes of very preterm birth. Acta Obstet Gynecol Scand. 2005;84(6):572-7.
52. Mitchell EA, Thompson JM, Robinson E, Wild CJ, Becroft DM, Clark PM, et al. Smoking, nicotine and tar and risk of small for gestational age babies. Acta paediatrica (Oslo, Norway : 1992). 2002;91(3):323-8.
53. Agrawal A, Scherrer JF, Grant JD, Sartor CE, Pergadia ML, Duncan AE, et al. The effects of maternal smoking during pregnancy on offspring outcomes. Preventive medicine. 2010;50(1-2):13-8.
54. Talati A, Wickramaratne PJ, Wesselhoeft R, Weissman MM. Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry research. 2017;252:346-52.
55. Slotkin TA. Fetal nicotine or cocaine exposure: which one is worse? The Journal of pharmacology and experimental therapeutics. 1998;285(3):931-45.
56. Tiesler CM, Heinrich J. Prenatal nicotine exposure and child behavioural problems. Eur Child Adolesc Psychiatry. 2014;23(10):913-29.
57. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry. 2001;40(6):630-41.
58. Talati A, Wickramaratne PJ, Wesselhoeft R, Weissman MM. Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry research. 2017;252:346-52.

59. Slotkin TA, Ryde IT, Tate CA, Seidler FJ. Lasting effects of nicotine treatment and withdrawal on serotonergic systems and cell signaling in rat brain regions: separate or sequential exposure during fetal development and adulthood. Brain research bulletin. 2007;73(4-6):259-72.
60. Taylor AE, Carslake D, de Mola CL, Rydell M, Nilsen TIL, Bjørngaard JH, et al. Maternal Smoking in Pregnancy and Offspring Depression: a cross cohort and negative control study. Scientific reports. 2017;7(1):12579.
61. Menezes AM, Murray J, László M, Wehrmeister FC, Hallal PC, Gonçalves H, et al. Happiness and depression in adolescence after maternal smoking during pregnancy: birth cohort study. PLoS One. 2013;8(11):e80370.
62. Meier SM, Plessen KJ, Verhulst F, Mors O, Mortensen PB, Pedersen CB, et al. Familial confounding of the association between maternal smoking during pregnancy and internalizing disorders in offspring. Psychol Med. 2017;47(8):1417-26.
63. Cornelius MD, Goldschmidt L, Day NL. Prenatal cigarette smoking: Long-term effects on young adult behavior problems and smoking behavior. Neurotoxicology and Teratology. 2012;34(6):554-9.
64. Sutin AR, Flynn HA, Terracciano A. Maternal cigarette smoking during pregnancy and the trajectory of externalizing and internalizing symptoms across childhood: Similarities and differences across parent, teacher, and self reports. J Psychiatr Res. 2017;91:145-8.
65. Monshouwer K, Huizink AC, Harakeh Z, Raaijmakers QA, Reijneveld SA, Oldehinkel AJ, et al. Prenatal smoking exposure and the risk of behavioral problems and substance use in adolescence: the TRAILS study. Eur Addict Res. 2011;17(6):342-50.
66. Dolan CV, Geels L, Vink JM, van Beijsterveldt CE, Neale MC, Bartels M, et al. Testing Causal Effects of Maternal Smoking During Pregnancy on Offspring's Externalizing and Internalizing Behavior. Behav Genet. 2016;46(3):378-88.
67. Palmer RHC, Bidwell LC, Heath AC, Brick LA, Madden PAF, Knopik VS. Effects of Maternal Smoking during Pregnancy on Offspring Externalizing Problems: Contextual Effects in a Sample of Female Twins. Behavior genetics. 2016;46(3):403-15.
68. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal Smoking and Early Childhood Conduct Problems: Testing Genetic and Environmental Explanations of the Association. Archives of General Psychiatry. 2004;61(8):836-43.
69. Brion MJ, Victora C, Matijasevich A, Horta B, Anselmi L, Steer C, et al. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics. 2010;126(1):e57-65.
70. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, et al. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. Development and psychopathology. 2008;20(1):139-64.
71. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch Gen Psychiatry. 2004;61(8):836-43.
72. Silberg JL, Parr T, Neale MC, Rutter M, Angold A, Eaves LJ. Maternal smoking during pregnancy and risk to boys' conduct disturbance: an examination of the causal hypothesis. Biol Psychiatry. 2003;53(2):130-5.
73. Goldschmidt L, Cornelius MD, Day NL. Prenatal cigarette smoke exposure and early initiation of multiple substance use. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012;14(6):694-702.
74. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. Addiction. 2006;101(9):1313-22.
75. Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicology and teratology. 2005;27(2):267-77.
76. De Genna NM, Goldschmidt L, Richardson GA, Cornelius MD, Day NL. Prenatal exposure to tobacco and cannabis, early cannabis initiation, and daily dual use of combustible cigarettes and cannabis during young adulthood. Addictive Behaviors. 2021;116:106820.

77. Rydell M, Magnusson C, Cnattingius S, Granath F, Svensson AC, Galanti MR. Exposure to Maternal Smoking During Pregnancy as a Risk Factor for Tobacco Use in Adult Offspring. American Journal of Epidemiology. 2014;179(12):1409-17.
78. Rydell M, Magnusson C, Cnattingius S, Granath F, Svensson AC, Galanti MR. Exposure to maternal smoking during pregnancy as a risk factor for tobacco use in adult offspring. Am J Epidemiol. 2014;179(12):1409-17.
79. 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.
80. Menezes AM, Gonçalves H, Anselmi L, Hallal PC, Araújo CL. Smoking in early adolescence: evidence from the 1993 Pelotas (Brazil) Birth Cohort Study. J Adolesc Health. 2006;39(5):669-77.
81. Menezes AM, Hallal PC, Horta BL. Early determinants of smoking in adolescence: a prospective birth cohort study. Cad Saude Publica. 2007;23(2):347-54.
82. Murray KW, Duggan A. Understanding Confounding in Research. Pediatrics in Review. 2010;31(3):124.
83. Rogers A, Obst S, Teague SJ, Rossen L, Spry EA, Macdonald JA, et al. Association Between Maternal Perinatal Depression and Anxiety and Child and Adolescent Development: A Meta-analysis. JAMA Pediatrics. 2020;174(11):1082-92.
84. Rasic D, Hajek T, Alda M, Uher R. Risk of Mental Illness in Offspring of Parents With Schizophrenia, Bipolar Disorder, and Major Depressive Disorder: A Meta-Analysis of Family High-Risk Studies. Schizophrenia Bulletin. 2014;40(1):28-38.
85. Rees S, Channon S, Waters CS. The impact of maternal prenatal and postnatal anxiety on children's emotional problems: a systematic review. European child & adolescent psychiatry. 2019;28(2):257-80.
86. Fergusson DM, Lynskey MT. The effects of maternal depression on child conduct disorder and attention deficit behaviours. Soc Psychiatry Psychiatr Epidemiol. 1993;28(3):116-23.
87. Halligan SL, Murray L, Martins C, Cooper PJ. Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. J Affect Disord. 2007;97(1-3):145-54.
88. Dachew BA, Scott JG, Mamun A, Alati R. Hypertensive disorders of pregnancy and the risk of anxiety disorders in adolescence: Findings from the Avon Longitudinal Study of Parents and Children. J Psychiatr Res. 2019;110:159-65.
89. Dachew BA, Scott JG, Betts K, Mamun A, Alati R. Hypertensive disorders of pregnancy and the risk of offspring depression in childhood: Findings from the Avon Longitudinal Study of Parents and Children. Dev Psychopathol. 2020;32(3):845-51.
90. Maher GM, O'Keeffe GW, Kearney PM, Kenny LC, Dinan TG, Mattsson M, et al. Association of Hypertensive Disorders of Pregnancy With Risk of Neurodevelopmental Disorders in Offspring: A Systematic Review and Meta-analysis. JAMA Psychiatry. 2018;75(8):809-19.
91. Burnett AC, Anderson PJ, Cheong J, Doyle LW, Davey CG, Wood SJ. Prevalence of psychiatric diagnoses in preterm and full-term children, adolescents and young adults: a meta-analysis. Psychol Med. 2011;41(12):2463-74.
92. Al-Sahab B, Saqib M, Hauser G, Tamim H. Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. BMC Pregnancy and Childbirth. 2010;10(1):24.
93. Muhajarine N, D'Arcy C, Edouard L. Prevalence and predictors of health risk behaviours during early pregnancy: Saskatoon Pregnancy and Health Study. Canadian journal of public health = Revue canadienne de sante publique. 1997;88(6):375-9.
94. Stewart DE, Streiner DL. Cigarette smoking during pregnancy. Canadian journal of psychiatry Revue canadienne de psychiatrie. 1995;40(10):603-7.
95. Nagahawatte NT, Goldenberg RL. Poverty, maternal health, and adverse pregnancy outcomes. Ann N Y Acad Sci. 2008;1136:80-5.
96. Heaman MI, Chalmers K. Prevalence and correlates of smoking during pregnancy: a comparison of aboriginal and non-aboriginal women in manitoba. Birth. 2005;32(4):299-305.

97. Knopik VS. Maternal smoking during pregnancy and child outcomes: real or spurious effect? Developmental neuropsychology. 2009;34(1):1-36.
98. Rogers JM. Tobacco and pregnancy. Reproductive toxicology (Elmsford, NY). 2009;28(2):152-60.
99. Wu S, Wu F, Ding Y, Hou J, Bi J, Zhang Z. Advanced parental age and autism risk in children: a systematic review and meta-analysis. Acta Psychiatrica Scandinavica. 2017;135(1):29-41.
100. Kabir Z, Connolly GN, Alpert HR. Secondhand smoke exposure and neurobehavioral disorders among children in the United States. Pediatrics. 2011;128(2):263-70.
101. Richmond-Rakerd LS, Slutske WS, Heath AC, Martin NG. Genetic and environmental influences on the ages of drinking and gambling initiation: evidence for distinct aetiologies and sex differences. Addiction (Abingdon, England). 2014;109(2):323-31.
102. De Genna NM, Goldschmidt L, Day NL, Cornelius MD. Prenatal and Postnatal Maternal Trajectories of Cigarette Use Predict Adolescent Cigarette Use. Nicotine Tob Res. 2016;18(5):988-92.
103. Homel J, Warren D. The Relationship Between Parent Drinking and Adolescent Drinking: Differences for Mothers and Fathers and Boys and Girls. Subst Use Misuse. 2019;54(4):661-9.
104. Kingsbury M, Weeks M, MacKinnon N, Evans J, Mahedy L, Dykxhoorn J, et al. Stressful Life Events During Pregnancy and Offspring Depression: Evidence From a Prospective Cohort Study. J Am Acad Child Adolesc Psychiatry. 2016;55(8):709-16.e2.
105. Hill SY, Lowers L, Locke-Wellman J, Shen SA. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol. 2000;61(5):661-8.
106. MacKinnon N, Kingsbury M, Mahedy L, Evans J, Colman I. The Association Between Prenatal Stress and Externalizing Symptoms in Childhood: Evidence From the Avon Longitudinal Study of Parents and Children. Biol Psychiatry. 2018;83(2):100-8.
107. Roza SJ, Verhulst FC, Jaddoe VW, Steegers EA, Mackenbach JP, Hofman A, et al. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int J Epidemiol. 2009;38(3):680-9.
108. Chudal R, Brown AS, Gissler M, Suominen A, Sourander A. Is maternal smoking during pregnancy associated with bipolar disorder in offspring? Journal of affective disorders. 2015;171:132-6.
109. Streissguth AP, Barr HM, Kogan J, Bookstein FL. Understanding the occurrence of secondary disabilities in clients with fetal alcohol syndrome (FAS) and fetal alcohol effects (FAE). Final report to the Centers for Disease Control and Prevention (CDC). 1996:96-06.
110. Lynch ME, Kable JA, Coles CD. Effects of prenatal alcohol exposure in a prospective sample of young adults: Mental health, substance use, and difficulties with the legal system. Neurotoxicology and teratology. 2017;64:50-62.
111. Kesmodel U. Binge drinking in pregnancy--frequency and methodology. Am J Epidemiol. 2001;154(8):777-82.

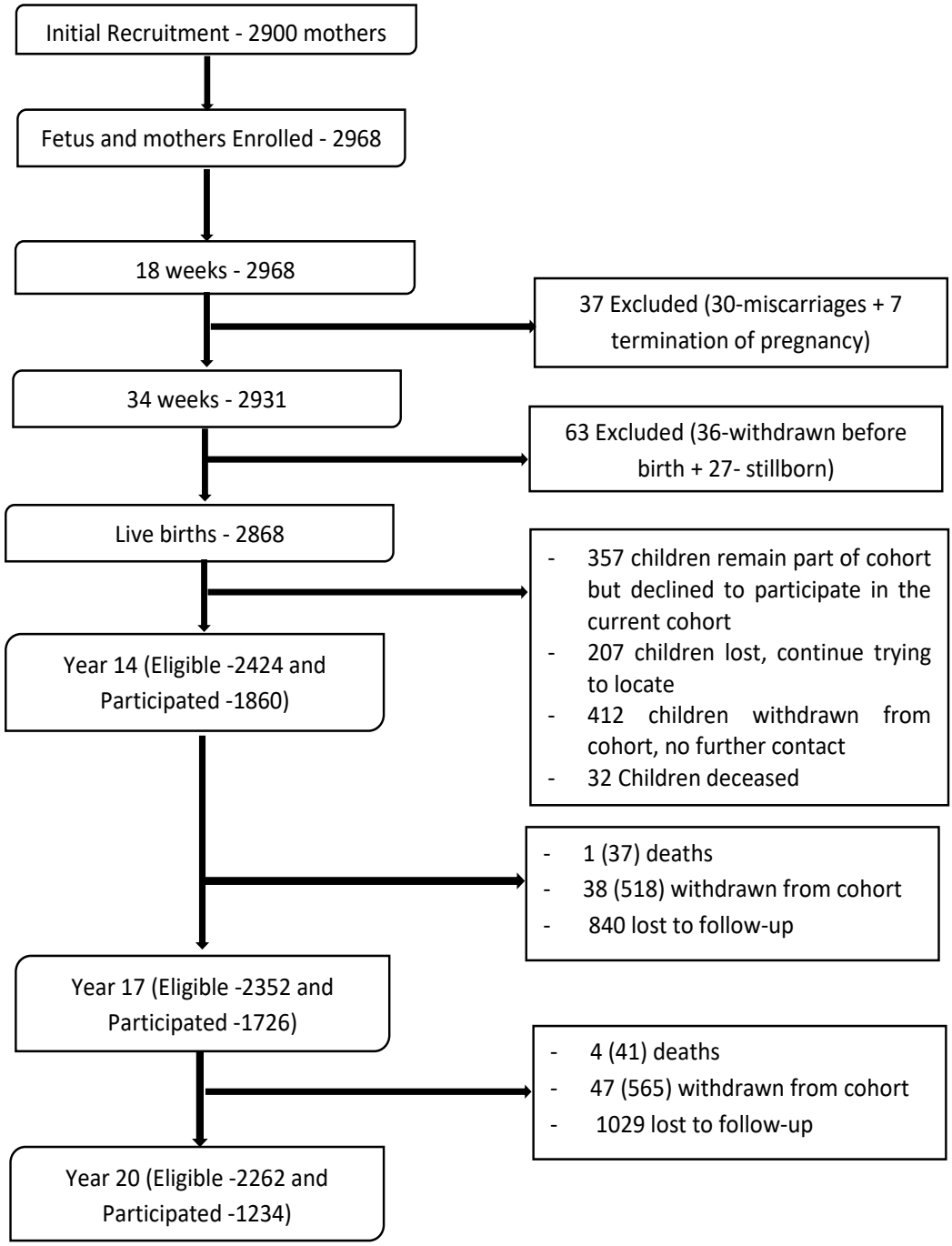
Chapter 3: Methodology

Chapter 3: Methodology

This chapter provides a concise summary of study design, participants, measures used and data sources. Subsequent chapters include a more comprehensive description of methods that have been followed to answer the specific research questions addressed in this project.

1.1 Overview of data source, study design, and population

To address the specific aims of this thesis, several electronic databases, and the Raine Study were used as potential data sources. More specifically, the electronic databases such as MEDLINE/PubMed, SCOPUS, PsycINFO and EMBASE were used as data sources for 3 systematic reviews and with 2 including meta-analyses. Data for primary studies were obtained from the Raine Study (Table 1). The Raine study is an ongoing prospective multigenerational cohort of pregnancy, childhood, adolescence, and adulthood (1, 2). The Raine Study is a well-known prospective cohort with extensive data collection on prenatal and environmental exposures and biological factors that can impact the health, development, and wellbeing of offspring. More comprehensive descriptions of the Raine Study have been published elsewhere (3) and also available at the study website (https://rainestudy.org.au/). Between 1989 and 1991, a total of 2730 pregnant women attending King Edward Memorial Hospital and nearby private clinics in Perth and expecting to give birth at the hospital and intending to remain in Western Australia were recruited between 16-20 weeks of gestation (3). From August 1989 to April 1992, these pregnancies resulted in a total of 2868 live births including 138 multiple pregnancies. This figure represents 94% of the initial recruitment sample (n=2900) (Figure 1). In this thesis we drew datasets regarding the perinatal and life course environmental exposures, and psychological and risky behavioural outcomes of participants. Perinatal and life course environmental exposures dataset included socio-demographic and economic variables, obstetric related variables, preeclampsia, and pregnancy adverse outcomes. Psychological datasets included maternal and child mental health, such as depression, anxiety and conduct disorder symptoms. In addition, the dataset included maternal use of alcohol and tobacco as well as alcohol, tobacco and cannabis use in adolescents. Offspring behavioural and mental health outcomes were assessed at age 14, 17 and 20 years. Alcohol, tobacco, and cannabis use were assessed at age of 17 years. This study was approved by the Human Research Ethics Committees (HREC) of the University of Western Australia. Written informed consent was obtained from each study participant at enrolment and at each subsequent assessment after the details of the procedures had been fully described. Pregnant women and their children are referred to as Generation 1(Gen1) and 2 (Gen2) of the Raine Study, respectively.



Source from Straker et al (1)

Figure 1. Showing the characteristics of study participants at each follow-up from birth to 20 years.

3.2 Measures

3.2.1 Measure for prenatal alcohol and tobacco exposures (Gen1)

At 18 and 34 weeks of gestations, pregnant mothers self-reported the number of spirits, glasses of wine, cans or 375-ml bottles of low to full strength beer consumed during the first three months of pregnancy and they were currently drinking, respectively. These data converted into a continuous variable indicating the total number of standard drinks of alcohol consumed per week. Based on the National Health and Medical Research Council (NHMRC) guidelines of 2009, one standard drink in Australia constitutes 10 grams of absolute alcohol (4), which is approximately equal to 285 mL of full strength beer (4.8% alcohol), 425 mL of low strength beer (2.7% alcohol), 375mL of mid strength beer (3.5% alcohol), 100 mL of champagne (12% alcohol), 330 mL of spirits (40% alcohol), 275 mL bottle of ready-to-drink beverage (5% alcohol) and 100 mL of wine (red - 13% alcohol, and white – 11.5% alcohol). There has been no widely accepted standard on the amount of alcohol that represent light to heavy drinking during prenatal period. As a result, we used NHMRC guidelines of 2009 (4) and several other studies were used as a reference to categorize prenatal alcohol exposure.

At same time points in pregnancy, pregnant mothers also reported the numbers of cigarettes they had smoked per day during the first and third trimesters of pregnancy. These data were used to categorize pregnant mothers as either non-smokers or smokers. Further, a study was conducted by Stick et al. to validate self-reports of prenatal tobacco exposure (5). In that study, cotinine was measured in serum from 238 pregnant mothers who reported cigarette smoking during the first three months of pregnancy (6). Cotinine is a biomarker of nicotine which accumulates in the body as a result of tobacco smoke exposure (7). Unlike nicotine, cotinine remains in the body system for several days (8), suggesting measuring cotinine is much better when compared to measuring nicotine. Evidence from that validation study (5) showed strong agreement between maternal self-reported prenatal tobacco exposure and measured serum cotinine concentration.

3.2.2 Measure for outcomes

As detailed below, well-accepted, standardized, and validated measurement tools were used to ascertain adverse mental health and substance use outcomes in children and young adults such as depression, anxiety, conduct disorder symptoms and alcohol, tobacco, and cannabis use.

Depressive symptoms at age of 17 years were measured using the Beck Depression Inventory for Youth (BDI-Y). The BDI-Y has been shown to be a reliable and valid tool to measure depressive symptoms (9) as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV-TR) for diagnoses of major depressive disorders in children

and adolescents (10). The BDI-Y incorporates 20 Likert scale items relating to depressed moods that have been experienced over the past 2 weeks. Its raw scores are transformed into summary scores (0 to 60) with higher scores suggesting a greater degree of depressive symptoms. In this study, summary scores were dichotomized as 'depressed' or 'not depressed' using the recommended cut-off score points (normal ≤13; mild-severe depression ≥14) (9). Experiencing symptoms of anxiety in young adults at the age of 20 years was ascertained by a short form of the Depression Anxiety Stress Scale (DASS 21). DASS is a 42-item scale designed by the University of New South Wales to measure depression, anxiety and stress (11, 12). The DASS-21 score was multiplied by two to obtain the normal DASS-42 score. This scale consists of 21 items, of which seven items measure anxiety symptoms, which were answered based on four-point frequency scales suggesting the severity of the specific symptoms (13, 14). It has shown high internal consistency for the anxiety subscale (Cronbach's alpha=0.76) (11, 12) in different settings (15, 16). In our study, participants were considered to be experiencing symptoms of anxiety according to the recommended severity thresholds, which is a DASS score of 8 and above (11, 12). Conduct Disorder symptoms at age of 14 years were measured using the Diagnostic Statistical Manual of Mental Disorders (DSM) oriented scales of the Child Behavioral Checklist (CBCL) (17). It has been reported that the DSM-oriented CBCL scales provide significantly better agreement with clinical DSM diagnoses than the syndrome scales (17). Furthermore, a previous epidemiological study that tested the diagnostic accuracy of DSM oriented CBCL scales in diagnosing conduct disorder found that such scales better differentiated between cases and non-cases of CD than conventional CBCL scales (18).

Alcohol, tobacco, and cannabis use at 17 years of age were measured by using a self-reported questionnaire developed by the Raine Study to capture risky behaviours in adolescents. Adolescents were asked, "Have you ever drunk six or more alcoholic drinks at one time or drunk so much alcohol that you vomited?" We grouped adolescents who responded "yes, more than once" to above question as 'harmful alcohol users' whereas those reported "never" or "only once" were used as a reference control group. This classification has been used in a previous study to categorize "harmful" and "non-harmful alcohol use" in the same cohort (19). We were also guided by the current NHMRC guidelines that recommend "healthy men and women should drink no more than ten standard drinks per week and no more than four standard drinks on any one day"(20). Nevertheless, it should be noted that the current guidelines recommend no alcohol use by those aged under 18 years. Adolescents were also asked to report whether or not they had smoked tobacco in the past four weeks. We grouped adolescents who

replied “yes” to above question as ‘current tobacco users’ whereas those reported “no” or “never smoked” were used as a reference control group. This categorization has been used in a previous study that used the same cohort data (19). Current tobacco use was reported as tobacco smoking in this thesis. Cannabis use at 17 years of age was measured by using a self-reported questionnaire developed to capture risky behaviours in adolescents. Adolescents were asked, “How often do you use cannabis (marijuana) for non-medical purposes?” We grouped adolescents who responded daily, weekly and monthly use to the above question as ‘current cannabis users’ whereas those reported ‘never’ and ‘once over one year ago’ were categorized as non-current cannabis users/abstainers. A previous study from the same cohort has used a similar classification to categorize cannabis use in adolescents at age of 17 years (19). Current cannabis use was reported as cannabis use in this thesis. Further to examine whether the associations between prenatal alcohol and tobacco exposures and offspring cannabis use differ when the way cannabis use differed in the sensitivity analysis, cannabis use was defined as non-users/abstainers, lifetime users (cannabis use once over one year ago) and current users (daily/weekly/monthly use).

3.2.3 Measure for confounders and covariates

In this thesis, the decision to include all potential confounders and relevant covariates in the multivariable regression models was guided by the following criteria. First, variables that fulfill confounding variable criteria, affect the association between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. Second, variables that are available in our dataset (Figure 4). Moreover, all other variables which were identified in previous studies and available in our dataset were considered as covariates and confounders (Figure 5).

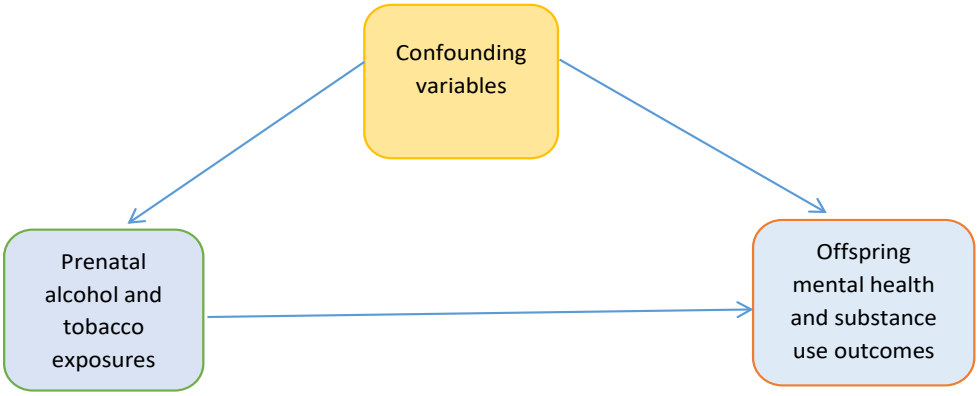


Figure 2. Schematic presentation of the relationship between exposures, confounders, and outcomes.

3.2.3.1 Parental mental health problems

Parental mental health problems that are found to be associated with prenatal alcohol and tobacco exposures and offspring mental health and substance use problems were included in sequential models. These mental health problems included maternal depressive and anxiety symptoms, maternal history of mental health problems during pregnancy and paternal emotional problems. Maternal depressive and anxiety symptoms (Gen1) were ascertained by Depression Anxiety Stress Scale (DASS 42) at 14 years of follow-up. This scale is a 42-items questionnaire often used to depict depression, anxiety and stress symptoms in adults. The internal consistency was reported be excellent for depression (.89) and anxiety (.76) subscales (11, 12). We grouped mothers who scored $\geq$ 10 and $\geq$ 8 as having clinically significant depressive and anxiety symptoms, respectively using the recommended conventional severity thresholds. Maternal self-reported history of maternal mental health problems assessed during pregnancy was also included in this study. Paternal lifetime history of emotional problems was assessed (yes/no) at the 13 years follow-up phase using a self-reported item.

3.2.3.2 Adverse pregnancy and birth outcomes

Adverse pregnancy and birth outcomes such as preeclampsia (yes/no), low birthweight and preterm birth were also included in the multivariable regression models. Low birthweight operationalized as a birthweight of less than 2,500g and preterm birth as birth before 37 completed weeks (Figure 3).

3.2.3.3 Childhood sleep and existing mental health problems

Findings from epidemiological studies reported that maternal prenatal tobacco smoking was associated with an increased risk of sleep problems in offspring (21), which in turn results in mental health problems such as anxiety in offspring (22). Therefore, we included childhood sleep problems (Gen2) in our study. Childhood sleep problems, anxious/depressed behaviors and aggressive behaviors at the age of 10 years was measured using the child behavioural checklist (CBCL).

3.2.3.4 Sociodemographic and other factors

The risk factors that influence the decision to consume alcohol and tobacco during pregnancy were also included in this study. The variables related to maternal sociodemographic position were obtained from baseline questionnaires completed by pregnant mothers at 18 weeks of gestation. These were: maternal education, ethnicity, maternal age during pregnancy, marital status, pre-pregnancy substance use, paternal smoking status during the mother's pregnancy (yes/no) and family income. Non-pathological factors included pregnancy plan, sex of child and parity.

3.2.3.5 Parental substance use

Data were also available on paternal tobacco smoking during partner's pregnancy, maternal postnatal alcohol, and tobacco use. At 18 weeks of pregnancy, mothers of study participants were reported the average number of cigarettes their partners (fathers of the study adolescents and young adults) had smoked per day during their pregnancy. Paternal tobacco smoking during partners' pregnancy was used as a proxy for environmental tobacco smoke exposure. Maternal postnatal tobacco (yes/no) were assessed at 14 and 16 years of follow-up. Mothers of study participants were also reported the average number of standard drinks of alcohol consumed per week at 14 and 16 years of follow-ups.

3.3 Data analysis

Bivariate and multivariate log-binomial, negative binomial, and multinomial logit models were used to examine the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes. The inverse variance weighted random effect meta-analysis models were also used to combine studies included in the meta-analyses. To better examine the role of covariates and confounders in the association between exposures and outcomes, covariates and confounders have been included as adjustment variables in sequential models. Relative risks (RR) were used for measures of association and P-value < 0.05 was set for statistical significance. Negative binomial regression was used to estimate the risk as incidence rate ratios (IRR) of CD symptoms in offspring. All statistical analyses were conducted in the Comprehensive Meta-Analysis 3.0 (CMA) and Stata 16.1. Moreover, we employed multivariate imputation by chained equation using the STATA "mice" command to minimize the possibility of bias due to attrition, drawing data on sociodemographic factors collected at 18-weeks of gestation. In the multivariate imputation, 50 cycles of regression switching were used to generate 50 imputed datasets. The potential explanatory variables (except predictors and outcome variables) along with auxiliary variables predictive of incomplete variables were included in the regression model and imputed, and analyses were repeated for each imputation before being combined. The resulting Monte Carlo errors (<5%) of the standard error, suggested 50 imputed datasets were sufficient. Such approach results unbiased estimates and provides more validity than ad hoc approaches to missing data. Further, the use of available data, preserving sample size and statistical power with standard statistical software are additional advantages of such approach. However, the validity of the multiple imputation results will be questionable if there is an incompatibility between the imputation model and the analysis model, or if the imputation model is less general than the analysis

model. More comprehensive descriptions of statistical approaches and additional sensitivity analyses were explained in respective chapters.

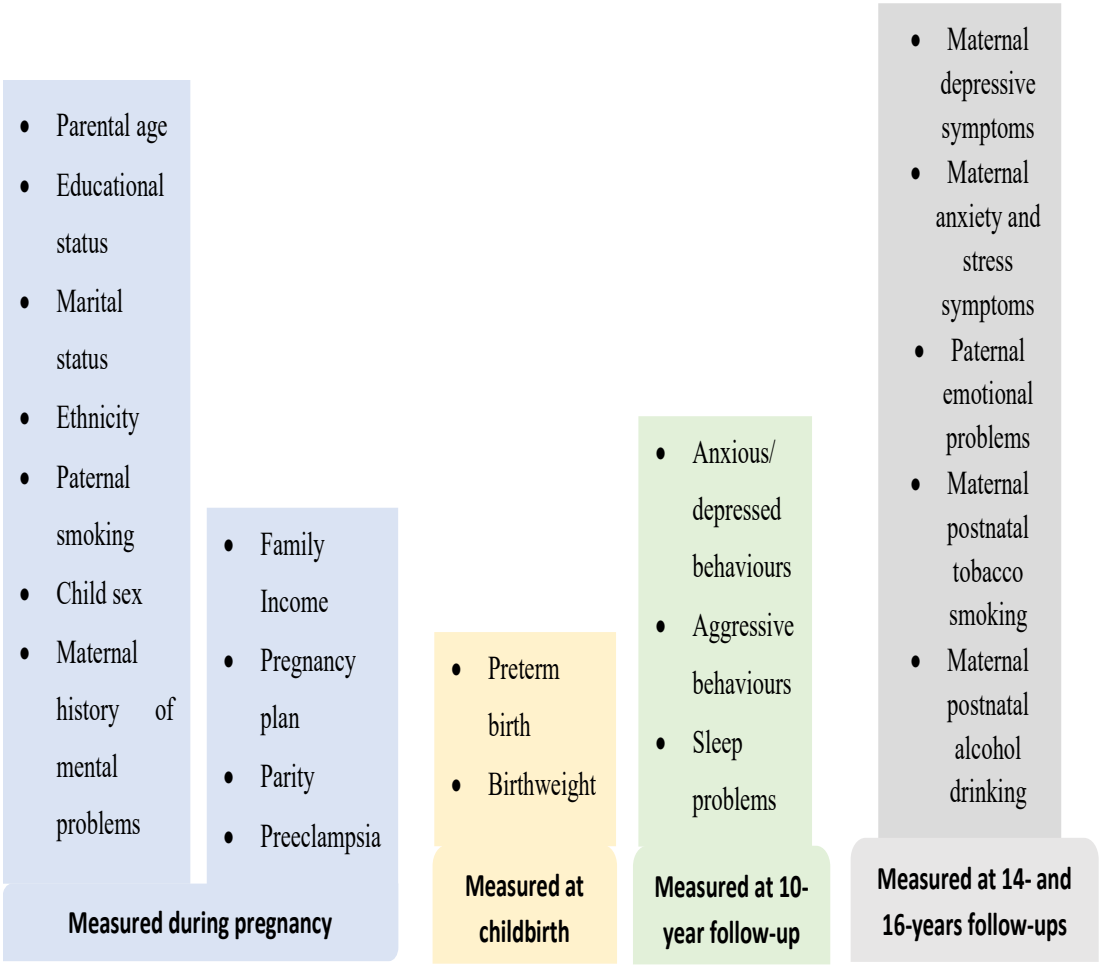


Figure 4. List of all relevant variables that are included in this study (outcomes of interest were not shown here)

Table 1. Summary of exposure variables, offspring outcomes, data sources and analysis of studies included in the thesis.

Study full title	Chapter	Data source/s	Outcome variables	Data analysis	Published at
Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis	4	PubMed, PsycINFO, EMBASE, SCOPUS	Mood disorders	Random effect meta-analysis	Social Psychiatry and Psychiatric Epidemiology
Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study.	4	The Raine Study	Depressive symptoms	Log-binomial regression	Journal of Affect Disorders
Prenatal Tobacco and Alcohol Exposures and the Risk of Anxiety Symptoms in Young Adulthood: a Population-Based cohort study	4	The Raine Study	Anxiety symptoms in young adults	Log-binomial regression	Psychiatry research
Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: Findings from the Raine Study.	5	The Raine Study	Conduct disorder symptoms	Negative-binomial regression	Journal of psychiatric research
Prenatal alcohol exposure and offspring subsequent alcohol use: a systematic review	6	PubMed, PsycINFO, EMBASE, SCOPUS	Alcohol use	Narrative data synthesis	Drug and Alcohol Dependence
Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study.	6	The Raine Study	Harmful alcohol use	Log-binomial regression	Drug and Alcohol Dependence
Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-Analysis.	7	PubMed, PsycINFO, EMBASE, SCOPUS	Tobacco smoking (several outcomes)	Random effect meta-analysis	Drug and Alcohol Dependence
Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence.	7	The Raine Study	Tobacco smoking	Log-binomial regression (negative control)	Addictive Behaviors
Prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring: Findings from a population-based cohort study	8	The Raine Study	Cannabis use	Log-binomial regression, multinomial logit models	Neurotoxicology and Teratology

References

1. Straker L, Mountain J, Jacques A, White S, Smith A, Landau L, et al. Cohort Profile: The Western Australian Pregnancy Cohort (Raine) Study-Generation 2. Int J Epidemiol. 2017;46(5):1384-5j.
2. Newnham JP, Evans SF, Michael CA, Stanley FJ, Landau LI. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet (London, England). 1993;342(8876):887-91.
3. Dontje ML, Eastwood P, Straker L. Western Australian pregnancy cohort (Raine) Study: Generation 1. BMJ Open. 2019;9(5):e026276.
4. NHMRC. Australian guidelines to reduce health risks from drinking alcohol: Commonwealth of Australia. 2009. p. Pages 2, 3.
5. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. The Lancet. 1996;348(9034):1060-4.
6. Sharma P, Sane N, Anand SD, Marimutthu P, Benegal V. Assessment of cotinine in urine and saliva of smokers, passive smokers, and nonsmokers: Method validation using liquid chromatography and mass spectrometry. Indian journal of psychiatry. 2019;61(3):270-6.
7. Moran VE. Cotinine: Beyond that Expected, More than a Biomarker of Tobacco Consumption. Frontiers in pharmacology. 2012;3:173-.
8. Raja M, Garg A, Yadav P, Jha K, Handa S. Diagnostic Methods for Detection of Cotinine Level in Tobacco Users: A Review. J Clin Diagn Res. 2016;10(3):ZE04-ZE6.
9. Beck JS, Beck AT, Jolly BJ. Beck youth inventories of emotional and social impairment." The Psychological Corporation, San Atonio , TX (2001). 2001.
10. APA. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR, Washington, DC: American Psychiatric Association. 2000.
11. Lovibond SH, Lovibond P. Manual for the Depression Anxiety Stress Scales (DASS). University of New South Wales. 1993.
12. Akin A, Citin B. The Depression Anxiety and StressScale (DASS): The study of Validityand Reliability. Educational Sciences: Theory & Practice. 2007;7(1):260-8.
13. Le MTH, Tran TD, Holton S, Nguyen HT, Wolfe R, Fisher J. Reliability, convergent validity and factor structure of the DASS-21 in a sample of Vietnamese adolescents. PloS one. 2017;12(7):e0180557-e.
14. Tully PJ, Zajac IT, Venning AJ. The Structure of Anxiety and Depression in a Normative Sample of Younger and Older Australian Adolescents. J Abnorm Child Psychol. 2009;37(5):717.
15. Szabó M. The short version of the Depression Anxiety Stress Scales (DASS-21): factor structure in a young adolescent sample. J Adolesc. 2010;33(1):1-8.
16. Lee J, Lee EH, Moon SH. Systematic review of the measurement properties of the Depression Anxiety Stress Scales-21 by applying updated COSMIN methodology. Qual Life Res. 2019;28(9):2325-39.
17. Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol. 2003;32(3):328-40.
18. Hudziak JJ, Copeland W, Stanger C, Wadsworth M. Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: a receiver-operating characteristic analysis. J Child Psychol Psychiatry. 2004;45(7):1299-307.
19. Moore SE, Norman RE, Sly PD, Whitehouse AJO, Zubrick SR, Scott J. Adolescent peer aggression and its association with mental health and substance use in an Australian cohort. Journal of Adolescence. 2014;37(1):11-21.
20. NHMRC. Draft Australian Guidelines to Reduce Health Risks from Drinking Alcohol, 2020, https://www.nhmrc.gov.au/health-advice/alcohol 2020.
21. O'Callaghan F, O'Callaghan M, Scott JG, Najman J, Al Mamun A. Effect of maternal smoking in pregnancy and childhood on child and adolescent sleep outcomes to 21 years: a birth cohort study. BMC Pediatrics. 2019;19(1):70.
22. McMakin DL, Alfano CA. Sleep and anxiety in late childhood and early adolescence. Current opinion in psychiatry. 2015;28(6):483-9.

Chapter 4: Prenatal alcohol and tobacco exposures and offspring depression and anxiety

Chapter 4: Prenatal alcohol and tobacco exposures and offspring depression and anxiety

This chapter included three papers that examined the association between prenatal alcohol and tobacco exposures and the risk of mood disorders, depressive and anxiety symptoms in their offspring during childhood, adolescence, and young adulthood. The first paper examined the risk of mood disorders such as depressive and bipolar disorders in offspring exposed to prenatal tobacco using a systematic review and meta-analysis of published studies on the topic. The second paper tested the association between maternal prenatal alcohol and tobacco exposures and the risk of depressive symptoms in late adolescence using data from the Raine Study. The third paper examined the prospective association between maternal prenatal alcohol and tobacco exposures and the risk of experiencing symptoms of anxiety in young adults, which is also based on the data from the Raine Study. All papers included in this chapter have been published in the Social Psychiatry and Psychiatric Epidemiology; Journal of affective disorders, and Psychiatry Research. All studies included in this chapter addressed the following research objectives: to systematically review previous epidemiological research on the associations between prenatal tobacco exposures and offspring mental health outcomes; test associations between maternal prenatal alcohol and tobacco exposures and the risk of depressive symptoms in adolescents at the age of 17 years; and examine the association between prenatal alcohol and tobacco exposures and the risk of experiencing anxiety symptoms in young adulthood.

Paper 1: **Duko B**, Ayano G, Pereira G, Betts K, Alati R. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology. 2020;55(12):1549-62.

Paper 2: **Duko B**, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study. Journal of Affective Disorders. 2021; 279:426-33.

Paper 3: **Duko B,** Pereira G, Tait RJ, Newnham J, Betts K, Alati R**.** Prenatal Tobacco and Alcohol Exposures and the Risk of Anxiety Symptoms in Young Adulthood: a Population-Based Cohort Study. Psychiatry Research 2022; 310:114466.

4.1 Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis

Published manuscript and formal citation

Duko B, Ayano G, Pereira G, Betts K, Alati R. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Social Psychiatry and Psychiatric Epidemiology. 2020;55(12):1549-62.

Supplementary material associated with this article can be found, in the online version, at **https://doi.org/10.1007/s00127-020-01949-y.**

Study purpose: Although it is plausible that offspring born to mothers using tobacco during pregnancy may have increased risk of mood disorders, epidemiological studies have reported mixed results including null, detrimental, and protective effects. This systematic review and meta-analysis was conducted to examine the magnitude and consistency of associations reported between prenatal tobacco use and mood disorders in offspring.

Social Psychiatry and Psychiatric Epidemiology (2020) 55:1549–1562
https://doi.org/10.1007/s00127-020-01949-y

REVIEW

Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis

Bereket Duko[1] · Getinet Ayano[1] · Gavin Pereira[1,2,3] · Kim Betts[1] · Rosa Alati[1,4]

Received: 24 March 2020 / Accepted: 1 September 2020 / Published online: 7 September 2020

Abstract

Purpose It is plausible that offspring born to mothers using tobacco during pregnancy may have increased risk of mood disorders (depression and bipolar disorders); however, mixed results have been reported. We conducted a systematic review and meta-analysis to investigate the magnitude and consistency of associations reported between prenatal tobacco use and mood disorders in offspring.

Methods We systematically searched EMBASE, SCOPUS, PubMed and Psych-INFO for studies on mood disorders and prenatal tobacco use. Methodological quality of studies was assessed with the revised Newcastle–Ottawa Scale. We estimated pooled relative risk (RR) with inverse variance weighted random-effects meta-analysis. We performed leave-one-out analyses, and stratified analyses by a subgroup (depression and bipolar disorder). Potential publication bias was assessed by inspection of the funnel plot and Egger's test for regression asymmetry. This study protocol was prospectively registered in PROSPERO (CRD42017060037).

Results Eight cohort and two case–control studies were included in the final meta-analysis. We found an increased pooled relative risk of mood disorders in offspring exposed to maternal prenatal tobacco use RRs 1.43 (95% CI 1.27–1.60) compared to no prenatal tobacco use. Similarly, the pooled relative risks of bipolar and depressive disorders in offspring were 1.44, (95% CI 1.15–1.80) and 1.44, (95% CI 1.21–1.71), respectively. Moreover, the pooled estimated risk of mood disorders was not significantly attenuated in the studies that reported sibling comparison results [RR = 1.21 (95% CI 1.04–1.41)].

Conclusion Taken together, there was strong evidence for a small (RR < 2) association between prenatal tobacco use and mood disorders in offspring.

Keywords Mood disorders · Bipolar disorder · Depression · Offspring · Prenatal · Tobacco · Systematic review · Meta-analysis

Introduction

Mood disorders, also known as affective disorders, are a group of mental health disorders consisting of bipolar and major depressive disorders [1, 2] which can impair the psycho-social

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00127-020-01949-y) contains supplementary material, which is available to authorized users.

✉ Bereket Duko
b.adema@postgrad.curtin.edu.au

Getinet Ayano
g.yaya@postgrad.curtin.edu.au

Gavin Pereira
Gavin.F.Pereira@curtin.edu.au

Kim Betts
Kim.Betts@curtin.edu.au

Rosa Alati
Rosa.Alati@curtin.edu.au

[1] School of Public Health, Curtin University, Kent Street, Bentley, WA 6102, Australia

[2] Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, 15 Hospital Ave, Nedlands, WA 6009, Australia

[3] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway

[4] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, QLD 4068, Australia

functioning of individuals and significantly affect their quality of life [3]. A 6% lifetime prevalence of depression has been reported globally [4] and the global mental health survey conducted across 11 countries in America, Europe and Asia using the World Health Organization Composite International Diagnostic Interview (WHO-CIDI) version 3.0 reported a 2.4% lifetime prevalence of bipolar disorders [5].

Observational studies and randomized controlled trials have been unable to confirm the causes of mood spectrum disorders [6]. However, it has been hypothesized that the imbalances of certain neurotransmitters which are important regulators of the bodily functions [7], genetic factors [5] and environmental factors [1] can significantly contribute to mood disorders. In addition, it has been reported that maternal lifestyle behaviors during pregnancy may result in mental and behavioral problems in offspring via early programming of the developing brain [8].

Tobacco use during pregnancy is one of such behaviours, which may increase risk of mood or other mental disorders through direct pathways [9, 10]. For example, tobacco modulates nicotinic acetylcholine receptors in the brain and results in alterations in the neurodevelopmental trajectory of widespread pathways [9]. Further, a systematic review conducted to test the association between smoking and depressive disorders revealed adverse associations in more than a third of the included studies [11]. However, the level to which observed offspring mental health problems constitute a direct effect of exposure of tobacco remains unclear [12–14].

Tobacco is a commonly used legal drug during pregnancy [15] with epidemiological studies indicating this exposure may increase the risk of bipolar [16–18] and depressive disorders [19–22] in offspring. However, additional studies have produced inconsistent findings. For example, no association was found with internalizing behaviours, namely depression and withdrawal, among children in one study [23], while another study found a higher risk of depression only among prenatally exposed boys but no increased risk in females [24]. There is also suggestion of associations in the opposite direction. For instance, a retrospective cohort study conducted in the USA found that prenatal tobacco exposure was linked with lower risk of mood disorders [25]. Variability in assessment methods of mental health outcomes may explain these inconsistencies. Therefore, we conducted a systematic review and meta-analysis to assess the magnitude and consistency of associations reported between prenatal tobacco use and mood disorders in offspring.

Methods

Research design

This systematic review and meta-analysis followed the standards of quality for reporting a Meta-analysis Of Observational Studies in Epidemiology (MOOSE) [26, 27] and the Preferred Reporting Items for Systematic review and Meta-Analysis guidelines (PRISMA) [28]. The literature search strategy, study selection, data extraction, and synthesis were compiled with a pre-defined protocol which was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number of CRD42017060037 (https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=146976).

Literature search strategy

We systematically searched the following electronic databases with no language and date limits: EMBASE, SCOPUS, PubMed and Psych-INFO. An extensive search of these databases was conducted in August 2019. The search terms and keywords were: "(cigarette use OR cigarette smoking OR cigarette exposure OR tobacco use OR tobacco exposure OR nicotine use OR nicotine exposure OR substance use OR substance exposure) AND (prenatal OR antenatal OR pregnancy OR maternal) AND (offspring OR adolescents OR youths OR young OR child OR childhood OR young adults) AND (mental disorders OR internalizing behaviours OR depression OR bipolar disorder OR mood disorders OR depressive disorders OR severe mental illness OR hypomania OR mania OR mental illness OR mental disorder OR psychiatric disorders OR psychiatric morbidity)".

Eligibility criteria

The following inclusion criteria were set to include the studies in this systematic review and meta-analysis: (1) case–control or cohort studies, (2) the exposure of interest was prenatal tobacco use, (3) the outcome of interest was mood disorders, namely bipolar and major depressive disorders, (4) measured outcomes using odds ratio (OR) or relative risk (RR) estimates with 95% confidence intervals (CIs) or data to calculate these were reported. We were interested in offspring outcomes, namely depression and bipolar disorders, rather than a group of behavioral problems such as internalizing behaviours (anxious/depressed/withdrawal). Case reports, editorials, comments, abstracts of meeting or conferences, letters and studies conducted on animals were excluded from the review.

Data extraction

Two reviewers (BD and GA) independently conducted an electronic database searching and screening of titles as well as abstracts. The data extraction was performed based on the standardized data extraction form. Data were extracted systematically from each study: the first author name, year of publication, study characteristics including study design, measurement of bipolar or depressive disorder, trimester in which smoking initiated, country in which the study was conducted, confounders, point estimates of risk such as odds ratios (OR) or relative risk (RR) with 95% Confidence Intervals (CI) in accordance with the PRISMA guidelines [28]. Any sources of mental health outcomes, either self-report or maternal report or clinical report, were included in the review. Reviewer conflicts and issues raised during data extraction were resolved by discussion.

Study quality

The methodological quality of all selected studies was assessed using the revised Newcastle–Ottawa Scale (NOS) [29]. The quality assessment was done by two independent reviewers (BD and GA). NOS is a scale which is recommended for the quality assessment of observational studies such as cohort and case–control studies. It uses three standard grading categories such as high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3). These points were calculated using the following items namely: group selection (four items), comparability between the groups (one item), and outcome and exposure assessment (three items). Based on the scale, a maximum of one star could be given for each item in the group selection, outcome and exposure assessment categories as well as a maximum of two stars could be given for comparability. Conflicting scores among two reviewers were resolved by consensus and discussion.

Data synthesis and analysis

A meta-analysis was conducted using a Comprehensive Meta-Analysis (CMA) software version 3.0 [30]. All studies that reported an effect size were included in the meta-analysis. If multiple estimates were presented in the studies, RR were reported in this review. Only three studies conducted a separate analysis for the effects of moderate (< 10 cigarettes per day) and high tobacco smoking (≥ 10 cigarettes per day) during pregnancy on offspring mood disorders. We have included the estimates of high prenatal tobacco use of these studies in our pooled analysis to ensure sufficient exposure contrast. We have combined the included studies using inverse variance weighted random-effect meta-analysis model to estimate the association between exposure and account for heterogeneity across the studies [31]. We performed a subgroup and sensitivity analysis to identify the potential source of heterogeneity. We further conducted an additional analysis for those studies that reported sibling comparison results. We stratified analyses by outcomes (depression and bipolar disorders). To identify studies that were influential on the pooled estimate, we ran a leave-one-out sensitivity analysis, whereby one study was removed at a time and the pooled estimate was re-estimated on the remaining studies [32]. The magnitude of statistical heterogeneity between studies was evaluated using the Q- and I^2-statistic [30]. The scores of 25%, 50% and 75% were considered to refer low, moderate and high heterogeneity between studies, respectively [33]. Potential publication bias was assessed by inspection of the funnel plot and Egger's test for regression asymmetry [34].

Results

Study selection

A total of 3987 articles were identified by our initial literature search. Seventeen additional studies were obtained via a manual search from the reference lists of other studies. Of these, 585 were duplicates, depression and bipolar disorders were not measured as an outcome in 12 studies, in 10 studies depression was as assessed as an internalizing behaviours, and 3380 studies were found not to be related to the subject from title and abstract review. A total of 39 articles were retrieved for further screening and resulting in a total of 10 studies for a meta-analysis (Fig. 1).

Characteristics of included studies

The studies included in the systematic review and meta-analysis were published between September 2000 [35] and October 2017 [36, 37]. Among the included studies, four studies were conducted in the USA [18, 25, 35, 37], one in Sweden [16], two in Finland [20, 38], one in Denmark [39], one in Brazil [22] and one study was based in the UK and combined the data of the four birth cohorts including Avon Longitudinal Study of Parents and Children (ALSPAC, UK), Nord-Trondelag Health Study (HUNT, Norway), the Pelotas 1982 birth cohort (Brazil) and Swedish Sibling Health Cohort (Sweden) [36]. Eight were cohort studies [16, 18, 20, 22, 25, 35, 36, 39] and two were nested case–control studies [37, 38]. Three studies reported the additional sibling analysis results. Four studies assessed the risk of bipolar disorder in offspring exposed to prenatal tobacco use [16, 18, 37, 38] while seven studies assessed the risk of depression [20, 22, 25, 35–37, 39]. Four studies adjusted for maternal alcohol use during pregnancy. Five studies recruited the study

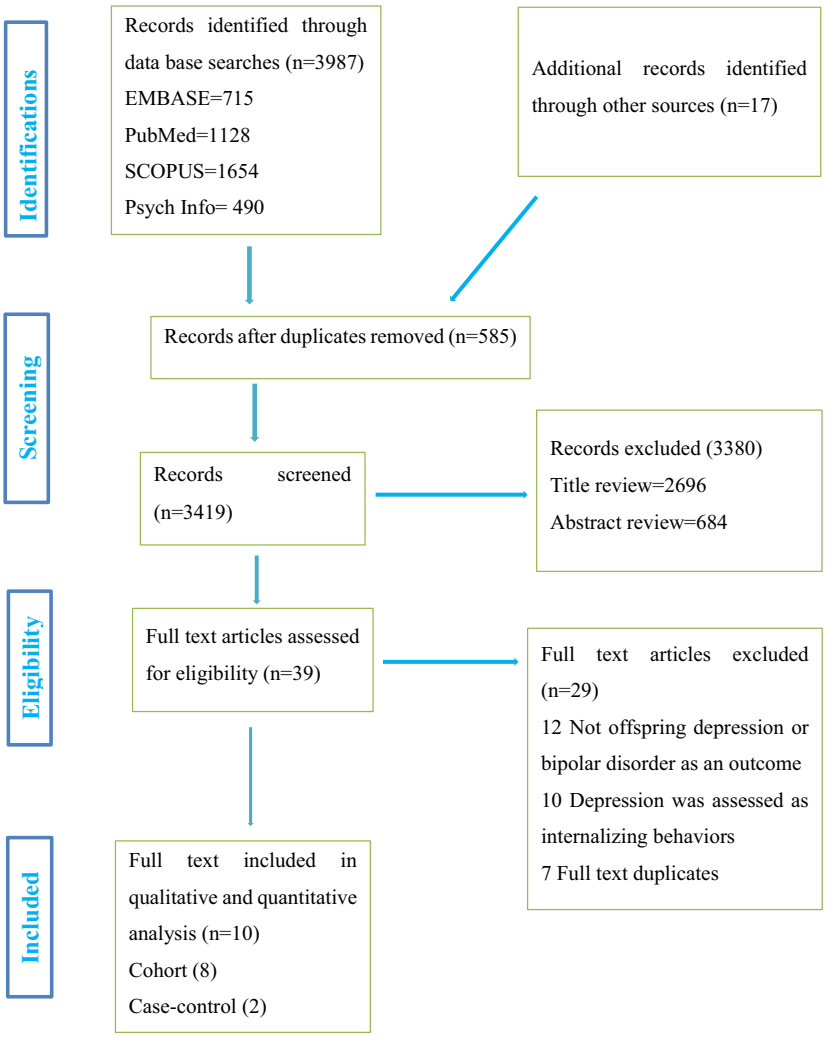


Fig. 1 PRISMA flowchart of review search

participants from clinical setting, whereas five studies from population-based registers. The sample size of the included studies ranges from 77 to approximately 1,312,516 participants (Table 1).

Outcome measures

Out of 10 studies included in the systematic review, three studies used the International Classification of Diseases and Related Health Problems, 10th edition (ICD-10) manual [20, 38, 39], one study used both ICD-9 and 10 [16], two studies used the fourth revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) [18, 37], two studies used the Schedule for Affective Disorders and Schizophrenia (SADS) [25, 35], one study used the Mini-International Psychiatric Interview (MINI) [22] and one study based in UK and combined the data of four birth cohorts used the Clinical Interview Schedule-Revised (CIS-R) (ALSPAC), Hospital Anxiety and Depression Scale (HADS) (HUNT) and Mini-International Psychiatric Interview (MINI) (Pelotas) [36] to screen and diagnose mood disorders in offspring.

The studies included in the review have screened or diagnosed mood disorders namely depression and bipolar disorders in offspring at different follow-up periods. For example, bipolar disorder was diagnosed in offspring between ages 10 and 30 years [16, 18, 37, 38]. Depressive disorder was screened and diagnosed in offspring at age ranges from 8 to 41 years [20, 22, 25, 35–37, 39]. For instance, a study conducted in the USA assessed depression in offspring at

Table 1 Characteristics of studies included in the current systematic review and meta-analysis

First author, year	Country	Study characteristics	Prenatal tobacco exposure assessed at	Outcome in offspring	Outcome assessed in offspring at/ follow-up period	Outcome ascertained by	Adjusted OR/RR (95% CI)	Adjusted for
Quinn et al., 2017	Sweden	This study analyzed a population register data via birth cohort of 1,680,219 individuals born in Sweden from January 1, 1983 to December 31, 2001	1st trimester	Bipolar disorder	Included offspring with age ≥ 12 years	International Classification of Diseases, 9th Revision, and International Statistical Classification of Diseases and Related Health Problems, 10th Revision	1.19 (1.12–1.25) (High prenatal tobacco use) 1.34 (1.26–1.43) (Moderate prenatal tobacco use)	Offspring sex, parity, maternal and paternal age at childbirth, education, maternal and paternal hospitalization for severe mental illness: substance use disorders and suicidal behavior, any criminal conviction and nationality
Talati et al., 2013	USA	This is a cohort of the Child Health and Development Study with live offspring that were enrolled at Kaiser Permanente Medical Care Plan, Northern California Region from 1959 to 1966 ($n = 214$)	Any time during pregnancy	Bipolar disorder	Cohort follow-up 1959–1966	Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)	2.01 (1.48–2.53)	Lifetime psychopathology such as; anxiety, emotional problems, psychoneuroses, hypochondriasis, neurasthenia, alcoholism, drug addiction or habituation, mental deficiency, or mental disorders. Lifetime diagnoses of schizophrenia or other psychotic disorders, affective disorder, and postpartum depression.
Chudal et al., 2015	Finland	A nested case–control study derived from all singleton live births in Finland between January 1st 1987 and December 31st 1998 (Finnish Prenatal study of Bipolar Disorders) (Cases = 724, Controls = 1419)	2nd trimester	Bipolar disorder	Offspring born between 1987 and 1988 were treated and diagnosed at 2008 and the mean age offspring at diagnosis of cases was 17.4 years	International Classification of Diseases, 9th Revision, and International Statistical Classification of Diseases and Related Health Problems, 10th Revision	1.14 (0.88–1.49)	Maternal age, maternal education, maternal psychiatry history, paternal psychiatry history

Table 1 (continued)

First author, year	Country	Study characteristics	Prenatal tobacco exposure assessed at	Outcome in offspring	Outcome assessed in offspring at/ follow-up period	Outcome ascertained by	Adjusted OR/RR (95% CI)	Adjusted for
Talati et al., 2017	USA	This study followed a 3-generation cohort of offspring of families with and without major depressive disorder over six assessment waves spanning up to 30 years ($n=238$)	Any time during pregnancy	Depression	The mean follow-up age was 27.7 years	Semi-structured schedule for Affective disorders and schizophrenia (SADS)-life time version for adults or the child version for ages 6–17 years	1.34 (0.77–2.31)	Offspring age at last interview, risk status, sex, maternal psychiatric illness, familial history for depression
Ekblad et al., 2010	Finland	This study used the data from a Finnish Medical Birth Register and included the 1987–1989 birth cohorts. (n=175,869)	1st trimester	Mood disorder	Included offspring with age between 18 and 26 years	International Statistical Classification of Diseases and Related Health Problems, 10th Revision	1.65 (1.54–1.76) (High prenatal tobacco use) 1.93 (1.78–2.10) (Moderate prenatal tobacco use)	Child's sex, gestational age, birth weight, and 5-min Apgar score and maternal age, parity, and psychiatric diagnosis before the child's birth
Hill et al., 2000	USA	A longitudinal prospective study of 150 children/ adolescents age 8–18 years	Any time during pregnancy	Depression	Included offspring with the ages of 8–18 years	Schedule for Affective Disorders and Schizophrenia for School-Aged Children (K-SADS)	3.43 (1.06–11.09)	Familial risk, prenatal alcohol use, other substance use
Menezes et al., 2013	Brazil	A birth cohort study of Pelotas with 5249 participants	Any time during pregnancy	Depression	Included offspring at 18 years of follow-up	Mini-International Neuropsychiatric Interview (MINI)	2.11 (1.31–3.40) (High prenatal tobacco use) 1.38 (1.03–1.84) (Moderate prenatal tobacco use)	Family income at birth, planned pregnancy, partner support of pregnancy, alcohol use during pregnancy, type of delivery, partner's smoking during pregnancy and mother's Strengths and Difficulties Questionnaire (SRQ) at age 11 years old

Table 1 (continued)

First author, year	Country	Study characteristics	Prenatal tobacco exposure assessed at	Outcome in offspring	Outcome assessed in offspring at/follow-up period	Outcome ascertained by	Adjusted OR/RR (95% CI)	Adjusted for
Taylor et al., 2017	UK	This study was based in UK and combined the data of four birth cohorts: Avon Longitudinal Study of Parents and Children (ALSPAC, UK), Nord-Trondelag Health Study (HUNT, Norway), the Pelotas 1982 birth cohort and Swedish Sibling Health Cohort	At 2nd and 3rd trimesters in ALSPAC, Trimester is not clear in HUNT, Anytime during pregnancy in Pelotas 1982, At 1st trimester in Swedish Sibling Health Cohort	Depression	Included offspring at 18 years in ALSPAC, 30 years in the Pelotas, 32.4 ± 8.6 years in HUNT, Not specified in Swedish Sibling Health Cohort	Clinical Interview Schedule—Revised (CIS-R) (ALSPAC), Hospital Anxiety and Depression Scale (HADS) (HUNT) and Mini-International Psychiatric Interview (MINI) (Pelotas 1982).	1.20 (1.08–1.34)	Age, sex, maternal age, partner social class, maternal education, maternal antenatal depression and anxiety, paternal depression and anxiety during pregnancy, parity, housing tenure, crowding, household income, assets index, partner smoking
Meier et al., 2017	Denmark	This study used data from a record linkage of six Danish population-based registries (nationwide cohort) of 957,635 individuals born in Denmark between 1991 and 2007	1st trimester	Depression	They followed offspring born between 1991 and 2007 from the 5th year birthday until offspring develop depression	International Statistical Classification of Diseases and Related Health Problems, 10th Revision	1.29 (1.22–1.36)	Calendar year of birth, gender, parity, parental age at time of birth, parental income, parental education, and parental psychiatric history
Biederman et al., 2017	USA	A case–control family study of children, recruited male and female age between 6 and 17 years (Exposed = 96, Non-exposed = 400)	1st trimester	Depression Bipolar disorder	The study recruited offspring aged 6–17 years	Diagnostic and Statistical Manual of Mental Disorders, Third and Fourth Edition, Text Revision (DSM-IV-TR)	1.71 (1.02–2.87) 1.56 (0.87–2.81)	Maternal age, race/ethnicity, Attention deficit hyperactivity disorder (ADHD) in offspring, parental antisocial personality and maladaptive parenting

age of 8–18 years [35]; whereas, the mean follow-up age of offspring in another similar study in the same country was 27.7 years [25] (Table 1).

Quality assessment of included studies

The revised Newcastle–Ottawa scale (NOS) was used to evaluate the quality of the included studies and the points were given based on the following criteria: Selection process (0–4 points), the comparability of the cohorts (0–2 points) and the identification of the exposures and the outcomes of research participants (0–3 points). The NOS score of ≥ 7 of 9 was considered of high quality in this review. Based on the averages of the scores given by two independent reviewers, all of the included studies scored ≥ 7 of 9 points (Supplementary file 1).

Prenatal tobacco exposure and risk of mood disorders

There was significant heterogeneity among the included studies ($I^2 = 81.22\%$; $Q = 52.24$; P value < 0.01), justifying our use of a random effect model. Prenatal tobacco use was associated with risk of mood disorders in offspring with a pooled adjusted RR of 1.43, (95% CI 1.27–1.60) (Fig. 2). Based on the stratification of the analysis by the type of outcomes in offspring, the pooled RR in offspring with bipolar disorder and depression was 1.44 (95% CI 1.15–1.80) and 1.44 (95% CI 1.21–1.71), respectively. We observed significant heterogeneity in bipolar disorder ($I^2 = 70.72\%$; $Q = 10.25$; P value $= 0.02$) as well as in depressive disorder ($I^2 = 86.03\%$; $Q = 42.96$; P value < 0.01).

Confounding variables in multivariable models

Apart from the studies conducted in Brazil [22] and in the USA [37], all other studies fully or partially adjusted for maternal psychiatric history, paternal psychiatric history, maternal lifetime psychopathology, parental psychiatric history and maternal mental illness before or during pregnancy. The majority of the studies adjusted for the following variables in common: maternal education, age, maternal race, parity, gestational age, offspring age and sex, family income, partner social class, partner support and planned pregnancy. Four studies adjusted for prenatal alcohol use whereas only one study adjusted for other prenatal substance use including alcohol. Further, one study [37] adjusted for Attention Deficit Hyperactivity Disorder (ADHD) in offspring, parental antisocial personality and maladaptive parenting style (Table 1).

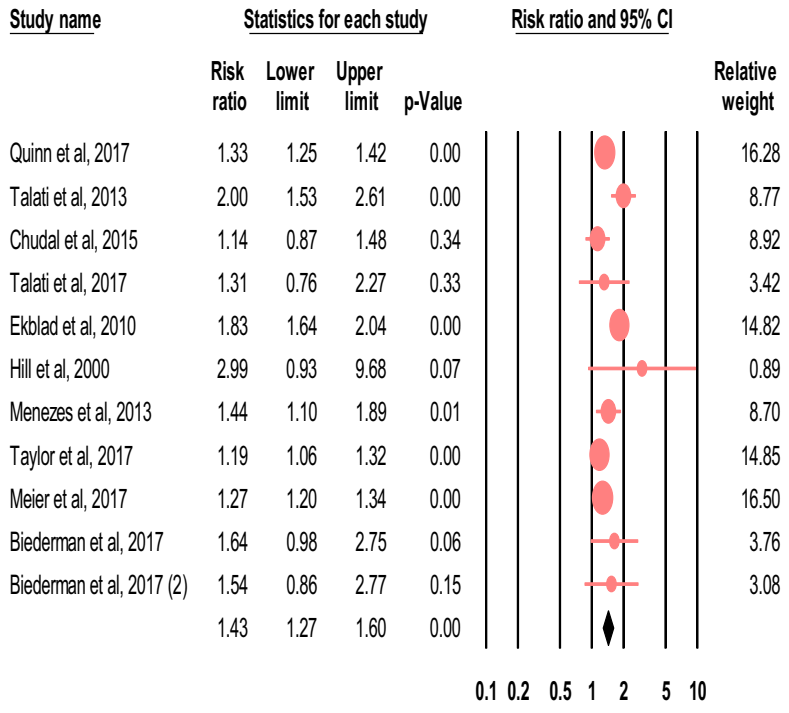


Fig. 2 Forest plot depicting the risk of mood disorders in offspring exposed to prenatal tobacco use: a meta-analysis

Publication bias

In the overall meta-analysis of the risk of mood disorders among offspring exposed to prenatal tobacco use, both visual inspection of the funnel plot (symmetric) and Egger's regression test provided no evidence of potential publication bias ($B = 1.155$, SE = 1.026, $P = 0.289$) (Fig. 3). Similarly, Egger's test was not statistically significant for both subgroups: $B = 1.196$, SE = 2.864, $P = 0.748$ and $B = 1.388$, SE = 1.959, $P = 0.518$ for bipolar and depressive disorders, respectively.

Subgroup and sensitivity analysis

Associations did not substantially change by the specific outcome of interest (bipolar and depression), the study setting, adjustment for prenatal alcohol use, socio-economic positions and reported dose-response effects of prenatal tobacco use. We performed an outcome specific analysis using the type of outcomes in offspring. The risk of bipolar disorder RR = 1.44 (95% CI 1.15–1.80) was similar when compared to depressive disorder RR = 1.44 (95% CI 1.21–1.71). However, the risk of mood disorders was greater in the studies that recruited the study participants from a clinical setting RR = 1.55 (95% CI 1.33–1.81) when compared to those recruited from population-based registers RR = 1.21 (95% CI 1.10–1.33). Similarly, the risk of mood disorders was greater in the studies that did not adjust for the residual confounding by socio-economic positions such as maternal age, education, parental income and social class RR = 1.80 (95% CI 1.47–2.20) when compared to those adjusted for socio-economic positions RR = 1.36 (95% CI 1.20–1.53). The risk of mood disorders was not significantly differed when studies included the adjustment for the confounding effect of prenatal alcohol exposure. For example, the risk of mood disorders in offspring exposed to prenatal tobacco use was RR = 1.57 (95% CI 1.23–1.99) and RR = 1.36 (95% CI 1.14–1.63) in the subgroup analysis of studies that adjusted or not adjusted for prenatal alcohol use, respectively. Further, to identify the possible effects of mood disorders in offspring, we also applied the analysis to studies that reported dose-related effects of prenatal tobacco use. We observed a greater risk of mood disorders in offspring exposed to high prenatal tobacco use RR = 1.54 (95% CI 1.46–1.62) when compared to moderate prenatal tobacco use RR = 1.36 (95% CI 1.30–1.42) (Table 2). The risk of mood disorders was not significantly attenuated when we limit the analysis to the studies that reported sibling comparison results. The relative risk of mood disorders in offspring exposed to prenatal tobacco use was RR = 1.21 (95% CI 1.04–1.41) in the studies that reported sibling comparison results. Moreover, the pooled estimated RR varied between 1.33 (95% CI 1.22–1.43) and 1.47 (95% CI 1.27–1.70) after removal of a single study at a time, which indicated that the findings were not influenced substantially by any single study (Supplementary file 2).

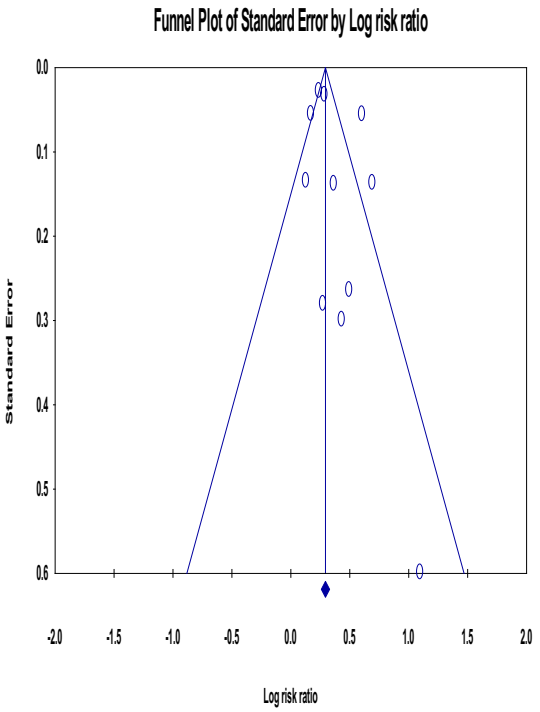


Fig. 3 Funnel plot for publication bias of the meta-analysis for prenatal tobacco exposure and risk of mood disorders in offspring

Discussion

Main findings

This systematic review and meta-analysis explored the risk of mood disorders in offspring exposed to prenatal tobacco use reported by eight cohort studies and two nested case–control studies. We found some evidence for a small association (RR < 2) with mood disorders in offspring. We also noted that exposure to higher levels of prenatal tobacco use was associated with an increased risk of mood disorders in offspring when compared to moderate exposure. For all studies, outcomes in offspring were prospectively collected and measured using well-accepted standardized and validated screening and diagnostic tools.

Table 2 Subgroup and sensitivity analysis of the included studies

Subgroups	No. of studies	RR	95% CI	Heterogeneity within the studies (I^2, Q and P value)			Heterogeneity between groups (P value)
				Q value	I^2 (%)	P value	
Type of outcomes in offspring							
Bipolar	4	1.44	1.15–1.80	10.25	70.72	0.02	< 0.01
Depression	6	1.44	1.21–1.71	42.96	86.03	< 0.01	
Studies adjusted for any maternal psychiatric history and lifetime psychopathology							
Yes	7	1.41	1.24–1.61	52.17	86.58	< 0.01	< 0.01
No	3	1.49	1.19–1.86	0.207	0.00	0.90	
Studies adjusted for socio-economic positions such as maternal age, education, social class and parental income							
Yes	6	1.36	1.20–1.53	41.95	88.08	< 0.01	< 0.01
No	4	1.80	1.47–2.20	2.95	0.00	0.56	
Studies adjusted for maternal alcohol use during pregnancy							
Yes	4	1.57	1.23–1.99	10.27	70.79	0.016	< 0.001
No	6	1.36	1.14–1.63	42.26	88.17	< 0.01	
Studies reported dose-related effects of prenatal tobacco use							
High (> 10 cigarettes/day)	3	1.54	1.46–1.62	48.89	95.909	< 0.01	< 0.001
Moderate (≤ 10 cigarettes/day)	3	1.36	1.30–1.42	54.92	96.358	< 0.01	
Study participants recruitment							
Recruited from clinical setting	4	1.55	1.33–1.81	46.63	86.85	< 0.01	< 0.001
Recruited from community setting	6	1.21	1.10–1.33	2.02	0.00	0.56	
Studies reported sibling comparison results							
Yes	3	1.21	1.04–1.41	5.18	65.31	0.05	N/A

Possible biological mechanisms

Although the mechanisms underlying the association between prenatal tobacco use and mood disorders in offspring are not yet confirmed, a number of plausible mechanisms have been proposed [9, 10, 40–44]. One suggested mechanism is that the deleterious effects of the many hazardous compounds present in tobacco smoke can cross the placenta, affect the developing brain and alter neurodevelopmental trajectories [10, 40–43]. This pathway is characterized by excessive stimulation of serotonergic and dopaminergic receptors and the corresponding over-stimulation during pregnancy may alter sensitivity [9, 44] leading to impaired neural growth and circuit formation [9]. Thus, nicotine may directly interact with neural circuits linked with mood regulation [45] and contribute to mood disorders in offspring.

Exposure to prenatal tobacco use may also be linked with epigenetic changes in the offspring [46–48], in which modifications impact DNA expression through the chromatin remodelling and DNA methylation [49], without altering DNA sequences [50]. The epigenetic changes associated with prenatal tobacco use may include epigenetic regulation of genes involved in the hypothalamic–pituitary–adrenocortical axis (HPA) [47]. This over-stimulation of the axis is often seen in persons with mood disorders [51] has been suggested as a possible explanation for the causal pathway of prenatal tobacco exposure [52]. This is also supported by animal models, which showed that prenatal exposure to nicotine can induce HPA-axis hypersensitivity in offspring rats through the intrauterine programming of up-regulation of hippocampal GAD67 [53] and this may result in depression-like behavior in adolescent female rats that exposed to prenatal nicotine use [54].

Potential for confounding

The risk of mood disorders in offspring exposed to prenatal tobacco use may be due to a range of confounding, namely psychiatric problems in mothers and families [55–57]. For example, in the Avon Longitudinal Study of Parents and Children (ALPAC), the association between prenatal tobacco use and child psychological problems at the age of 4 years disappeared after adjusting for maternal and paternal psychopathology along with other covariates, suggesting that the association was due to confounding influences not prenatal tobacco exposure [58]. Similarly, a study assessing the risk of bipolar disorder in offspring exposed to prenatal tobacco use found a risk association in an unadjusted model [OR 1.41 (95% CI 1.12–1.79)], whereas reported no evidence for an association after adjusting for maternal psychiatric history [38]. In contrast, in a population-based study

that adjusted for maternal and parental history of severe mental illness [16], the risk of bipolar disorder was largely attenuated but the association remained significant. Further, a population-based longitudinal study of Finnish reported the increased risk association between prenatal tobacco use and depression in offspring even after adjusting for maternal psychiatric diagnoses before child birth [20]. Similarly, a study that assessed prenatal tobacco use and bipolar disorder in offspring showed an increased risk of bipolar disorder in offspring after adjusting for potential confounders, such as; lifetime psychopathology, diagnoses of schizophrenia or other psychotic disorders, affective disorder, and postpartum depression [18]. This is also supported by epidemiological evidence from sibling analysis, for example [39]. In our meta-analysis, the pooled estimated risk of mood disorders was not significantly attenuated in the studies that reported sibling comparison results [RR = 1.21 (95% CI 1.04–1.41)]. Moreover, these findings are supported by reports that mothers could pass liability genes to offspring that may translate to associations between prenatal tobacco use and offspring behaviors [59].

We noted that all studies included in the review except studies from the UK [36] and Brazil [22] did not use paternal smoking as a robustness analyses to demonstrate the maternal effect resulted from a biological mechanism. One UK-based study that combined data from ALSPAC, HUNT, and the Pelotas 1982 birth cohort reported no association for paternal prenatal tobacco use and offspring depression [36]. Further, this finding was corroborated by another study [22].

Epidemiologic evidence also suggested that children born to mothers smoking during pregnancy are more likely to be exposed to second-hand smoke in childhood and may develop adverse outcomes [60, 61]. The environmental, individual and familial factors which predispose children to post-birth tobacco smoke have been associated with increased risk of neurobehavioral disorders in offspring [11, 61, 62]. For example, a systematic review and meta-analysis conducted to test the association between smoking and resultant depressive disorders found adverse associations, through which tobacco smoking was linked with later depressive disorders in more than a third of the included studies [11]. This finding is complimented by evidence suggesting that prolonged exposure to tobacco use or smoke may increase the individual vulnerability to have depression in later life [63, 64]. Therefore, considering these factors in the analysis may enable to differentiate the effects of in utero exposure to tobacco smoke from second-hand or passive smoking during pregnancy that have influenced the expression of childhood behavioral problems [65, 66].

Furthermore, more comprehensive adjusting for residual confounding by socio-economic positions may statistically correct the estimate of the effects of prenatal tobacco use on offspring adverse mental health and behavioural outcomes [58]. Some of the studies included in the current meta-analysis accounted for a range of residual confounding by socio-economic position that may influence the link between prenatal tobacco use and risk of mood disorders in offspring [16, 20, 22, 36, 38, 39]. Evidence from epidemiologic studies have shown that women who use tobacco during pregnancy have lower educational attainment and socioeconomic status including family income compared to non-smoking pregnant women [24, 67–71]. These have also been found to be associated with internalizing behaviors such as depression in offspring [41, 60]. For instance, in a study that combined data of four birth cohorts, both prenatal tobacco use and depression in offspring were associated with lower maternal education and social class [36]. This is also corroborated by a population-based cohort study testing associations between maternal smoking during pregnancy and internalizing behaviours where a risk association is found in unadjusted analysis [OR 1.60 (95% CI 1.60–2.10)]; whereas, no association is seen after adjustment for parental educational attainment and family income [OR 1.22 (95% CI 0.90–1.63)] [72], suggesting parental socioeconomic positions accounted for the greater risk of internalizing behaviours in offspring [24]. In our meta-analysis, we also found a similar pattern in which the risk of mood disorder in offspring was moderately attenuated in the studies that adjusted for socio-economic position explaining some part of the reported association between prenatal tobacco use and mood disorders in offspring.

Differences among the studies included in the meta-analysis

Although we found an association between prenatal tobacco use and mood disorders in offspring, it should be noted that the variations between the included studies led to a moderate level of heterogeneity in this meta-analysis. The type of mood disorders in offspring, the adjustment for prenatal alcohol use, outcomes measured at different time points and with different assessment methods, residual confounding by socio-economic positions, the setting as well as the level of prenatal tobacco exposure may have contributed to variability in the risk of mood disorders in offspring exposed to prenatal tobacco use. Nevertheless, the pooled RR estimate remained similar after the removal of a single study at a time in our leave-one-out sensitivity analysis, which indicated that the findings were not influenced substantially by any single study. Further, the subgroup analysis and sensitivity analysis appeared to support the robustness of our findings.

Strength and limitations

This systematic review and meta-analysis has the following strengths: we have used a predefined search strategy

and data extraction protocol, as well as the methodological quality of the included studies, was checked by two independent reviewers. By doing so, we have minimized possible reviewer bias. We conducted subgroup and sensitivity analysis as well as leave-one-out-sensitivity analysis to identify the small study effect and the risk of heterogeneity. Further, we also conducted an additional analysis for those studies that reported sibling comparison results. In addition, the outcomes in offspring were measured using the standard and validated screening and diagnostic tools such as the ICD 9/10, DSM IV, SADS, MINI, CIS-R and HADS that provided well-validated assessments of mood disorders in offspring. However, the following limitations should be taken into consideration while interpreting these results. First, we did not analyze gender-, age- and study design-specific effect estimates due to a lack of sufficient and consistent data from the included studies. Second, the confounding effect of lifetime maternal mental health problems or mental health problems during pregnancy was not consistently adjusted in the included studies. Third, only three studies reported the effects of moderate and high tobacco smoking during pregnancy on offspring mood disorders and this might reduce the precision of the estimate. Fourth, in some studies, the follow-up period may be too short to find validated and diagnosed mood disorders and this may be contributed to underreporting due to a later manifestation of the outcome. Fifth, the prenatal tobacco exposure periods varied and for some studies the time of exposure during pregnancy that was investigated was not reported. Further, majority of the included studies had no information about smoking cessation. The consequence of this is that there will be a fraction of women who might have been classified as non-smokers but stopped smoking when they became aware of their pregnancy usually around mid-first trimester, or they were classified as smokers yet did not smoke after becoming aware of their pregnancy.

Conclusion

Although the etiology of mood disorders has not been established, this systematic review and meta-analysis provided some evidence for a small (RR < 2) association between prenatal tobacco use and mood disorders in offspring. However, it should be noted that the sparsity of studies on the topic and the potential for bias limits more conclusive inference.

Acknowledgements We are so grateful to the Curtin University for providing us a wide range of available online databases.

Author contributions BD conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed quality, conducted a meta-analysis, and wrote the first draft of the manuscript. GA reviewed abstracts and assessed the methodological quality of the included studies. GP reviewed the protocol, reviewed data extraction, data analysis and contributed to subsequent drafts of the manuscript. KB reviewed data extraction, data analysis and contributed to subsequent drafts of the manuscript. RA reviewed the protocol, reviewed data extraction, and synthesis and contributed to subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Funding No external funding obtained for this systematic review and meta-analysis.

Availability of data and material All data generated or analyzed during this review were included in this article and attached as supplementary files.

Compliance with ethical standards

Conflict of interest All authors have no conflicts of interest to disclose.

Code availability Comprehensive Meta-Analysis (CMA) version 3.0 was used to analyze the data.

References

1. Sadock BJ, Sadock VA, Ruiz P (2015) Kaplan and Sadock's synopsis of psychiatry 11th edition: behavioral sciences/clinical psychiatry, book chapter 8. Wolters Kluwer, Alphen aan den Rijn
2. American Psychiatric Association (2000) Diagnostic and statistical manual of mental disorders: DSM-IV-TR. American Psychiatric Association, Washington, DC
3. Malhi GS, Mann JJ (2018) Depression. Lancet 392(10161):2299–2312
4. Kessler RC, Bromet EJ (2013) The epidemiology of depression across cultures. Annu Rev Public Health 34(1):119–138
5. Merikangas KR, Jin R, He JP, Kessler RC, Lee S, Sampson NA et al (2011) Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68(3):241–251
6. James SB, Alcott SV (2007) Mood disorders. Kaplan & Sadock's synopsis of psychiatry: behavioral sciences/clinical psychiatry, 10th edn. Lippincott Williams & Wilkins, Philadelphia, pp 530–533
7. Thase ME (2009) Neurobiological aspects of depression. In: Gotlib IH, Hammen CL (eds) Handbook of depression. The Guilford Press, New York, pp 187–217
8. Kim DR, Bale TL, Epperson CN (2015) Prenatal programming of mental illness: current understanding of relationship and mechanisms. Curr Psychiatry Rep 17(2):5
9. Slotkin TA, Tate CA, Cousins MM, Seidler FJ (2006) Prenatal nicotine exposure alters the responses to subsequent nicotine administration and withdrawal in adolescence: serotonin receptors and cell signaling. Neuropsychopharmacology 31(11):2462–2475
10. Slotkin TA (1998) Fetal nicotine or cocaine exposure: which one is worse? J Pharmacol Exp Ther 285(3):931–945
11. Fluharty M, Taylor AE, Grabski M, Munafò MR (2017) The association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tobacco Res 19(1):3–13
12. Al Mamun A, O'Callaghan FV, Alati R, O'Callaghan M, Najman JM, Williams GM et al (2006) Does maternal smoking during pregnancy predict the smoking patterns of young adult offspring? A birth cohort study. Tob Control 15(6):452–457

13. D'Onofrio BM, Singh AL, Iliadou A, Lambe M, Hultman CM, Grann M et al (2010) Familial confounding of the association between maternal smoking during pregnancy and offspring criminality: a population-based study in Sweden. Arch Gen Psychiatry 67(5):529–538
14. Knopik VS, McGeary J, Nugent N, Francazio S, Heath AC (2010) Smoking during pregnancy, maternal xenobiotic metabolism genes, and child externalizing behavior: a case-crossover design. Behav Genet 40(6):799–800
15. Lange S, Probst C, Rehm J, Popova S (2018) National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. Lancet Glob Health 6(7):e769–e776
16. Quinn PD, Rickert ME, Weibull CE, Johansson ALV, Lichtenstein P, Almqvist C et al (2017) Association between maternal smoking during pregnancy and severe mental illness in offspring. JAMA Psychiatry 74(6):589–596
17. Sutin AR, Flynn HA, Terracciano A (2017) Maternal cigarette smoking during pregnancy and the trajectory of externalizing and internalizing symptoms across childhood: similarities and differences across parent, teacher, and self reports. J Psychiatr Res 91:145–148
18. Talati A, Bao Y, Kaufman J, Shen L, Schaefer CA, Brown AS (2013) Maternal smoking during pregnancy and bipolar disorder in offspring. Am J Psychiatry 170(10):1178–1185
19. Ashford J, van Lier PA, Timmermans M, Cuijpers P, Koot HM (2008) Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. J Am Acad Child Adolesc Psychiatry 47(7):779–787
20. Ekblad M, Gissler M, Lehtonen L, Korkeila J (2010) Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Arch Gen Psychiatry 67(8):841–849
21. Indredavik MS, Brubakk A-M, Romundstad P, Vik T (2007) Prenatal smoking exposure and psychiatric symptoms in adolescence. Acta Paediatr 96(3):377–382
22. Menezes AMB, Murray J, Laszlo M, Wehrmeister FC, Hallal PC, Goncalves H et al (2013) Happiness and depression in adolescence after maternal smoking during pregnancy: birth cohort study. PLoS One 8(11):e80370
23. Monshouwer K, Huizink AC, Harakeh Z, Raaijmakers QA, Reijneveld SA, Oldehinkel AJ et al (2011) Prenatal smoking exposure and the risk of behavioral problems and substance use in adolescence: the TRAILS study. Eur Addict Res 17(6):342–350
24. Dolan CV, Geels L, Vink JM, van Beijsterveldt CE, Neale MC, Bartels M et al (2016) Testing causal effects of maternal smoking during pregnancy on offspring's externalizing and internalizing behavior. Behav Genet 46(3):378–388
25. Talati A, Wickramaratne PJ, Wesselhoeft R, Weissman MM (2017) Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry Res 252:346–352
26. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D et al (2000) Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis of observational studies in epidemiology (MOOSE) group. Jama 283(15):2008–2012
27. Reviews UOYCF (2009) Dissemination. Systematic reviews: CRD's guidance for undertaking reviews in health care. University of York, Centre for Reviews & Dissemination
28. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M et al (2015) Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst Rev 4:1
29. Wells GA, Shea B, O'Connell D, Peterson J, Welch V, Losos M et al (2017) The Newcastle–Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. The Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp. Accessed 27 Apr 2019
30. Borenstein M, Hedges L, Higgins J, Rothstein H (2005) Comprehensive meta-analysis version 2. Biostat, Englewood, p 104
31. Borenstein M, Hedges LV, Higgins JP, Rothstein HR (2010) A basic introduction to fixed-effect and random-effects models for meta-analysis. Res Synth Methods 1(2):97–111
32. Patsopoulos NA, Evangelou E, Ioannidis JP (2008) Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int J Epidemiol 37(5):1148–1157
33. Higgins JP, Thompson SG, Deeks JJ, Altman DG (2003) Measuring inconsistency in meta-analyses. BMJ (Clin Res Ed) 327(7414):557–560
34. Egger M, Davey Smith G, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. BMJ (Clin Res Ed) 315(7109):629–634
35. Hill SY, Lowers L, Locke-Wellman J, Shen S (2000) Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol 61(5):661–668
36. Taylor AE, Carslake D, De Mola CL, Rydell M, Nilsen TIL, Bjørngaard JH et al (2017) Maternal smoking in pregnancy and offspring depression: a cross cohort and negative control study. Sci Rep 7(1):1–8
37. Biederman J, Martelon M, Woodworth KY, Spencer TJ, Faraone SV (2017) Is maternal smoking during pregnancy a risk factor for cigarette smoking in offspring? A longitudinal controlled study of adhd children grown up. J Atten Disord 21(12):975–985
38. Chudal R, Brown AS, Gissler M, Suominen A, Sourander A (2015) Is maternal smoking during pregnancy associated with bipolar disorder in offspring? J Affect Disord 171:132–136
39. Meier SM, Plessen KJ, Verhulst F, Mors O, Mortensen PB, Pedersen CB et al (2017) Familial confounding of the association between maternal smoking during pregnancy and internalizing disorders in offspring. Psychol Med 19:1–10. https://doi.org/10.1017/S0033291716003627
40. Lambers DS, Clark KE (1996) The maternal and fetal physiologic effects of nicotine. Semin Perinatol 20(2):115–126
41. Rogers JM (2009) Tobacco and pregnancy. Reprod Toxicol (Elmsf NY) 28(2):152–160
42. Levin ED, Slotkin TA (1998) Chapter 34—developmental neurotoxicity of nicotine. In: Slikker W, Chang LW (eds) Handbook of developmental neurotoxicology. Academic Press, San Diego, pp 587–615
43. Slikker W, Xu ZA, Levin ED, Slotkin TA (2005) Mode of action: disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction—developmental neurotoxicity of nicotine. Crit Rev Toxicol 35(8–9):703–711
44. Ernst M, Moolchan ET, Robinson ML (2001) Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry 40(6):630–641
45. Suter M, Ma J, Harris A, Patterson L, Brown KA, Shope C et al (2011) Maternal tobacco use modestly alters correlated epigenome-wide placental DNA methylation and gene expression. Epigenetics 6(11):1284–1294
46. Richmond RC, Simpkin AJ, Woodward G, Gaunt TR, Lyttleton O, McArdle WL et al (2015) Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Hum Mol Genet 24(8):2201–2217
47. Stroud LR, Papandonatos GD, Rodriguez D, McCallum M, Salisbury AL, Phipps MG et al (2014) Maternal smoking during pregnancy and infant stress response: test of a prenatal programming hypothesis. Psychoneuroendocrinology 48:29–40

48. Knopik VS, Maccani MA, Francazio S, McGeary JE (2012) The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol 24(4):1377–1390
49. Tehranifar P, Wu H-C, McDonald JA, Jasmine F, Santella RM, Gurvich I et al (2018) Maternal cigarette smoking during pregnancy and offspring DNA methylation in midlife. Epigenetics 13(2):129–134
50. Klose RJ, Bird AP (2006) Genomic DNA methylation: the mark and its mediators. Trends Biochem Sci 31(2):89–97
51. Varghese FP, Brown ES (2001) The hypothalamic-pituitary-adrenal axis in major depressive disorder: a brief primer for primary care physicians. Prim Care Companion J Clin Psychiatry 3(4):151–155
52. Mello AF, Mello MF, Carpenter LL, Price LH (2003) Update on stress and depression: the role of the hypothalamic-pituitary-adrenal (HPA) axis. Rev Bras Psiquiatr (Sao Paulo Braz 1999) 25(4):231–238
53. He X, Lu J, Dong W, Jiao Z, Zhang C, Yu Y et al (2017) Prenatal nicotine exposure induces HPA axis-hypersensitivity in offspring rats via the intrauterine programming of up-regulation of hippocampal GAD67. Arch Toxicol 91(12):3927–3943
54. Zhang C, Fan SJ, Sun AB, Liu ZZ, Liu L (2019) Prenatal nicotine exposure induces depression like behavior in adolescent female rats via modulating neurosteroid in the hippocampus. Mol Med Rep 19(5):4185–4194
55. Lieb R, Isensee B, Höfler M, Pfister H, Wittchen H-U (2002) Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. Arch Gen Psychiatry 59(4):365–374
56. Halligan SL, Murray L, Martins C, Cooper PJ (2007) Maternal depression and psychiatric outcomes in adolescent offspring: a 13-year longitudinal study. J Affect Disord 97(1–3):145–154
57. Hannigan LJ, Eilertsen EM, Gjerde LC, Reichborn-Kjennerud T, Eley TC, Rijsdijk FV et al (2018) Maternal prenatal depressive symptoms and risk for early-life psychopathology in offspring: genetic analyses in the Norwegian Mother and Child Birth Cohort Study. Lancet Psychiatry 5(10):808–815
58. Brion M-J, Victora C, Matijasevich A, Horta B, Anselmi L, Steer C et al (2010) Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics 126(1):e57–e65
59. Kuja-Halkola R, D'Onofrio BM, Larsson H, Lichtenstein P (2014) Maternal smoking during pregnancy and adverse outcomes in offspring: genetic and environmental sources of covariance. Behav Genet 44(5):456–467
60. Knopik VS (2009) Maternal smoking during pregnancy and child outcomes: real or spurious effect? Dev Neuropsychol 34(1):1–36
61. Kabir Z, Connolly GN, Alpert HR (2011) Secondhand smoke exposure and neurobehavioral disorders among children in the United States. Pediatrics 128(2):263–270
62. Tiesler CMT, Heinrich J (2014) Prenatal nicotine exposure and child behavioural problems. Eur Child Adolesc Psychiatry 23(10):913–929
63. Markou A, Kosten TR, Koob GF (1998) Neurobiological similarities in depression and drug dependence: a self-medication hypothesis. Neuropsychopharmacology 18(3):135–174
64. Rose JE, Behm FM, Ramsey C, Ritchie JC Jr (2001) Platelet monoamine oxidase, smoking cessation, and tobacco withdrawal symptoms. Nicotine Tob Res 3(4):383–390
65. Schlotz W, Phillips DI (2009) Fetal origins of mental health: evidence and mechanisms. Brain Behav Immun 23(7):905–916
66. Thapar A, Rutter M (2009) Do prenatal risk factors cause psychiatric disorder? Be wary of causal claims. Br J Psychiatry J Ment Sci 195(2):100–101
67. Al-Sahab B, Saqib M, Hauser G, Tamim H (2010) Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. BMC Pregnancy Childbirth 10(1):24
68. Muhajarine N, D'Arcy C, Edouard L (1997) Prevalence and predictors of health risk behaviours during early pregnancy: Saskatoon Pregnancy and Health Study. Can J Public Health Revue Canadienne de Sante Publique. 88(6):375–379
69. Stewart DE, Streiner DL (1995) Cigarette smoking during pregnancy. Can J Psychiatry Revue Canadienne de Psychiatrie 40(10):603–607
70. Nagahawatte NT, Goldenberg RL (2008) Poverty, maternal health, and adverse pregnancy outcomes. Ann N Y Acad Sci 1136:80–85
71. Heaman MI, Chalmers K (2005) Prevalence and correlates of smoking during pregnancy: a comparison of aboriginal and non-aboriginal women in manitoba. Birth 32(4):299–305
72. Roza SJ, Verhulst FC, Jaddoe VWV, Steegers EAP, Mackenbach JP, Hofman A et al (2008) Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int J Epidemiol 38(3):680–689

4.2 Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study

Published manuscript and formal citation

Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study. Journal of Affective Disorders. 2021; 279:426-33.

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.jad.2020.10.030.

Study purpose: Evidence from epidemiological studies indicated that prenatal alcohol and tobacco exposures may increase the risk of internalizing behaviors in offspring. However, additional epidemiological studies have produced inconsistent results. Variability in assessment methods of internalizing behaviors and incomplete adjustment for potential confounders may explain these conflicting results. Further, those available studies had not examined specific sub-types of internalizing behaviors such as depressive symptoms but rather relied on aggregated internalizing and externalizing behaviors. Moreover, there has been a dearth of studies that have examined the association between prenatal alcohol and tobacco exposures and depression in adolescent offspring. Therefore, this study aimed to fill a gap in the literature by examining the prospective associations between prenatal alcohol and tobacco exposures and the risk of depressive symptoms in adolescent offspring using large prospective cohort in Western Australia.

Journal of Affective Disorders 279 (2021) 426–433

Contents lists available at ScienceDirect

Journal of Affective Disorders

journal homepage: www.elsevier.com/locate/jad

Research paper

Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study

Bereket Duko[a,*], Gavin Pereira[a,b,c], Kim Betts[a], Robert J. Tait[d], John Newnham[e], Rosa Alati[a,f]

[a] School of Public Health, Curtin University, Kent Street, Bentley WA 6102, Australia
[b] Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, 15 Hospital Ave, Nedlands WA 6009, Australia
[c] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley WA 6102, Australia
[e] Division of Obstetrics and Gynecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands WA 6009, Australia
[f] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland 4068 Australia

ARTICLE INFO

Keywords:
depression
alcohol
tobacco
adolescent
pregnancy
the Raine Study

ABSTRACT

Background: Prenatal alcohol and tobacco exposures have been associated with adverse mental health consequences in offspring. The objective of this study was to test the associations between maternal prenatal alcohol and tobacco exposures and depressive symptoms in the offspring, adjusting for a wide range of potential confounders.

Methods: We used data from 1168 mother-offspring pairs from the Raine Study based in Perth, Western Australia. Depressive symptoms at age 17 years were measured using the Beck Depression Inventory for Youth (BDI-Y). Associations between prenatal alcohol and tobacco use and the risk of depressive symptoms in offspring were estimated by risk ratios (RR) derived with multivariable log-binomial regression.

Results: Among offspring who were assessed for depressive symptoms, 5% were born to mothers who consumed six or more standard drinks of alcohol per week during pregnancy and 20% were exposed to prenatal tobacco. After adjustment for confounders, depressive symptoms at the age of 17 years remained associated with maternal alcohol use of six or more standard drinks per week [RR 1.59 (95% CI: 1.11-2.26)] and any tobacco use [RR 1.36 (95% CI: 1.05-1.79)] during the first trimester of pregnancy.

Conclusion: Offspring exposed to prenatal alcohol and tobacco use had greater risks of depressive symptoms compared with unexposed offspring, suggesting early screening and prevention of these exposures could possibly reduce depressive symptoms in offspring.

1. Introduction

Depression is one of the most common mental health problems occurring among adolescents (Polanczyk, Salum et al. 2015) but often left undiagnosed (Thapar, Collishaw et al. 2012). Generally, the clinical features of depression are similar in both adolescents and adults (Lewinsohn, Pettit et al. 2003). However, epidemiological evidence indicates that the prevalence of unrecognized depression in adolescents is much higher than adults (Leaf, Alegria et al. 1996). Adolescents with depression can experience mood disturbance or irritability, loss of interest or pleasure in nearly all activities, feeling of guilt or fatigue, low self-esteem (Sadock BJ, Sadock VA et al. 2015) and this in turn can lead to poor concentration and impairments in social and academic skills (Sadock BJ, Sadock VA et al. 2015), substance use disorders (Keenan-Miller, Hammen et al. 2007), other mental health problems and even suicide (APA 2000, Sadock BJ, Sadock VA et al. 2015). Thus, identifying potential risk factors of depression is critical to direct preventive strategies in addressing adolescent and adult adverse mental health outcomes (Davey and McGorry 2019).

Although the precise causal mechanisms for depression remain elusive, several risk factors have been associated with its progression (James and Alcott 2007). Imbalances of certain neurotransmitters (Thase 2009), genetic factors (Merikangas, Jin et al. 2011) and environmental factors (Sadock BJ, Sadock VA et al. 2015) are some of those risk factors which may increase the risk of depression in offspring. Other studies suggest that *in utero* exposure to stressful life events (Lau and Eley 2008) and family history of depression (Loechner, Sfärlea et al. 2019) are robust risk factors that contribute to the development of depression in offspring.

Modifiable *in utero* exposures include prenatal alcohol and tobacco

* Corresponding author. Bereket Duko, School of Public Health, Curtin University, Kent Street, Bentley, Perth, 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.jad.2020.10.030
Received 22 May 2020; Received in revised form 7 September 2020; Accepted 12 October 2020
Available online 16 October 2020

use (Hill, Lowers et al. 2000, Slotkin, Tate et al. 2006). Findings from epidemiological studies indicated that prenatal alcohol and tobacco exposure may increase the risk of depression in offspring (Hill, Lowers et al. 2000, Ekblad, Gissler et al. 2010, Menezes, Murray et al. 2013) but previous studies have reported conflicting results (Sayal, Heron et al. 2007, Robinson, Oddy et al. 2010, Dolan, Geels et al. 2016, Talati, Wickramaratne et al. 2017). A population-based retrospective cohort study investigated the association between prenatal tobacco exposure and behavioral problems in adolescence (Monshouwer, Huizink et al. 2011). This study reported no association for internalizing behaviors among children exposed to maternal tobacco (> 10 cigarettes/day) at any time during pregnancy. In contrast, a retrospective cohort study conducted in the USA found that exposure to maternal tobacco use at any time during pregnancy (yes/no) was linked with a lower risk of mood disorders (Talati, Wickramaratne et al. 2017). Further, a population-based cohort study of 9086 offspring born to mothers using alcohol (<1 glass per week) in the first trimester of pregnancy reported gender-specific associations, such that prenatal alcohol use was linked with internalizing behaviors in girls only (Sayal, Heron et al. 2007).

Variability in assessment methods of depression may explain these conflicting results. Some prospective cohort studies that have investigated the effects of prenatal alcohol and tobacco exposure on risk of mental health outcomes assessed only total scores of externalizing and internalizing rather than subscale scores of individual mental health problems such as depressive symptoms (Roza, Verhulst et al. 2009, Robinson, Oddy et al. 2010). Furthermore, some previous studies may have over-estimated risk due to bias introduced by selection of hospitalized participants, recall bias from retrospective exposure assessment years after pregnancy; and from incomplete adjustment for immediate pregnancy outcomes such as preterm birth and low birthweight (Menezes, Murray et al. 2013), mental health status in parents (Roza, Verhulst et al. 2009, Dolan, Geels et al. 2016) and child postnatal exposure to tobacco smoke (Meier, Plessen et al. 2017). Finally, there has been a paucity of studies have investigated the association between prenatal alcohol and tobacco use and depression in offspring. Therefore, the aim of this study was to test the associations between alcohol and tobacco use during pregnancy and depressive symptoms in offspring from a large prospective cohort.

2. Methods

2.1. Study design and participants

This study used data from the Raine Study, a prospective multigenerational observational study. The Raine Study began with 2730 pregnant mothers (generation 1) who were recruited between 16-20 weeks of pregnancy visiting King Edward Memorial Hospital (KEMH) in Perth, Western Australia. These pregnancies resulted in births to 2868 children between August 1989 and April 1992. We excluded 138 children with multiple gestation. The final study cohort consisted of those who completed the mental health assessment at age of 17 years (generation 2) (n = 1168). The Raine Study data collection, recruitment and enrolment procedures have been published elsewhere (Newnham, Evans et al. 1993, Dontje, Eastwood et al. 2019). Human research ethical approval for the study was gained from the Human Research Ethics Committees (HREC) of the Princess Margaret Hospital for Children and King Edward Memorial Hospital in Western Australia. At each follow-up assessment, written informed consent was gained from each study participants after the nature of the procedures had been fully explained.

2.2. Measures

2.2.1. Outcome: Depressive symptoms at age of 17 years

Depressive symptoms at age of 17 years were measured using the Beck Depression Inventory for Youth (BDI-Y). The BDI-Y has been shown to be a reliable and valid tool to measure depressive symptoms (Beck et al., 2001), as described in the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, (DSM-IV-TR) for diagnoses of major depressive disorders in children and adolescents (APA 2000). The BDI-Y incorporates 20 Likert scale items relating to depressed moods that have been experienced over the past 2 weeks. Its raw scores are transformed into summary scores (0 to 60) with higher scores suggesting a greater degree of depressive symptoms. In this study, summary scores were dichotomized as 'depressed' or 'not depressed' using the recommended cut-off score points (normal ≤13; mild-severe depression ≥14) (Beck et al., 2001).

2.2.2. Exposure: Prenatal alcohol and tobacco use

At 18 and 34 weeks of gestations, pregnant mothers reported the number of nips of spirits, glasses of wine, cans or 375-ml bottles of low to full strength beer consumed during the first three months of pregnancy and they were currently drinking respectively. We converted these data into a continuous variable showing the total number of standard drinks of alcohol consumed per week. Based on the National Health and Medical Research Council (NHMRC) guidelines of 2009, one standard drink constitutes 10 grams of absolute alcohol (NHMRC 2009). There has been no universally accepted standard on the levels of alcohol that represent light to heavy drinking during pregnancy. As a result, we used NHMRC guidelines of 2009 as a reference to categorize prenatal alcohol use. Subsequently, prenatal alcohol use was defined as non-use, light use (1-2 standard drinks/week), moderate use (3-5 standard drinks/week) and heavy use (≥ 6 standard drinks/week) during the first and third trimesters of pregnancy. Similarly, maternal self-reported data on prenatal tobacco use (at 18 and 34 weeks) was used to categorize pregnant mothers as either non-smoker or smoker. Based on previous studies (Menezes, Hallal et al. 2007, Menezes, Murray et al. 2013) and to further investigate dose-response associations, we further defined prenatal tobacco use as "non-smoker"(reference group), "<15 cigarettes/day" and ≥ 15 cigarettes/day. Self-reported maternal smoking status during the first three months of pregnancy showed strong agreement with measured serum cotinine level on a random sample of 238 pregnant mothers tested in the Raine study (Stick, Burton et al. 1996).

2.2.3. Confounding Variables

The confounding variables for adjustment in our analyses included factors that have been reported to have an association with both the exposures (prenatal alcohol and tobacco use) and the risk of depressive symptoms in adolescents; marital status, maternal education, family income and ethnicity (McLaughlin, Costello et al. 2012, Reiss 2013), maternal age (Aitken, Hewitt et al. 2016), parity (Lahti, Eriksson et al. 2014), pre-term birth (Pyhälä, Wolford et al. 2017), maternal depression or depressive symptoms (Loechner, Sfärlea et al. 2019), low birthweight (Nomura, Wickramaratne et al. 2007, De Mola, De França et al. 2014), planned pregnancy (Menezes, Murray et al. 2013) and paternal smoking during pregnancy. Maternal sociodemographic indicators were obtained from prenatal questionnaires completed by mothers during pregnancy at 18 weeks of gestation: maternal education (schooling up to 12 years, trade certificate / apprenticeship, professional registration/ college diploma and university degree), ethnicity (Caucasian and non-Caucasian), maternal age at conception, marital status (married, never married, de-facto and widowed/divorced/separated), paternal smoking status during the mother's pregnancy (yes/no) and family income (low income < $24,000 per annum (pa) and moderate to high income > $24,000 pa). Planned pregnancy (yes/no), parity (nulliparous or multiparous) and maternal history of mental health problems at conception (yes/no) were obtained from questionnaires also administered to mothers during pregnancy. Preterm birth (<37 weeks of gestation) (yes/no), sex of a child (male/female), and birth weight (low-birth weight (< 2.5 kg), normal birth-weight

(2.5-3.99 kg) and high-birth weight (>4.0 kg)) were obtained from the birth and neonatal database. Pregnant mothers also reported postnatal tobacco smoking (yes/no) at 13 years of follow-up. Mothers were also assessed for depressive symptoms at 13 years follow-up using the Depression Anxiety Stress Scales (DASS). The DASS is a 42-item scale designed to measure symptoms of depression, anxiety and stress. The internal consistency for the total scale is .93 (sub-scale; depression .89) (Akin and Citin, 2007). The scale was dichotomized as depressed (≤ 9) or not depressed (normal ≥ 10) using the recommended conventional severity thresholds.

2.3. Statistical analyses

2.3.1. Main analysis

Associations between prenatal alcohol and tobacco use and the risk of depressive symptoms in offspring were tested using univariate log-binomial regression models, computing risk ratios (RR) with STATA 16.0 (StataCorp 2019). To further explore which risk factors contributed to the effects reported by previous studies, we fitted multivariate log-binomial regression models to separately estimate changes in estimated effects attributable to varying extent of adjustment. Firstly, we produced unadjusted estimates. Next, we adjusted for sociodemographic and non-pathologic risk factors (maternal age at conception, marital status, maternal education, and ethnicity, family income at conception, parity, planned pregnancy, and sex of child; Model 1). Then we adjusted for both sociodemographic and non-pathologic risk factors and predisposition to psychiatric conditions (maternal history of mental illness at conception, maternal depressive symptoms and maternal smoking at 13 years of follow-up; Model 2). To this model, we separately added adjustment for adverse pregnancy outcomes (preterm birth and birth weight; Model 3) and paternal smoking status during pregnancy as a negative control exposure (Model 4). In the final model, we adjusted for all of these risk factors (Model 5). We conducted an additional sensitivity analysis by limiting our analysis to offspring exposed to third trimester (at 34 weeks) prenatal alcohol and tobacco use.

2.3.2. Bias and missing data

We employed multivariate imputation by chained equation using the STATA "mice" command to minimize the possibility of bias due to attrition (Sterne, White et al. 2009), drawing data on sociodemographic factors collected at 18 weeks of gestation. In the multivariate imputation, 50 cycles of regression switching were used to generate 50 imputed datasets. The potential explanatory variables along with auxiliary variables predictive of incomplete variables were included in the regression model and imputed, and analyses were repeated for each imputation before being combined. The resulting Monte Carlo errors (<5%) of the standard error, suggested 50 imputed datasets were sufficient.

3. Results

3.1. Characteristics of pregnant mothers and children

Among mothers included in the analysis, 49.1% were nulliparous, 56.2% planned their pregnancy, 20% smoked tobacco and 5% consumed six or more standard drinks of alcohol per week within the first three months of pregnancy. The prevalence of maternal depressive symptoms assessed at 13 years of follow-up was 10.7%. Further, in comparison to those mothers with complete data, mothers of offspring who were excluded due to lost to follow-up were more likely to be married, younger during conception, non-Caucasians and more likely to report low income per annum, and less likely to report history of mental health problems during conception. Fathers of offspring with missing data were more likely to be tobacco smokers during pregnancy (Table 1). Moreover, mother of offspring with depressive symptoms at the age of 17 years were more likely to report divorce or separation, low

Table 1
Characteristics of mothers and children with complete data on depressive symptoms compared with those with incomplete data at the age of 17 years.

Variables included in the model	Completed data on depression (n=1168)		Missed/lost follow-up (n=1700)		*p-value
	n	%	*N*	%	
Maternal age at conception					0.489
< 20 years	70	5.99	214	12.59	
20-25 years	209	17.89	409	24.06	
25-30 years	341	29.19	522	30.71	
30-35 years	353	30.23	380	22.35	
≥ 35 years	195	16.70	175	10.29	
Marital status					0.361
Married	833	72.69	975	58.81	
Never married	114	9.95	252	15.20	
Defacto	167	14.57	362	21.83	
Separate/divorce/widow	32	2.79	69	4.16	
Ethnicity					0.723
Caucasian	1034	90.23	1439	86.79	
Non-Caucasian	112	9.77	219	13.21	
Family income at conception					0.149
≤ 24,000 AUD	427	37.26	894	53.92	
> 24,000 AUD	719	62.74	764	46.08	
Parity					0.057
Nulliparous	561	49.12	784	47.09	
Multiparous	581	50.88	881	52.91	
Current pregnancy					0.063
Planned	644	56.20	866	52.23	
Not planned	502	43.80	792	47.77	
Previous history of maternal mental illness					0.128
Yes	28	6.21	38	2.29	
No	1118	93.79	1620	97.71	
Preterm birth					0.674
Yes	74	6.46	143	8.62	
No	1071	93.64	1515	91.38	
Birthweight					0.462
Low birth weight (< 2.5K.G)	86	7.37	166	9.82	
Normal birthweight (2.5 -3.99K.G)	973	83.38	1377	81.43	
High birthweight (≥ 4.0K.G)	108	9.25	148	8.75	
Child's sex					0.08
Male	580	49.66	874	51.41	
Female	588	50.34	826	48.59	
Maternal depression at 13 years of follow-up					0.09
Depressed	116	10.71	70	10.00	
Normal	967	89.29	630	90.00	
Maternal prenatal tobacco use (at first trimester)					0.02
Non-smoker	918	80.01	1130	68.15	
< 15 cigarettes/day	132	11.5	304	18.3	
≥ 15 cigarettes/day	96	8.5	224	13.5	
Maternal prenatal tobacco use (at third trimester)					0.04
Non-smoker	889	81.6	1016	69.6	
< 15 cigarettes/day	152	14.0	313	21.4	
≥ 15 cigarettes/day	48	4.4	131	9.0	
Paternal smoking during pregnancy					0.069
Smoker	367	32.02	771	46.50	
Non-smoker	779	67.98	887	53.50	
Maternal prenatal alcohol use (at first trimester)				0.045	0.045
Non-use	580	50.61	945	57.00	
1-2 standard drinks/week	408	35.60	462	27.86	
3-5 standard drinks/week	103	8.99	132	7.96	
≥ 6 standard drinks/ week	55	4.80	119	7.18	

(*continued on next page*)

Table 1 (*continued*)

Variables included in the model	Completed data on depression ($n=1168$)		Missed/lost follow-up ($n=1700$)		*p-value
	n	%	*N*	%	
Maternal prenatal alcohol use (at third trimester)					0.529
Non-use	650	62.8	972	70.3	0.529
1-2 standard drinks/week	291	28.2	292	21.1	
3-5 standard drinks/week	60	5.8	69	5.0	
≥ 6 standard drinks/ week	33	3.2	49	3.5	

*p-values corresponds to Pearson's chi-square test.

family income per annum, alcohol and tobacco use during pregnancy when compared to mothers of offspring without depressive symptoms (Supplementary file 1 for Table 1).

Of the 1168 offspring who were assessed for depressive symptoms at age of 17 years, 50.3% were females, 7.4% were of low birthweight and 6.5% were born pre-term. The mean age (± SD) of pregnant mothers at conception was 28.1 (± 5.9) years.

3.2. Association between prenatal alcohol and tobacco use and the risk of depressive symptoms in offspring

Prevalence of depressive symptoms among offspring at age of 17 years was 23.3%. Univariate analysis revealed that offspring born to mothers using six or more standard drinks of alcohol during pregnancy the first three months of pregnancy were 1.43 times more likely to have depressive symptoms at age of 17 years when compared to those who did not drink (RR = 1.43; 95% (1.01-2.16)). Similarly, offspring exposed to prenatal tobacco use (any use) were 1.38 times more likely to have depressive symptoms at age of 17 years when compared to those unexposed (RR = 1.38; 95% (1.09-1.74)) (Table 2). The risks of depressive symptoms in offspring increased in magnitude and precision with increasing exposure to prenatal tobacco use (Supplementary file 1 for Table 2). We found relative risks (RR) of 1.43 (95% CI: 1.04-1.96) and 1.50 (95% CI: 1.07-2.12) for offspring exposed to prenatal tobacco use of < 15 cigarettes/day and ≥15 cigarettes/day respectively. The above estimates were not sensitive to control for sociodemographic, predisposition to maternal mental health status, adverse pregnancy outcomes as mediators, or paternal smoking during pregnancy. Analyses repeated using the imputed dataset resulted in similar estimates (Supplementary file 2 for Table 2). However, we found insufficient evidence for associations between prenatal alcohol and tobacco use and depressive symptoms in offspring when we limit our analysis to offspring exposed to maternal alcohol and tobacco use during the third trimester (34 weeks) of pregnancy (Supplementary file 3 for Table 2). Moreover, the interaction test revealed no interaction between both predictor variables (p-value = 0.26), suggesting either prenatal alcohol or tobacco exposure is independently associated with depressive symptoms in the offspring.

4. Discussion

4.1. Prenatal alcohol use and risk of depressive symptoms in offspring

We prospectively investigated the associations between maternal prenatal alcohol use and the risk of depressive symptoms in offspring at age 17 years. Although the amount of alcohol consumed by mothers during the first three months of pregnancy increased the risks of depressive symptoms in offspring, we only observed statistically significant associations in offspring exposed to maternal alcohol use of six or more standard drinks per week during the first three months of pregnancy. These associations persisted after controlling for a wide range of risk factors and potential confounders. Although we found insufficient statistical evidence for increased risks of depressive symptoms in offspring exposed to less maternal alcohol consumption during the first trimester of pregnancy, the dose-response pattern we found prevents us from assuming that there is safe level of alcohol consumption during pregnancy.

The finding of this study was consistent with evidence from several studies. A study of data from 14,062 mother-offspring pairs in the Avon Longitudinal Study of Children and Parents (ALSPAC) (Easey, Timpson et al. 2020) reported that offspring born to mothers consumed any alcohol during the first three months of pregnancy were more likely to report greater symptoms of depression. Furthermore, a prospective cohort study that investigated the relationship between episodic heavy or binge alcohol use during the prenatal period (≥4 drinks per day) and adverse mental health outcomes in 4610 offspring at age of 11 years also observed dose-response associations (Sayal, Heron et al. 2014), whereas low to moderate levels of prenatal alcohol exposure were not associated with offspring mental health problems. In contrast, a few previous studies have produced conflicting

Table 2
Association between prenatal alcohol and tobacco use (first trimester) and depressive symptoms in offspring at the age of 17 years.

Predictor Variables	Risk Ratio (95%CI) Unadjusted	Adjusted for Model 1	Model 2	Model 3	Model 4	Model 5	
Prenatal alcohol use (first trimester)	Non-use	Reference	Reference	Reference	Reference	Reference	Reference
	≤ 2 standard drinks/week	1.01(0.80-1.27)	1.04(0.83-1.30)	1.02(0.81-1.30)	1.03(0.82-1.31)	1.03(0.82-1.30)	1.04(0.82-1.32)
	3-5 standard drinks/ week	1.15(0.81-1.64)	1.10(0.77-1.57)	1.12(0.78-1.62)	1.14(0.78-1.66)	1.11(0.78-1.59)	1.16(0.80-1.68)
	≥ 6 standard drinks/week	1.43(1.01-2.16)	1.56(1.14-2.12)	1.55(1.09-2.21)	1.59(1.14-2.22)	1.46(1.02-2.12)	1.59(1.11-2.26)
Prenatal tobacco use (first trimester)	Non-smoker	Reference	Reference	Reference	Reference	Reference	Reference
	Smoker (any)	1.38 (1.09–1.74)	1.38(1.09-1.73)	1.40(1.08-1.81)	1.40(1.08-1.81)	1.37(1.05-1.79)	1.36(1.05-1.79)
	< 15 cigs/day	1.27(1.01-1.72)	1.33(1.01-1.75)	1.52(1.10-2.08)	1.50(1.10-2.04)	1.33(1.01-1.65)	1.43(1.04-1.96)
	≥ 15 cigs/day	1.51(1.11-2.06)	1.46(1.09-1.96)	1.62(1.19-2.23)	1.60(1.17-2.20)	1.45(1.05-1.90)	1.50(1.07-2.12)

Key: Model 1: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, and sex of child.
Model 2: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception and maternal depression and smoking at 13 years of follow-up.
Model 3: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception, maternal depression and smoking at 13 years of follow-up, preterm birth, and birth weight.
Model 4: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception, maternal depression and smoking at 13 years of follow-up, and paternal smoking status during pregnancy.
Model 5: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception, maternal depression and smoking at 13 years of follow-up, preterm birth, birth weight, and paternal smoking status during pregnancy.

results (Barr, Bookstein et al. 2006, Robinson, Oddy et al. 2010). A study examined the association between prenatal alcohol use and the risk of internalizing and externalizing behavioral problems in offspring at age of 2, 5, 8, 10, and 14 years (Robinson, Oddy et al. 2010). This study reported that offspring exposed to maternal alcohol use of six or more standard drinks during the first three months of pregnancy were less likely to develop internalizing behavioral problems when compared to non-exposed and occasional use. However, this study combined 'non-prenatal alcohol use' with 'occasional prenatal alcohol use' as a reference control group as well as used parent report of Child Behavior Checklist (CBCL) to ascertain outcomes in offspring. Conversely, parent reporting of CBCL showed low correlation compared to child ratings (Konold, Walthall et al. 2004). Moreover, epidemiological evidence also suggests that depressive symptoms in offspring might be more observable than externalizing behaviors in late adolescence (Zahn–Waxler, Klimes–Dougan et al. 2000).

We did not observe an association between maternal alcohol use at 34 weeks of gestation and depressive symptoms in offspring. Our finding is consistent with the existing literature showing differences between trimesters for associations between maternal prenatal alcohol use and internalizing behaviours in offspring, with the risk of mental health problems in offspring was not increased when the authors limited the analysis to the third trimester of pregnancy alcohol exposure (O'Leary, Nassar et al. 2010), suggesting how prenatal alcohol exposure may affect the developing foetus at different trimesters of pregnancy.

Prenatal exposure to alcohol may increase the risk of depressive symptoms in offspring through different physiological mechanisms. Alcohol exposure in pregnancy may result in dose-dependent constriction of blood vessels in the placenta which in turn may increase blood pressure and lower placenta weight (Jones, Leichter et al. 1981, Burd, Roberts et al. 2007). Increased placental vasoconstriction may result in placental and fetal hypoxia (Shamshirsaz, Paidas et al. 2012). Reports from previous studies suggested that prenatal hypoxia may results in some impairments in dopamine pathways which can persist to adulthood (Chen, Herrera-Marschitz et al. 1997). These physiological alterations may significantly affect the function of dopamine neurotransmitter (Dunlop and Nemeroff 2007) and contribute to the development of depressive symptoms in offspring.

Evidence from animal studies suggested that prenatal alcohol exposure may be linked to mood and behavioral disturbances in offspring (O'Connor 2014, Brancato, Castelli et al. 2018). A study that administered 5.8 g/kg of ethanol (alcohol) to pregnant mice during preimplantation phase reported significant growth retardation and physical malformations in nearly all viable embryos (Padmanabhan and Hameed 1988), suggesting teratogenic effects of alcohol exposure during the preimplantation period. Another study found that for female rats, heavy prenatal alcohol exposure during pregnancy induced affective (depressive) phenotypes in both mothers and their offspring (Brancato, Castelli et al. 2018).

4.2. Prenatal tobacco use and risk of depressive symptoms in offspring

Our results also indicated that the risk of depressive symptoms was 50% higher for offspring born to mothers who smoked tobacco during pregnancy the first trimester of pregnancy than for those whose mothers did not smoke during pregnancy. Again, these associations persisted after controlling for a wide range of potential risk factors and confounders. These findings indicated that the observed adverse association between smoking tobacco during pregnancy and risk of depressive symptoms in their offspring was independent of socio-demographic variation, predisposition to depression and paternal smoking during pregnancy. Moreover, the association did not appear to be mediated by the effects of smoking on adverse pregnancy outcomes. Similar to prenatal alcohol exposure, we found a null association for late pregnancy (at 34 weeks) exposure to tobacco.

The finding of this study was consistent with evidence from some previous studies (Ashford, van Lier et al. 2008, Robinson, McLean et al. 2010, Moylan, Gustavson et al. 2015, Biederman, Martelon et al. 2017), but not all (Batstra, Hadders-Algra et al. 2003, Chudal, Brown et al. 2015, Talati, Wickramaratne et al. 2017). A study from the USA examined the association between prenatal tobacco use and psychopathology in offspring with a mean follow-up of 27.7 years (Talati, Wickramaratne et al. 2017). The USA based study reported small associations in the opposite direction, suggesting male offspring born to mothers smoking 10 or more cigarettes/day during pregnancy are protected from mood disorders or are less likely to develop mood disorders. However, the study had a very small sample size (n = 238). Further, a study from the Dutch birth cohort including a total of 1186 singleton births aged between 5.5 and 11 years assessed the associations between prenatal tobacco use and behavioral problems in offspring (Batstra, Hadders-Algra et al. 2003). This study reported no associations between prenatal tobacco use (any time during pregnancy) and internalizing behaviors in offspring. This lack of association may be due to using parent and teacher reported data to ascertain outcomes in offspring. This is also complemented by a study that investigated the measurement structure of the Child Behavior Checklist (CBCL) and reported low correlations between parent and teacher ratings of behavioral problems in children (Konold, Walthall et al. 2004).

The mechanism underlying the association between prenatal tobacco use and the risk of depressive symptoms in offspring remain unclear. However, a number of plausible physiological mechanisms have been suggested. One suggested mechanism involves the hazardous effects of over 4000 chemical ingredients present in tobacco smoke (Blood-Siegfried and Rende 2010). Such chemicals as carbon monoxide, aldehydes and nicotine can cross the placenta and blood-brain barrier and consequently result in a deleterious influence on fetal brain development (Rose 2006). This can minimize the neuronal area in numerous regions of the hippocampus (a complex brain structure with major role of learning and memory), and prompt permanent modifications to the brain cell structure, which persist into young adulthood (Roy and Sabherwal 1998). Furthermore, evidence from *in vivo* studies has suggested that prenatal tobacco exposure may affect the function of dopamine and serotonin (Muneoka, Ogawa et al. 1997, Muneoka, Ogawa et al. 2001, Cowen and Browning 2015), neurotransmitters that have been robustly linked to behavioral and mental health problems in humans.

Epidemiological evidence also suggests that exposure to tobacco smoking in the prenatal period may be associated with epigenetic changes in the offspring (Knopik, Maccani et al. 2012, Stroud, Papandonatos et al. 2014, Richmond, Simpkin et al. 2015). For example, a study that examined epigenome-wide methylation in cord blood of newborns exposed to prenatal tobacco smoking collected from the Norwegian Mother and Child Cohort Study, identified methylated cytosine–phosphate–guanine (CpGs) in the offspring (Joubert, Haberg et al. 2012). This is also corroborated by evidence from a recent study that investigated the effects of prenatal tobacco use on DNA methylation among adolescents participating in 17-year follow-up of the Raine Study (Rauschert, Melton et al. 2019). This study reported that prenatal tobacco exposure prompted permanent changes to DNA methylation in the adolescent offspring, which are not significantly modified by paternal smoking during pregnancy and maternal postnatal smoking. The epigenetic changes in DNA methylation may result in over-stimulation of the hypothalamic-pituitary-adrenocortical axis (HPA) (Stroud, Papandonatos et al. 2014). The corresponding over-stimulation of the axis induces intrauterine programming of up-regulation of hippocampal GAD67 (He, Lu et al. 2017) and may result in depressive symptoms in offspring (Zhang, Fan et al. 2019).

Postnatal environmental risk factors may play an important role in the progression of depressive symptoms in the adolescents. For example, findings from epidemiological studies proposed that adolescents may be exposed to postnatal parental tobacco use and develop adverse

mental health outcomes (Knopik 2009, Kabir, Connolly et al. 2011). Most recently, a study of data from 37,505 adolescents aged 12 − 15 years from 2003–2008 Global School-Based Student Health Survey that included 22 low- and middle-income countries reported that exposure to second-hand tobacco smoking increased the prevalence of depressive symptoms from 23.0% to 28.9% (Jacob, Smith et al. 2020). However, the effects of prenatal tobacco use on offspring depressive symptoms remained significant when we further adjusted the models for postnatal maternal tobacco use at 13 years of follow-up.

4.3. Strengths and limitations of the study

This study has the following strengths. Prenatal alcohol and tobacco exposures and the risk of depressive symptoms in offspring were prospectively collected and measured using well-accepted standardized and validated screening tools. Depressive symptoms in offspring were measured using the BDI-Y, a valid and reliable tool which is aligned with the DSM-IV manual to diagnose major depressive disorders in adolescents. Serum cotinine levels were previously measured in a random sample of 238 of the pregnant mothers and there was strong agreement with self-reported maternal smoking status during pregnancy (Stick, Burton et al. 1996). A wide range of confounders were included in the prenatal period with a relatively large sample size. Our study also had the following limitations. Although not all pregnant mothers who smoked and drank alcohol engage in illicit drug use, such illicit drug use would be correlated with smoking and alcohol consumption but unfortunately we did not have these data to include in the adjusted models. Loss to follow-up in this study was relatively high, although can be expected for such a long period of follow-up of the cohort and this may have introduced bias. However, the patterns of prenatal alcohol and tobacco use did not differ between those lost to follow-up and those retained in the study. This suggests that attrition is unlikely to have introduced substantial bias. Nonetheless, we employed multivariate imputation with chained equations to minimize bias and found similar results after imputation. Although we were not able to adjust specifically for maternal and paternal mental health problems during pregnancy, but we were able to control for previous maternal mental health problems during pregnancy and maternal depressive symptoms at 13 year follow-up of the cohort as proxies for offspring predisposition to psychiatric conditions. Moreover, we did not adjust for adolescents' risk factors for mental health problems such as substance use, in that we assumed that further adjustment for risk factors which are not confounders may inflate the variance of the estimate and produce less precise estimates (Greenland, Daniel et al. 2016).

5. Conclusion

Offspring exposed to prenatal alcohol and tobacco use had greater risks of depressive symptoms compared with unexposed offspring. Although a number of studies of adolescents with prenatal alcohol and tobacco exposure have focused mainly on externalizing behaviors, the findings of our study add to the accumulating body of evidence that such adolescents should also be monitored for the possible development of depressive symptoms. Further epidemiological and mechanistic studies are warranted to elucidate specific causal pathways.

Funding

There are no additional funding received to disclose for this publication.

CRediT authorship contribution statement

Bereket Duko: Conceptualization, Data curation, Formal analysis, Software, Methodology, Project administration, Investigation, Visualization, Writing - original draft, Writing - review & editing. **Gavin Pereira:** Data curation, Methodology, Investigation, Software, Visualization, Supervision, Writing - review & editing. **Kim Betts:** Data curation, Methodology, Investigation, Software, Visualization, Supervision, Writing - review & editing. **Robert J. Tait:** Data curation, Methodology, Investigation, Visualization, Writing - review & editing. **John Newnham:** Data curation, Methodology, Investigation, Visualization, Writing - review & editing. **Rosa Alati:** Data curation, Methodology, Investigation, Software, Visualization, Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors acknowledge the Raine Study participants and their family. We also acknowledge the Raine Study team for data collection and cohort coordination. The National Health and Medical Research Council (NHMRC) for long term contribution to funding the Raine Study since initiation, the Raine Medical Research Foundation, The University of Western Australia (UWA), Curtin University, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University andThe University of Notre Dame Australia are acknowledged for providing funding for core management of the Raine Study. The 17 year follow-up of the Raine Cohort was supported by the National Health and Medical Research Council Program grant #353514, Project Grants #1099655 and #1173991. Bereket Duko is funded by Curtin University through Curtin International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. The funders had no role in the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.jad.2020.10.030.

References

Aitken, Z., Hewitt, B., Keogh, L., LaMontagne, A.D., Bentley, R., Kavanagh, A.M., 2016. "Young maternal age at first birth and mental health later in life: Does the association vary by birth cohort? Social Science & Medicine 157, 9–17.

Akin, A, Citin, B., 2007. "The Depression Anxiety and StressScale (DASS): The study of Validityand Reliability. Educational Sciences: Theory & Practice 7 (1), 260–268.

APA, 2000. Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR. DC: American Psychiatric Association, Washington.

Ashford, J., van Lier, P.A., Timmermans, M., Cuijpers, P., Koot, H.M., 2008. "Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. J Am Acad Child Adolesc Psychiatry 47 (7), 779–787.

Barr, H.M., Bookstein, F.L., O'Malley, K.D., Connor, P.D., Huggins, J.E., Streissguth, A.P., 2006. "Binge drinking during pregnancy as a predictor of psychiatric disorders on the structured clinical interview for DSM-IV in young adult offspring. American Journal of Psychiatry 163 (6), 1061–1065.

Batstra, L., Hadders-Algra, M., Neeleman, J., 2003. "Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: prospective evidence from a Dutch birth cohort. Early Human Development 75 (1), 21–33.

Beck, J.S., Beck, A.T., Jolly, B.J., 2001. Beck youth inventories of emotional and social impairment. The Psychological Corporation, San Atonio, TX.

Biederman, J., Martelon, M., Woodworth, K., Spencer, T.J., Faraone, S.V., 2017. "Is maternal smoking during pregnancy a risk factor for cigarette smoking in offspring? A longitudinal controlled study of ADHD children grown up. Journal of Attention Disorders 21 (12), 975–985.

Blood-Siegfried, J., Rende, E.K., 2010. "The Long-Term Effects of Prenatal Nicotine Exposure on Neurologic Development. Journal of Midwifery and Women's Health 55 (2), 143–152.

Brancato, A., Castelli, V., Cavallaro, A., Lavanco, G., Plescia, F., Cannizzaro, C., 2018. "Pre-conceptional and Peri-Gestational Maternal Binge Alcohol Drinking Produces

Inheritance of Mood Disturbances and Alcohol Vulnerability in the Adolescent Offspring. Frontiers in psychiatry 9 150-150.
Burd, L., Roberts, D., Olson, M., Odendaal, H., 2007. "Ethanol and the placenta: A review. The Journal of Maternal-Fetal & Neonatal Medicine 20 (5), 361–375.
Chen, Y., Herrera-Marschitz, M., Bjelke, B., Blum, M., Gross, J., Andersson, K., 1997. "Perinatal asphyxia-induced changes in rat brain tyrosine hydroxylase-immunoreactive cell body number: effects of nicotine treatment. Neurosci Lett 221 (2-3), 77–80.
Chudal, R., Brown, A.S., Gissler, M., Suominen, A., Sourander, A., 2015. "Is maternal smoking during pregnancy associated with bipolar disorder in offspring? Journal of Affective Disorders 171, 132–136.
Cowen, P.J., Browning, M., 2015. "What has serotonin to do with depression? World psychiatry: official journal of the World Psychiatric Association (WPA) 14 (2), 158–160.
Davey, C.G., McGorry, P.D., 2019. "Early intervention for depression in young people: a blind spot in mental health care. The Lancet Psychiatry 6 (3), 267–272.
De Mola, C.L., De França, G.V.A., de Avila Quevedo, L., Horta, B.L., 2014. "Low birth weight, preterm birth and small for gestational age association with adult depression: systematic review and meta-analysis. British Journal of Psychiatry 205 (5), 340–347.
Dolan, C., Geels, L., Vink, J., Beijsterveldt, C., Neale, M., Bartels, M., Boomsma, D.I., 2016. "Testing causal effects of maternal smoking during pregnancy on offspring's externalizing and internalizing behavior. Behavior Genetics 46 (3), 378–388.
Dontje, M.L., Eastwood, P., Straker, L., 2019. "Western Australian pregnancy cohort (Raine) Study: Generation 1. BMJ Open 9 (5) e026276.
Dunlop, B.W., Nemeroff, C.B., 2007. "The Role of Dopamine in the Pathophysiology of Depression. Archives of General Psychiatry 64 (3), 327–337.
Easey, K.E., Timpson, N.J., Munafò, M.R., 2020. Association of Prenatal Alcohol Exposure and Offspring Depression: A Negative Control Analysis of Maternal and Partner Consumption. Alcoholism: Clinical and Experimental Research n/a(n/a).
Ekblad, M., Gissler, M., Lehtonen, L., Korkeila, J., 2010. "Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Archives of General Psychiatry 67 (8), 841–849.
Greenland, S., Daniel, R., Pearce, N., 2016. "Outcome modelling strategies in epidemiology: traditional methods and basic alternatives. International Journal of Epidemiology 45 (2), 565–575.
He, X., Lu, J., Dong, W., Jiao, Z., Zhang, C., Yu, Y., Zhang, Z., Wang, H., Xu, D., 2017. "Prenatal nicotine exposure induces HPA axis-hypersensitivity in offspring rats via the intrauterine programming of up-regulation of hippocampal GAD67. Arch Toxicol 91 (12), 3927–3943.
Hill, S.Y., Lowers, L., Locke-Wellman, J., Shen, S.A., 2000. "Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol 61 (5), 661–668.
Jacob, L., Smith, L., Jackson, S.E., Haro, J.M., Shin, J.I., Koyanagi, A., 2020. "Secondhand Smoking and Depressive Symptoms Among In-School Adolescents. American Journal of Preventive Medicine 58 (5), 613–621.
James, S.B., Alcott, S.V., 2007. Mood disorders, in Kaplan & Sadock's Synopsis of Psychiatry: Behavioral Sciences/Clinical Psychiatry, 10th Edition. Lippincott Williams & Wilkins, pp. 530–533 page.
Jones, P.J.H., Leichter, J., Lee, M., 1981. "Placental blood flow in rats fed alcohol before and during gestation. Life Sciences 29 (11), 1153–1159.
Joubert, B.R., Haberg, S.E., Nilsen, R.M., Wang, X., Vollset, S.E., Murphy, S.K., Huang, Z., Hoyo, C., Midttun, O., Cupul-Uicab, L.A., Ueland, P.M., Wu, M.C., Nystad, W., Bell, D.A., Peddada, S.D., London, S.J., 2012. "450K epigenome-wide scan identifies differential DNA methylation in newborns related to maternal smoking during pregnancy. Environ Health Perspect 120 (10), 1425–1431.
Kabir, Z., Connolly, G.N., Alpert, H.R., 2011. "Secondhand smoke exposure and neurobehavioral disorders among children in the United States. Pediatrics 128 (2), 263–270.
Keenan-Miller, D., Hammen, C.L., Brennan, P.A., 2007. "Health outcomes related to early adolescent depression. J Adolesc Health 41 (3), 256–262.
Knopik, V.S., 2009. "Maternal smoking during pregnancy and child outcomes: real or spurious effect? Developmental neuropsychology 34 (1), 1–36.
Knopik, V.S., Maccani, M.A., Francazio, S., McGeary, J.E., 2012. "The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Development and psychopathology 24 (4), 1377–1390.
Konold, T.R., Walthall, J.C., Pianta, R.C., 2004. "The Behavior of Child Behavior Ratings: Measurement Structure of the Child Behavior Checklist Across Time, Informants, and Child Gender. Behavioral Disorders 29 (4), 372–383.
Lahti, M., Eriksson, J.G., Heinonen, K., Kajantie, E., Lahti, J., Wahlbeck, K., Tuovinen, S., Pesonen, A.-K., Mikkonen, M., Osmond, C., Räikkönen, K., 2014. "Maternal Grand Multiparity and the Risk of Severe Mental Disorders in Adult Offspring. PloS one 9 (12) e114679-e114679.
Lau, J.Y.F., Eley, T.C., 2008. "Disentangling gene-environment correlations and interactions on adolescent depressive symptoms. Journal of child psychology and psychiatry, and allied disciplines 49 (2), 142–150.
Leaf, P.J., Alegria, M., Cohen, P., Goodman, S.H., Horwitz, S.M., Hoven, C.W., Narrow, W.E., Vaden-Kiernan, M., Regier, D.A., 1996. "Mental health service use in the community and schools: results from the four-community MECA Study. Methods for the Epidemiology of Child and Adolescent Mental Disorders Study. J Am Acad Child Adolesc Psychiatry 35 (7), 889–897.
Lewinsohn, P.M., Pettit, J.W., Joiner, Jr, T.E., Seeley, J.R., 2003. "The symptomatic expression of major depressive disorder in adolescents and young adults. J Abnorm Psychol 112 (2), 244–252.
Loechner, J., Sfärlea, A., Starman, K., Oort, F., Thomsen, L.A., Schulte-Körne, G., Platt, B., 2019. "Risk of Depression in the Offspring of Parents with Depression: The Role of Emotion Regulation, Cognitive Style, Parenting and Life Events. Child Psychiatry & Human Development.
McLaughlin, K.A., Costello, E.J., Leblanc, W., Sampson, N.A., Kessler, R.C., 2012. "Socioeconomic Status and Adolescent Mental Disorders. American Journal of Public Health 102 (9), 1742–1750.
Meier, S., Plessen, K., Verhulst, F., Mors, O., Mortensen, P., Pedersen, C., Agerbo, E., 2017. "Familial confounding of the association between maternal smoking during pregnancy and internalizing disorders in offspring. Psychological Medicine 47 (8), 1417–1426.
Menezes, A.M., Hallal, P.C., Horta, B.L., 2007. "Early determinants of smoking in adolescence: a prospective birth cohort study. Cad Saude Publica 23 (2), 347–354.
Menezes, A.M., Murray, J., Laszlo, M., Wehrmeister, F.C., Hallal, P.C., Goncalves, H., Assuncao, M.C., Menezes, C.B., Barros, F.C., 2013. "Happiness and depression in adolescence after maternal smoking during pregnancy: birth cohort study. PLoS One 8 (11) e80370.
Merikangas, K.R., Jin, R., He, J.P., Kessler, R.C., Lee, S., Sampson, N.A., Viana, M.C., Andrade, L.H., Hu, C., Karam, E.G., Ladea, M., Medina-Mora, M.E., Ono, Y., Posada-Villa, J., Sagar, R., Wells, J.E., Zarkov, Z., 2011. "Prevalence and correlates of bipolar spectrum disorder in the world mental health survey initiative. Arch Gen Psychiatry 68 (3), 241–251.
Monshouwer, K., Huizink, A.C., Harakeh, Z., Raaijmakers, Q.A., Reijneveld, S.A., Oldehinkel, A.J., Verhulst, F.C., Vollebergh, W.A., 2011. "Prenatal smoking exposure and the risk of behavioral problems and substance use in adolescence: the TRAILS study. Eur Addict Res 17 (6), 342–350.
Moylan, S., Gustavson, K., Øverland, S., Karevold, E.B., Jacka, F.N., Pasco, J.A., Berk, M., 2015. "The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: The Norwegian mother and child cohort study. BMC Medicine 13 (1).
Muneoka, K., Ogawa, T., Kamei, K., Mimura, Y., Kato, H., Takigawa, M., 2001. Nicotine exposure during pregnancy is a factor which influences serotonin transporter density in the rat brain. Eur J Pharmacol 411 (3), 279–282.
Muneoka, K., Ogawa, T., Kamei, K., Muraoka, S., Tomiyoshi, R., Mimura, Y., Kato, H., Suzuki, M.R., Takigawa, M., 1997. "Prenatal nicotine exposure affects the development of the central serotonergic system as well as the dopaminergic system in rat offspring: involvement of route of drug administrations. Brain Res Dev Brain Res 102 (1), 117–126.
Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. "Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342 (8876), 887–891.
NHMRC (2009). Australian guidelines to reduce health risks from drinking alcohol: Commonwealth of Australia. Pages. 2, 3. Available at http://www.nhmrc.gov.au/guidelines/publications/ds10.
Nomura, Y., Wickramaratne, P.J., Pilowsky, D.J., Newcorn, J.H., Bruder-Costello, B., Davey, C., Fifer, W.P., Brooks-Gunn, J., Weissman, M.M., 2007. "Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression. Comprehensive psychiatry 48 (5), 470–478.
O'Leary, C.M., Nassar, N., Zubrick, S.R., Kurinczuk, J.J., Stanley, F., Bower, C., 2010. "Evidence of a complex association between dose, pattern and timing of prenatal alcohol exposure and child behaviour problems. Addiction 105 (1), 74–86.
O'Connor, M.J., 2014. "Mental Health Outcomes Associated with Prenatal Alcohol Exposure: Genetic and Environmental Factors. Current Developmental Disorders Reports 1 (3), 181–188.
Padmanabhan, R., Hameed, M.S., 1988. "Effects of acute doses of ethanol administered at pre-implantation stages on fetal development in the mouse. Drug Alcohol Depend 22 (1-2), 91–100.
Polanczyk, G.V., Salum, G.A., Sugaya, L.S., Caye, A., Rohde, L.A., 2015. "Annual Research Review: A meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. Journal of Child Psychology and Psychiatry 56 (3), 345–365.
Pyhälä, R., E. Wolford, H. Kautiainen, S. Andersson, P. Bartmann, N. Baumann, A.-M. Brubakk, K. A. I. Evensen, P. Hovi, E. Kajantie, M. Lahti, R. J. Van Lieshout, S. Saigal, L. A. Schmidt, M. S. Indredavik, D. Wolke and K. Räikkönen (2017). "Self-Reported Mental Health Problems Among Adults Born Preterm: A Meta-analysis." Pediatrics 139(4): e20162690.
Rauschert, S., Melton, P.E., Burdge, G., Craig, J.M., Godfrey, K.M., Holbrook, J.D., Lillycrop, K., Mori, T.A., Beilin, L.J., Oddy, W.H., Pennell, C., Huang, R.-C., 2019. "Maternal Smoking During Pregnancy Induces Persistent Epigenetic Changes Into Adolescence, Independent of Postnatal Smoke Exposure and Is Associated With Cardiometabolic Risk. Frontiers in Genetics 10, 770.
Reiss, F., 2013. "Socioeconomic inequalities and mental health problems in children and adolescents: A systematic review. Social Science & Medicine 90, 24–31.
Richmond, R.C., Simpkin, A.J., Woodward, G., Gaunt, T.R., Lyttleton, O., McArdle, W.L., Ring, S.M., Smith, A.D.A.C., Timpson, N.J., Tilling, K., Davey Smith, G., Relton, C.L., 2015. "Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Human molecular genetics 24 (8), 2201–2217.
Robinson, M., McLean, N.J., Oddy, W.H., Mattes, E., Bulsara, M., Li, J., Zubrick, S.R., Stanley, F.J., Newnham, J.P., 2010. "Smoking cessation in pregnancy and the risk of child behavioural problems: a longitudinal prospective cohort study. J Epidemiol Community Health 64 (7), 622–629.
Robinson, M., Oddy, W.H., McLean, N.J., Jacoby, P., Pennell, C.E., de Klerk, N.H., Zubrick, S.R., Stanley, F.J., Newnham, J.P., 2010. "Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. Bjog 117 (9), 1139–1150.
Rose, J.E., 2006. "Nicotine and nonnicotine factors in cigarette addiction. Psychopharmacology (Berl) 184 (3-4), 274–285.
Roy, T.S., Sabherwal, U., 1998. "Effects of gestational nicotine exposure on hippocampal morphology. Neurotoxicol Teratol 20 (4), 465–473.

Roza, S.J., Verhulst, F.C., Jaddoe, V.W., Steegers, E.A., Mackenbach, J.P., Hofman, A., Tiemeier, H., 2009. "Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int J Epidemiol 38 (3), 680–689.
Sadock, BJ, Sadock, VA, R., P., 2015. Kaplan and Sadock's Synopsis of psychiatry, 11th edition. behavioral sciences/clinical psychiatry, pp. 8 Book chapter.
Sayal, K., Heron, J., Draper, E., Alati, R., Lewis, S.J., Fraser, R., Barrow, M., Golding, J., Emond, A., Davey Smith, G., Gray, R., 2014. "Prenatal exposure to binge pattern of alcohol consumption: mental health and learning outcomes at age 11. Eur Child Adolesc Psychiatry 23 (10), 891–899.
Sayal, K., Heron, J., Golding, J., Emond, A., 2007. "Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. Pediatrics 119 (2) e426-434.
Shamshirsaz, A.A., Paidas, M., Krikun, G., 2012. "Preeclampsia, hypoxia, thrombosis, and inflammation. J Pregnancy 2012, 374047.
Slotkin, T.A., Tate, C.A., Cousins, M.M., Seidler, F.J., 2006. "Prenatal nicotine exposure alters the responses to subsequent nicotine administration and withdrawal in adolescence: Serotonin receptors and cell signaling. Neuropsychopharmacology 31 (11), 2462–2475.
StataCorp (2019). "Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC.".
Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A.M., Carpenter, J.R., 2009. "Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.
Stick, S.M., Burton, P.R., Gurrin, L., Sly, P.D., LeSouëf, P.N., 1996. "Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. The Lancet 348 (9034), 1060–1064.
Stroud, L.R., Papandonatos, G.D., Rodriguez, D., McCallum, M., Salisbury, A.L., Phipps, M.G., Lester, B., Huestis, M.A., Niaura, R., Padbury, J.F., Marsit, C.J., 2014. "Maternal smoking during pregnancy and infant stress response: test of a prenatal programming hypothesis. Psychoneuroendocrinology 48, 29–40.
Talati, A., Wickramaratne, P.J., Wesselhoeft, R., Weissman, M.M., 2017. "Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry Res 252, 346–352.
Thapar, A., Collishaw, S., Pine, D.S., Thapar, A.K., 2012. "Depression in adolescence. Lancet (London, England) 379 (9820), 1056–1067.
Thase, M.E., 2009. "Neurobiological aspects of depression. In: Gotlib, I.H., Hammen, C.L. (Eds.), Handbook of depression, Eds. US: The Guilford Press, New York, NY, pp. 187–217.
Zahn–Waxler, C., Klimes–Dougan, B., Slattery, M.J., 2000. "Internalizing problems of childhood and adolescence: Prospects, pitfalls, and progress in understanding the development of anxiety and depression. Development and Psychopathology 12 (3), 443–466.
Zhang, C., Fan, S.J., Sun, A.B., Liu, Z.Z., Liu, L., 2019. "Prenatal nicotine exposure induces depressionlike behavior in adolescent female rats via modulating neurosteroid in the hippocampus. Mol Med Rep 19 (5), 4185–4194.

4.3 Prenatal tobacco and alcohol exposures and the risk of anxiety symptoms in young adulthood: a population-based cohort study

Published manuscript and formal citation

Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal Tobacco and Alcohol Exposures and the Risk of Anxiety Symptoms in Young Adulthood: a Population-Based Cohort Study. Psychiatry research; 310: 114466.

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.psychres.2022.114466.

Study purpose: Existing epidemiological studies have linked prenatal tobacco and alcohol exposures with internalizing behaviours in children and adolescents with inconsistent findings, suggesting the necessity of well-balanced longitudinal studies with relatively larger sample size to produce more precise estimates. Moreover, to our knowledge, there is no previous study that has investigated the associations between prenatal alcohol exposure and the risk of anxiety symptoms in young adulthood. Therefore, this study was conducted to fill this gap in literature by testing the prospective associations between prenatal alcohol and tobacco exposures and the risk of experiencing symptoms of anxiety in young adulthood using relatively large sample size.

Psychiatry Research 310 (2022) 114466

Contents lists available at ScienceDirect

Psychiatry Research

journal homepage: www.elsevier.com/locate/psychres

Prenatal tobacco and alcohol exposures and the risk of anxiety symptoms in young adulthood: A population-based cohort study

Bereket Duko [a,*], Gavin Pereira [a,b,c], Robert J. Tait [d], Kim Betts [a], John Newnham [e], Rosa Alati [a,f]

[a] Curtin School of Population Health, Curtin University, Kent Street, Bentley WA 6102, Australia
[b] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[c] enAble Institute, Curtin University, Kent Street, Bentley, Western Australia 6102, Australia
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley WA 6102, Australia
[e] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands WA 6009, Australia
[f] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland 4068 Australia

ARTICLE INFO

Keywords:
Tobacco
Alcohol
Pregnancy
Young adulthood
Anxiety symptoms
The Raine Study

ABSTRACT

Background: Epidemiological studies have linked prenatal tobacco and alcohol exposures to internalizing behaviours in children and adolescents with inconsistent findings. Dearth of epidemiological studies have investigated the associations with the risk of experiencing symptoms of anxiety in young adulthood.
Methods: Study participants ($N = 1190$) were from the Raine Study, a population-based prospective birth cohort based in Perth, Western Australia. Data on prenatal tobacco and alcohol exposures were available for the first and third trimesters of pregnancy. Experiencing symptoms of anxiety in young adulthood at age 20 years was measured by a short form of the Depression Anxiety Stress Scale (DASS 21). Relative risk (RR) of experiencing symptoms of anxiety in young adulthood for prenatal tobacco and alcohol exposures were estimated with log binomial regression.
Results: After adjusting for potential confounders, we observed increased risks of experiencing symptoms of anxiety in young adults exposed to prenatal tobacco in the first trimester [RR = 1.52, 95% CI: 1.12–2.06, p-value < 0.01] and third trimester [RR = 1.53, 95% CI: 1.10–2.13, p-value = 0.02]. However, we found insufficient statistical evidence for an association between first trimester [RR = 1.01, 95% CI: 0.76–1.22, p-value = 0.90] and third trimester [RR = 1.03, 95% CI: 0.80–1.34, p-value = 0.91] prenatal exposure to alcohol and the risk of experiencing symptoms of anxiety in young adults. There was a dose response association between prenatal tobacco exposure and increasing anxiety symptoms in offspring.
Conclusion: The findings of this study suggest that an association between prenatal tobacco exposure and risk of anxiety symptoms remains apparent into young adulthood.

1. Background

Anxiety disorder is one the most commonly diagnosed mental health problems in young adults (Yang et al., 2021). Recent estimates from the Global Burden of Diseases 2019 study suggest that anxiety disorder is responsible for about 28.68 million disability-adjusted life years (DALYs) in adolescents and young adults (Vos et al., 2020). Young adults suffering from anxiety disorder can experience excessive and uncontrollable fear and worry, panic attacks, cold flushes, and restlessness or feeling tense, avoiding perceived threats and obsessive thinking (Craske et al., 2009). A number of studies have reported that anxiety disorder is also a major predictor of personal and social difficulties (Sareen et al., 2005; Stroud et al., 2014), lack of interest in learning and poor academic performance in exams (Vitasari et al., 2010), increased risk of substance use disorders (Smith and Book, 2008) and suicidal ideation and attempt (Nepon et al., 2010). Rigorously identifying early-life presumptive risk factors of this disorder is therefore critically important to direct early preventive strategies and alleviate such burden later in life.

Although the exact cause of anxiety disorder is not fully understood, it has been speculated that a mixture of biological, genetic, psychological, social and environmental factors are believed to contribute to anxiety symptoms, which can progress to anxiety disorder (Michael et al., 2007; Beesdo et al., 2010; Munir and T, 2021). Evidence from epidemiological studies that support the elements of the developmental

* Corresponding author: Curtin School of Population Health, Curtin University, Kent Street, Bentley, Perth, Western Australia 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.psychres.2022.114466
Received 11 October 2021; Received in revised form 18 January 2022; Accepted 19 February 2022
Available online 20 February 2022

origin of health and disease hypothesis suggests that the majority of these risk factors could appear in early life (Tierney and Nelson, 2009), which in turn lead to the elevated risk of diseases and disorders (Barker, 2007).

Prenatal tobacco and alcohol exposures feature prominently among such factors, which are antecedent to several mental health and behavioural problems in offspring later in life (Easey et al., 2019; Duko et al., 2020; Duko Pereira et al., 2021). Epidemiological evidence suggests that offspring exposed to prenatal tobacco may have an elevated risk of internalizing behaviours compared to non-exposed offspring (Ashford et al., 2008; Moylan et al., 2015; Moylan et al., 2015; Duko et al., 2020). Similarly, findings from *in vivo* studies provide evidence that prenatal exposure to alcohol (ethanol) could result in anxiety like behaviours in offspring at various ages (Kleiber et al., 2011; Brocardo et al., 2012; Cullen et al., 2013). Studies on human have however reported inconsistence results (Sayal et al., 2007; Robinson et al., 2010; Day et al., 2013; Niclasen et al., 2014; Silva et al., 2015; Ichikawa et al., 2018; Duko et al., 2021). For example, a systematic review that examined the link between prenatal alcohol exposure and offspring anxiety/depression in 13 studies did not find sufficient evidence to support such associations (Easey et al., 2019). Supporting these explanations, a meta-analysis that tested the association between prenatal alcohol exposure and offspring mental health problems also presented inconclusive evidence and suggested the necessity of further studies to rule out the possibility of confounding (Flak et al., 2014).

Inconsistent results across previous studies may be due to variability in the way anxiety symptoms have been measured in the studies. Most longitudinal studies that have tested the association between prenatal tobacco and alcohol exposures and offspring anxiety symptoms reported results for associations with a total score for internalizing behaviours, without presenting the subscale scores of individual mental health problems such as anxiety symptoms (Roza et al., 2009; Robinson et al., 2010), making the replication of findings more problematic. Further, evidence suggests that socioeconomic positions can influence the initiation and continued use of tobacco and alcohol during pregnancy (Bobo and Husten, 2000; Gilman et al., 2008; Wendell, 2013), suggesting that prenatal tobacco and alcohol exposures are more likely to be affected by similar socio-economic confounding. Moreover, to our knowledge, there is no study that has examined the associations between prenatal tobacco and alcohol exposures and the risk of anxiety symptoms in young adulthood. The aim of this study was to estimate the association between prenatal tobacco and alcohol exposures and the risk of experiencing symptoms of anxiety in young adulthood.

2. Methods

2.1. Study design and participants

Participants were from the Raine Study, a multi-generational prospective cohort of 2730 pregnant women (Gen1) and their offspring (Gen2) (Newnham et al., 1993; Straker et al., 2017). These women received antenatal care at King Edward Memorial Hospital and nearby private clinics in Perth, Western Australia between 1989 and 1992, and delivered a total of 2868 live-births including 138 multiple births. Complete data were available for 1190 mother-offspring pairs at 20 years of follow-up. This study was approved by the Human Research Ethics Committees of the University of Western Australia. Written informed consent was gained from the study participants at enrolment and each follow-up assessment after the details of the study procedures had been fully described.

2.2. Exposure: prenatal tobacco and alcohol exposures (Gen1)

At 18 and 34 weeks of pregnancy, mothers were asked to report the total number of cigarettes they had smoked per day during the first and third trimesters of pregnancy, respectively. We used these data to classify mothers as either non-smokers or smokers during pregnancy. Cotinine, a metabolite of nicotine, is considered as a gold standard (biomarker) for evaluation of tobacco smoking or exposure to tobacco smoke (Moran, 2012). A validation study was conducted by Stick et al., to validate self-reports of prenatal tobacco exposure (Stick et al., 1996). In that study, cotinine was measured in serum from 238 pregnant mothers who self-reported tobacco smoking during the first three months of pregnancy. Results of that study suggested good agreement between self-reported prenatal tobacco exposure and measured serum cotinine concentration. To further test dose-related responses of prenatal tobacco exposure: 'light/moderate exposure' was defined as prenatal tobacco exposure of 1–9 cigarettes per day whereas 'heavy exposure' was defined as $\geq$ 10 cigarettes per day during pregnancy (Ashford et al., 2008; Duko et al., 2021). At the same time point in pregnancy, mothers also reported an average of the total number of standard drinks of alcohol consumed per week during the first and third trimesters of pregnancy. Based on the National Health and Medical Research Council guidelines of 2009 (NHMRC, 2009), one standard drink in Australia constitutes 10 gs of absolute alcohol. Subsequently, we defined prenatal alcohol exposure as: non-drinker (category 1), up to three standard drinks of alcohol per week (category 2); and four or more standard drinks of alcohol per week (category 3) separately for the first and third trimesters of pregnancy. The same categorization was applied in our previous study that tested the link between maternal prenatal alcohol exposure and harmful alcohol use in adolescent offspring (Duko et al., 2020).

2.3. Outcome: anxiety symptoms in young adults (Gen2)

Experiencing symptoms of anxiety in young adults at the age of 20 years was measured by a short form of the Depression Anxiety Stress Scale (DASS 21). DASS is a 42-item scale designed by the University of New South Wales to measure depression, anxiety and stress (Lovibond and Lovibond, 1993; Akin and Citin, 2007). DASS-21 score was multiplied by two in order to obtain the normal DASS-42 score. This scale consists of 21 items, of which seven items measure anxiety symptoms, which were answered based on four-point frequency scales suggesting the severity of the specific symptoms (Tully et al., 2009; Le et al., 2017). It has shown fairly high internal consistency for the anxiety subscale (Cronbach's alpha = 0.76) (Lovibond and Lovibond, 1993; Akin and Citin, 2007) in different settings (Szabó, 2010; Lee et al., 2019). In our study, participants were considered to be experiencing symptoms of anxiety according to the recommended severity thresholds, which is a DASS score of 8 and above (Lovibond and Lovibond, 1993; Akin and Citin, 2007).

2.4. Confounding and mediating factors

Measures at baseline consisted of maternal socioeconomic positions: maternal age (< 20 years, 20–24.99 years, 25–29.99 years, 30–34.99 years and $\geq$ 35 years); marital status (married, never married, de-facto and widowed/divorced/separated); maternal educational attainment (schooling up to 12 years, trade certificate / apprenticeship, professional registration/ college diploma and university degree); ethnicity (Caucasian and non-Caucasian); average annual family income (low income $\leq$ AUD $24,000 and moderate to high income > AUD $24,000), paternal tobacco smoking during partner's pregnancy (yes/no) and sex of child (male/female). We also included immediate adverse pregnancy and birth outcomes such as hypertensive disorder of pregnancy/pre-eclampsia (yes/no); birth weight (low-birth weight (< 2.5 kg), normal birth-weight (2.5–3.99 kg) and high-birth weight ($\geq$4.0 kg)) and preterm birth (<37 weeks of gestation) (yes/no). Evidence from some emerging studies suggests that prenatal tobacco exposure was associated with an increased risk of sleep problems in offspring (O'Callaghan et al., 2019), which in turn results in anxiety symptoms in offspring (McMakin and Alfano, 2015). Offspring sleep problem at the age of 10 years was

measured using the child behavioural checklist (CBCL) (Achenbach and Rescorla, 2001). Studies have also shown that maternal anxiety symptoms might be associated with offspring anxiety symptoms (Rees et al., 2019). Mothers of the study participants were also assessed for symptoms of anxiety at 16 years of follow-up using DASS-42 (Lovibond and Lovibond, 1993; Akin and Citin, 2007). Further, mothers also reported their postnatal tobacco smoking status at 14 years of follow-up (yes/no).

2.5. Statistical analysis

Associations between prenatal tobacco and alcohol exposures and the risk of experiencing symptoms of anxiety in young adults were examined by generalized linear models (GLM) fitted using log binomial regression to estimate relative risks (RRs). We added different risk factors sequentially as adjustment variables in separate models to explore the role of potential confounders and mediators. We added prenatal tobacco and alcohol exposures separately to unadjusted models. We adjusted these models by maternal age at conception, education, marital status, race and family income, paternal prenatal tobacco smoking during partner's pregnancy and child sex (Model 1). Next, we added pre-eclampsia, birthweight, and preterm birth to Model 1 to remove their potential mediating effects (Model 2). We separately added an indicator for offspring sleep problems at 10 years of follow-up, maternal postnatal tobacco smoking at the age of 14 years and maternal anxiety symptoms at 16 years of follow-up to Model 1 to further remove their effects (Model 3). Model 4 was adjusted for all confounders and mediators. We repeated all analyses removing the first trimester prenatal tobacco and alcohol exposures from the models and replacing them with third trimester prenatal tobacco and alcohol exposures to determine risks in terms of gestational periods. As a sensitivity analysis, we used multiple imputations using chained equations to account for the missing data (Tan et al., 2018). Missing data was imputed using the "mice" STATA command (Royston, 2005; Sterne et al., 2009) and produced fifty imputed datasets. All covariates and mediators along with auxiliary variables used in the final model were included in the imputation model and analyses were repeated.

3. Results

3.1. Characteristics of study participants

The prevalence of maternal tobacco smoking and alcohol drinking during the first trimester of pregnancy were 27.0% and 45.6% respectively. In comparison to non-smoker pregnant mothers, mothers who smoked tobacco during the first trimester of pregnancy were more likely to be never married or living in a de-facto relationship, report low annual family income, have low educational attainment, report postnatal tobacco smoking at 14 years of follow-up and anxiety symptoms at 16 years of follow-up as well as have partners who were tobacco smokers during their pregnancy. In contrast, mothers who reported alcohol use during the first trimester of pregnancy were more likely to be married, report moderate or high annual income, relatively higher educational attainment/level and were less likely to experience symptoms of anxiety at 16 years of follow-up (**Table 1**).

Out of the 304 offspring who reported experiencing symptoms of anxiety at 20 years of follow-up; 26% had been exposed to pre-eclampsia, 6% had been born preterm, 7.4% were of low birthweight, 27.3% were exposed to the first trimester prenatal tobacco use and 24% were exposed to maternal postnatal tobacco smoking at 14 years of follow-up (**Table 2**).

Table 1
Characteristics of mothers and offspring comparing by exposure to the first trimester prenatal tobacco and alcohol use at baseline.

Variables included in the model		First trimester prenatal tobacco				First trimester prenatal alcohol			
		Non-exposed (n = 2048)		Exposed (756)		Non-exposed (n = 1525)		Exposed (n = 1279)	
		n	%	n	%	n	%	n	%
Maternal age at baseline	< 20 years	154	7.5	125	16.5	178	11.7	101	7.9
	20–25 years	387	18.9	216	28.5	363	23.8	240	18.8
	25–30 years	637	31.1	211	28.0	464	30.4	384	30.0
	30–35 years	563	27.5	146	19.3	354	23.2	355	27.8
	≥ 35 years	307	15.0	58	7.7	166	10.9	199	15.6
Marital status	Married	1509	73.7	299	39.5	1028	67.4	780	61.0
	Never married	183	8.9	183	24.2	174	11.4	192	15.0
	Defacto	303	14.8	226	30.0	275	18.2	254	20.0
	Separate/divorce/widow	53	2.6	48	6.3	48	3.1	53	4.0
Annual family income	≤ 24,000 AUD	840	41.0	481	63.6	765	50.1	556	43.5
	> 24,000 AUD	1208	59.0	275	36.4	760	49.9	723	56.5
Mothers' Education status at baseline	Schooling Up to year 12	1108	56.1	575	76.0	957	62.8	726	56.8
	Trade certificate/ apprenticeship	204	10.0	42	5.6	116	7.6	130	10.2
	Professional registration/College Diploma	361	17.6	87	11.5	224	14.7	224	17.5
	University degree	375	18.3	52	6.9	228	15.0	199	15.6
Mothers' ethnicity	Caucasian	1772	86.5	701	92.7	1268	83.1	1205	94.2
	Non-Caucasian	276	13.5	55	7.3	257	16.9	74	5.8
Paternal tobacco smoking during pregnancy	Non-smoker	1435	70.0	231	30.5	910	60.0	756	59.1
	Smoker	613	30.0	525	69.5	615	40.0	523	40.9
Pre-eclampsia	No	1479	72.4	599	79.4	1120	73.5	958	75.1
	Yes	565	27.6	155	20.6	403	26.5	317	24.9
Preterm birth	No	1899	92.8	689	90.9	1393	91.3	1193	93.3
	Yes	148	7.2	69	9.1	132	8.7	85	6.7
Birthweight	Low birth weight	132	6.4	79	10.5	125	8.2	86	6.7
	Normal birthweight	1701	83.2	627	83.6	1252	82.4	1076	84.4
	High birthweight	212	10.4	44	5.9	143	9.4	113	8.9
Offspring sleep problem at 10 years	No	1487	96.8	417	94.6	988	96.1	916	96.5
	Yes	49	3.2	24	5.4	40	3.9	33	3.5
Maternal anxiety symptoms at 16 years of follow-up	No anxiety symptom	992	90.0	242	85.5	602	86.7	632	91.5
	Anxiety symptoms	109	10.0	42	14.5	92	13.3	59	8.5
Maternal tobacco smoking at 14 years of follow-up	Non-smoker	1229	90.2	272	69.8	711	78.8	636	74.8
	Smoker	133	9.8	118	30.2	191	21.2	214	25.2

Table 2
Characteristics of mothers and offspring comparing the major covariates among offspring with and without anxiety symptoms at the age of 20 years.

Variables included in the model		Offspring anxiety symptoms			
		None		Yes	
		n	%	*n*	%
Maternal age at baseline	< 20 years	50	5.4	17	5.5
	20–25 years	155	17.1	58	18.6
	25–30 years	280	30.8	77	24.8
	30–35 years	270	29.7	102	32.8
	≥ 35 years	154	17.0	57	18.3
Marital status	Married	672	75.8	211	69.4
	Never married	76	8.6	27	8.8
	Defacto	114	12.9	57	18.8
	Separate/divorce/ widow	24	2.7	9	3.0
Mothers' ethnicity	Caucasian	796	89.8	268	88.2
	Non-Caucasian	90	10.2	36	11.8
Annual family income at conception	≤ 24,000 AUD	304	34.3	119	39.1
	> 24,000 AUD	582	65.7	185	60.9
Mothers' education status at baseline	Schooling Up to year 12	432	48.8	168	55.3
	Trade certificate/ apprenticeship	105	11.9	27	8.8
	Professional registration/College Diploma	164	18.5	48	15.8
	University degree	185	20.8	61	20.1
Pre-eclampsia	No	667	75.5	223	74.0
	Yes	216	24.5	80	26.0
Preterm birth	No	816	92.2	286	94.1
	Yes	69	7.8	18	5.9
Birthweight	Low birth weight	78	8.6	23	7.4
	Normal birthweight	750	82.6	265	85.8
	High birthweight	80	8.8	21	6.8
Child sex	Male	452	49.7	117	37.6
	Female	457	50.3	194	62.4
Offspring childhood sleep problem at 10 years of follow-up	Non-sleep problem	821	97.2	274	97.5
	Sleep problem	24	2.8	7	2.5
Maternal prenatal tobacco use (1st trimester)	Non-smoker	736	83.0	221	72.7
	Smoker	150	17.0	83	27.3
Maternal prenatal tobacco use (3rd trimester)	Non-smoker	707	85.0	215	75.4
	Smoker	126	15.0	70	24.6
Maternal prenatal alcohol use (1st trimester)	Non-drinker	450	50.8	145	47.7
	Drinker	436	49.2	159	51.3
Maternal prenatal alcohol use (3rd trimester)	Non-drinker	484	61.6	159	58.0
	Drinker	302	38.4	115	42.0
Maternal postnatal tobacco smoking at 14 years of follow-up	Non-smoker	661	82.0	202	76.0
	Smoker	146	18.0	64	24.0
Maternal anxiety symptoms at 16 years of follow-up	Normal	761	94.7	237	89.8
	Anxiety symptoms	43	5.3	27	10.2

3.2. Association between prenatal tobacco and alcohol exposures and the risk of anxiety symptoms in young adulthood

We observed higher risk of experiencing symptoms of anxiety in the unadjusted analysis in young adult offspring exposed to prenatal tobacco use during the first trimester [RR = 1.54, 95% CI: 1.25–1.90] and third trimester of pregnancy [RR 1.53, 95% CI: 1.23–1.91]. In contrast, we observed insufficient statistical evidence for an association between the first trimester [RR = 1.10, 95% CI: 0.90–1.33] and third trimester [RR = 1.12, 95% CI: 0.91–1.37] prenatal alcohol exposure and the risk of experiencing symptoms of anxiety in young adulthood **(Table 3)**.

After adjusting for maternal age at conception, education, marital status, race, family income, child sex and paternal prenatal tobacco smoking, the association between the first trimester and third trimester prenatal tobacco exposure and risk of experiencing symptoms of anxiety in offspring remained virtually unchanged (Model 1). Further statistical adjustment of this model for pre-eclampsia, preterm birth and birthweight to remove their mediation role produced very slight attenuation in the estimates for first trimester [RR = 1.45, 95% CI: 1.15–1.83] and third trimester [RR = 1.43, 95% CI: 1.12–1.84] prenatal tobacco exposures (Model 2). We did not observe substantial changes after full adjustment (Model 4).

We observed that the risk of experiencing symptoms of anxiety in young adulthood increased with the level of exposure to prenatal tobacco and alcohol use. Notably, we observed increased relative risks (RR) of 1.50 (95% CI: 1.05–2.17) and 1.60 (95% CI: 1.07–2.42) for offspring exposed to < 10 cigarettes/day and ≥10 cigarettes/day in the first trimester of pregnancy respectively. We also noted slight increment in point estimates (RR) in offspring exposed to prenatal alcohol use of four or more drinks per week during the first and third trimesters of pregnancy but found insufficient evidence for associations. Moreover, the results remained essentially unchanged after we repeated the analysis after full adjustment with the imputed dataset **(Supplementary file 1).**

4. Discussion

This study prospectively examined the association between prenatal tobacco and alcohol exposures and the risk of experiencing symptoms of anxiety in young adulthood at the age of 20 years using a population-based birth cohort in Australia. To our knowledge, this is the first longitudinal study to investigate the associations between prenatal tobacco and alcohol exposures and risk of anxiety symptoms in young adults. Our results suggest that young adults of mothers who reported tobacco smoking during the first and third trimesters of pregnancy were at a greater risk for experiencing symptoms of anxiety at the age of 20 years. We observed that the risk of experiencing symptoms of anxiety was 50% higher for those exposed compared to non-exposed. These results were robust to statistical adjustment after sequentially adjusting for potential confounders and were independent of pathways involving preeclampsia, low birthweight, and preterm birth. A dose-response association was also observed between prenatal tobacco exposure and the risk of experiencing symptoms of anxiety in young adults. This explanation was further substantiated by the greater relative risk for those exposed to prenatal tobacco smoking of more than 10 cigarettes per day compared to those exposed to fewer cigarettes during pregnancy. In contrast, we found insufficient statistical evidence for associations between prenatal alcohol exposure in the first and third trimester and the risk of experiencing symptoms of anxiety in young adults.

Our findings are consistent with the results of several studies that reported association between prenatal tobacco exposure and risk of internalizing behaviours such as anxiety symptoms in children and adolescents (Indredavik et al., 2007; Ashford et al., 2008; Ekblad et al., 2010; Robinson et al., 2010; Moylan et al., 2015). A population-based prospective cohort study from the Netherlands examined the association between prenatal tobacco exposure and internalizing behaviour in children aged 5 to 18 years (n = 400) and observed an association with internalizing behaviours after controlling for maternal socioeconomic status and mental health problems, child social and attention problems as well as existing externalizing behaviour (Ashford et al., 2008). This was also corroborated by observations from a large longitudinal study of 175,869 young adults from the Finnish medical birth register that reported an increased risk of being diagnosed with any psychiatric disorder including anxiety disorder in offspring exposed to prenatal tobacco use (Ekblad et al., 2010). In supporting our findings, that study also observed dose-response relationship in which the risk of being diagnosed with any psychiatric disorder increased with the level of exposure to maternal prenatal tobacco smoking. Nonetheless, some studies found null associations (Höök et al., 2006; Brion et al., 2010). For instance, a prospective study that combined the data of two birth cohorts namely the Avon Longitudinal Study of Parents and Children and Brazilian Pelotas study reported insufficient statistical evidence for

Table 3
Associations between prenatal tobacco and alcohol exposures and offspring anxiety symptoms at age of 20 years (n = 1190).

Prenatal exposures	Relative Risk (95%CI)					P-value for Model 4
	Unadjusted	Model 1	Model 2	Model 3	Model 4	
First trimester prenatal tobacco						
Any tobacco exposure	1.54 (1.25–1.90)	1.47 (1.17–1.84)	1.45 (1.15–1.83)	1.49 (1.10–2.03)	1.52 (1.12–2.06)	< 0.01
1–9 Cigarettes /day	1.53 (1.18–1.98)	1.46 (1.13–1.95)	1.46 (1.10–1.94)	1.46 (1.02–2.11)	1.50 (1.05–2.17)	.01
> 10 Cigarettes/day	1.56 (1.17–2.07)	1.49 (1.08–1.98)	1.46 (1.07–2.00)	1.59 (1.06–2.40)	1.60 (1.07–2.42)	.03
Third trimester prenatal tobacco						
Any tobacco exposure	1.53 (1.23–1.91)	1.42 (1.10–1.81)	1.43 (1.12–1.84)	1.49 (1.07–2.08)	1.53 (1.10–2.13)	.02
1–9 Cigarettes/day	1.47 (1.09–1.99)	1.42 (1.04–1.94)	1.42 (1.04–1.95)	1.46 (1.01–2.18)	1.46 (1.02–2.12)	.03
> 10 Cigarettes/day	1.57 (1.20–2.10)	1.43 (1.04–1.97)	1.48 (1.08–2.04)	1.56 (1.03–2.36)	1.62 (1.10–2.38)	.01
First trimester prenatal alcohol						
Any alcohol exposure	1.10 (0.90–1.33)	1.07 (0.88–1.30)	1.07 (0.88–1.30)	1.01 (0.79–1.23)	1.01 (0.76–1.22)	.90
≤ 3 standard drinks/week	1.04 (0.77–1.39)	1.00 (0.72–1.29)	1.01 (0.70–1.27)	1.00 (0.55–1.17)	1.00 (0.54–1.15)	.81
> 4 standard drinks/week	1.12 (0.91–1.38)	1.12 (0.90–1.38)	1.12 (0.91–1.39)	1.04 (0.81–1.33)	1.04 (0.81–1.35)	.15
Third trimester prenatal alcohol						
Any alcohol exposure	1.12 (0.91–1.37)	1.11 (0.89–1.38)	1.09 (0.88–1.35)	1.06 (0.82–1.36)	1.03 (0.80–1.34)	.91
≤ 3 standard drinks/week	1.10 (0.88–1.38)	1.02 (0.73–1.44)	1.00 (0.71–1.42)	1.00 (0.98–1.45)	1.01 (0.68–1.47)	.50
> 4 standard drinks/week	1.14 (0.82–1.60)	1.15 (0.91–1.44)	1.13 (0.89–1.42)	1.08 (0.83–1.42)	1.08 (0.83–1.40)	.10

Foot note: non-users were used as a reference control for all above categories.
NB: Analyses were run separately by trimester but reported together for ease of presentation.
Model 1: maternal age at conception, education, marital status, race, family income and paternal prenatal smoking.
Model 2: added pre-eclampsia, preterm birth, birthweight to Model 1.
Model 3: separately added offspring sleep problem at 10 years of follow-up, maternal postnatal tobacco smoking at 14 years follow-up and anxiety symptoms at 16 years of follow-up to Model 1.
Model 4 (fully adjusted model): included maternal age at conception, education, marital status, family income, maternal race, paternal prenatal tobacco smoking, pre-eclampsia, preterm birth, birthweight and maternal postnatal tobacco smoking at 14 years follow-up and anxiety symptoms at 16 years of follow-up.

association between prenatal tobacco smoking and internalizing problems in preschool children at 4 years of age after adjusting for maternal socioeconomic status, parental psychopathology and alcohol consumption (Brion et al., 2010). Similarly, in the Generation R study from the Netherlands the association between maternal smoking during pregnancy and offspring internalizing behaviours disappeared after adjusting for family income, parental education level and psychopathology and child gender (Roza et al., 2009). These lack of evidence for associations in the aforementioned studies may reflect varying offspring ages of assessment and variations in the included confounders. Most notably, evidence from epidemiological studies showed that anxiety symptoms are more noticeable as the age of children and adolescent increases (Zahn-Waxler et al., 2000) and this may potentially limit the capacity of such studies to find associations among younger children with follow-up that ends prior to young adulthood.

We observed insufficient statistical evidence for an association between prenatal alcohol exposure and the risk of experiencing symptoms of anxiety in young adults, which is consistent with the results from several previous studies that have produced mixed results (Kelly et al., 2013; Skogerbø et al., 2013; Niclasen et al., 2014; Lund et al., 2019). A study of data from 37,315 mother-children pairs in the Danish National Birth Cohort found that children born to mothers who consumed five or more alcohol units during the first trimester (AOR = 0.93, 95% CI:0.84–1.03) and third trimester (AOR = 0.86, 95% CI:0.51–1.57) of pregnancy were less likely to report emotional/anxiety symptoms (Niclasen et al., 2014). Furthermore, in a large sibling comparison study that used data from the Norwegian Mother and Child Cohort (MoBa), the association between prenatal alcohol exposure and offspring anxious as well as emotional behavioural problems at the age of five years disappeared after sibling control (Lund et al., 2019). Although we found insufficient statistical evidence for an association between prenatal alcohol exposure and offspring anxiety symptoms in our study; slight increments in risk estimates (RR) in offspring exposed to higher levels of alcohol during the first and third trimesters of pregnancy limits us from concluding that there is safe level of alcohol consumption during the prenatal period in relation to future anxiety symptoms in offspring. It is also plausible that the effects of prenatal alcohol exposure have longer latency, thereby requiring further follow-up to observe associations.

Although the mechanisms explaining the link between prenatal tobacco exposure and the risk of anxiety symptoms in offspring are not fully understood, several putative mechanisms have been suggested. One proposed mechanism is that prenatal exposure to tobacco smoke may result in DNA methylation and dysregulated expression of microRNA (Knopik et al., 2012; Stroud et al., 2014; Richmond et al., 2015). Most recently, a prospective longitudinal study that examined the link between maternal prenatal tobacco smoking and DNA methylation in adolescent offspring reported irreversible changes in DNA methylation, which were not sensitive to control for maternal postnatal tobacco smoking and paternal tobacco smoking during pregnancy (Rauschert et al., 2019). The corresponding modifications in DNA methylation may result in over-stimulation of the hypothalamic-pituitary-adrenal (HPA) axis via intrauterine programming of up-regulation of the hippocampus, a brain structure embedded deep into the temporal lobe (He et al., 2017). Such alterations in the HPA axis have been linked to the onset of anxiety symptoms in childhood that endure into adulthood (Faravelli et al., 2012; Tafet and Nemeroff, 2020).

Another possible explanation is that prenatal exposure to tobacco smoke affects placental vasculature (Pintican et al., 2019) and places expectant mothers and their fetuses at increased risk of hypertensive disorders of pregnancy (Roberts and Escudero, 2012), low birth weight (Agrawal et al., 2010; Talati et al., 2017), preterm birth (Kyrklund--Blomberg et al., 2005) and small for gestational age outcomes (Mitchell et al., 2002), which in turn may result in several mental health problems in offspring via mediating the effects of prenatal tobacco exposure (Ernst et al., 2001; Herrmann et al., 2008; Dachew et al., 2020). This hypothesized pathway has been further supported by the results of a meta-analysis that summarized the findings of six prospective cohort studies from five different countries (Pyhälä et al., 2017). In that meta-analysis, preterm born adults with very low birth weight were more likely to experience mental health problems such as anxiety. Although we noted slight attenuation in the risk estimates after controlling for the mediating role of low birthweight, preterm birth and preeclampsia, the association remained evident, suggesting that an indirect pathway does not completely explain the associations observed in our study.

It is also possible that the association we observed between prenatal tobacco exposure and the risk of experiencing symptoms of anxiety in the offspring may be explained by several factors such as maternal

anxiety symptoms and postnatal tobacco smoking as well as child sleep problems. A large number of epidemiological studies have documented that the risks of developing anxiety disorders are substantially greater in the close relatives of affected probands when compared to healthy controls (Hettema et al., 2001; Hettema et al., 2005; Shimada-Sugimoto et al., 2015; Gottschalk and Domschke, 2017). Most notably, close relatives of probands with anxiety disorders are at four to six-fold increased risk for anxiety disorders when compared to healthy controls (Hettema et al., 2001). Nonetheless, the genetic liability to anxiety disorders ranged from 30–40% (Hettema et al., 2005), suggesting that other presumptive risk factors such as prenatal tobacco smoking may explain the remaining proportion. Further, prenatal tobacco smoking was also associated with an increased risk of sleep problems in offspring during childhood (Stone et al., 2010; O'Callaghan et al., 2019) and this in turn may lead to anxiety disorders in adulthood (Gregory et al., 2005; McMakin and Alfano, 2015). In support of this explanation, we also noted some attenuation in the strength of observed associations after controlling for maternal anxiety symptoms measured at 16 years of follow-up, suggesting predisposition to maternal anxiety symptoms may explain some part of the associations reported in our study.

The association between prenatal tobacco exposure and the risk of experiencing symptoms of anxiety may be due to confounding by maternal and family socio-economic positions such as maternal age, education and family income (Muhajarine et al., 1997; Al-Sahab et al., 2010). Evidence from epidemiological studies has indicated that mothers who reported tobacco smoking during pregnancy were likely to have lower family income and educational attainment compared to non-smoking pregnant mothers (Heaman and Chalmers, 2005; Al-Sahab et al., 2010). These have been associated with mental health problems in offspring (Maughan et al., 2004; Quinn et al., 2017; Duko et al., 2020). Moreover, in a recent meta-analysis, the association between prenatal tobacco smoking and offspring mood disorders was moderately attenuated in the included studies that controlled for such socio-economic risk factors (Duko et al., 2020). In contrast, we observed negligible differences in risk estimates after adjusting for maternal covariates such as maternal age, education, and family income.

Major strengths of this study include: the prospective measures of prenatal alcohol and tobacco exposures; the use of relatively larger sample size; the use of a standardized, well-accepted and validated measurement tool to assess anxiety symptoms in offspring; comprehensive inclusion of a number of confounding and mediating risk factors in our sequential statistical models; validation of self-reported prenatal tobacco exposure status with biomarker of tobacco smoke; and the additional estimation of risks by gestational period of exposure. Nonetheless, the findings of this study should be viewed considering several caveats. Data on second trimester prenatal tobacco and alcohol exposure were not available and these would have allowed us to produce estimates for whole pregnancy exposure. A proportion of the study participants were lost to follow-up, although this can be expected from such a long-term prospective longitudinal study, and this may have introduced bias. However, the results remained essentially unchanged after we repeated the analysis with the imputed dataset. We were not able to control for maternal and paternal psychiatric disorders during pregnancy, but we adjusted for maternal anxiety symptoms measured at 16 years follow-up as proxies for offspring predisposition to anxiety symptoms. Finally, future studies could consider control for genetic predisposition, which may be achieved via Mendellian Randomization studies or via the use of sibling comparisons as such designs may potentially elucidate pathways that are independent of genetic and other environmental risk factors.

Role of funding sources

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Bereket Duko: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Validation, Visualization, Writing – original draft, Writing – review & editing. **Gavin Pereira:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **Robert J. Tait:** Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. **Kim Betts:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing. **John Newnham:** Data curation, Investigation, Methodology, Resources, Validation, Visualization, Writing – review & editing. **Rosa Alati:** Data curation, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – review & editing.

Declarations of Competing Interest

None.

Acknowledgments

We would like to acknowledge the Raine Study participants and their families for their ongoing participation in the study and the Raine Study team for cohort co-ordination and data collection. We also thank the National Health and Medical Research Council (NHMRC) for their long-term contribution to funding the study over the last 30 years. The core management of the Raine Study is funded by the University of Western Australia, Curtin University, Telethon Kids Institute, Women and Infants Research Foundation, Edith Cowan University, Murdoch University, the University of Notre Dame Australia and the Raine Medical Research Foundation. Bereket Duko is a recipient of Curtin University International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. Gavin Pereira was funded by NHMRC grants# 1099655 and 1173991, and the Research Council of Norway through Centre of Excellence, grant #262700. The funders had no role in the data collection, study design, the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2022.114466.

References

Achenbach, T., Rescorla, L., 2001. Manual For the ASEBA School-Age Forms and Profiles. University of Vermont, Burlington, VT, 2001Research Center for Children, Youth, and Families.

Agrawal, A., S.cherrer, J.F., G.rant, J.D., S.artor, C.E., P.ergadia, M.L., D.uncan, A.E., Madden, P.A.F., H.aber, J.R., Jacob, T., B.ucholz, K.K., Xian, H., 2010. The effects of maternal smoking during pregnancy on offspring outcomes. Prev. Med. 50 (1–2), 13–18.

Akin, A., Citin, B., 2007. The Depression Anxiety and StressScale (DASS): the study of Validityand Reliability. Edu. Sci. 7 (1), 260–268.

Al-Sahab, B., Saqib, M., Hauser, G., Tamim, H., 2010. Prevalence of smoking during pregnancy and associated risk factors among Canadian women: a national survey. BMC Preg. Childbirth 10 (1), 24.

Ashford, J., v.an Lier, P.A., Timmermans, M., Cuijpers, P., K.oot, H.M., 2008. Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. J. Am. Acad. Child. Adolesc. Psychiatry 47 (7), 779–787.

Barker, D.J., 2007. The origins of the developmental origins theory. J. Intern. Med. 261 (5), 412–417.

Beesdo, K., Pine, D.S., Lieb, R., Wittchen, H.-U., 2010. Incidence and risk patterns of anxiety and depressive disorders and categorization of generalized anxiety disorder. Arch. Gen. Psychiatry 67 (1), 47–57.

Bobo, J.K., Husten, C., 2000. Sociocultural influences on smoking and drinking. Alcohol Res. Health 24 (4), 225–232.

Brion, M.J., Victora, C., Matijasevich, A., Horta, B., Anselmi, L., Steer, C., Menezes, A.M., Lawlor, D.A., Smith, G.D., 2010. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics 126 (1), e57–e65.
Brocardo, P.S., Boehme, F.., Patten, A., Cox, A., Gil-Mohapel, J., C.hristie, B.R., 2012. Anxiety- and depression-like behaviors are accompanied by an increase in oxidative stress in a rat model of fetal alcohol spectrum disorders: protective effects of voluntary physical exercise. Neuropharmacology 62 (4), 1607–1618.
Craske, M.G., Rauch, S.L., Ursano, R., Prenoveau, J., Pine, D.S., Zinbarg, R.E., 2009. What is an anxiety disorder? Depress Anxiety 26 (12), 1066–1085.
Cullen, C.L., Burne, T.H., Lavidis, N.A., Moritz, K.M., 2013. Low dose prenatal ethanol exposure induces anxiety-like behaviour and alters dendritic morphology in the basolateral amygdala of rat offspring. PLoS One 8 (1), e54924.
Dachew, B.A., Scott, J.G., Mamun, A., Alati, R., 2020. Hypertensive disorders of pregnancy and emotional and behavioural problems in children: a longitudinal population-based study. Eur. Child Adolesc. Psychiatry 29 (10), 1339–1348.
Day, N.L., Helsel, A., Sonon, K., Goldschmidt, L., 2013. The association between prenatal alcohol exposure and behavior at 22 years of age. Alcohol. Clin. Exp. Res. 37 (7), 1171–1178.
Duko, B., Ayano, G., Pereira, G., Betts, K., Alati, R., 2020. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Soc. Psychiatry Psychiatr. Epidemiol. 55 (12), 1549–1562.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2021. Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study. J. Affect. Disord. 279, 426–433.
Easey, K.E., Dyer, M.L., T.impson, N.J., Munafò, M.R., 2019. Prenatal alcohol exposure and offspring mental health: a systematic review. Drug Alcohol Depend. 197, 344–353.
Ekblad, M., Gissler, M., Lehtonen, L., Korkeila, J., 2010. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Arch. Gen. Psychiatry 67 (8), 841–849.
Ernst, M., Moolchan, E.T., Robinson, M.L., 2001. Behavioral and neural consequences of prenatal exposure to nicotine. J. Am. Acad. Child Adolesc. Psychiatry 40 (6), 630–641.
Faravelli, C., Lo Sauro, C., Godini, L., Lelli, L., Benni, L., Pietrini, F., Lazzeretti, L., Talamba, G.A., Fioravanti, G., Ricca, V., 2012. Childhood stressful events, HPA axis and anxiety disorders. World J. Psychiatry 2 (1), 13–25.
Flak, A.L., Su, S., Bertrand, J., Denny, C.H., Kesmodel, U.S., Cogswell, M.E., 2014. The association of mild, moderate, and binge prenatal alcohol exposure and child neuropsychological outcomes: a meta-analysis. Alcohol. Clin. Exp. Res. 38 (1), 214–226.
Gilman, S.E., Breslau, J.., S.ubramanian, S.V., Hitsman, B., K.oenen, K.C., 2008. Social factors, psychopathology, and maternal smoking during pregnancy. Am. J. Public Health 98 (3), 448–453.
Gottschalk, M.G., Domschke, K., 2017. Genetics of generalized anxiety disorder and related traits. Dialogues Clin. Neurosci. 19 (2), 159–168.
Gregory, A.M., Caspi, A., Eley, T.C., Moffitt, T.E., Oconnor, T.G., Poulton, R., 2005. Prospective longitudinal associations between persistent sleep problems in childhood and anxiety and depression disorders in adulthood. J. Abnorm. Child Psychol. 33 (2), 157–163.
He, X., Lu, J., Dong, W., Jiao, Z., Zhang, C., Yu, Y., Zhang, Z., Wang, H., Xu, D., 2017. Prenatal nicotine exposure induces HPA axis-hypersensitivity in offspring rats via the intrauterine programming of up-regulation of hippocampal GAD67. Arch. Toxicol. 91 (12), 3927–3943.
Heaman, M.I., Chalmers, K., 2005. Prevalence and correlates of smoking during pregnancy: a comparison of aboriginal and non-aboriginal women in manitoba. Birth 32 (4), 299–305.
Herrmann, M., King, K., Weitzman, M., 2008. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. Curr. Opin. Pediatr. 20 (2), 184–190.
Hettema, J.M., Neale, M.C., Kendler, K.S., 2001a. A review and meta-analysis of the genetic epidemiology of anxiety disorders. Am. J. Psychiatry 158 (10), 1568–1578.
Hettema, J.M., M.C. Neale and K. S.J. A.J. o. P. Kendler (2001). "A review and meta-analysis of the genetic epidemiology of anxiety disorders." 158(10): 1568–1578.
Hettema, J.M., Prescott, C.A., Myers, J.M., Neale, M.C., Kendler, K.S., 2005. The structure of genetic and environmental risk factors for anxiety disorders in men and women. Arch. Gen. Psychiatry 62 (2), 182–189.
Höök, B., Cederblad, M., Berg, R., 2006. Prenatal and postnatal maternal smoking as risk factors for preschool children's mental health. Acta Paediatr. 95 (6), 671–677.
Ichikawa, K., Fujiwara, T., Kawachi, I., 2018. Prenatal alcohol exposure and child psychosocial behavior: a sibling fixed-effects analysis. Front. Psychiatry 9, 570. -570.
Indredavik, M.S., Brubakk, A.-M., Romundstad, P., Vik, T., 2007. Prenatal smoking exposure and psychiatric symptoms in adolescence. Acta Paediatrica (Oslo, Norway: 1992) 96 (3), 377–382.
Kelly, Y., Iacovou, M., Quigley, M.A., Gray, R., Wolke, D., Kelly, J., Sacker, A., 2013. Light drinking versus abstinence in pregnancy – behavioural and cognitive outcomes in 7-year-old children: a longitudinal cohort study. BJOG 120 (11), 1340–1347.
Kleiber, M.L., Wright, E., Singh, S.M., 2011. Maternal voluntary drinking in C57BL/6 J mice: advancing a model for fetal alcohol spectrum disorders. Behav. Brain Res. 223 (2), 376–387.
Knopik, V.S., Maccani, M.A., Francazio, S., McGeary, J.E., 2012. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev. Psychopathol. 24 (4), 1377–1390.
Kyrklund-Blomberg, N.B., Granath, F., Cnattingius, S., 2005. Maternal smoking and causes of very preterm birth. Acta Obstet. Gynecol. Scand. 84 (6), 572–577.
Le, M.T.H., Tran, T.D., Holton, S., Nguyen, H.T., Wolfe, R., Fisher, J., 2017. Reliability, convergent validity and factor structure of the DASS-21 in a sample of Vietnamese adolescents. PLoS One 12 (7), e0180557. -e0180557.
Lee, J., L.ee, E.H., M.oon, S.H., 2019. Systematic review of the measurement properties of the Depression Anxiety Stress Scales-21 by applying updated COSMIN methodology. Qual. Life Res. 28 (9), 2325–2339.
Lovibond, S.H., Lovibond, P., 1993. Manual For the Depression Anxiety Stress Scales (DASS). University of New South Wales.
Lund, I.O., Moen Eilertsen, E.., G.jerde, L.C., Røysamb, E., Wood, M., Reichborn-Kjennerud, T., Ystrom, E., 2019. Is the association between maternal alcohol consumption in pregnancy and pre-school child behavioural and emotional problems causal? Multiple approaches for controlling unmeasured confounding. Addiction 114 (6), 1004–1014.
Maughan, B., Taylor, A., Caspi, A., M.offitt, T.E., 2004. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch. Gen. Psychiatry 61 (8), 836–843.
McMakin, D.L., Alfano, C.A., 2015. Sleep and anxiety in late childhood and early adolescence. Curr. Opin. Psychiatry 28 (6), 483–489.
Michael, T., Zetsche, U., Margraf, J., 2007. Epidemiology of anxiety disorders. Psychiatry 6 (4), 136–142.
Mitchell, E.A., Thompson, J.M., Robinson, E., W.ild, C.J., B.ecroft, D.M., C.lark, P.M., Glavish, N., P.attison, N.S., Pryor, J.E., 2002. Smoking, nicotine and tar and risk of small for gestational age babies. Acta Paediatr. 91 (3), 323–328.
Moran, V.E., 2012. Cotinine: beyond that Expected, More than a Biomarker of Tobacco Consumption. Front. Pharmacol. 3, 173. -173.
Moylan, S., Gustavson, K., Øverland, S., K.arevold, E.B., J.acka, F.N., P.asco, J.A., Berk, M., 2015a. The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: the Norwegian Mother and Child Cohort Study. BMC Med. 13, 24. -24.
Moylan, S., Gustavson, K., Øverland, S., Karevold, E.B., Jacka, F.N., Pasco, J.A., Berk, M., 2015b. The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: the Norwegian Mother and Child Cohort Study. BMC Med. 13 (1), 24.
Muhajarine, N., D'Arcy, C., Edouard, L., 1997. Prevalence and predictors of health risk behaviours during early pregnancy: saskatoon pregnancy and health study. Canad. J. Public Health 88 (6), 375–379.
Munir, S., Takov, V., 2021. Generalized Anxiety Disorder. [Updated 2021 May 8]. StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2021 Jan-. Available from: https://www.ncbi.nlm.nih.gov/books/NBK441870/.
Nepon, J., Belik, S.-L., Bolton, J., Sareen, J., 2010. The relationship between anxiety disorders and suicide attempts: findings from the National Epidemiologic Survey on Alcohol and Related Conditions. Depress. Anxiety 27 (9), 791–798.
Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342 (8876), 887–891.
NHMRC, 2009. Australian Guidelines to Reduce Health Risks from Drinking alcohol: Commonwealth of Australia. Pages 2, 3. Available at. http://www.nhmrc.gov.au/guidelines/publications/ds10.
Niclasen, J., Andersen, A.-M.N., Strandberg-Larsen, K., Teasdale, T.W., 2014a. Is alcohol binge drinking in early and late pregnancy associated with behavioural and emotional development at age 7 years? Eur. Child Adolesc. Psychiatry 23 (12), 1175–1180.
Niclasen, J., Andersen, A.M., Strandberg-Larsen, K., Teasdale, T.W., 2014b. Is alcohol binge drinking in early and late pregnancy associated with behavioural and emotional development at age 7 years? Eur. Child. Adolesc. Psychiatry 23 (12), 1175–1180.
O'Callaghan, F., O'Callaghan, M., S.cott, J.G., Najman, J., Al Mamun, A., 2019. Effect of maternal smoking in pregnancy and childhood on child and adolescent sleep outcomes to 21 years: a birth cohort study. BMC Pediatr 19 (1), 70.
Pintican, D., Poienar, A.A., Strilciuc, S., Mihu, D., 2019. Effects of maternal smoking on human placental vascularization: a systematic review. Taiwan. J. Obstetr. Gynecol. 58 (4), 454–459.
Pyhälä, R., Wolford, E., Kautiainen, H., Andersson, S., Bartmann, P., Baumann, N., Brubakk, A.-M., Evensen, K.A.I., Hovi, P., Kajantie, E., Lahti, M., V.an Lieshout, R.J., Saigal, S., S.chmidt, L.A., I.ndredavik, M.S., Wolke, D., Räikkönen, K., 2017. Self-reported mental health problems among adults born preterm: a meta-analysis. Pediatrics, e20162690.
Quinn, P.D., Rickert, M..E., W.eibull, C.E., Johansson, A.L.V., Lichtenstein, P., Almqvist, C., Larsson, H., I.liadou, A.N., D.'Onofrio, B.M., 2017. Association between maternal smoking during pregnancy and severe mental illness in offspring. JAMA Psychiatry 74 (6), 589–596.
Rauschert, S., Melton, P.E., Burdge, G., Craig, J.M., Godfrey, K.M., Holbrook, J.D., Lillycrop, K., Mori, T.A., Beilin, L.J., Oddy, W.H., Pennell, C., Huang, R.-C., 2019. Maternal smoking during pregnancy induces persistent epigenetic changes into adolescence, independent of postnatal smoke exposure and is associated with cardiometabolic risk. Front. Genet. 10, 770.
Rees, S., Channon, S., Waters, C.S., 2019. The impact of maternal prenatal and postnatal anxiety on children's emotional problems: a systematic review. Eur. Child Adolesc. Psychiatry 28 (2), 257–280.
Richmond, R.C., Simpkin, A.J., Woodward, G., Gaunt, T.R., Lyttleton, O., McArdle, W.L., Ring, S.M., Smith, A.D.A.C., Timpson, N.J., Tilling, K., Smith, G.D., Relton, C.L., 2015. Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Hum. Mol. Genet. 24 (8), 2201–2217.
Roberts, J.M., Escudero, C., 2012. The placenta in preeclampsia. Pregnancy Hypertens. 2 (2), 72–83.

Robinson, M., McLean, N.J., Oddy, W.H., Mattes, E., Bulsara, M., Li, J., Zubrick, S.R., Stanley, F.J., Newnham, J.P., 2010a. Smoking cessation in pregnancy and the risk of child behavioural problems: a longitudinal prospective cohort study. J. Epidemiol. Community Health 64 (7), 622–629.
Robinson, M., Oddy, W.H., McLean, N.J., Jacoby, P., Pennell, C.E., de Klerk, N.H., Zubrick, S.R., Stanley, F.J., Newnham, J.P., 2010b. Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. BJOG 117 (9), 1139–1150.
Robinson, M., Oddy, W.H., McLean, N.J., Jacoby, P., Pennell, C.E., de Klerk, N.H., Zubrick, S.R., Stanley, F.J., Newnham, J.P., 2010c. Low–Moderate prenatal alcohol exposure and risk to child behavioral development: a prospective cohort study. Obstet. Gynecol. Surv. 65 (12).
Royston, P., 2005. Multiple imputation of missing values: update of ice. Stata J. 5 (4), 527–536.
Roza, S.J., Verhulst, F.C., Jaddoe, V.W., Steegers, E.A., Mackenbach, J.P., Hofman, A., Tiemeier, H., 2009a. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int. J. Epidemiol. 38 (3), 680–689.
Roza, S.J., Verhulst, F.C., Jaddoe, V.W.V., Steegers, E.A.P., Mackenbach, J.P., Hofman, A., Tiemeier, H., 2009b. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. Int. J. Epidemiol. 38 (3), 680–689.
Sareen, J., Cox, B.J., Clara, I., Asmundson, G.J., 2005. The relationship between anxiety disorders and physical disorders in the U.S. National Comorbidity Survey. Depress Anxiety 21 (4), 193–202.
Sayal, K., Heron, J., Golding, J., Emond, A., 2007. Prenatal alcohol exposure and gender differences in childhood mental health problems: a longitudinal population-based study. Pediatrics 119 (2), e426–e434.
Shimada-Sugimoto, M., Otowa, T., Hettema, J.M., 2015. Genetics of anxiety disorders: genetic epidemiological and molecular studies in humans. Psychiatry Clin. Neurosci. 69 (7), 388–401.
Silva, D., Houghton, S., Hagemann, E., Bower, C., 2015. Comorbidities of attention deficit hyperactivity disorder: pregnancy risk factors and parent mental health. Community Ment. Health J. 51 (6), 738–745.
Skogerbø, Å., Kesmodel, U.S., Denny, C.H., Kjaersgaard, M.I.S., Wimberley, T., Landrø, N. I., Mortensen, E.L., 2013. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on behaviour in 5-year-old children: a prospective cohort study on 1628 children. BJOG 120 (9), 1042–1050.
Smith, J.P., Book, S.W., 2008. Anxiety and substance use disorders: a review. Psychiatric Times 25 (10), 19–23.
Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A. M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.
Stick, S.M., Burton, P.R., Gurrin, L., Sly, P.D., LeSouëf, P.N., 1996. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet North Am. Ed. 348 (9034), 1060–1064.
Stone, K.C., LaGasse, L.L., Lester, B.M., Shankaran, S., Bada, H.S., Bauer, C.R., Hammond, J.A., 2010. Sleep problems in children with prenatal substance exposure: the maternal lifestyle study. Arch. Pediatr. Adolesc. Med. 164 (5), 452–456.
Straker, L., Mountain, J., Jacques, A., White, S., Smith, A., Landau, L., Stanley, F., Newnham, J., Pennell, C., Eastwood, P., 2017. Cohort profile: the western australian pregnancy cohort (raine) study-generation 2. Int. J. Epidemiol. 46 (5), 1384–1385j.
Stroud, L.R., Papandonatos, G..D., Rodriguez, D., McCallum, M., Salisbury, A.L., Phipps, M.G., Lester, B., Huestis, M.A., Niaura, R., Padbury, J.F., Marsit, C.J., 2014. Maternal smoking during pregnancy and infant stress response: test of a prenatal programming hypothesis. Psychoneuroendocrinology 48, 29–40.
Szabó, M., 2010. The short version of the Depression Anxiety Stress Scales (DASS-21): factor structure in a young adolescent sample. J. Adolesc. 33 (1), 1–8.
Tafet, G.E., Nemeroff, C.B., 2020. Pharmacological treatment of anxiety disorders: the role of the HPA axis. Front. Psychiatry 11, 443. -443.
Talati, A., Wickramaratne, P.J., Wesselhoeft, R., Weissman, M.M., 2017. Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry Res. 252, 346–352.
Tan, F.E.S., Jolani, S., Verbeek, H., 2018. Guidelines for multiple imputations in repeated measurements with time-dependent covariates: a case study. J. Clin. Epidemiol. 102, 107–114.
Tierney, A.L., Nelson 3rd, C.A., 2009. Brain development and the role of experience in the early years. Zero Three 30 (2), 9–13.
Tully, P.J., Zajac, I.T., Venning, A.J., 2009. The structure of anxiety and depression in a normative sample of younger and older australian adolescents. J. Abnorm. Child Psychol. 37 (5), 717.
Vitasari, P., Wahab, M.N.A., Othman, A., Herawan, T., Sinnadurai, S.K., 2010. The relationship between study anxiety and academic performance among engineering students. Procedia - Soc. Behav. Sci. 8, 490–497.
Vos, T., Lim, S.S., Abbafati, C., Abbas, K.M., Abbasi, M., Abbasifard, M., et al., 2020. Global burden of 369 diseases and injuries in 204 countries and territories, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet North Am. Ed. 396 (10258), 1204–1222.
Wendell, A.D., 2013. Overview and epidemiology of substance abuse in pregnancy. Clin. Obstet. Gynecol. 56 (1), 91–96.
Yang, X., Fang, Y., Chen, H., Zhang, T., Yin, X., Man, J., Yang, L., Lu, M., 2021. Global, regional and national burden of anxiety disorders from 1990 to 2019: results from the Global Burden of Disease Study 2019. Epidemiol. Psychiatric Sci. 30, e36.
Zahn-Waxler, C., Klimes-Dougan, B., Slattery, M.J., 2000. Internalizing problems of childhood and adolescence: prospects, pitfalls, and progress in understanding the development of anxiety and depression. Dev. Psychopathol. 12 (3), 443–466.

Chapter 5: Prenatal tobacco exposure and offspring conduct disorder

Chapter 5: Prenatal tobacco exposure and offspring conduct disorder

Published manuscript and formal citation

Duko B, Pereira G, Tait RJ, Newnham J, Betts K, Alati R. Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: Findings from the Raine Study. Journal of Psychiatric Research. 2021; 142:1-8.

Study Purpose: Epidemiological studies have linked prenatal tobacco exposure to offspring conduct disorder symptoms but with inconsistent findings. Further examination of maternal and paternal tobacco smoking during pregnancy may give vital clues to the etiological basis for conduct disorder symptoms. If maternal tobacco smoking during pregnancy, but not paternal tobacco smoking, is linked to an increased risk of conduct disorder symptoms in offspring, this observation may provide support for a biological pathway. Conversely, if maternal and paternal tobacco smoking during pregnancy are both associated with an increased risk of this disorder, this would suggest the influence of environmental and/or lifestyle factors or unmeasured confounding. Therefore, the present study focused on examining the association between maternal prenatal tobacco smoking and conduct disorder symptoms in offspring using paternal prenatal tobacco smoking as a proxy for environmental tobacco smoke exposure.

Journal of Psychiatric Research 142 (2021) 1–8

Contents lists available at ScienceDirect

Journal of Psychiatric Research

journal homepage: www.elsevier.com/locate/jpsychires

Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: Findings from the Raine Study

Bereket Duko [a,*], Gavin Pereira [a,b], Robert J. Tait [c], John Newnham [d], Kim Betts [a], Rosa Alati [a,e]

[a] Curtin School of Population Health, Curtin University, Kent Street, Bentley, WA, 6102, Australia
[b] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[c] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA, 6102, Australia
[d] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands, WA, 6009, Australia
[e] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland, 4068, Australia

ARTICLE INFO

Keywords:
Tobacco
Pregnancy
Adolescents
Offspring
Conduct disorder symptoms
The raine study

ABSTRACT

Background: Emerging epidemiological evidence suggests that offspring born to mothers who smoked tobacco during pregnancy may have elevated risk of developing conduct disorder (CD) symptoms. We examined associations between maternal and paternal tobacco smoking during pregnancy and CD symptoms in offspring at the age of 14 years.

Methods: We obtained data from the Raine Study, a multi-generational cohort study based in Western Australia. DSM-oriented scale of the Child Behavior Checklist (CBCL) was used to measure CD symptoms in offspring. Negative binomial regression was used to estimate the rate ratio (risks) (RR) of CD symptoms in offspring. We also produced the E-values to investigate the extent of unmeasured confounding. Paternal smoking during pregnancy was used as a proxy for environmental tobacco smoke exposure.

Results: Complete data were available for 1747 mother-offspring and 1711 father-offspring pairs. After adjusting for potential confounders, we found elevated risks (rates) of CD symptoms in offspring born to mothers smoking tobacco during the first trimester [RR 1.52 (95 % CI: 1.24–1.87)], third trimester [RR 1.36 (95 % CI: 1.09–1.69)] and during both trimesters of pregnancy [RR 1.50 (95 % CI: 1.19–1.90)]. The rates of CD symptoms in offspring increased with the level of exposure to maternal smoking during pregnancy. However, we noted insufficient statistical evidence for an association between paternal smoking during pregnancy and CD symptoms in offspring.

Conclusion: The associations we found for maternal but not paternal smoking may suggest a biological mechanism for intrauterine tobacco exposure on the risk of CD symptoms in offspring. Early interventions assisting pregnant mothers to quit tobacco smoking, or avoid smoking initiation, have potential to contribute health benefits to both mothers and their offspring.

1. Background

Conduct disorder (CD) is one of the most common behavioural problems that is diagnosed in children and adolescents under the age of 18 years (APA 2013). It is characterized by repetitive and persistent pattern of behaviours whereby affected individuals can manifest aggression against people or animals, destroy properties or other serious violations of societal norms (APA 2013; Erskine et al., 2013). It has been reported that CD is an antecedent to academic under-achievement, poor interpersonal relationships, sexually transmitted infections, and a range of social difficulties, mental health problems, substance abuse and addiction, as well as suicidal ideation and suicide attempt (Loeber et al., 2000; Biederman et al., 2008; APA 2013; Wei et al., 2016; Fairchild 2018; Lin et al., 2020). Further, existing evidence suggests that approximately 40 % of boys and 25 % of girls with CD may eventually develop antisocial personality disorder in adulthood (Black 2015). Thus, identifying early-life presumptive risk factors of CD is critically important to propose appropriate primary prevention and intervention strategies for adolescents that are prone to this disorder.

Although the exact cause of CD remains unclear, it has been proposed that a combination of genetic, biological, environmental, social and psychological factors play a significant role in its development (Slotkin

* Corresponding author. Curtin School of Population Health, Curtin University, Kent Street, Bentley, Perth, WA, 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.jpsychires.2021.07.030
Received 22 April 2021; Received in revised form 30 June 2021; Accepted 18 July 2021
Available online 20 July 2021

2004; Martin et al., 2007; APA 2013; Blair et al., 2014). Amongst other factors, early factors occurring during the prenatal environment, may result in mental health and behavioural problems in offspring by exerting programming influences on the brain of the fetus (Kim et al., 2015). Maternal prenatal tobacco exposure is one such adversity, with an estimated prevalence of 20–30 % (Lamy and Thibaut 2010), is believed to increase risk of CD in offspring (Gatzke-Kopp and Beauchaine 2007).

Epidemiological evidence from prospective longitudinal studies suggests that offspring exposed to prenatal tobacco may have an increased risk of CD compared to non-exposed offspring (Maughan et al., 2004; Brion et al., 2010; Palmer et al., 2016). A study based on two birth cohorts, the Brazilian Pelotas and the Avon Longitudinal Study of Parents and Children (ALSPAC), reported an increased risk of CD in offspring exposed to prenatal tobacco after controlling for socioeconomic positions, parental psychopathology as well as adjusting for paternal smoking during pregnancy (Brion et al., 2010). Also, a meta-analysis conducted in 2018 showed an increased risk of CD in offspring exposed to prenatal tobacco use (Ruisch et al., 2018). On the other hand, there is also evidence of no associations between exposure to maternal tobacco use during pregnancy and greater risk of CD in offspring (Silberg et al., 2003; Maughan et al., 2004; D'Onofrio et al., 2008; Agrawal et al., 2010).

These conflicting results across previous studies may be due to variability in the extent to which risk factors have been controlled. For instance, lower socioeconomic position, race, maternal education and age during conception (Mathews 2001; Bowes et al., 2013), preterm birth and low birthweight (Nomura et al., 2007; Johnson and Marlow 2011), maternal mental health problems such as depression and anxiety (Dagher and Shenassa 2012; Pooler et al., 2013; Cui et al., 2020), maternal alcohol use during pregnancy (Larkby et al., 2011) and postnatal tobacco smoking (Hutchinson et al., 2010) have been associated with maternal prenatal tobacco exposure and offspring conduct disorder, suggesting studies that did not control for these factors may have produced biased results.

Moreover, an investigation of maternal and paternal smoking during pregnancy may give some evidence to clarify the etiological basis for CD. If maternal smoking during pregnancy but not paternal smoking is linked with an increased risk of CD in offspring, this may provide more support for a pathway via *in utero* exposure. However, if exposure to both maternal and paternal tobacco is linked with an increased risk of CD, it may indicate either (i) a role of both *in utero* exposure and

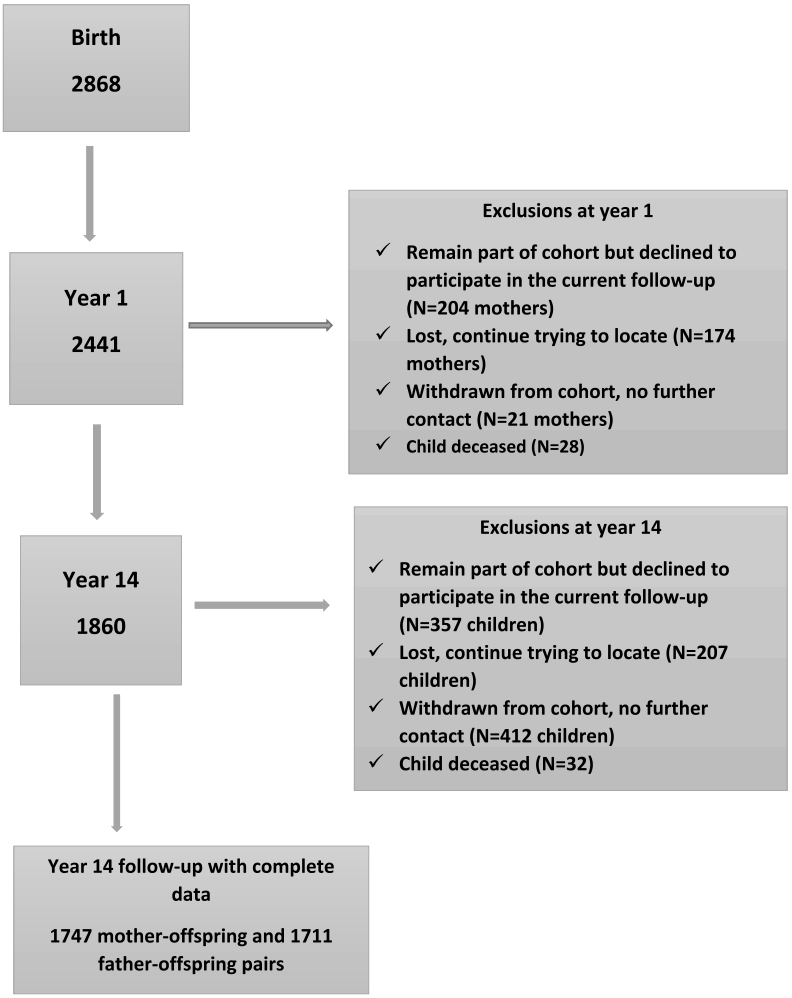


Fig. 1. Showing study participants of the current study at each follow-up from birth to 14 years.

environmental tobacco smoke exposure or (ii) the presence of unmeasured confounding. Therefore, the present study focused on investigating the association between maternal tobacco smoking during pregnancy and CD symptoms in offspring using paternal tobacco smoking during partners' pregnancy as a proxy for environmental tobacco smoke exposure. We hypothesized that maternal smoking during pregnancy will be associated with an increased risk of conduct disorder symptoms in offspring at the age of 14 years after adjusting for available confounders.

2. Methods

2.1. Study design and participants

We used data from the Raine Study, which is an ongoing population-based prospective cohort of pregnancy, childhood, adolescence and adulthood (Newnham et al., 1993; Straker et al., 2017). Between 1989 and 1992, a total of 2730 pregnant women (Gen1) visiting King Edward Memorial Hospital (KEMH) and nearby private clinics in Perth, Western Australia were recruited between 16 and 20 weeks of pregnancy and had 2868 live-born. Complete data were available for 1747 mother-offspring (Gen 1-Gen 2) and 1711 father-offspring pairs (Fig. 1). This study was approved by the Human Research Ethics Committees (HREC) of the University of Western Australia. Written informed consent was obtained from each study participant at enrollment and at each subsequent assessment after the details of the procedures had been fully described.

2.2. Exposure: prenatal tobacco exposure (Gen1)

At 18 and 34 weeks of gestation, pregnant mothers self-reported the number of cigarettes they had smoked per day during the first and the third trimesters of pregnancy respectively. We used this data to categorize pregnant mothers as either non-smoker or smoker. In order to validate questionnaire responses on cigarette-smoke exposure, cotinine was measured in serum from 238 pregnant mothers who reported cigarette smoking during the first three months of pregnancy (Sharma et al., 2019). Cotinine is a predominant metabolite (biomarker) of nicotine which accumulates in the body as a result of tobacco exposure (Moran 2012). Epidemiological evidence from the validation study (Stick et al., 1996) revealed strong agreement between maternal self-reported prenatal tobacco exposure and measured serum cotinine concentration. To further explore dose-related effects of prenatal tobacco exposure, 'light/moderate exposure' was defined as prenatal tobacco exposure of 1–9 cigarettes per day whereas 'heavy exposure' was defined as $\geq$ 10 cigarettes per day during pregnancy (Gaysina et al., 2013). To further estimate risks in terms of gestational age at exposure, we have produced the following categories; 'no exposure throughout pregnancy', 'first trimester (Trim-1) exposure', 'third trimester (Trim-3) exposure' and, 'both first and third trimesters (Trim-1 and 3) exposures'. At 18 weeks of pregnancy, pregnant mothers also reported that the average number of cigarettes their partners (fathers of the study adolescents) had smoked per day during their pregnancy. These data have been used to categorize partners of pregnant mothers as either non-smoker or smoker. Paternal prenatal tobacco exposure was used as a proxy for environmental tobacco smoke exposure.

2.3. Outcome: conduct disorder symptoms (Gen2)

Conduct Disorder symptoms at age of 14 years were measured using the Diagnostic Statistical Manual of Mental Disorders (DSM) oriented scales of the Child Behavioural Checklist (CBCL) (Achenbach et al., 2003). It has been reported that the DSM-oriented CBCL scales would provide significantly better agreement with clinical DSM diagnoses than the syndrome scales (Achenbach et al., 2003). Furthermore, a previous epidemiological study that tested the diagnostic accuracy of DSM oriented CBCL scales in diagnosing conduct disorder found that such scales better differentiated between cases and non-cases of CD (Hudziak et al., 2004). In this study, CD symptom scores were appeared to be skewed in the distribution (mean = 1.66 and variance = 8.83).

2.4. Confounders

We adjusted for confounders that were identified in previous studies and available in our dataset. These include maternal socioeconomic positions such as marital status, age, maternal and paternal education, family income, ethnicity (race), parity (Murray and Farrington 2010; Shaw and Shelleby 2014; Zondervan-Zwijnenburg et al., 2020), preterm birth and low birthweight (Langley et al., 2007; Lærum et al., 2019), maternal alcohol use during pregnancy (Ruisch et al., 2018) and parental mental health problems (Fergusson and Lynskey 1993). Maternal, paternal and child early life covariates that were measured at baseline include maternal and paternal age during pregnancy of the study child, marital status, educational level, family income at conception, ethnicity (race), parity, maternal alcohol use during pregnancy, hypertension/pre-eclampsia (yes/no), sex of child, preterm birth and low birthweight. Mothers of the study participants were asked to report any history of mental health problems during pregnancy (yes/no). Further, they were also assessed for depressive and anxiety symptoms at 14 years of follow-up using the 'Depression Anxiety Stress Scales (DASS).' The DASS is a validated 42-item screening scale constructed to assess symptoms of depression, anxiety and stress (Akin and Citin, 2007). In the current study, mothers of study participants were classified as suffering symptoms of depression and anxiety under the recommended conventional severity thresholds (DASS scores >10 and > 8) respectively (Lovibond and Lovibond 1995). Additionally, paternal lifetime history of emotional/mental health problems was measured at 14 years of follow-up as well.

2.5. Statistical analysis

To account for over dispersion, negative binomial regression was used to estimate unadjusted and adjusted rate ratios (RR) and 95 % confidence interval (CI) for the associations between prenatal tobacco exposure and risk of CD symptoms in offspring with STATA 16.0 (StataCorp 2019). To facilitate comparison with previous studies and to better investigate the role of potential confounders, risk factors were sequentially added as adjustment variables in separate models. First, we included maternal and paternal prenatal tobacco exposure individually. Next, we mutually-adjusted these two models of maternal and paternal prenatal tobacco exposure for one another. We then estimated the difference in estimates after fitting the models with all variables. Model 1 was adjusted by maternal and paternal education, maternal age during pregnancy, race (ethnicity), family income, parity, hypertension/pre-eclampsia (yes/no), maternal alcohol use during the first and third trimesters of pregnancy and sex of child. Then, we added birthweight and preterm birth (mediators) to Model 1 (Model 2). Evidence suggests that offspring of parents with mental health and substance use problems are at increased risk for a conduct disorder symptoms. To further explore this, we separately added history of maternal mental health problems during pregnancy, maternal depressive and anxiety symptoms and paternal history of emotional problems (anxiety and depression) at 14 years follow-up to Model 1(Model 3). Model 4 was fully adjusted for all covariates. We repeated analysis excluding first trimester prenatal tobacco exposure from the models and adding third trimester prenatal tobacco exposure to estimate risks in terms of gestational age. We conducted a sensitivity analysis to calculate the E-values to test the potential effect of unmeasured confounding (Haneuse et al., 2019). The E-value is the minimum strength of association on the risk-ratio estimate the extent of an unmeasured confounder possibly will require to have with both the exposure and outcome to fully explain away or nullify the reported associations based on measured confounders (VanderWeele and Ding 2017; Linden et al.,

2020). As a sensitivity analysis, missing data was imputed with *multiple imputation by chained equations* using the "mice" STATA command (Royston 2005; Sterne et al., 2009) and produced 50 imputed datasets.

3. Results

3.1. Characteristics of study participants

The mean age (±SD) of the pregnant women (mothers) during conception was 28.07 (± = 5.92). The prevalence of maternal smoking during the first and third trimesters of pregnancy was 27.0 % and 25.3 % respectively. Paternal tobacco smoking during partners' pregnancy was reported by 47.0 % of fathers. Of total pregnant mothers, 48.0 % were nulliparous, 64.5 were married, 6.2 % were consuming six or more standard drinks of alcohol per week within the first three months of pregnancy and 41.2 % reported an average annual family income of ≤24,000 A$ (Table 1). Of the total offspring, 50.7 % were females, 7.7 % were born pre-term (<37 weeks) and 8.8 % were of low birthweight (<2.5 K.G). At 14 years of follow-up, 10.4 % of mothers reported depressive symptoms whereas 2.1 % of fathers reported emotional problems.

3.2. Association between prenatal tobacco exposure and CD symptoms in offspring

We found the increased rates of CD symptoms in the univariate analysis among offspring born to mothers smoking tobacco during the first trimester [RR 1.84 (95 % CI: 1.52–2.22)], third trimester [RR 1.67 (95 % CI: 1.35–2.03)] and during both trimesters of pregnancy [RR 1.79 (95 % CI: 1.45–2.21)]. Similarly, paternal smoking during partner's pregnancy was associated with an increased risk of CD symptoms in offspring at the age of 14 years [RR 1.56 (95 % CI: 1.34–1.87)] (Table 2). These estimates were slightly attenuated when we mutually-adjusted for maternal and paternal smoking during pregnancy but remained statistically significant for the first trimester [RR 1.65 (95 % CI: 1.35–2.01)], third trimester [RR 1.47 (95 % CI: 1.18–1.82)] and both trimesters of pregnancy [RR 1.58 (95 % CI: 1.26–1.98)] as well as paternal smoking during partner's pregnancy [RR 1.35(95 % CI: 1.12–1.64)]. Further statistical adjustment of this model by maternal and paternal education, maternal age during pregnancy, race, family income, parity, maternal alcohol use during the first and third trimesters of pregnancy and sex of child did not substantially change the estimates for first trimester [RR 1.51 (95 % CI: 1.23–1.85)], third trimester [RR 1.41 (95 % CI: 1.13–1.75)] and both trimesters of pregnancy exposure [RR 1.52 (95 % CI: 1.21–1.91)] but we noted insufficient statistical evidence for an association between paternal smoking and CD symptoms in offspring [RR 1.18 (95 % CI: 0.87–1.40)](Model 1). In the fully adjusted model (Model 4), the estimates did not substantially change. Further, we observed the increased rates of CD symptoms in offspring with increasing exposure to maternal tobacco smoking in the first, third and during both trimesters of pregnancy. For example, we found the increased rates (RR) of 1.41 (95 % CI: 1.04–1.89) and 2.00(95 % CI: 1.35–2.96) for offspring born to mothers smoking < 9 cigarettes/day and ≥10 cigarettes/day respectively during both trimesters of pregnancy. Moreover, we repeated analysis using the imputed dataset and results remained unchanged (Supplementary file 1 for Table 2).

3.3. Sensitivity analysis (E-values)

We also run a sensitivity analysis to produce the E-values to test the potential effect of unmeasured confounding for fully adjusted model (Model 4). It has been suggested that for rate-ratio (RR) measures of non-negative continuous outcomes, the respective E-values for point estimates and confidence interval can be obtained by replacing the risk ratio with the rate ratio in the E-value formula (VanderWeele and Ding 2017; Linden et al., 2020). Based on this assumption, statistical evidence from

Table 1
Characteristics of mothers and children included in the analysis (at baseline).

Variables included in the model		Frequency (n)	Percent (%)
Ethnicity (race)	Caucasian	2473	88.3
	Non-Caucasian	331	11.7
Mothers' Education level at conception	Schooling Up to 12 years	1683	60.0
	Trade certificate/ apprenticeship	246	8.8
	Professional registration/College Diploma	448	16.0
	University degree	427	15.2
Fathers' Education level at conception	Schooling Up to 12 years	767	33.6
	Trade certificate/ apprenticeship	667	29.3
	Professional registration/College Diploma	355	15.6
	University degree	491	21.5
Mothers' age at conception	<20 years	284	9.9
	20–24.99 years	618	21.6
	25–29.99 years	863	30.1
	30–34.99 years	733	25.6
	≥35 years	370	12.9
Parity	Nulliparous	1342	47.9
	Multiparous	1462	52.1
Family income at conception	≤24,000 AUD	1155	41.2
	>24,000 AUD	1649	58.8
Marital status	Married	1808	64.5
	Single	366	13.1
	Defacto	529	18.9
	Separate/divorce/ widow	101	3.6
Previous history of maternal mental illness	Yes	66	2.4
	No	2738	97.7
Hypertension/pre-eclampsia	Yes	720	25.7
	No	2078	74.3
Child's sex	Male	1454	50.7
	Female	1414	49.3
Preterm birth	Yes	217	7.7
	No	2586	92.3
Birthweight	Low birth weight (<2.5 K.G)	252	8.8
	Normal birthweight (2.5–3.99 K.G)	2350	82.2
	High birthweight (≥4.0 K.G)	256	8.9
Maternal prenatal alcohol use (at first trimester)	Non-use	1525	54.4
	1-2 standard drinks/ week	870	31.0
	3-5 standard drinks/ week	235	8.4
	≥6 standard drinks/ week	174	6.2
Maternal prenatal alcohol use (at third trimester)	Non-use	1622	67.1
	1-2 standard drinks/ week	583	24.1
	3-5 standard drinks/ week	129	5.3
	≥6 standard drinks/ week	82	3.4
Maternal prenatal tobacco exposure (at first trimester)	Non-smoker	2048	73.0
	1-9 cigarettes/day	436	15.6
	≥10 cigarettes/day	320	11.4
Maternal prenatal tobacco exposure (at third trimester)	Non-smoker	1905	74.7
	1-9 cigarettes/day	325	12.8
	≥10 cigarettes/day	319	12.5
Paternal prenatal tobacco exposure at 1st and 3rd trimester	Non-smoker	1450	52.9
	1-9 cigarettes/day	417	15.2
	≥10 cigarettes/day	870	31.8
Maternal depressive symptoms at 14 years of follow-up	Depressed	186	10.4
	Non-depressed	1597	89.6

(*continued on next page*)

Table 1 (*continued*)

Variables included in the model		Frequency (n)	Percent (%)
Maternal anxiety symptoms at 14 years of follow-up	Anxiety symptoms	124	6.9
	Non-anxiety symptoms	1659	93.1
Paternal emotional problems at 14 years of follow-up	Emotional problems	38	2.1
	No emotional problems	1761	97.9

our E-values suggested that the risk ratio (rate ratio) of the relationship between an unmeasured confounder and (i) maternal tobacco smoking during pregnancy (both trimesters) and CD symptoms in offspring would need to be at least 3.50 for each association to explain away or nullify the associations we found in this study (Table 3).

4. Discussion

This study prospectively tested the association between prenatal tobacco exposure and the risk of CD symptoms in offspring at the age of 14 years. We found that offspring exposed to maternal tobacco smoking during the first trimester, third trimester and both trimesters of pregnancy were at increased risk for CD symptoms when compared to non-exposed, with higher rates of CD symptoms observed with increasing levels of exposure, suggestive of a dose-response relationship. This interpretation was strengthened by the greater RR for those smoking more than 10 cigarettes per day compared to those smoking fewer cigarettes. Moreover, these estimates were robust to control for potential confounders. Paternal tobacco smoking during partner's pregnancy had no notable effect on CD symptoms in offspring, suggesting that maternal tobacco smoking during pregnancy may have *in utero* effects on offspring CD symptoms.

If the findings of this study are confirmed, it is possible that early screening and prevention of maternal prenatal tobacco smoking could reduce CD symptoms in offspring. There is already strong evidence for a range of adverse outcomes from exposure to prenatal tobacco smoke *in utero* (Office on Smoking and Health (US), 2006; Duko et al., 2020) and during childhood. The association with adolescent CD provides further impetus for targeting cessation and support programs during the child bearing years.

The finding of this study was consistent with the results from prospective longitudinal studies that have reported an increased risk of CD symptoms in offspring born to mothers who smoked tobacco during pregnancy (Maughan et al., 2004; Brion et al., 2010; Palmer et al., 2016; Ruisch et al., 2018). A study using data from the Brazilian Pelotas and the ALSPAC study from the UK found that maternal tobacco smoking during pregnancy was associated with a 1.82-fold and a 1.24-fold increased odds of externalizing/CD symptoms in offspring respectively after controlling for potential confounders including parental psychopathology (Brion et al., 2010). Consistent with our finding, that study also presented insufficient evidence for an association between paternal smoking during partner's pregnancy and offspring CD symptoms in both cohorts. This was also corroborated by evidence from a recent systematic review and meta-analysis that found a similar result (AOR = 2.06 (95 % CI: 1.67–2.54)) (Ruisch et al., 2018). It is also worth noting that other studies did not produce similar findings (Silberg et al., 2003; Maughan et al., 2004; D'Onofrio et al., 2008; Agrawal et al., 2010). A study from the US reported insufficient evidence for an increased risk of CD symptoms in offspring exposed to maternal smoking during pregnancy (Agrawal et al., 2010). However, that study assessed maternal tobacco smoking using a retrospective method, which could have introduced exposure misclassification due to recall bias, thereby contributing to less precise estimates.

Several putative mechanisms have been suggested to elucidate the link between prenatal tobacco exposure and CD symptoms in offspring. One suggested mechanism involves the neurotoxic effects of the chemical compounds found in tobacco smoke (Slikker et al., 2005). These

Table 2
Association between prenatal tobacco exposure and conduct disorder symptoms in offspring at the age of 14 years.

Prenatal tobacco exposure		Rate Ratios (95%CI)					
		Unadjusted	Adjusted for				
			Each other	Model 1	Model 2	Model 3	Model 4
Maternal smoking at first trimester	Non-smoker	Reference	Reference	Reference	Reference	Reference	Reference
	Smoker (any)	1.84 (1.52–2.22)	1.65 (1.35–2.01)	1.51 (1.23–1.85)	1.50 (1.21–1.84)	1.53 (1.25–1.88)	1.52 (1.24–1.87)
	1-9 Cigs/day	1.74 (1.38–2.20)	1.58 (1.24–2.00)	1.41 (1.10–1.80)	1.40 (1.09–1.78)	1.43 (1.12–1.83)	1.41 (1.10–1.81)
	≥10 Cigs/day	1.97 (1.50–2.60)	1.76 (1.33–2.33)	1.66 (1.25–2.21)	1.66 (1.25–2.20)	1.68 (1.27–2.23)	1.68 (1.26–2.22)
Maternal smoking at third trimester[a]	Smoker (any)	1.67 (1.35–2.03)	1.47 (1.18–1.82)	1.41 (1.13–1.75)	1.37 (1.10–1.71)	1.38 (1.12–1.73)	1.36 (1.09–1.69)
	1-9 Cigs/day	1.40 (1.07–1.83)	1.33 (1.04–1.70)	1.28 (1.01–1.64)	1.25 (1.01–1.60)	1.24 (1.00–1.59)	1.22 (1.01–1.56)
	≥10 Cigs/day	1.94 (1.48–2.56)	1.87 (1.29–2.71)	1.75 (1.22–2.53)	1.72 (1.20–2.48)	1.79 (1.25–2.57)	1.76 (1.22–2.53)
Maternal smoking at first and third trimesters	Smoker (any)	1.79(1.45–2.21)	1.58 (1.26–1.98)	1.52 (1.21–1.91)	1.48 (1.18–1.87)	1.54 (1.22–1.93)	1.50 (1.19–1.90)
	1-9 Cigs/day	1.66(1.26–2.20)	1.45 (1.08–1.94)	1.41 (1.04–1.89)	1.36 (1.01–1.84)	1.37 (1.01–1.86)	1.33 (1.03–1.87)
	≥10 Cigs/day	2.22(1.50–3.30)	2.06 (1.38–3.08)	2.00 (1.35–2.96)	1.95 (1.32–2.90)	2.08 (1.40–3.07)	2.04 (1.38–3.01)
Paternal smoking	Smoker (any)	1.56 (1.34–1.87)	1.35 (1.12–1.64)	1.18 (0.87–1.40)	1.14 (0.84–1.39)	1.13 (0.86–1.38)	1.03 (0.82–1.37)

[a] Analyses were run separately by trimester but demonstrated together for ease of presentation.
Key:Each other: paternal and maternal prenatal tobacco exposure.
Model 1: maternal age at conception, education, marital status, annual family income, parity, ethnicity (race), and maternal alcohol use during pregnancy (first and third trimester), Hypertension/pre-eclampsia (yes/no) and sex of child.
Model 2: added preterm birth and low birthweight to model 1.
Model 3: Separately added history of maternal psychiatric disorder during conception, maternal depression, and anxiety at 13 years of follow-up and paternal history of emotional problems (anxiety and depression) at 13 years of follow-up.
Model 4: Adjusted for all risk factors.

Table 3
Sensitivity analysis (E-values) for the association between maternal prenatal tobacco exposure and the risk of CD symptoms in offspring for fully adjusted Model.

Maternal Prenatal tobacco exposure		Rate Ratio (RRs) (95 % CI)	E-value	
			For Point Estimate	For Confidence Interval
Maternal prenatal tobacco exposure at first trimester	Smoker (any)	1.52 (1.24–1.87)	2.41	1.79
	1-9 Cigs/day	1.41 (1.10–1.81)	2.17	1.43
	≥10 Cigs/day	1.68 (1.26–2.22)	2.75	1.83
Maternal prenatal tobacco exposure at third trimester	Smoker (any)	1.36 (1.09–1.69)	2.06	1.40
	1-9 Cigs/day	1.22 (1.01–1.56)	1.74	1.11
	≥10 Cigs/day	1.76 (1.22–2.53)	2.92	1.74
Maternal prenatal tobacco exposure at both trimesters	Smoker (any)	1.50 (1.19–1.90)	2.37	1.67
	1-9 Cigs/day	1.33 (1.03–1.87)	1.99	1.21
	≥10 Cigs/day	2.04 (1.38–3.01)	3.50	2.10

Note: Analyses were run separately by trimester but demonstrated together for ease of presentation.

chemicals can easily cross the placenta (Pastrakuljic et al., 1998) and the levels of these chemicals in amniotic fluid and fetal serum found to be higher than corresponding maternal serum concentrations (Luck and Nau 1984). This may results in activation of nicotinic acetylcholine receptors (nAChRs) in the early periods of fetal brain development (Atluri et al., 2001) and contribute to apoptosis and mitotic abnormalities (Wickström 2007), which in turn may contribute to dysregulation in neurodevelopment via disruption of the intensity or timing of neurotrophic actions (Navarro et al., 1989) and thereby result in mental and behavioural disorders in offspring (Ernst et al., 2001; Duko et al., 2021).

Prenatal exposure to tobacco smoke may be linked with epigenetic modifications in offspring (Knopik et al., 2012; Richmond et al., 2015). A study of 800 mother-offspring pairs in the ALSPAC found an association between maternal smoking during pregnancy and offspring DNA methylation as well as a dose-dependent association with respect to duration and intensity of smoking (Richmond et al., 2015). Similarly, a recent finding from the Raine cohort showed that maternal tobacco smoking during pregnancy prompted irreversible changes in DNA methylation in offspring that was independent of paternal tobacco smoking during pregnancy, adolescent tobacco smoking and maternal postnatal tobacco smoking (Rauschert et al., 2019). DNA methylation in offspring may result in dysregulation of the hypothalamic-pituitary-adrenocortical axis (HPA) (Lee and Sawa 2014). A preponderance of studies have reported that such alterations in HPA axis regulation have been associated with behavioural disorders, including CD in offspring (Ruttle et al., 2011; Platje et al., 2013; Fairchild et al., 2018).

Parental mental health problems are important contributors in the development of CD symptoms in offspring. For example, a study of data from 2674 adult female and male twins from the 'Children of Twins' (COT) in the US found an association between parental depression and an increased risk of CD symptoms in children and adolescents (Silberg et al., 2010). Further, a study that used data from the World Mental Health Surveys included 51,507 participants from ten high income, six upper-middle income and six low/lower-middle income countries also produced similar results (McLaughlin et al., 2012). Similarly, we also found that further adjustment for history of maternal mental health problems during conception, maternal and paternal mental health problems at 13 years of follow-up slightly attenuated observed estimates but did not appear to affect the reported associations.

The current study has several strengths, including the prospective measures of maternal tobacco smoking during first and third trimesters of pregnancy; the use of prospective longitudinal study with a relatively large sample size; validation of self-reported maternal tobacco smoking status with biomarkers of tobacco smoking (e.g. cotinine); use of a standardized and widely used measurement scale (DSM-oriented) to measure offspring outcomes; comprehensive statistical adjustment for potential maternal and paternal early life covariates; examination of the mediating roles of preterm birth and low birthweight in the association between exposure and outcome; comparison of maternal and paternal tobacco smoking during pregnancy; additional analysis to identify risks in terms of gestational age; and the calculation of E-values to explore the potential effect of unmeasured confounding. However, the following limitations should be kept in mind when interpreting the results of this study. This study did not have data on second trimester maternal smoking during pregnancy or prior history of parental arrests. We were not able to control for parental mental health diagnosis and parental externalizing behavioural problems, but we were able to adjust for lifetime history of maternal mental health problems that was assessed during pregnancy, maternal depressive and anxiety symptoms as well as paternal emotional problems at 14 years follow-up as proxies for offspring predisposition to behavioural disorders.

Finally, the associations that we have reported may not necessarily reflect maternal tobacco smoking during pregnancy. Future studies could consider pre-conception exposure, and genetic predisposition to smoking using Mendellian Randomization. The pertinent remaining question is whether CD symptoms in offspring can be minimized by maternal smoking cessation during pregnancy, or avoidance of smoking take-up. Taken together with the current body of knowledge on prenatal tobacco smoking and CD symptoms, our findings provide support for such a future study.

5. Conclusion

Our findings suggest that offspring exposed to maternal tobacco smoking during the first, third and both trimesters of pregnancy were associated with increased rates of CD symptoms when compared to unexposed offspring. However, we found insufficient statistical evidence for an association between paternal smoking during pregnancy and CD symptoms in offspring. Early screening and interventions assisting pregnant mothers to quit tobacco smoking, or avoid smoking take-up, have potential to contribute health benefits for both mothers and their offspring.

Funding sources

There was no additional funding received to disclose for this publication.

CRediT author statement

Bereket Duko: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Project administration; Software; Visualization; Roles/Writing – original draft; Writing – review & editing. Gavin Pereira, Conceptualization; Data curation, Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing. Kim Betts: Conceptualization; Data curation, Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing. Rosa Alati: Conceptualization; Data curation, Methodology; Resources; Supervision; Validation; Visualization; Writing – review & editing. Robert J. Tait: Conceptualization; Data curation, Methodology; Resources; Validation; Visualization; Writing – review & editing. John Newnham: Conceptualization; Data curation, Methodology; Resources; Validation; Visualization; Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are sincerely grateful for all the Raine Study participants and their family who were involved in this study. We also acknowledge the Raine Study team including data collectors, data officers, clerical staff, data and cohort managers, research scientists and volunteers for data collection and cohort coordination. The National Health and Medical Research Council (NHMRC) for long term contribution to funding the Raine Study since initiation, the Raine Medical Research Foundation, The University of Western Australia (UWA), Curtin University, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University and The University of Notre Dame Australia are acknowledged for providing funding for core management of the Raine Study. The 14 year follow-up of the Raine Cohort was supported by the NHMRC (Sly et al. ID 211912) and NHMRC Program Grant (Stanley et al. ID 003209). Bereket Duko is funded by Curtin University through Curtin International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. The funders had no role in the data collection, study design, the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpsychires.2021.07.030.

References

Achenbach, T.M., Dumenci, L., Rescorla, L.A., 2003. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J. Clin. Child Adolesc. Psychol. 32 (3), 328–340.
Agrawal, A., Scherrer, J.F., Grant, J.D., Sartor, C.E., Pergadia, M.L., Duncan, A.E., Madden, P.A.F., Haber, J.R., Jacob, T., Bucholz, K.K., Xian, H., 2010. The effects of maternal smoking during pregnancy on offspring outcomes. Prev. Med. 50 (1–2), 13–18.
Akin, A., Citin, B., 2007. The depression anxiety and StressScale (DASS): the study of validityand reliability. Educ. Sci. Theor. Pract. 7 (1), 260–268.
APA, 2013. American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders, fifth ed.
Atluri, P., Fleck, M.W., Shen, Q., Mah, S.J., Stadfelt, D., Barnes, W., Goderie, S.K., Temple, S., Schneider, A.S., 2001. Functional nicotinic acetylcholine receptor expression in stem and progenitor cells of the early embryonic mouse cerebral cortex. Dev. Biol. 240 (1), 143–156.
Biederman, J., Petty, C.R., Dolan, C., Hughes, S., Mick, E., Monuteaux, M.C., Faraone, S. V., 2008. The long-term longitudinal course of oppositional defiant disorder and conduct disorder in ADHD boys: findings from a controlled 10-year prospective longitudinal follow-up study. Psychol. Med. 38 (7), 1027–1036.
Black, D.W., 2015. The natural history of antisocial personality disorder. Can. J. Psychiatr. 60 (7), 309–314.
Blair, R.J., Leibenluft, E., Pine, D.S., 2014. Conduct disorder and callous-unemotional traits in youth. N. Engl. J. Med. 371 (23), 2207–2216.
Bowes, L., Chollet, A., Fombonne, E., Galéra, C., Melchior, M., 2013. Lifecourse SEP and tobacco and cannabis use. Eur. J. Publ. Health 23 (2), 322–327.
Brion, M.J., Victora, C., Matijasevich, A., Horta, B., Anselmi, L., Steer, C., Menezes, A.M., Lawlor, D.A., Davey Smith, G., 2010. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics 126 (1), e57–65.
Cui, M., Kimura, T., Ikehara, S., Dong, J.-Y., Ueda, K., Kawanishi, Y., Kimura, T., Iso, H., 2020. Prenatal tobacco smoking is associated with postpartum depression in Japanese pregnant women: the Japan environment and children's study. J. Affect. Disord. 264, 76–81.
D'Onofrio, B. M., Van Hulle, C.A., Waldman, I.D., Rodgers, J.L., Harden, K.P., Rathouz, P.J., Lahey, B.B., 2008. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. Dev. Psychopathol. 20 (1), 139–164.
Dagher, R.K., Shenassa, E.D., 2012. Prenatal health behaviors and postpartum depression: is there an association? Arch. Wom. Ment. Health 15 (1), 31–37.
Duko, B., Ayano, G., Pereira, G., Betts, K., Alati, R., 2020. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Soc. Psychiatr. Psychiatr. Epidemiol. 55 (12), 1549–1562.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2021. Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study. J. Affect. Disord. 279, 426–433.
Ernst, M., Moolchan, E.T., Robinson, M.L., 2001. Behavioral and neural consequences of prenatal exposure to nicotine. J. Am. Acad. Child Adolesc. Psychiatry 40 (6), 630–641.
Erskine, H.E., Ferrari, A.J., Nelson, P., Polanczyk, G.V., Flaxman, A.D., Vos, T., Whiteford, H.A., Scott, J.G., 2013. Epidemiological modelling of attention-deficit/hyperactivity disorder and conduct disorder for the Global Burden of Disease Study 2010. JCPP (J. Child Psychol. Psychiatry) 54 (12), 1263–1274.
Fairchild, G., 2018. Adult outcomes of conduct problems in childhood or adolescence: further evidence of the societal burden of conduct problems. Eur. Child Adolesc. Psychiatr. 27 (10), 1235–1237.
Fairchild, G., Baker, E., Eaton, S., 2018. Hypothalamic-pituitary-Adrenal Axis function in children and adults with severe antisocial behavior and the impact of early adversity. Curr. Psychiatr. Rep. 20 (10), 84-84.
Fergusson, D.M., Lynskey, M.T., 1993. The effects of maternal depression on child conduct disorder and attention deficit behaviours. Soc. Psychiatr. Psychiatr. Epidemiol. 28 (3), 116–123.
Gatzke-Kopp, L.M., Beauchaine, T.P., 2007. Direct and passive prenatal nicotine exposure and the development of externalizing psychopathology. Child Psychiatr. Hum. Dev. 38 (4), 255–269.
Gaysina, D., Fergusson, D.M., Leve, L.D., Horwood, J., Reiss, D., Shaw, D.S., Elam, K.K., Natsuaki, M.N., Neiderhiser, J.M., Harold, G.T., 2013. Maternal smoking during pregnancy and offspring conduct problems: evidence from 3 independent genetically sensitive research designs. JAMA psychiatry 70 (9), 956–963.
Haneuse, S., VanderWeele, T.J., Arterburn, D., 2019. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. J. Am. Med. Assoc. 321 (6), 602–603.
Hudziak, J.J., Copeland, W., Stanger, C., Wadsworth, M., 2004. Screening for DSM-IV externalizing disorders with the Child Behavior Checklist: a receiver-operating characteristic analysis. JCPP (J. Child Psychol. Psychiatry) 45 (7), 1299–1307.
Hutchinson, J., Pickett, K.E., Green, J., Wakschlag, L.S., 2010. Smoking in pregnancy and disruptive behaviour in 3-year-old boys and girls: an analysis of the UK Millennium Cohort Study. J. Epidemiol. Community 64 (1), 82–88.
Johnson, S., Marlow, N., 2011. Preterm birth and childhood psychiatric disorders. Pediatr. Res. 69 (8), 11–18.
Kim, D.R., Bale, T.L., Epperson, C.N., 2015. Prenatal programming of mental illness: current understanding of relationship and mechanisms. Curr. Psychiatr. Rep. 17 (2), 5.
Knopik, V.S., Maccani, M.A., Francazio, S., McGeary, J.E., 2012. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev. Psychopathol. 24 (4), 1377–1390.
Lærum, A.M.W., Reitan, S.K., Evensen, K.A.I., Lydersen, S., Brubakk, A.-M., Skranes, J., Indredavik, M.S., 2019. Psychiatric symptoms and risk factors in adults born preterm with very low birthweight or born small for gestational age at term. BMC Psychiatr. 19 (1), 223.
Lamy, S., Thibaut, F., 2010. [Psychoactive substance use during pregnancy: a review]. Encephale 36 (1), 33–38.
Langley, K., Holmans, P.A., van den Bree, M.B.M., Thapar, A., 2007. Effects of low birth weight, maternal smoking in pregnancy and social class on the phenotypic manifestation of Attention Deficit Hyperactivity Disorder and associated antisocial behaviour: investigation in a clinical sample. BMC Psychiatr. 7 (1), 26.
Larkby, C.A., Goldschmidt, L., Hanusa, B.H., Day, N.L., 2011. Prenatal alcohol exposure is associated with conduct disorder in adolescence: findings from a birth cohort. J. Am. Acad. Child Adolesc. Psychiatry 50 (3), 262–271.
Lee, R.S., Sawa, A., 2014. Environmental stressors and epigenetic control of the hypothalamic-pituitary-adrenal axis. Neuroendocrinology 100 (4), 278–287.
Lin, Y.T., Hsu, J.W., Huang, K.L., Tsai, S.J., Su, T.P., Li, C.T., Lin, W.C., Chen, T.J., Bai, Y. M., Chen, M.H., 2020. Sexually transmitted infections among adolescents with conduct disorder: a nationwide longitudinal study. Eur. Child Adolesc. Psychiatr. https://doi.org/10.1007/s00787-020-01605-5.
Linden, A., Mathur, M.B., VanderWeele, T.J., 2020. Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: the evalue package. STATA J. 20 (1), 162–175.
Loeber, R., Burke, J.D., Lahey, B.B., Winters, A., Zera, M., 2000. Oppositional defiant and conduct disorder: a review of the past 10 years, part I. J. Am. Acad. Child Adolesc. Psychiatry 39 (12), 1468–1484.
Lovibond, P.F., Lovibond, S.H., 1995. The structure of negative emotional states: comparison of the depression anxiety stress scales (DASS) with the beck depression and anxiety inventories. Behav. Res. Ther. 33 (3), 335–343.
Luck, W., Nau, H., 1984. Exposure of the fetus, neonate, and nursed infant to nicotine and cotinine from maternal smoking. N. Engl. J. Med. 311 (10), 672.
Martin, A., Volkmar, F.R., Lewis, M., 2007. Lewis's Child and Adolescent Psychiatry : a Comprehensive Textbook. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia.
Mathews, T.J., 2001. Smoking during pregnancy in the 1990s. Natl. Vital Stat. Rep. 49 (7), 1–14.
Maughan, B., Taylor, A., Caspi, A., Moffitt, T.E., 2004a. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch. Gen. Psychiatr. 61 (8), 836–843.

Maughan, B., Taylor, A., Caspi, A., Moffitt, T.E., 2004b. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch. Gen. Psychiatr. 61 (8), 836–843.
McLaughlin, K.A., Gadermann, A.M., Hwang, I., Sampson, N.A., Al-Hamzawi, A., Andrade, L.H., Angermeyer, M.C., Benjet, C., Bromet, E.J., Bruffaerts, R., Caldas-de-Almeida, J.M., de Girolamo, G., de Graaf, R., Florescu, S., Gureje, O., Haro, J.M., Hinkov, H.R., Horiguchi, I., Hu, C., Karam, A.N., Kovess-Masfety, V., Lee, S., Murphy, S.D., Nizamie, S.H., Posada-Villa, J., Williams, D.R., Kessler, R.C., 2012. Parent psychopathology and offspring mental disorders: results from the WHO World Mental Health Surveys. Br. J. Psychiatry : J. Ment. Sci. 200 (4), 290–299.
Moran, V.E., 2012. Cotinine: beyond that expected, more than a biomarker of tobacco consumption. Front. Pharmacol. 3, 173-173.
Murray, J., Farrington, D.P., 2010. Risk factors for conduct disorder and delinquency: key findings from longitudinal studies. Can. J. Psychiatr. 55 (10), 633–642.
Navarro, H.A., Seidler, F.J., Eylers, J.P., Baker, F.E., Dobbins, S.S., Lappi, S.E., Slotkin, T. A., 1989. Effects of prenatal nicotine exposure on development of central and peripheral cholinergic neurotransmitter systems. Evidence for cholinergic trophic influences in developing brain. J. Pharmacol. Exp. Therapeut. 251 (3), 894–900.
Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342 (8876), 887–891.
Nomura, Y., Wickramaratne, P.J., Pilowsky, D.J., Newcorn, J.H., Bruder-Costello, B., Davey, C., Fifer, W.P., Brooks-Gunn, J., Weissman, M.M., 2007. Low birth weight and risk of affective disorders and selected medical illness in offspring at high and low risk for depression. Compr. Psychiatr. 48 (5), 470–478.
Palmer, R.H.C., Bidwell, L.C., Heath, A.C., Brick, L.A., Madden, P.A.F., Knopik, V.S., 2016. Effects of maternal smoking during pregnancy on offspring externalizing problems: contextual effects in a sample of female twins. Behav. Genet. 46 (3), 403–415.
Pastrakuljic, A., Schwartz, R., Simone, C., Derewlany, L.O., Knie, B., Koren, G., 1998. Transplacental transfer and biotransformation studies of nicotine in the human placental cotyledon perfused in vitro. Life Sci. 63 (26), 2333–2342.
Platje, E., Jansen, L.M., Raine, A., Branje, S.J., Doreleijers, T.A., de Vries-Bouw, M., Popma, A., van Lier, P.A., Koot, H.M., Meeus, W.H., Vermeiren, R.R., 2013. Longitudinal associations in adolescence between cortisol and persistent aggressive or rule-breaking behavior. Biol. Psychol. 93 (1), 132–137.
Pooler, J., Perry, D.F., Ghandour, R.M., 2013. Prevalence and risk factors for postpartum depressive symptoms among women enrolled in WIC. Matern. Child Health J. 17 (10), 1969–1980.
Rauschert, S., Melton, P.E., Burdge, G., Craig, J.M., Godfrey, K.M., Holbrook, J.D., Lillycrop, K., Mori, T.A., Beilin, L.J., Oddy, W.H., Pennell, C., Huang, R.-C., 2019. Maternal smoking during pregnancy induces persistent epigenetic changes into adolescence, independent of postnatal smoke exposure and is associated with cardiometabolic risk. Front. Genet. 10 (770).
Richmond, R.C., Simpkin, A.J., Woodward, G., Gaunt, T.R., Lyttleton, O., McArdle, W.L., Ring, S.M., Smith, A.D., Timpson, N.J., Tilling, K., Davey Smith, G., Relton, C.L., 2015. Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Hum. Mol. Genet. 24 (8), 2201–2217.
Royston, P., 2005. Multiple imputation of missing values: update of ice. STATA J. 5 (4), 527–536.
Ruisch, I.H., Dietrich, A., Glennon, J.C., Buitelaar, J.K., Hoekstra, P.J., 2018. Maternal substance use during pregnancy and offspring conduct problems: a meta-analysis. Neurosci. Biobehav. Rev. 84, 325–336.
Ruttle, P.L., Shirtcliff, E.A., Serbin, L.A., Fisher, D.B., Stack, D.M., Schwartzman, A.E., 2011. Disentangling psychobiological mechanisms underlying internalizing and externalizing behaviors in youth: longitudinal and concurrent associations with cortisol. Horm. Behav. 59 (1), 123–132.
Office on Smoking and Health (US), 2006. The Health Consequences of Involuntary Exposure to Tobacco Smoke: A Report of the Surgeon General. Centers for Disease Control and Prevention (US), Atlanta (GA).
Sharma, P., Sane, N., Anand, S.D., Marimutthu, P., Benegal, V., 2019. Assessment of cotinine in urine and saliva of smokers, passive smokers, and nonsmokers: method validation using liquid chromatography and mass spectrometry. Indian J. Psychiatr. 61 (3), 270–276.
Shaw, D.S., Shelleby, E.C., 2014. Early-starting conduct problems: intersection of conduct problems and poverty. Annu. Rev. Clin. Psychol. 10, 503–528.
Silberg, J.L., Maes, H., Eaves, L.J., 2010. Genetic and environmental influences on the transmission of parental depression to children's depression and conduct disturbance: an extended Children of Twins study. J. Child Psychol. Psychiatry Allied Discip. 51 (6), 734–744.
Silberg, J.L., Parr, T., Neale, M.C., Rutter, M., Angold, A., Eaves, L.J., 2003. Maternal smoking during pregnancy and risk to boys' conduct disturbance: an examination of the causal hypothesis. Biol. Psychiatr. 53 (2), 130–135.
Slikker, W., Xu, Z.A., Levin, E.D., Slotkin, T.A., 2005. Mode of action: disruption of brain cell replication, second messenger, and neurotransmitter systems during development leading to cognitive dysfunction—developmental neurotoxicity of nicotine. Crit. Rev. Toxicol. 35 (8–9), 703–711.
Slotkin, T.A., 2004. Cholinergic systems in brain development and disruption by neurotoxicants: nicotine, environmental tobacco smoke, organophosphates. Toxicol. Appl. Pharmacol. 198 (2), 132–151.
StataCorp, 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.
Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A. M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.
Stick, S.M., Burton, P.R., Gurrin, L., Sly, P.D., LeSouëf, P.N., 1996. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 348 (9034), 1060–1064.
Straker, L., Mountain, J., Jacques, A., White, S., Smith, A., Landau, L., Stanley, F., Newnham, J., Pennell, C., Eastwood, P., 2017. Cohort profile: the western Australian pregnancy cohort (raine) study-generation 2. Int. J. Epidemiol. 46 (5), 1384–1385j.
VanderWeele, T.J., Ding, P., 2017. Sensitivity analysis in observational research: introducing the E-value. Ann. Intern. Med. 167 (4), 268–274.
Wei, H.-T., Lan, W.-H., Hsu, J.-W., Bai, Y.-M., Huang, K.-L., Su, T.-P., Li, C.-T., Lin, W.-C., Chen, T.-J., Chen, M.-H., 2016. Risk of suicide attempt among adolescents with conduct disorder: a longitudinal follow-up study. J. Pediatr. 177, 292–296.
Wickström, R., 2007. Effects of nicotine during pregnancy: human and experimental evidence. Curr. Neuropharmacol. 5 (3), 213–222.
Zondervan-Zwijnenburg, M.A.J., Veldkamp, S.A.M., Neumann, A., Barzeva, S.A., Nelemans, S.A., van Beijsterveldt, C.E.M., Branje, S.J.T., Hillegers, M.H.J., Meeus, W.H.J., Tiemeier, H., Hoijtink, H.J.A., Oldehinkel, A.J., Boomsma, D.I., 2020. Parental age and offspring childhood mental health: a multi-cohort, population-based investigation. Child Dev. 91 (3), 964–982.

Chapter 6: Prenatal alcohol exposure and offspring subsequent alcohol use

Chapter 6: Prenatal alcohol exposure and offspring subsequent alcohol use

This chapter included two papers that comprehensively tested the association between prenatal alcohol exposure and offspring subsequent alcohol use during childhood, adolescence, and young adulthood. The first paper systematically reviewed the literature on the association between prenatal alcohol exposure and subsequent alcohol use in the offspring. Based on the findings from that systematic review, the second paper included in this chapter has compared the effects of pre-pregnancy and post-pregnancy maternal alcohol exposures on offspring subsequent alcohol use with prenatal alcohol exposure using progressive models. These studies addressed the following research objectives: to systematically review previous epidemiological research on the associations between prenatal alcohol exposure and offspring subsequent alcohol use; and to examine the associations between maternal prenatal alcohol exposure and offspring subsequent alcohol use using population-based cohort study.

Paper 1: **Duko B**, Pereira G, Tait RJ, Newnham J, Bedaso A, Betts K, Alati R. Prenatal alcohol exposure and offspring subsequent alcohol use: a systematic review. Drug and Alcohol Dependence

Paper 2: **Duko B**, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study. Drug and Alcohol Dependence. 2020; 217:108305**.**

6.1 Prenatal alcohol exposure and offspring subsequent alcohol use: a systematic review

Published manuscript and formal citation

Duko B, Pereira G, Tait RJ, Bedaso A, Betts K, Alati R. Prenatal alcohol exposure and offspring subsequent alcohol use: a systematic review. Drug and Alcohol Dependence. 2022; 232:109324

Supplementary material associated with this article can be found, in the online version, at **https://doi.org/10.1016/j.drugalcdep.2022.109324**.

Study purpose: Epidemiological studies examining the association between prenatal alcohol exposure and offspring subsequent alcohol use have produced inconsistent results. Therefore, summarizing the findings of those studies are imperative to avail epidemiological evidence more accessible to decision makers. Moreover, the association between maternal prenatal alcohol exposure and offspring subsequent alcohol use has not be systematically reviewed to date. To fill this gap in literature, this systematic review was performed to examine the association between prenatal alcohol exposure and offspring subsequent alcohol use. This is the first comprehensive systematic review that has investigated the prospective association between prenatal alcohol exposure and offspring subsequent alcohol use.

Drug and Alcohol Dependence 232 (2022) 109324

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Review

Prenatal alcohol exposure and offspring subsequent alcohol use: A systematic review

Bereket Duko [a,*,1], Gavin Pereira [a,b,c], Robert J. Tait [c,d], Asres Bedaso [e], John Newnham [f], Kim Betts [a], Rosa Alati [a,g]

[a] Curtin School of Population Health, Curtin University, Kent Street, Bentley, WA 6102, Australia
[b] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[c] enAble Institute, Curtin University, Kent Street, Bentley, WA 6102, Australia
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA 6102, Australia
[e] Australian Centre for Public and Population Health Research, School of Public Health, Faculty of Health, University of Technology Sydney, Ultimo, NSW, Australia
[f] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands, WA 6009, Australia
[g] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Qld 4068 Australia

ARTICLE INFO

Keywords:
Alcohol use
Alcohol use initiation
Offspring
Prenatal
Systematic review

ABSTRACT

Background: Prenatal alcohol exposure has been found to be associated with adverse physical and mental health outcomes in postnatal life, but the evidence is equivocal as to whether such exposure increases the risk of subsequent alcohol use in the offspring. We systematically reviewed the literature on the association between prenatal alcohol exposure and subsequent alcohol use in the offspring.

Methods: Relevant primary studies were identified via systematic search of PubMed/Medline, SCOPUS, EMBASE and Psych-INFO databases. Articles were also retrieved by reviewing reference lists of the identified studies. Literature searches did not have language and date limits but were restricted to human studies. The revised Newcastle-Ottawa Scale was used to evaluate the methodological quality of the studies included in this review. The protocol of this study was prospectively registered in the PROSPERO.

Results: Twelve observational studies, published between 1998 and 2020, were included in the final review. Eight studies (66.7%) reported an increased risk of alcohol use or increased level of alcohol drinking, two studies (16.7%) reported an increased risk of alcohol use disorder and one study (8.3%) reported an increased odds of alcohol sipping in offspring exposed to maternal prenatal alcohol use compared to non-exposed. However, one study (8.3%) reported insufficient statistical evidence for an association between prenatal alcohol exposure and offspring subsequent alcohol use. However, it should be noted that the large amount of variability across studies included in this review may limit more conclusive inference.

Conclusion: The findings of this review suggest a positive link between prenatal alcohol exposure and offspring's subsequent alcohol use. However, further mechanistic studies that allow stronger causal inference are warranted to further elucidate specific causal pathways.

1. Introduction

Alcohol use disorder is one of the leading modifiable causes of global disease burden and disability. Estimates from the Global Burden of Disease (GBD) study suggested that 2.8 million deaths and 6.0% of the total disability adjusted life years (DALYs) among men and 1.6% among women were attributable to alcohol use disorder (Griswold et al., 2018). Alcohol use disorder has been consistently linked to physical trauma and injury (Weil et al., 2018), unplanned and unwanted pregnancy (Connery et al., 2014), different types of criminal behaviours (Felson and Staff, 2010), prevalent sexual transmitted infections such as HIV, hepatitis C and others (Wilson et al., 2014; Scott-Sheldon et al., 2016), poor academic achievement (El Ansari et al., 2013, Tembo et al., 2017), several mental health problems (Kuria et al., 2012; Tembo et al., 2017) and even suicidal ideation and attempt (Darvishi et al., 2020), making it an alarming global public health concern. An early detection of the

* Correspondence to: Curtin School of Population Health, Curtin University, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).
[1] Present Address: Kent Street, Bentley, Perth, Western Australia 6102

https://doi.org/10.1016/j.drugalcdep.2022.109324
Received 9 November 2021; Received in revised form 17 January 2022; Accepted 17 January 2022
Available online 20 January 2022

modifiable determinants of alcohol use disorder is therefore paramount to guide prevention and intervention efforts and better address this public health problem.

The precise causes of alcohol use disorder remain unclear. Epidemiological evidence from genetic sensitive examinations found an approximately three-to four-fold increased risk of alcohol use disorder in offspring of those with alcohol use disorder (Edenberg and Foroud, 2013). Similarly, a meta-analysis that synthesized the results of twelve twin and five adoption studies found that the heritability of alcohol use disorder was as high as 50%, suggesting the remaining proportion may be accounted by early-life environmental and developmental factors such as the prenatal environment (Verhulst et al., 2015). Maternal prenatal alcohol exposure is one such modifiable risk factor with an estimated prevalence of 9.8% globally, with the highest reported prevalence in Ireland, UK, Denmark, Belarus and Russia, which ranged from 60.4% to 36.5% (Popova et al., 2017).

Evidence from several longitudinal studies suggest that offspring exposed to prenatal alcohol use may have increased risk of harmful alcohol use (Duko et al., 2020), alcohol use disorder (Alati et al., 2006; O'Brien and Hill, 2014), alcohol use problems (Baer et al., 2003), persistence of alcohol drinking (Cornelius et al., 2016), alcohol use (Pfinder et al., 2014), increased levels of alcohol drinking (Goldschmidt et al., 2019) and alcohol sipping (Lees et al., 2020) in offspring compared to non-exposed. Nonetheless, additional studies presented inconsistent results (Goldschmidt et al., 2019; Zaso et al., 2021). A study of data from 608 mother-offspring pairs in the Maternal Health Practices and Child Development (MHPCD) project found that young adults exposed to prenatal alcohol use were more likely to report two or more symptoms of alcohol use disorder at 22 years of age, but not alcohol use disorder (Goldschmidt et al., 2019). Further, a study based on the Avon Longitudinal Study of Parents and Children (ALSPAC) found insufficient evidence for association between prenatal alcohol exposure and offspring alcohol initiation after adjusting for parental demographic covariates and confounders (Zaso et al., 2021).

Heterogeneity across studies in the ascertainment of prenatal alcohol exposure, offspring subsequent alcohol use and the level of control for potential confounders and covariates may underpin these conflicting results. To date, two theoretical and narrative reviews have been conducted to examine the effects of prenatal substance use on offspring subsequent substance consumption (Spear and Molina, 2005; Dodge et al., 2019). Of these reviews, the first review exclusively focuses on the in vivo studies whereas the second review gives the general overview of the effects of prenatal substance use on offspring subsequent substance use (Dodge et al., 2019). To our knowledge, however, there is no comprehensive systematic review on the subject. More specific, comprehensive and up to date systematic reviews are warranted as such reviews are based on the results of systematic literature searches, whereby minimize selection bias (Jahan et al., 2016). We, therefore, conducted this systematic review to examine the association between prenatal alcohol exposure and offspring subsequent alcohol use.

2. Methods

2.1. Study design

This systematic review followed the methodological framework suggested by the Preferred Reporting Items for Systematic review and Meta-Analysis guidelines (PRISMA) (Moher et al., 2015; Page et al., 2021). The literature search strategy, relevant study selection, data extraction and results were guided by a pre-defined study protocol, which was prospectively registered in the PROSPERO with the registration number-CRD42021279084 (https://www.crd.york.ac.uk/prospero/export_details_pdf.php).

2.2. Data sources and literature searches

Systematic searches in PubMed/Medline, SCOPUS, EMBASE and Psych-INFO were conducted to identify relevant studies which examined the association between prenatal alcohol exposure and offspring subsequent alcohol use. Literature searches did not have language and date limits but were restricted to human studies. The search terms and keywords were: "(alcohol use OR alcohol drinking OR alcohol exposure OR alcohol consumption OR substance use OR substance exposure) AND (prenatal OR antenatal OR maternal OR pregnancy OR gestational OR *in utero*) AND (offspring OR adolescents OR youths OR young OR child OR childhood OR young adults) AND (alcohol use OR alcohol sipping OR alcohol initiation OR alcohol dependence OR alcohol use disorder OR level of drinking OR persistent drinking OR harmful alcohol use OR alcohol use)". Articles were also retrieved by reviewing reference lists of the identified studies and other reviews.

2.3. Eligibility criteria

All relevant studies were included in this systematic review based on the following inclusion criteria: 1) the exposure of interest was maternal prenatal alcohol use, 2) the outcome of interest was offspring subsequent alcohol use (including alcohol sipping, alcohol initiation, alcohol use disorder, alcohol consumption or level of alcohol drinking), 3) studies were conducted using case-control, cohort, case-cohort, nested case control or cross-sectional designs. Non-peer reviewed articles, editorials, case reports, commentaries, letters, and conference proceedings were excluded from the review. Screening of study eligibility was conducted by two independent reviewers.

2.4. Data extraction

Two independent reviewers (BD and AB) extracted the first author name, year of publication, country in which the study was conducted, study characteristics such as study design, sample size, maternal alcohol use quantification, offspring outcome and age of assessment, tools used to ascertain outcomes in offspring, confounders and covariates included in the fully adjusted model, point estimates such as odds ratio (OR) or relative risk (RR) with 95% Confidence Intervals (CI) in accordance with the PRISMA guidelines (Moher et al., 2015). Any sources of alcohol use outcomes in offspring either self-report or maternal report or clinical report was included in the review. Reviewer conflicts and issues raised during data screening and extraction were resolved by discussion.

2.5. Study quality

The methodological quality of each study was checked using the revised Newcastle-Ottawa Scale (NOS) (Wells et al., 2017). Additionally, a modified version of the NOS was used to check the methodological quality of cross-sectional studies included in this review (Modesti et al., 2016). To minimize possible reviewer bias, two independent reviewers conducted the methodological quality assessment. The NOS uses three standard grading categories: high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3). These scores were derived from the cumulative sum of the following broad perspectives: selection of the study groups (four items); comparability between the groups (one item); ascertainment of outcome and exposure variables (three items). With exception of comparability between the groups, a maximum of one point could be given to all broad perspectives. Contrasting scores between two reviewers were resolved by through discussion.

2.6. Rationale for not conducting meta-analysis

There has been no universally accepted standard on the definition of low, moderate, heavy or binge alcohol drinking during the prenatal period, making comparison between the studies more complex. Further,

studies included in this review differed vastly in the way they have categorized or classified prenatal alcohol exposure. Moreover, there were also substantial differences between studies in defining Standard Drinks which varied from 8 to 20 g of pure alcohol according to their respective country's alcohol use guidelines. The decision not to undertake a meta-analysis was based on the extent of such heterogeneity between studies.

2.7. Data synthesis

As we have noted in the aforementioned section, we conducted a narrative data synthesis as the studies included in this review differed vastly in the way they have categorized or classified prenatal alcohol exposure and offspring outcomes. The data synthesis was guided by the methods described on the Conduct of Narrative Synthesis in Systematic Reviews (Popay et al., 2006). For the studies that reported multiple estimates, the estimate (RR/OR/COR and 95%CI) with the most extensive adjustment were used to check the direction of association between the exposure and outcome. In the studies that did not report effect estimates, we have used p-values of respective studies to declare statistical significance (p-value < 0.05) for an association. For studies that reported risk estimates in terms of gestational week (categorised as trimester 1, trimester 2 and trimester 3) but not for whole pregnancy period, the estimates for the first trimester (trimester 1) prenatal alcohol exposure were considered for this review as mounting body of evidence suggests that some developmental periods (e.g. first trimester) are particularly responsive to the teratogenic effects of prenatal alcohol exposure (Wallén et al., 2021).

3. Results

3.1. Study selection

Our initial literature search retrieved a total of 3732 records. After removing duplicates, 2837 records were retained for titles and abstracts screening. A total of 2796 articles were excluded at titles and abstracts screening stage as they did not appear to be related to the topic. We conducted final review on 12 studies after excluding 29 full-text articles due to the following reasons: 25 studies did not report alcohol use as an outcome in the offspring; three studies were duplicates; and one was a review study (Fig. 1).

3.2. Characteristics of included studies

The primary studies included in this systematic review were published between 1998 and 2020. Of studies included in the systematic review; three studies were conducted in Australia (Alati et al., 2006; Alati et al., 2008; Duko et al., 2020), seven in the US (Baer et al., 1998; Baer et al., 2003; O'Brien and Hill, 2014; Cornelius et al., 2016; Lynch et al., 2017; Goldschmidt et al., 2019; Lees et al., 2020), one in UK (Zaso et al., 2021) and one in Germany (Pfinder et al., 2014). Two studies were based on the Mater-University of Queensland Study of Pregnancy (MUSP) cohort (Alati et al., 2006; Alati et al., 2008), two studies were based on the Seattle Prospective Longitudinal Study on Alcohol and Pregnancy (SPLP) (Baer et al., 1998; Baer et al., 2003) and another two studies were based on the Maternal Health Practices and Child Development (MHPCD) project (Cornelius et al., 2016; Goldschmidt et al., 2019) but measured varying offspring outcomes at different ages. One study each was based on the Western Australian pregnancy birth cohort (the Raine Study) (Duko et al., 2020), the Avon Longitudinal Study of Parents and Children (ALSPAC) (Zaso et al., 2021), the Germany Health Interview and Examination Survey for Children and Adolescent (the KiGGS study) (Pfinder et al., 2014) and the Adolescent Brain Cognitive Development Study (the ABCD study) (Lees et al., 2020). All studies included in this review were from high-income countries. Ten studies used cohort designs whereas two studies used cross-sectional data. The

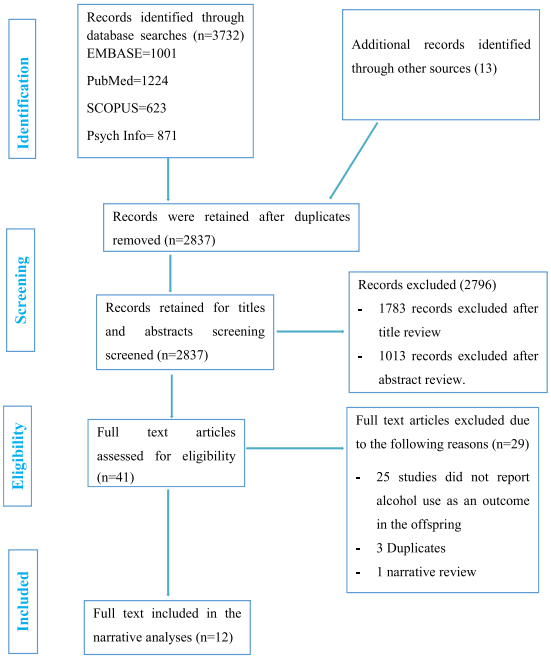


Fig. 1. PRISMA flowchart of review search.

sample size of the studies included in this review ranged between 209 and 10,119 study participants (Table 1).

3.3. Prenatal alcohol exposure

All of the studies included in this review used a categorical measure to ascertain prenatal alcohol exposure. Of these, three studies used a binary exposure (yes/no) to ascertain maternal prenatal alcohol exposure (O'Brien and Hill, 2014; Pfinder et al., 2014; Lynch et al., 2017). The remaining nine studies used varying level of categorizations to define low/moderate and high/binge maternal alcohol exposure during the prenatal period, which limited the ability to undertake a meta-analysis. Of twelve studies, three studies reported risk estimates for the first and third trimesters of pregnancy (Goldschmidt et al., 2019; Duko et al., 2020; Zaso et al., 2021), two studies reported for early (before six months) and late pregnancy exposures (Alati et al., 2006; Alati et al., 2008), two studies reported for mid-pregnancy exposure (Baer et al., 1998; Baer et al., 2003), one study reported for first and second trimesters of pregnancy exposures (Cornelius et al., 2016), one study reported for early pregnancy and whole pregnancy exposures (Lees et al., 2020) and three studies reported for whole pregnancy prenatal alcohol exposure (O'Brien and Hill, 2014; Pfinder et al., 2014; Lynch et al., 2017) (Table 1).

3.4. Offspring subsequent alcohol use

Out of twelve studies, three used the fourth revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR) (Alati et al., 2006; O'Brien and Hill, 2014; Goldschmidt et al., 2019), one used the 25-items Alcohol Dependence Scale (Baer et al., 2003), one study used Alcohol Use Disorders Identification Test (Zaso et al., 2021), one study used both laboratory test results and self-reports of alcohol use (Lynch et al., 2017) and, six used self-reported questionnaires designed by the respective studies to ascertain subsequent alcohol use in offspring. Studies included in this review examined subsequent alcohol

Table 1
Summary of studies included in this systematic review.

First Author/ year	Country	Study design	Sample size	Prenatal alcohol use defined as	Prenatal alcohol use assessed at	Outcome in offspring (name of outcome, age, and measurement scale)	Covariates and confounders considered in the final model	Adjusted odds ratio (AOR) /Relative risk (RR)/ Rate ratio (IRR) or equivalent	Summary of findings
Duko 2020	Australia	Prospective cohort (the Raine Study)	1200	Categorical: non-drinkers, < 4 standard units/week, > 4 standard units/week	1st and 3rd trimesters	Harmful alcohol use at 17 years of age in offspring ascertained by self-reported questionnaire	Maternal age at conception, education, marital status, race, family income, planned pregnancy, low birthweight, preterm birth, sex of child, maternal and paternal smoking during pregnancy, maternal depressive, anxiety and stress symptoms at 13 years of follow-up, offspring aggressive behaviours at 10 years and anxious/ depressed behaviours at 16 years of follow-up, maternal alcohol and tobacco use at 16 years of follow-up.	1.86 (1.16 – 2.96) for > 4 standard units/week	Offspring exposed to maternal prenatal alcohol use of four or more standard drinks of alcohol in the first and third trimesters are at increased risk of harmful alcohol use.
Lees 2020	US	Cross-sectional (the ABCD study	10,119	Categorical: Exposed: low-level alcohol use during early pregnancy (~0 –7 weeks), Heavier-level use during early pregnancy (~0 –7 weeks)	Early pregnancy and throughout pregnancy	Preadolescent alcohol sipping at 9–10.9 years ascertained by self-reported questionnaire	Sex, age, race, parental education, marital status, and income	AOR: 1.7: 95% CI (1.4–2.0), p < 0.001 for heavier-level use during pregnancy	This study suggested that prenatal alcohol use could play an important role in alcohol sipping among offspring by ages 9–10 years.
Zaso 2020	UK	Prospective cohort (ALSPAC)	2640	Heavy drinking (>4 U.K. units in a drinking day)	At 18 weeks and 32 weeks of pregnancy	Adolescent alcohol use at age of 17 years ascertained by AUDIT	Adolescent: sex and childhood stressful eventsMother: social class, depression history, drinking during childhood, smoking and marijuana useMothers partner: social class, depression history, drinking in pregnancy, smoking and marijuana use	(IRR: 1.00, 95%CI [0.93,1.08] for prenatal heavy drinking exposure	Adolescents who were prenatally exposed to heavy drinking appeared to be less protected by later alcohol initiation than those who were not exposed in utero. Prenatal heavy drinking exposure moderated associations of the age of alcohol initiation with alcohol quantity and heavy drinking frequency but not adolescent alcohol frequency or AUDIT score.
Goldschmidt 2019	US	Prospective cohort (the MHPCD)	608	Categorical: Exposed: ADV ≥ 1, Non-exposed: ADV < 1	1st and 3rd trimesters	Increased level of alcohol drinking in offspring at 22 years ascertained by DSM IV	Race, gender, employment, family history of alcohol problems and stressful life events	1.84 [1.17–2.88] for ADV ≥ 1 alcohol drinking volume (ADV)	Maternal prenatal alcohol use of ≥ 1 drinks/day in the first trimester was associated with increased levels of alcohol

(*continued on next page*)

Table 1 (*continued*)

First Author/ year	Country	Study design	Sample size	Prenatal alcohol use defined as	Prenatal alcohol use assessed at	Outcome in offspring (name of outcome, age, and measurement scale)	Covariates and confounders considered in the final model	Adjusted odds ratio (AOR) /Relative risk (RR)/ Rate ratio (IRR) or equivalent	Summary of findings
									drinking in offspring. Maternal prenatal alcohol use of ≥ 1 drinks/day in the first and third trimesters was linked to two or more symptoms of Alcohol Use Disorder.
Lynch 2017	US	Prospective cohort	182	Prenatal alcohol exposure (who drank at least one ounce of absolute alcohol per week or no prenatal alcohol exposure	Whole pregnancy	Alcohol use in offspring ascertained by both laboratory test results and self-reports of alcohol use	Adult's report of negative life stress, adult educational level achieved, gender and other prenatal exposures (tobacco, marijuana, and cocaine)	Effect size not reported	Young adults exposed to prenatal alcohol use but not cognitively affected, had more alcohol use problem.
Cornelius 2016	US	Prospective cohort study (the MHPCD)	917	Categorical: Exposed: > 1 alcoholic drinks/week, Non-exposed: < 1 drinks/ week	First and second trimesters	Adolescent alcohol use at 16 years of age ascertained by self-reported questionnaire	Race, maternal age, parental strictness, childhood maltreatment exposure, exposure to violence	Cumulative odds ratio: 1.70, P < 0.010	Prenatal alcohol exposure predicted the level of alcohol drinking among the adolescent offspring.
O'Brien 2014	US	Retrospective cohort study	209	Prenatal alcohol exposure or no prenatal alcohol exposure	Whole pregnancy	Alcohol use disorders in offspring ascertained by DSM IV	Socio-economic status, gender, prenatal cigarette exposure, and prenatal exposure to other drugs (cigarette (nicotine), marijuana)	Effect size not reported	Prenatal alcohol exposure was significantly associated with offspring alcohol-use disorders.
Pfinder 2013	Germany	Cross sectional study (the KiGGS study)	5922	Prenatal alcohol exposure or no prenatal alcohol exposure	Whole pregnancy	Adolescent alcohol intake between 11 and 17 years ascertained by self-reported questionnaire	Gender, age, ethnicity, socio-economic status, quality of life within the family, parental smoking, school failure, friends who smoke and maternal smoking during pregnancy	AOR: 2.18 (1.53, 3.10), p < 0.001	The findings this study suggested that low to moderate levels of maternal alcohol consumption during pregnancy were a risk factor for adolescent alcohol intake, with stronger associations in females.
Alati 2008	Australia	Prospective cohort study (MUSP)	5115	Categorical: > 3 glasses during pregnancy	Maternal alcohol use in early pregnancy (since become pregnant) and Maternal alcohol use in late pregnancy (in the last 3 month)	Child's Alcohol use at 14 years of age ascertained by self-reported questionnaire	Child's behaviour at age 5, drinking before pregnancy and at age 5.	2.74 (1.70–4.22) for > 3 glasses/ occasion (early pregnancy)	Offspring born to mothers who consumed > 3 glasses of alcohol during pregnancy were at increased risk of reporting drinking of > 3 glasses when compared with those whose mothers reported no drinking or drinking up to 2 glasses.
Alati 2006	Australia	Prospective cohort study (MUSP)	2138	Categorical: Exposed: > 3 glasses	Early pregnancy (before 6 months) and	Alcohol use disorder at 21 years (early and late onset) in	Sex, smoking over time, birth weight, gestational age, maternal	2.95 (1.62–5.36) for > 3 glasses/	Prenatal alcohol exposure (early pregnancy) was associated with

(*continued on next page*)

Table 1 (*continued*)

First Author/ year	Country	Study design	Sample size	Prenatal alcohol use defined as	Prenatal alcohol use assessed at	Outcome in offspring (name of outcome, age, and measurement scale)	Covariates and confounders considered in the final model	Adjusted odds ratio (AOR) /Relative risk (RR)/ Rate ratio (IRR) or equivalent	Summary of findings
					late pregnancy (after 6 months)	offspring ascertained by DSM IV	education, age, and marital status at the antenatal visit, maternal anxiety at the 5-year follow-up and maternal depression and child behaviour at the 14-year follow-up	occasion (early pregnancy)	the risk of developing early-onset and late onset alcohol use disorders at age 21 years.
Baer 2003	US	Prospective cohort study (SPLS)	419	Categorical: > 5 drinks per occasion	Mid pregnancy	Alcohol use problems at 21 years in offspring ascertained by 25 item-Alcohol Dependence Scale	Family history alcohol problems, gender, nicotine exposure, other prenatal exposures, and postnatal parental use of drugs.	Effect size not reported.	Prenatal alcohol exposure was related with offspring alcohol use problems at the age of 21 years.
Baer 1998	US	Prospective cohort study (SPLS)	439	Categorical: > 5 drinks per occasion	Mid pregnancy	Adolescent alcohol use at 14–16 years ascertained by self-reported questionnaire	Family history, parity, prenatal nicotine, age at the exam, self-esteem, parenting style control, parenting style effectiveness	Effect size not reported.	Prenatal alcohol exposure was identified as one of risk factor for adolescent's alcohol involvement and alcohol-related problem.

Foot note:
ABCD: Adolescent Brain Cognitive Development Study
ADV: Alcohol Drinking Volume
DSM IV: Diagnostic and Statistical Manual of Mental Disorders, fourth edition
KiGGS: Germany Health Interview and Examination Survey for Children and Adolescent
MHPCD: Maternal Health Practices and Child Development
MUSP: Mater-University of Queensland Study of Pregnancy
SPLS: Seattle Prospective Longitudinal Study on Alcohol and Pregnancy

use in offspring at age between 9 and 38 years. Mixed adverse outcome measure was reported in the included studies. Most notably, offspring alcohol use adverse outcome were reported as alcohol use disorder in two studies (Alati et al., 2006; O'Brien and Hill, 2014), harmful alcohol use (Duko et al., 2020), alcohol use problems (Baer et al., 2003; Lynch et al., 2017), persistence of alcohol drinking (Cornelius et al., 2016), alcohol use (Pfinder et al., 2014), increased levels of alcohol drinking (Goldschmidt et al., 2019), alcohol sipping (Lees et al., 2020) and alcohol use initiation (Zaso et al., 2021) in offspring exposed to prenatal alcohol use (Table 1).

3.5. Quality assessment of included studies

The methodological quality of the included studies was checked by the revised version Newcastle-Ottawa scale. The NOS parameters such as selection process including the identification of the exposure, the comparability of the cohorts and ascertainment of outcomes were used to give points to each study. Based on the NOS scoring guide, a study considered to be followed high methodological quality when it got a total score of > 7 of 9. Subsequently, all of the studies included in this review were rated as high quality based on the averages provided by two independent reviewers (Supplementary file 1 and 2).

3.6. Summary of results

A total of twelve primary studies examining the association between prenatal alcohol exposure and offspring subsequent alcohol use were included in the current systematic review. Of these, eleven studies (91.7%) reported an increased risk of alcohol use disorder or increased level of alcohol drinking or alcohol sipping in offspring exposed to prenatal alcohol use. More specifically, two studies reported an increased risk of alcohol use disorder, eight studies reported an increased risk of harmful alcohol use or increased level of alcohol drinking or early alcohol initiation, and one study reported an increased odds of alcohol sipping, with outcomes assessed between age 9 and 38 years in offspring exposed to prenatal alcohol use. However, one study (8.3%) found insufficient statistical evidence for an association between prenatal alcohol exposure and offspring subsequent alcohol early initiation. However, it should be noted that the large amount of variability across studies included in this review may limit more conclusive inference.

In the Raine Study, prenatal alcohol exposure increased the risk of harmful alcohol use in 17 years old adolescents. After adjusting for several confounders and covariates, offspring exposed to four or more standard drinks of alcohol per week during the first and third trimesters of pregnancy had a 1.86-fold increased risk of consuming alcohol at harmful levels (Duko et al., 2020). In the MHPCD cohort, prenatal alcohol exposure to one or more drinks of alcohol per day predicted persistent alcohol drinking in offspring at 16 years of age (Cornelius et al., 2016). In that study, the observed association was not mediated by offspring childhood externalizing problems. An additional study from the same cohort also observed similar findings such that prenatal alcohol exposure during the first and third trimesters has been associated with two or more symptoms of alcohol use disorders in offspring at the age of

22 years (Goldschmidt et al., 2019). In the MUSP cohort, prenatal alcohol consumption of three or more glasses a few times per month during early periods of pregnancy was associated with approximately a 3-fold increased risk of early and late-onset alcohol use disorders in offspring at 13–17 and 18–21 years of age, respectively (Alati et al., 2006). In another study from the same cohort that adjusted for pre-and post-pregnancy alcohol exposures, offspring born to mothers who reported alcohol consumption of three or more glasses during the prenatal period were 2.7 times more likely to report consumption of three or more alcoholic drinks at the age of 14 years (Alati et al., 2008). In the SPLP, maternal alcohol consumption of five or more standard drinks during mid-pregnancy has been associated with a composite measure of alcohol-related problems in offspring at age 14 years after controlling for family history of alcohol problems, parental postnatal alcohol use and other environmental potential confounders (Baer et al., 1998). An additional epidemiological study from the same cohort, prenatal alcohol exposure of five or more drinks during mid pregnancy predicted offspring alcohol drinking problems at the age of 21 years after adjusting for available covariates and confounders (Baer et al., 2003). In that study, the amount and frequency of alcohol drinking in young adults were not linked to maternal alcohol exposure during pregnancy. In the ABCD study, offspring exposed to any maternal alcohol use during early pregnancy were 1.7 times more likely to report alcohol sipping by ages 9–10 years (Lees et al., 2020). Similarly, in the KiGGS study, the odds of drinking alcohol in children and adolescents exposed to prenatal alcohol use increased approximately by 2-fold at ages between 11 and 17 years when compared to unexposed (Pfinder et al., 2014). In the prospective longitudinal study by O'Brien and Hill, prenatal alcohol exposure predicted alcohol use disorders in offspring at the mean age of 22.5 (+ 6.5) years (O'Brien and Hill, 2014). Similarly, an additional study from the US observed that young adults born to mothers who reported drinking at least one ounce of absolute alcohol per week during pregnancy had more alcohol use problems when compared to unexposed (Lynch et al., 2017). Nonetheless, a study of data from 2640 mothers-adolescents pairs in the ALSPAC observed that prenatal alcohol use of four or more units on more than 3–4 days during 18 or 32 weeks of pregnancy was not linked with offspring early alcohol initiation at 17 years of age after adjusting for several confounders including parental socio-demographic and mental health confounders (Zaso et al., 2021).

4. Discussion

This systematic review was conducted to investigate the association between maternal prenatal alcohol exposure and offspring subsequent alcohol use, by appraising available literature on the topic and describing their findings. The findings of this review suggest that prenatal alcohol exposure was associated with an increased risk of offspring subsequent alcohol use. These associations were observed for different types of subsequent alcohol use by offspring. With exception of a study by Zaso et al. (Zaso et al., 2021), the remaining of primary studies included in this review showed the detrimental effect of prenatal alcohol exposure on offspring subsequent alcohol use. There were also reports of dose-response associations. Therefore, the findings of this study provide further impetus for targeting interventions to stop drinking alcohol during pregnancy with several guidelines suggesting that there is no known safe amount and time during pregnancy to drink alcohol (Lim et al., 2019).

The precise mechanisms underpinning the association between prenatal alcohol exposure and offspring subsequent alcohol use remain uncertain. However, several putative mechanisms have been extensively replicated. One proposed mechanism explaining such association involves the teratogenic effect of ethanol that can readily cross both the placenta and fetal blood brain barrier (Singh et al., 2007) whereby it affects the morphology and function of the developing fetal brain (Lebel et al., 2011). This in turn hinders development of the central nervous system and results in a number of potential disabilities that persist at least into young adulthood (Carmichael Olson et al., 2001). This is also complimented by evidence from in vivo studies that suggest gestational exposure to ethanol could increase the propensity of offspring to consume more ethanol later in life (Spear and Molina, 2005). Similarly, an interventional study that administered 2.0 g/kg/day of ethanol (alcohol) to pregnant rats during gestational days 17–20 observed a two-fold increase in alcohol intake in those adolescent offspring that had been exposed to ethanol during gestation (Fabio et al., 2013). Additional epidemiological studies also observed similar results (Brancato et al., 2016; Brancato et al., 2018). In human studies such experimentation would not be ethical, so additional mechanistic studies are required to provide some clues on how alcohol exposure during prenatal period may impact subsequent alcohol use in the offspring. Mendelian randomization and negative control analysis feature prominently among such alternative studies, which can allow stronger causal inference. Mendelian randomization (MR) utilizes genetic variation as a natural experiment to examine the causal association between modifiable risk factors and adverse health outcomes in longitudinal data (Davies et al., 2018). Nonetheless, epidemiological evidence suggests that MR is not generally suitable approach in examining the association between prenatal alcohol exposure and behavioural outcomes in offspring as genetic variants currently identified for alcohol use suffered from weak instrument bias (Easey et al., 2019). Negative control analysis is an alternative approach that can be used as evidence to support inference as to whether a causal effect of the exposure on the outcome is present (Lipsitch et al., 2010; Sanderson et al., 2018; Easey et al., 2019). When examining the association between maternal prenatal alcohol exposure and offspring behavioural outcomes, maternal pre-and post-pregnancy alcohol exposures (Eilertsen et al., 2017; Duko et al., 2020) and paternal prenatal alcohol exposure (Easey et al., 2019) can be used as a negative control as such exposures are more likely to be affected by similar confounding, suggesting if an association with offspring alcohol use is found, it will be more likely due to maternal prenatal alcohol use.

An alternative explanation suggests that children and young adults may consume alcohol by emulating the behaviour of their parents (Haugland et al., 2021). A large study of 28,047 adults from the *Norwegian Counties Public Health Survey* reported that parental alcohol use problems modestly increased the odds of consuming alcohol in offspring (Haugland et al., 2021). To support this explanation, a meta-analysis that synthesized the results of seven prospective longitudinal studies also found that the odds of risky alcohol use increases approximately by two-folds in adolescents whose parents facilitated alcohol use by providing sips or tastes (Sharmin et al., 2017). Similarly, in this review studies that included parental (at least maternal) alcohol drinking during childhood in their fully adjusted model, also observed a moderate attenuation in the effect estimates, suggesting that postnatal environments such as this may also explain some portion of the association noted in this study.

Epidemiological studies also speculated that parental and offspring mental health problems may predispose individuals to consume alcohol (Weissman et al., 2006; Wu et al., 2006; Lamis et al., 2012). In a population-based prospective study from the US, maternal depressive symptoms measured before the onset of child adverse outcomes, significantly predicted an earlier age of alcohol use onset in offspring (Lamis et al., 2012). Similarly, in a longitudinal study of 1119 children aged between 10 and 13 years from the Boricua Youth Study in the US, early life depressive symptoms subsequently predicted an earlier onset of alcohol use after controlling for a number of confounders including parental psychopathology (Wu et al., 2006). In our review, some studies that considered such factors in their statistical models also reported slight attenuation in the risk estimates (Duko et al., 2020), suggesting parental and child mental health conditions might have some role in the observed associations.

Epidemiological evidence suggests that prenatal alcohol exposure has been associated with offspring behavioural and mental health problems (Easey et al., 2019; Duko et al., 2021). These behavioural and

mental health problems in childhood and adolescence are believed to be linked to substance use problems in young adulthood (Wu et al., 2006; Crum et al., 2008), suggesting that the association between prenatal alcohol exposure and offspring subsequent alcohol use is possibly mediated by mental health and behavioural problems in offspring (Dodge et al., 2019).

There are several caveats that should be considered when interpreting and generalizing the findings of this review. First, the associations observed in this review may not necessarily reflect the effects of prenatal alcohol exposure as such associations are substantially confounded by the maternal genome and behaviour. Most notably, there are some maternal genes that have been linked to the metabolism of alcohol during pregnancy have also been linked to adverse outcomes in offspring (Jacobson et al., 2006; Zuccolo et al., 2013). The presence of variants of alcohol dehydrogenase (ADH1B), linked with faster and efficient alcohol clearance may give some protection against hazardous effects of prenatal alcohol exposure (Zuccolo et al., 2013; Dodge et al., 2014). This implies that women with varying alcohol-related genotypes may have offspring with varying degrees of the disorder irrespective of the amount of alcohol consumed. Second, all studies included in this review are observational, such that their estimates may be affected by unmeasured confounders. Although well-designed and balanced observational studies could permit researchers to examine the effects of exposure on outcome when randomisation is not feasible, residual confounding remains a potential limitation for all studies. A practicable approach to reporting results in the presence of unmeasured and residual confounding is to either conduct a quantitative bias analysis (Lash et al., 2014) or compute E-values, which examine the extent of unmeasured confounding needed to explain away observed associations (VanderWeele and Ding, 2017; Linden et al., 2020). None of studies included in this review conducted a quantitative bias analysis or computed E-values. Third, the studies included in this review used varying definitions of low, moderate, heavy or binge prenatal alcohol exposure, making comparisons between studies problematic. We believe, to minimize such heterogeneity of prenatal alcohol definition, future studies need to report alcohol consumption levels in grams per week (g/week). Variability was also observed across the included studies regarding the timepoint at which prenatal alcohol exposure occurred (first, second or/and third trimester or all). Thus, it can be difficult to conclude from the evidence of this review at which stage of gestation maternal alcohol use has the greatest effect on offspring subsequent alcohol use. Fourth, measures of covariates and potential confounders varied widely across the included studies. These would have allowed us to compare and contrast the difference in estimates after inclusion or removal of covariates and confounders. Fifth, in some studies the length of the follow up period may have been too short to observe valid alcohol use outcome in offspring and this may be contributed to underreporting. In contrast, it is possible that an extended period of follow-up into adulthood may have resulted in such a high rate of alcohol consumption that analyses would have been of reduced power.

In summary, we noted evidence of positive association between prenatal alcohol exposure and offspring subsequent alcohol use. The findings of this study help to address a gap in the literature by systematically and comprehensively reviewing and describing the results of the existing epidemiological studies on the effects of prenatal alcohol exposure on offspring subsequent alcohol use aged 9–38 years. However, it should be noted that the epidemiological studies included in this review can suggest association between exposure and outcome but do not necessarily show evidence of causality on their own. Therefore, further studies that utilize sophisticated statistical approach are warranted to elucidate specific causal pathways.

CRediT authorship contribution statement

BD conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed quality, conducted analysis, and wrote the first draft of the manuscript. **AB** assisted data extraction of the included studies. **GP, RT, KB, JN and RA** reviewed the protocol, data extraction, narrative data synthesis and contributed to subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Author disclosures

None.

Role of funding

No external funding obtained for this systematic review.

Ethics approval

N/A.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Availability of data and material

All data generated during this review were included in this article.

Acknowledgment

We are so grateful to the Curtin University for providing us a wide range of available online databases. Bereket Duko is a recipient of Curtin University International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. Gavin Pereira was funded by NHMRC grants# 1099655 and 1173991, and the Research Council of Norway through Centre of Excellence grant #262700. The funders had no role in the data extraction, study design, the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.drugalcdep.2022.109324.

References

Alati, R., Al Mamun, A., Williams, G.M., O'Callaghan, M., Najman, J.M., Bor, W., 2006. "In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study.". Arch. Gen. Psychiatry 63 (9), 1009–1016.

Alati, R., Clavarino, A., Najman, J.M., O'Callaghan, M., Bor, W., Mamun, A.A., Williams, G.M., 2008. "The developmental origin of adolescent alcohol use: findings from the Mater University Study of Pregnancy and its outcomes.". Drug Alcohol Depend. 98 (1–2), 136–143.

Baer, J.S., Barr, H.M., Bookstein, F.L., Sampson, P.D., Streissguth, A.P., 1998. "Prenatal alcohol exposure and family history of alcoholism in the etiology of adolescent alcohol problems.". J. Stud. Alcohol 59 (5), 533–543.

Baer, J.S., Sampson, P.D., Barr, H.M., Connor, P.D., Streissguth, A.P., 2003. "A 21-Year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking.". Arch. Gen. Psychiatry 60 (4), 377–385.

Brancato, A., Castelli, V., Cavallaro, A., Lavanco, G., Plescia, F., Cannizzaro, C., 2018. "Pre-conceptional and peri-gestational maternal binge alcohol drinking produces inheritance of mood disturbances and alcohol vulnerability in the adolescent offspring.". Front. Psychiatry 9, 150.

Brancato, A., Plescia, F., Lavanco, G., Cavallaro, A., Cannizzaro, C., 2016. "Continuous and intermittent alcohol free-choice from pre-gestational time to lactation: focus on drinking trajectories and maternal behavior.". Front Behav. Neurosci. 10, 31.

Carmichael Olson, H., O'Connor, M.J., Fitzgerald, H.E., 2001. "Lessons learned from study of the developmental impact of parental alcohol use.". Infant Ment. Health J. 22 (3), 271–290.

Connery, H.S., Albright, B.B., Rodolico, J.M., 2014. Adolescent substance use and unplanned pregnancy: strategies for risk reduction. Obstet. Gynecol. Clin. North Am. 41 (2), 191–203.
Cornelius, M.D., Goldschmidt, L., Day, N.L., 2016. "Gestational alcohol exposure and other factors associated with continued teenage drinking.". Health Educ. Behav.: Off. Publ. Soc. Public Health Educ. 43 (4), 428–433.
Crum, R.M., Green, K.M., Storr, C.L., Chan, Y.-F., Ialongo, N., Stuart, E.A., Anthony, J.C., 2008. "Depressed mood in childhood and subsequent alcohol use through adolescence and young adulthood.". Arch. Gen. Psychiatry 65 (6), 702–712.
Darvishi, N., Farhadi, M., Haghtalab, T., Poorolajal, J., 2020. "Correction: alcohol-related risk of suicidal ideation, suicide attempt, and completed suicide: a meta-analysis.". PLOS ONE 15 (10), e0241874.
Davies, N.M., Holmes, M.V., Davey Smith, G., 2018. Reading mendelian randomisation studies: a guide, glossary, and checklist for clinicians. BMJ 362, k601.
Dodge, N.C., Jacobson, J.L., Jacobson, S.W., 2014. "Protective effects of the alcohol dehydrogenase-ADH1B*3 allele on attention and behavior problems in adolescents exposed to alcohol during pregnancy.". Neurotoxicol Teratol. 41, 43–50.
Dodge, N.C., Jacobson, J.L., Jacobson, S.W., 2019. "Effects of fetal substance exposure on offspring substance use.". Pediatr. Clin. North Am. 66 (6), 1149–1161.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2020. "Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study.". Drug Alcohol Depend. 217, 108305.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2021. "Prenatal alcohol and tobacco use and the risk of depression in offspring at age of 17 years: findings from the Raine Study.". J. Affect Disord. 279, 426–433.
Easey, K.E., Dyer, M.L., Timpson, N.J., Munafò, M.R., 2019. "Prenatal alcohol exposure and offspring mental health: a systematic review.". Drug Alcohol Depend. 197, 344–353.
Edenberg, H.J., Foroud, T., 2013. "Genetics and alcoholism.". Nat. Rev. Gastroenterol. Hepatol. 10 (8), 487–494.
Eilertsen, E.M., Gjerde, L.C., Reichborn-Kjennerud, T., Ørstavik, R.E., Knudsen, G.P., Stoltenberg, C., Czajkowski, N., Røysamb, E., Kendler, K.S., Ystrom, E., 2017. "Maternal alcohol use during pregnancy and offspring attention-deficit hyperactivity disorder (ADHD): a prospective sibling control study.". Int. J. Epidemiol. 46 (5), 1633–1640.
El Ansari, W., Stock, C., Mills, C., 2013. "Is alcohol consumption associated with poor academic achievement in university students?". Int. J. Prev. Med. 4 (10), 1175–1188.
Fabio, M.C., March, S.M., Molina, J.C., Nizhnikov, M.E., Spear, N.E., Pautassi, R.M., 2013. "Prenatal ethanol exposure increases ethanol intake and reduces c-Fos expression in infralimbic cortex of adolescent rats.". Pharmacol., Biochem., Behav. 103 (4), 842–852.
Felson, R.B., Staff, J., 2010. "The effects of alcohol intoxication on violent versus other offending.". Crim. Justice Behav. 37 (12), 1343–1360.
Goldschmidt, L., Richardson, G.A., De Genna, N.M., Cornelius, M.D., Day, N.L., 2019. "Prenatal alcohol exposure and offspring alcohol use and misuse at 22years of age: a prospective longitudinal study.". Neurotoxicol Teratol. 71, 1–5.
Griswold, M.G., Fullman, N., Hawley, C., Arian, N., Zimsen, S.R.M., Tymeson, H.D., Venkateswaran, V., Tapp, A.D., Forouzanfar, M.H., Salama, J.S., Abate, K.H., Abate, D., Abay, S.M., Abbafati, C., Abdulkader, R.S., Abebe, Z., Aboyans, V., Abrar, M.M., Acharya, P., Adetokunboh, O.O., Adhikari, T.B., Adsuar, J.C., Afarideh, M., Agardh, E.E., Agarwal, G., Aghayan, S.A., Agrawal, S., Ahmed, M.B., Akibu, M., Akinyemiju, T., Akseer, N., Asfoor, D.H.A., Al-Aly, Z., Alahdab, F., Alam, K., Albujeer, A., Alene, K.A., Ali, R., Ali, S.D., Alijanzadeh, M., Aljunid, S.M., Alkerwi, A. a, Allebeck, P., Alvis-Guzman, N., Amare, A.T., Aminde, L.N., Ammar, W., Amoako, Y.A., Amul, G.G.H., Andrei, C.L., Angus, C., Ansha, M.G., Antonio, C.A.T., Aremu, O., Ärnlöv, J., Artaman, A., Aryal, K.K., Assadi, R., Ausloos, M., Avila-Burgos, L., Avokpaho, E.F., Awasthi, A., Ayele, H.T., Ayer, R., Ayuk, T.B., Azzopardi, P.S., Badali, H., Badawi, A., Banach, M., Barker-Collo, S.L., Barrero, L.H., Basaleem, H., Baye, E., Bazargan-Hejazi, S., Bedi, N., Béjot, Y., Belachew, A.B., Belay, S.A., Bennett, D.A., Bensenor, I.M., Bernabe, E., Bernstein, R. S., Beyene, A.S., Beyranvand, T., Bhaumik, S., Bhutta, Z.A., Biadgo, B., Bijani, A., Bililign, N., Birlik, S.M., Birungi, C., Bizuneh, H., Bjerregaard, P., Bjørge, T., Borges, G., Bosetti, C., Boufous, S., Bragazzi, N.L., Brenner, H., Butt, Z.A., Cahuana-Hurtado, L., Calabria, B., Campos-Nonato, I.R., Campuzano, J.C., Carreras, G., Carrero, J.J., Carvalho, F., Castañeda-Orjuela, C.A., Castillo Rivas, J., Catalá-López, F., Chang, J.-C., Charlson, F.J., Chattopadhyay, A., Chaturvedi, P., Chowdhury, R., Christopher, D.J., Chung, S.-C., Ciobanu, L.G., Claro, R.M., Conti, S., Cousin, E., Criqui, M.H., Dachew, B.A., Dargan, P.I., Daryani, A., Das Neves, J., Davletov, K., De Castro, F., De Courten, B., De Neve, J.-W., Degenhardt, L., Demoz, G.T., Des Jarlais, D.C., Dey, S., Dhaliwal, R.S., Dharmaratne, S.D., Dhimal, M., Doku, D.T., Doyle, K.E., Dubey, M., Dubljanin, E., Duncan, B.B., Ebrahimi, H., Edessa, D., El Sayed Zaki, M., Ermakov, S.P., Erskine, H.E., Esteghamati, A., Faramarzi, M., Farioli, A., Faro, A., Farvid, M.S., Farzadfar, F., Feigin, V.L., Felisbino-Mendes, M.S., Fernandes, E., Ferrari, A.J., Ferri, C.P., Fijabi, D.O., Filip, I., Finger, J.D., Fischer, F., Flaxman, A.D., Franklin, R.C., Futran, N.D., Gallus, S., Ganji, M., Gankpe, F.G., Gebregergs, G.B., Gebrehiwot, T.T., Geleijnse, J.M., Ghadimi, R., Ghandour, L.A., Ghimire, M., Gill, P.S., Ginawi, I.A., Giref, A.Z.Z., Gona, P.N., Gopalani, S.V., Gotay, C.C., Goulart, A.C., Greaves, F., Grosso, G., Guo, Y., Gupta, R., Gupta, R., Gupta, V., Gutiérrez, R.A., Gvs, M., Hafezi-Nejad, N., Hagos, T.B., Hailu, G.B., Hamadeh, R.R., Hamidi, S., Hankey, G.J., Harb, H.L., Harikrishnan, S., Haro, J.M., Hassen, H.Y., Havmoeller, R., Hay, S.I., Heibati, B., Henok, A., Heredia-Pi, I., Hernández-Llanes, N.F., Herteliu, C., Hibstu, D. T.T., Hoogar, P., Horita, N., Hosgood, H.D., Hosseini, M., Hostiuc, M., Hu, G., Huang, H., Husseini, A., Idrisov, B., Ileanu, B.V., Ilesanmi, O.S., Irvani, S.S.N., Islam, S.M.S., Jackson, M.D., Jakovljevic, M., Jalu, M.T., Jayatilleke, A.U., Jha, R.P., Jonas, J.B., Jozwiak, J.J., Kabir, Z., Kadel, R., Kahsay, A., Kapil, U., Kasaeian, A., Kassa, T.D.D., Katikireddi, S.V., Kawakami, N., Kebede, S., Kefale, A.T., Keiyoro, P. N., Kengne, A.P., Khader, Y., Khafaie, M.A., Khalil, I.A., Khan, M.N., Khang, Y.-H., Khater, M.M., Khubchandani, J., Kim, C.-I., Kim, D., Kim, Y.J., Kimokoti, R.W., Kisa, A., Kivimäki, M., Kochhar, S., Kosen, S., Koul, P.A., Koyanagi, A., Krishan, K., Kuate Defo, B., Kucuk Bicer, B., Kulkarni, V.S., Kumar, P., Lafranconi, A., Lakshmana Balaji, A., Lalloo, R., Lallukka, T., Lam, H., Lami, F.H., Lan, Q., Lang, J.J., Lansky, S., Larsson, A.O., Latifi, A., Leasher, J.L., Lee, P.H., Leigh, J., Leinsalu, M., Leung, J., Levi, M., Li, Y., Lim, L.-L., Linn, S., Liu, S., Lobato-Cordero, A., Lopez, A.D., Lorkowski, S., Lotufo, P.A., Macarayan, E.R.K., Machado, I.E., Madotto, F., Magdy Abd El Razek, H., Magdy Abd El Razek, M., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malta, D.C., Mapoma, C.C., Martinez-Raga, J., Maulik, P.K., Mazidi, M., McKee, M., Mehta, V., Meier, T., Mekonen, T., Meles, K.G., Melese, A., Memiah, P.T.N., Mendoza, W., Mengistu, D.T., Mensah, G.A., Meretoja, T.J., Mezgebe, H.B., Miazgowski, T., Miller, T.R., Mini, G., Mirica, A., Mirrakhimov, E.M., Moazen, B., Mohammad, K.A., Mohammadifard, N., Mohammed, S., Monasta, L., Moraga, P., Morawska, L., Mousavi, S.M., Mukhopadhyay, S., Musa, K.I., Naheed, A., Naik, G., Najafi, F., Nangia, V., Nansseu, J.R., Nayak, M.S.D.P., Nejjari, C., Neupane, S., Neupane, S.P., Ngunjiri, J.W., Nguyen, C.T., Nguyen, L.H., Nguyen, T. H., Ningrum, D.N.A., Nirayo, Y.L., J, J., Noubiap, R., Ofori-Asenso, F.A., Ogbo, I.-H., Oh, O., Oladimeji, A.T., Olagunju, P.R., Olivares, B.O., Olusanya, J.O., Olusanya, A. M., Oommen, E., Oren, H.M., Orpana, D.D.V., Ortega-Altamirano, J.R., Ortiz, E., Ota, M.O., Owolabi, A.S., Oyekale, M.P.A., Pana, A., Park, E.-K., Parry, C.D.H., Parsian, H., Patle, A., Patton, G.C., Paudel, D., Petzold, M., Phillips, M.R., Pillay, J. D., Postma, M.J., Pourmalek, F., Prabhakaran, D., Qorbani, M., Radfar, A., Rafay, A., Rafiei, A., Rahim, F., Rahimi-Movaghar, A., Rahman, M., Rahman, M.A., Rai, R.K., Rajsic, S., Raju, S.B., Ram, U., Rana, S.M., Ranabhat, C.L., Rawaf, D.L., Rawaf, S., Reiner, R.C., Reis, C., Renzaho, A.M.N., Rezai, M.S., Roever, L., Ronfani, L., Room, R., Roshandel, G., Rostami, A., Roth, G.A., Roy, A., Sabde, Y.D., Saddik, B., Safiri, S., Sahebkar, A., Salama, J.S., Saleem, Z., Salomon, J.A., Salvi, S.S., Sanabria, J., Sanchez-Niño, M.D., Santomauro, D.F., Santos, I.S., Santric Milicevic, M.M.M., Sarker, A.R., Sarmiento-Suárez, R., Sarrafzadegan, N., Sartorius, B., Satpathy, M., Sawhney, M., Saxena, S., Saylan, M., Schaub, M.P., Schmidt, M.I., Schneider, I.J.C., Schöttker, B., Schutte, A.E., Schwendicke, F., Sepanlou, S.G., Shaikh, M.A., Sharif, M., She, J., Sheikh, A., Shen, J., Shiferaw, M.S., Shigematsu, M., Shiri, R., Shishani, K., Shiue, I., Shukla, S.R., Sigfusdottir, I.D., Silva, D.A.S., Silva, N.T.D., Silveira, D.G.A., Sinha, D.N., Sitas, F., Soares Filho, A.M., Soofi, M., Sorensen, R.J.D., Soriano, J.B., Sreeramareddy, C.T., Steckling, N., Stein, D.J., Sufiyan, M. a B., Sur, P.J., Sykes, B.L., Tabarés-Seisdedos, R., Tabuchi, T., Tavakkoli, M., Tehrani-Banihashemi, A., Tekle, M.G., Thapa, S., Thomas, N., Topor-Madry, R., Topouzis, F., Tran, B.X., Troeger, C.E., Truelsen, T.C., Tsilimparis, N., Tyrovolas, S., Ukwaja, K.N., Ullah, I., Uthman, O.A., Valdez, P.R., Van Boven, J.F.M., Vasankari, T.J., Venketasubramanian, N., Violante, F.S., Vladimirov, S.K., Vlassov, V., Vollset, S.E., Vos, T., Wagnew, F.W.S., Waheed, Y., Wang, Y.-P., Weiderpass, E., Weldegebreal, F., Weldegwergs, K.G., Werdecker, A., Westerman, R., Whiteford, H.A., Widecka, J., Wijeratne, T., Wyper, G.M.A., Xu, G., Yamada, T., Yano, Y., Ye, P., Yimer, E.M., Yip, P., Yirsaw, B.D., Yisma, E., Yonemoto, N., Yoon, S.-J., Yotebieng, M., Younis, M.Z., Zachariah, G., Zaidi, Z., Zamani, M., Zhang, X., Zodpey, S., Mokdad, A.H., Naghavi, M., Murray, C.J., L., Gakidou, E., 2018. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 392 (10152), 1015–1035.
Haugland, S.H., Carvalho, B., Stea, T.H., Strandheim, A., Vederhus, J.-K., 2021. "Associations between parental alcohol problems in childhood and adversities during childhood and later adulthood: a cross-sectional study of 28047 adults from the general population.". Subst. Abus. Treat., Prev., Policy 16 (1), 47.
Jacobson, S.W., Carr, L.G., Croxford, J., Sokol, R.J., Li, T.K., Jacobson, J.L., 2006. "Protective effects of the alcohol dehydrogenase-ADH1B allele in children exposed to alcohol during pregnancy.". J. Pedia 148 (1), 30–37.
Jahan, N., Naveed, S., Zeshan, M., Tahir, M.A., 2016. "How to conduct a systematic review: a narrative literature review.". Cureus 8 (11) e864-e864.
Kuria, M.W., Ndetei, D.M., Obot, I.S., Khasakhala, L.I., Bagaka, B.M., Mbugua, M.N., Kamau, J., 2012. "The association between alcohol dependence and depression before and after treatment for alcohol dependence.". ISRN Psychiatry 2012, 482802-482802.
Lamis, D.A., Malone, P.S., Lansford, J.E., Lochman, J.E., 2012. "Maternal depressive symptoms as a predictor of alcohol use onset and heavy episodic drinking in youths.". J. Consult. Clin. Psychol. 80 (5), 887–896.
Lash, T.L., Fox, M.P., MacLehose, R.F., Maldonado, G., McCandless, L.C., Greenland, S., 2014. "Good practices for quantitative bias analysis.". Int. J. Epidemiol. 43 (6), 1969–1985.
Lebel, C., Roussotte, F., Sowell, E.R., 2011. "Imaging the impact of prenatal alcohol exposure on the structure of the developing human brain.". Neuropsychol. Rev. 21 (2), 102–118.
Lees, B., Mewton, L., Stapinski, L.A., Teesson, M., Squeglia, L.M., 2020. "Association of prenatal alcohol exposure with preadolescent alcohol sipping in the ABCD study®.". Drug Alcohol Depend. 214, 108187.
Lim, A.W.Y., Van Schalkwyk, M.C.I., Maani Hessari, N., Petticrew, M.P., 2019. "Pregnancy, fertility, breastfeeding, and alcohol consumption: an analysis of framing and completeness of information disseminated by alcohol industry–funded organizations.". J. Stud. Alcohol Drugs 80 (5), 524–533.
Linden, A., Mathur, M.B., VanderWeele, T.J., 2020. "Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: The evalue package.". Stata J. 20 (1), 162–175.
Lipsitch, M., Tchetgen Tchetgen, E., Cohen, T., 2010. "Negative controls: a tool for detecting confounding and bias in observational studies.". Epidemiology 21 (3), 383–388.

Lynch, M.E., Kable, J.A., Coles, C.D., 2017. "Effects of prenatal alcohol exposure in a prospective sample of young adults: mental health, substance use, and difficulties with the legal system.". Neurotoxicology Teratol. 64, 50–62.
Modesti, P.A., Reboldi, G., Cappuccio, F.P., Agyemang, C., Remuzzi, G., Rapi, S., Perruolo, E., Parati, G., Settings, E.S.H.W.G. o C.R. i L.R., 2016. Anethnic differences in blood pressure in europe: a systematic review and meta-analysis. PLOS ONE 11 (1), e0147601.
Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. "Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement.". Syst. Rev. 4, 1.
O'Brien, J.W., Hill, S.Y., 2014. "Effects of prenatal alcohol and cigarette exposure on offspring substance u se in multiplex, alcohol-dependent families.". Alcohol., Clin. Exp. Res. 38 (12), 2952–2961.
Page, M.J., McKenzie, J.E., Bossuyt, P.M., Boutron, I., Hoffmann, T.C., Mulrow, C.D., Shamseer, L., Tetzlaff, J.M., Akl, E.A., Brennan, S.E., Chou, R., Glanville, J., Grimshaw, J.M., Hróbjartsson, A., Lalu, M.M., Li, T., Loder, E.W., Mayo-Wilson, E., McDonald, S., McGuinness, L.A., Stewart, L.A., Thomas, J., Tricco, A.C., Welch, V.A., Whiting, P., Moher, D., 2021. "The PRISMA 2020 statement: an updated guideline for reporting systematic reviews.". BMJ 372, n71.
Pfinder, M., Liebig, S., Feldmann, R., 2014. "Adolescents' use of alcohol, tobacco and illicit drugs in relation to prenatal alcohol exposure: modifications by gender and ethnicity.". Alcohol. Alcohol. 49 (2), 143–153.
Popay, J., Roberts, H., Sowden, A., Petticrew, M., Arai, L., Rodgers, M., Britten, N., Roen, K., Duffy, S., 2006. "Guidance on the conduct of narrative synthesis in systematic reviews.". A Prod. ESRC Methods Program. Version 1, b92.
Popova, S., Lange, S., Probst, C., Gmel, G., Rehm, J., 2017. "Estimation of national, regional, and global prevalence of alcohol use during pregnancy and fetal alcohol syndrome: a systematic review and meta-analysis." Lancet. Glob. Health 5 (3), e290–e299.
Sanderson, E., Macdonald-Wallis, C., Smith, G.Davey, 2018. Negative control exposure studies in the presence of measurement error: implications for attempted effect estimate calibration. Int. J. Epidemiol. 47 (2), 587–596.
Scott-Sheldon, L.A., Carey, K.B., Cunningham, K., Johnson, B.T., Carey, M.P., 2016. Alcohol use predicts sexual decision-making: a systematic review and meta-analysis of the experimental literature. AIDS Behav. 20 (Suppl 1(0 1)), S19–S39.
Sharmin, S., Kypri, K., Khanam, M., Wadolowski, M., Bruno, R., Mattick, R.P., 2017. "Parental supply of alcohol in childhood and risky drinking in adolescence: systematic review and meta-analysis.". Int. J. Environ. Res. Public Health 14 (3), 287.
Singh, A.K., Jiang, Y., Gupta, S., Benlhabib, E., 2007. "Effects of chronic ethanol drinking on the blood brain barrier and ensuing neuronal toxicity in alcohol-preferring rats subjected to intraperitoneal LPS injection. Alcohol Alcohol 42 (5), 385–399.
Spear, N.E., Molina, J.C., 2005. "Fetal or infantile exposure to ethanol promotes ethanol ingestion in adolescence and adulthood: a theoretical review.". Alcohol Clin. Exp. Res 29 (6), 909–929.
Tembo, C., Burns, S., Kalembo, F., 2017. "The association between levels of alcohol consumption and mental health problems and academic performance among young university students.". PloS One 12 (6) e0178142-e0178142.
VanderWeele, T.J., Ding, P., 2017. "Sensitivity analysis in observational research: introducing the e-value.". Ann. Intern Med 167 (4), 268–274.
Verhulst, B., Neale, M.C., Kendler, K.S., 2015. "The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies.". Psychol. Med. 45 (5), 1061–1072.
Wallén, E., Auvinen, P., Kaminen-Ahola, N., 2021. "The effects of early prenatal alcohol exposure on epigenome and embryonic development.". Genes 12 (7), 1095.
Weil, Z.M., Corrigan, J.D., Karelina, K., 2018. "Alcohol use disorder and traumatic brain injury.". Alcohol Res.: Curr. Rev. 39 (2), 171–180.
Weissman, M.M., Wickramaratne, P., Nomura, Y., Warner, V., Pilowsky, D., Verdeli, H., 2006. "Offspring of depressed parents: 20 years later.". Am. J. Psychiatry 163 (6), 1001–1008.
Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M.T.P., 2017. Newctle. -Ott. Scale (NOS) Assess. Qual. nonrandomised Stud. meta-Anal." Ott. Hosp. Res. Inst. ⟨http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp⟩.
Wilson, K.S., Odem-Davis, K., Shafi, J., Kashonga, F., Wanje, G., Masese, L., Mandaliya, K., Jaoko, W., McClelland, R.S., 2014. "Association between alcohol use and sexually transmitted infection incidence among kenyan women engaged in transactional sex.". AIDS Behav. 18 (7), 1324–1329.
Wu, P., Bird, H.R., Liu, X., Fan, B., Fuller, C., Shen, S., Duarte, C.S., Canino, G.J., 2006. "Childhood depressive symptoms and early onset of alcohol use.". Pediatrics 118 (5), 1907–1915.
Zaso, M.J., Youngentob, S.L., Park, A., 2021. "Characterizing the role of early alcohol reexposure in associations of prenatal alcohol exposure with adolescent alcohol outcomes.". Alcohol Clin. Exp. Res 45 (7), 1436–1447.
Zuccolo, L., Lewis, S.J., Smith, G.D., Sayal, K., Draper, E.S., Fraser, R., Barrow, M., Alati, R., Ring, S., Macleod, J., Golding, J., Heron, J., Gray, R., 2013. "Prenatal alcohol exposure and offspring cognition and school performance. A 'Mendelian randomization' natural experiment.". Int. J. Epidemiol. 42 (5), 1358–1370.

6.2 Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study

Published manuscript and formal citation

Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study. Drug and Alcohol Dependence. 2020; 217:108305.

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2020.108305.

Study purpose: The association between prenatal alcohol exposure and offspring subsequent alcohol use is highly correlated with some of the same risk factors commonly linked with adolescent alcohol use. This makes it problematic to identify the effects of pre-pregnancy, prenatal and post-natal maternal alcohol use on offspring subsequent alcohol use. Moreover, whether risk factors for harmful alcohol use can be traced back to the prenatal period is still unclear. As a result, the comparison of the effects of pre-pregnancy, prenatal and post-natal maternal alcohol use on offspring subsequent alcohol use may give some evidence to clarify the etiological basis for harmful alcohol use during adolescence. Therefore, the aim of this study was to examine whether prenatal exposures to alcohol in early and late pregnancy are independently associated with offspring harmful alcohol use at the age of 17 years using maternal pre-pregnancy and post-natal alcohol use as a negative control for intrauterine exposure.

Drug and Alcohol Dependence 217 (2020) 108305

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study

Bereket Duko [a,*], Gavin Pereira [a,b,c], Kim Betts [a], Robert J. Tait [d], John Newnham [e], Rosa Alati [a,f]

[a] School of Public Health, Curtin University, Kent Street, Bentley, WA 6102, Australia
[b] Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, 15 Hospital Ave, Nedlands, WA 6009, Australia
[c] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA 6102, Australia
[e] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands, WA 6009, Australia
[f] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland 4068 Australia

ARTICLE INFO

Keywords:
Alcohol
Pregnancy
Adolescents
Offspring
Harmful use
The Raine Study

ABSTRACT

Background: Epidemiological evidence suggests offspring exposed to prenatal alcohol are at increased risk of alcohol use disorders in adulthood. The evidence on the risk of developing harmful alcohol use in adolescence is less clear.

Methods: We used data from the Raine Study, a multi-generational birth cohort study, to examine the association between prenatal alcohol exposure and the risk of harmful alcohol use in offspring at the age of 17 years. Log binomial regression was used to estimate the relative risks (RRs) of harmful alcohol use in offspring exposed to maternal alcohol use in the first (early) and third (late) trimesters of pregnancy. Maternal pre-pregnancy alcohol use was used as a negative control for intrauterine exposure for comparison.

Results: Complete data were available for 1200 mother-offspring pairs. After adjustment for potential confounders, we found increased RRs of harmful alcohol use in offspring born to mothers who consumed four or more standard drinks of alcohol per week during the first trimester [RR 1.45(95% CI: 1.08−1.93)], third trimester [RR 1.34 (95% CI: 1.04–1.72)] and during both trimesters of pregnancy [RR 1.86 (95% CI: 1.16−2.96)]. Maternal pre-pregnancy alcohol use was not associated with an increased risk of harmful alcohol use in offspring [RR 1.15 (95% CI: 0.89−1.48)].

Conclusion: Observed associations for maternal prenatal alcohol exposure but not maternal pre-pregnancy alcohol use suggests a biological mechanism for intrauterine alcohol exposure on the risk of harmful alcohol use in the offspring.

1. Introduction

Harmful alcohol use is a major risk factor for a range of adverse outcomes across the life course. Reports from the recent Global Burden of Disease study suggested that harmful alcohol use contributes 5.1% to the global burden of disease and contributes to approximately 1 in 10 deaths of people aged 15–49 years (Griswold et al., 2018). Harmful alcohol use typically start in adolescence. For example, estimates from the Australian Institute of Health and Welfare (Australian Institute of Health and Welfare (AIHW, 2017) indicate that 9.1% of boys and 6.8% of girls aged between 12 and 17 years consume alcohol that exceeds the National Health and Medical Research Council (NHMRC) single occasion guidelines. Furthermore, harmful alcohol use during adolescence can be related to physical health problems such as injury (Hadland et al., 2017), unplanned pregnancy (Chapman and Wu, 2013), increased risk of contracting infectious diseases such as HIV, hepatitis C or others (Dembo et al., 2009), criminal involvement (Racz et al., 2015), mental health problems (Saban and Flisher, 2010; Mangerud et al., 2014) and suicide (Keyes et al., 2015). Therefore, rigorously identifying modifiable risk factors linked to harmful alcohol use is critically important to guide primary prevention and intervention strategies and alleviate hazardous consequences later in life (Onrust et al., 2016; Stockings et al., 2016).

Whether risk factors for harmful alcohol use can be traced back to the prenatal period is unclear. Prospective longitudinal studies examining the associations between prenatal alcohol exposure and the risk of harmful alcohol use in adolescents are scarce. Evidence from the

* Corresponding author.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.drugalcdep.2020.108305
Received 30 July 2020; Received in revised form 10 September 2020; Accepted 12 September 2020
Available online 20 September 2020

available studies suggests that offspring prenatally exposed to alcohol may have increased risk of alcohol use disorders when compared to non-exposed offspring (Alati et al., 2006, 2008; O'Brien and Hill, 2014; Goldschmidt et al., 2019). A prospective cohort study from Australia reported that offspring of mothers who consumed three or more drinks of alcohol per occasion during early pregnancy had approximately three-fold higher risks of developing alcohol use disorders at the age of 21 years when compared to offspring who were exposed to lighter consumption (Alati et al., 2006). Findings from the Maternal Health Practices and Child Development (MHPCD) study in the US showed that offspring exposed to prenatal alcohol were more likely to report increased levels of alcohol use at the age of 22 years (Goldschmidt et al., 2019). Similarly, the Seattle Prospective Longitudinal Study also reported a significant association between prenatal alcohol exposure and offspring problematic alcohol use at the age of 21 years (Baer et al., 2003).

Few studies have accounted for important risk factors such as low socio-economic position (Barr et al., 2006), parental mental health problems (Alati et al., 2006, 2008), maternal postnatal alcohol use (Alati et al., 2008), preterm birth and offspring birthweight (Alati et al., 2006, 2008), and existing mental health problems in offspring (Alati et al., 2006; Fergusson et al., 2007; Alati et al., 2008; Cornelius et al., 2016). In addition, the majority of existing studies have focused on ascertainment of alcohol use in young adults, with few studies on alcohol use in adolescence when harmful behavioral patterns are initiated. Finally, a paucity of studies has separated prenatal from postnatal exposure (Alati et al., 2008) or presented results for maternal pre-pregnancy alcohol use.

Moreover, the majority of previous studies have focused exclusively on prenatal exposure to alcohol in early pregnancy. Nonetheless, it has been proposed that the timing of those exposures are very important to identify risks in terms of gestational age at exposure (Kesmodel, 2001). The aim of this study was to test whether prenatal exposures to alcohol in early (the first trimester) and late (third trimester) (Generation 1) are independently associated with offspring harmful alcohol use at the age of 17 years (Generation 2) using maternal pre-pregnancy alcohol use as a negative control for intrauterine exposure.

2. Methods

2.1. Study design and participants

Data were obtained from the Raine Study, a multigenerational prospective study based in Perth, Australia. A total of 2730 pregnant mothers living in Western Australia and attending antenatal care between 16–20 weeks of gestation at King Edward Memorial Hospital (KEMH) and a nearby private clinic between 1989 and 1991 were enrolled. These pregnancies resulted in 2868 live births between August 1989 and April 1992. Complete data were available for 1200 mother-offspring pairs. The Raine Study participants' recruitment, enrolment, data collection and measurement strategies have been published in detail elsewhere (Newnham et al., 1993; Straker et al., 2017). Ethical approval for this study was gained from the Human Research Ethics Committees of the Princess Margaret Hospital for Children and King Edward Memorial Hospital in Western Australia. All parents and offspring gave written informed consent after the nature of the procedures had been fully explained.

2.2. Measures

2.2.1. Ascertainment of exposure: Prenatal alcohol exposure

At 18 and 34 weeks of gestation, pregnant mothers (Generation 1) reported an estimate of the total number of standard drinks of alcohol consumed per week during the first three months of pregnancy (early) and the total number of standard drinks they were currently drinking (late) respectively. Based on the NHMRC guidelines of 2009 (NHMRC, 2009), one Australian standard drink is equal to approximately 285 mL of full strength beer (4.8% alc), 375 mL of mid strength beer (3.5% alc), 425 mL of low strength beer (2.7% alc), 100 mL of wine (red - 13% alc, and white – 11.5% alc), 100 mL of champagne (12% alc), 330 mL of spirits (40% alc) and 275 mL bottle of ready-to-drink beverage (5% alcohol). There has been no universally accepted standard on the levels of alcohol that represent safe use during pregnancy. Based on this assumption and to further explore dose-response associations, we defined prenatal alcohol exposure as non-use (category 1), $\leq$ 3 standard drinks of alcohol per week (category 2) and $\geq$ 4 standard drinks of alcohol per week (category 3) during the first and third trimesters of pregnancy. To further elucidate and compare the timing of those exposures, we produced the following mutually exclusive categories; no exposure throughout pregnancy, first trimester (Trim-1) exposure only, third trimester (Trim-3) exposure only and, both first and third trimesters (Trim-1 and 3) exposures. Pregnant mothers also reported an average of the total number of standard drinks of alcohol consumed per week before becoming pregnant. We used the same category of prenatal alcohol exposure to define maternal pre-pregnancy alcohol use for comparison purposes. We used maternal pre-pregnancy alcohol use as a negative control for intrauterine exposure, in that we assumed that maternal pre-pregnancy alcohol use is likely to be influenced by similar unmeasured risk factors of prenatal alcohol use but not expected to have direct causal effect on offspring harmful alcohol use.

2.2.2. Ascertainment of outcome: Harmful alcohol use at the age of 17 years

Harmful alcohol use at 17 years of age (Generation 2) was assessed by using a self-reported questionnaire designed to depict risky behaviors in adolescents. Adolescents were asked, "Have you ever drunk six or more alcoholic drinks at one time or drunk so much alcohol that you vomited?" We grouped adolescents who responded "yes, more than once" to above question as 'harmful alcohol users' whereas those reported "never" or "only once" were used as a reference control group. This classification has been used in a previous study to categorize "harmful" and "non-harmful alcohol use" in the same cohort (Moore et al., 2014). We were also guided by the current NHMRC guidelines that recommend "healthy men and women should drink no more than ten standard drinks per week and no more than four standard drinks on any one day"(NHMRC, 2020).

2.2.3. Assessment of confounders

Confounders may explain an observed relationship between prenatal alcohol exposure and offspring harmful alcohol use (Murray and Duggan, 2010). Potential early life covariates included maternal age at conception (<20, 20–25, 25–29, 30–34, ≥35), maternal education (schooling up to 12 years, trade certificate / apprenticeship, professional registration/ college diploma and university degree), family income during pregnancy (low income < $24,000 per annum (pa) and moderate to high income ≥$24,000 pa), marital status (married, never married, de-facto and widowed/divorced/separated), ethnicity (Caucasian and non-Caucasian), planned pregnancy (yes/no) and paternal and maternal smoking (yes/no) during pregnancy were measured at the baseline. Childhood related factors such as child sex (male/female), preterm birth (<37 weeks), birthweight (<2.5 kg and ≥ 2.5 kg) were extracted from birth registrations. Maternal depressive, anxiety and stress symptoms at 13 years follow-up were measured using a short form of 'Depression Anxiety Stress Scale (DASS)'. The subscales for depression, anxiety and stress correspond to the diagnostic categories for mood disorders, panic disorder and generalized anxiety disorder respectively (Brown et al., 1997). This scale has excellent internal consistency for depression (range = .91–.97), anxiety (range = .81–.92) and stress (range = .88–.95) (Lovibond and Lovibond, 1995). In this study, mothers were considered to be experiencing symptoms of depression, anxiety and stress when recording a score of ≥10, ≥ 8 and ≥ 8 respectively (Lovibond and Lovibond, 1995). Harmful alcohol use in adolescents have been associated with postnatal exposures to family members' substance

use (Lee, Brook et al., 2016) and the existing mental health problems in adolescents (Bandiera et al., 2016; Pedrelli et al., 2016; Lechner et al., 2017). At 16 years of follow-up, postnatal maternal alcohol (non-use, ≤ 3 standard drinks of alcohol per week and ≥ 4 standard drinks of alcohol per week) and tobacco use (yes/no) were assessed. The self-reported existing mental health problems in adolescents included anxious/depressed and aggressive behavioral problems. These behaviors were assessed using the Child Behavior Checklist (CBCL4-18). The CBCL is an assessment tool which is aligned to the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (DSM IV) (Achenbach, 1999). This scale uses three-point Likert scale: not true, somewhat true and very true. The raw scores were changed into summary scores for classifying the behavioral and mental health problems of adolescents (Tearne et al., 2015). This scale has been applied in various studies across the world with good internal reliability, sensitivity of 83% and specificity of 67 % for a diagnosis of mental illness in the clinical setting (Zubrick et al., 1997; Tearne et al., 2015).

2.3. Statistical analysis

We used log-binomial regression models to estimate the effects of prenatal alcohol exposure on the risks of harmful alcohol use in offspring with STATA 16.1 (StataCorp, 2019). These models computed relative risks (RRs) as a measure of risk for harmful alcohol use. We separately fitted models with varying levels of adjustment. Model 1 was adjusted for maternal, paternal and child potential early life covariates such as maternal age at conception, education, marital status, race, family income, planned pregnancy, preterm birth, low birthweight, and sex of child, maternal and paternal smoking during pregnancy. Model 2 further adjusted by maternal depressive, anxiety and stress symptoms at 13 years of follow-up and child previous aggressive and existing anxious/depressed behavioral problems at 10 and 16 years of follow-up respectively. To further elucidate whether harmful alcohol drinking behavior is passed from mother to child through normalizing the behavior of alcohol drinking or smoking irrespective of prenatal exposures to alcohol, we separately added postnatal maternal alcohol and tobacco use at 16 years of follow-up to Model 1 (Model 3). In Model 4, we fully adjusted for all risk factors. We repeated analysis excluding early prenatal alcohol exposure from the models and adding late pregnancy exposure to alcohol to assess whether early and late prenatal exposures had significant impact on the overall analysis and identify of risks in terms of gestational age. We then used maternal pre-pregnancy alcohol use as a negative control for intrauterine exposure comparison. Next, we estimated the difference in estimates after fitting the models with all variables including the control variables. Moreover, to minimize the possibility of bias due to study participants' attrition, we ran multivariate imputation (Sterne et al., 2009) by chained equation using the STATA "mice" command to estimate imputed values for the missing datasets and repeated the analysis on the imputed datasets. Fifty cycles of regression switching were used and these generated 50 imputed datasets. All potential explanatory variables along with auxiliary variables used in the progressive regression models were included and imputed, and the analyses were repeated.

3. Results

3.1. Characteristics of study participants

A total of 1200 pregnant women along with their offspring were included the final analysis. Out of 1200 pregnant mothers, 72.4% were married, 90% were Caucasian, 56.2% planned their pregnancy and 37.2% had family income <24,000 AUD pa. At 13 years of follow-up, approximately 10.5%, 5.2% and 26.9% of pregnant mothers reported mild to severe form of depressive, anxiety and stress symptoms respectively. Among offspring ($n = 1200$) included in the analysis, 50.3% were females, 7.3% were of low birthweight, 6.5% were born preterm and 10% were born to mothers who consumed four or more standard drinks of alcohol per week during the first three months of pregnancy (Table 1).

3.2. Association between prenatal alcohol exposure and the risk of harmful alcohol use in offspring

We found the increased risks of harmful alcohol use in the unadjusted model among offspring born to mothers who consumed four or more standard drinks of alcohol per week during the first trimester [RR 1.50 (95% CI: 1.21−1.86)], third trimester [RR 1.41 (95% CI: 1.14−1.74)] and during both trimesters of pregnancy [RR 1.84 (95% CI: 1.31−2.60)]. We found insufficient statistical evidence for an increased risk of harmful alcohol use in offspring born to mothers who consumed three or less standard drinks of alcohol per week during the first and third trimesters of pregnancy (Table 2). Maternal pre-pregnancy alcohol consumption of four or more standard drinks per week was associated with an increased risk of harmful alcohol use in the offspring at the age of 17 years. The estimates were slightly attenuated when we adjusted for Model 1. Similarly, further adjustment of Model 1 by maternal depressive, anxiety and stress symptoms at 13 years of follow-up, offspring aggressive behaviors at 10 years and anxious/depressed behaviors at 16 years slightly attenuated the estimates for the first trimester and, third trimester exposures but slightly strengthened for the first and third (both) trimesters alcohol exposures and for maternal pre-pregnancy alcohol use (Model 2). In the fully adjusted model (Model 4), the estimates did not substantially change except for a slight attenuation in the exposure to both first and third trimesters [RR 1.86 (95% CI: 1.16−2.96)]. In contrast, we observed a null association between maternal pre-pregnancy alcohol use and risk of harmful alcohol use in offspring [RR 1.15 (95% CI: 0.89−1.48)]. The inclusion or removal of control variable in/from all sequential models produced no substantial difference in estimates. When we repeated all analyses using the imputed data, results remained unchanged (Supplementary file 1).

4. Discussion

We prospectively examined the association between prenatal alcohol exposure and the risk of harmful alcohol use in offspring at the age of 17 years. We found that offspring exposed to maternal alcohol use of four or more standard drinks per week during the first and third trimesters of pregnancy had an increased risk of harmful alcohol use at 17 years of age. These associations were not sensitive to varying levels of adjustment for potential confounders. We observed insufficient statistical evidence for an increased risk of harmful alcohol use in offspring exposed to less maternal alcohol consumption during the first and third trimesters of pregnancy. However, the risk of harmful alcohol use in offspring increased in magnitude and precision with increasing exposure to maternal alcohol use during pregnancy, suggesting that there is no safe level of prenatal alcohol use. Comparing maternal pre-pregnancy alcohol use and prenatal alcohol exposure, we observed stronger associations for intrauterine alcohol exposure and harmful alcohol use in offspring.

Whilst so far there are no studies that examined the risk of harmful alcohol use in adolescent offspring exposed to maternal prenatal alcohol using the methods we followed, there are a few studies that investigated this association in young and older adults (Baer et al., 2003; Alati et al., 2006, 2008; Goldschmidt et al., 2019). For example, a study using data from the 'Mater-University of Queensland Study of Pregnancy' (MUSP) found that early prenatal exposure to three or more alcoholic drinks per occasion increased the risks of Alcohol Use Disorders (AUD) in the offspring at the age of 21 years (Alati et al., 2006). The estimates of this study did not change substantially after adjusting for maternal age, education, and marital status during conception, sex, gestational age, birth weight, and maternal anxiety at 5 years of follow-up and maternal depression and child behavior at 14-years of follow-up as well as excluding subjects with fathers or siblings with alcohol-related

Table 1
Characteristics of mothers and children with complete data on harmful alcohol use at the age 17 years of follow-up.

Variables included in the model		Completed data on harmful alcohol use (n = 1200)		p-value*
		n	**%**	
Maternal education	Schooling Up to 12 years	519	43.3	0.7
	Trade certificate/ apprenticeship	230	19.2	
	Professional registration/College Diploma	218	18.2	
	University degree	233	19.4	
Maternal age at conception	< 20 years	73	6.0	0.06
	20–24.99 years	218	17.8	
	25–29.99 years	358	29.4	
	30–34.99 years	368	30.0	
	≥ 35 years	206	16.8	
Marital status	Married	869	72.4	0.4
	Never married	123	10.3	
	Defacto	176	14.7	
	Separate/divorce/ widow	32	2.6	
Ethnicity (race)	Caucasian	1079	90.0	0.02
	Non-Caucasian	121	10.0	
Family income at conception	≤ 24,000 AUD	447	37.2	0.8
	> 24,000 AUD	753	62.8	
Planned pregnancy	Yes	675	56.2	0.65
	No	525	43.8	
Preterm birth (<37 weeks)	Yes	78	6.5	0.25
	No	1121	93.5	
Birthweight	Low birth weight (< 2.5 K.G)	87	7.3	0.90
	Normal birthweight (≥ 2.5 K.G)	1113	92.7	
Sex of child	Male	596	49.7	0.8
	Female	604	50.3	
Maternal prenatal tobacco use	Smoker	235	19.6	0.08
	Non-smoker	965	80.4	
Paternal smoking during pregnancy	Smoker	381	31.8	0.07
	Non-smoker	819	68.2	
Maternal alcohol use in the first trimester only	Non-use	607	50.6	<0.01
	≤ 3 standard drinks/ week	473	39.4	
	≥ 4 standard drinks/ week	120	10.0	
Maternal alcohol use in the third trimester only	Non-use	678	59.8	<0.01
	≤ 3 standard drinks/ week	332	29.2	
	≥ 4 standard drinks/ week	124	11	
Maternal alcohol use in the first and third trimesters	Non-use	462	65.0	<0.01
	≤ 3 standard drinks/ week	218	30.8	
	≥ 4 standard drinks/ week	30	4.2	
Maternal pre-pregnancy alcohol use	Non-use	275	23.0	0.04
	≤ 3 standard drinks/ week	576	48.0	
	≥ 4 standard drinks/ week	349	29.0	
Maternal depression at 13 years of follow-up	Depressed	118	10.5	0.45
	Non-depressed	1014	89.5	
Maternal anxiety at 13 years of follow-up	Anxious	58	5.2	0.71
	Non-anxious	1074	94.8	
Maternal stress at 13 years of follow-up	Stressed	304	26.9	0.43
	Non-stressed	827	73.1	
Child anxious/depressed at 16 years of follow-up (n = 1200)		1200		0.22
Child aggressive behavior at 10 years of follow-up (n = 1156)		1156		0.08
Maternal smoking at 16 years of follow-up	Smoker	209	18.0	0.22
	Non-smoker	953	82.0	
Maternal alcohol use at 16 years of follow-up	Non-use	376	34.5	0.01
	≤ 3 standard drinks/ week	614	56.6	
	≥ 4 standard drinks/ week	98	8.90	

* p-values corresponds to Pearson's chi-square test.

problems. This is also corroborated by the results from the Seattle prospective cohort study that found the risk of alcohol dependence was higher at the age of 21 years in offspring exposed to maternal prenatal alcohol use compared to non-exposed (Baer et al., 2003). Most recently, a prospective cohort study that examined levels of alcohol consumption in young adults that were exposed to early and late pregnancy alcohol found a two to three-fold increased risks of alcohol drinking respectively (Goldschmidt et al., 2019). Consistently with these studies, our study suggests that *in utero* exposure to alcohol should be considered within the matrix of potential determinants for harmful alcohol use.

The mechanisms explaining the association between prenatal alcohol exposure and offspring harmful alcohol use remain elusive. However, several mechanisms have been proposed. The *developmental origins hypothesis* proposes that adaptation by the developing fetus to deleterious prenatal exposures could result in alterations in preterm brain morphology and function (Gluckman et al., 2010). Elements of this hypothesis have been supported by findings from studies that have reported modifications in fetal brain structure and function being associated with mental health and behavioral problems (Koob and Le Moal, 1997; Drevets et al., 2008). Maternal alcohol use during pregnancy is one such exposure that may contribute to behavioral problems in offspring (Kim et al., 2015).

Several studies have reported that the increased risks of alcohol use disorders were observed in close relatives of alcoholic probands when compared to healthy controls (Merikangas et al., 1998; Jacob et al., 2003; Edenberg and Foroud, 2013). Findings from genetic studies suggested that three-to four-fold increased risks of alcohol use disorders have been documented in children of those with alcohol use disorders (Edenberg and Foroud, 2013). Reports from twin and adoption studies also showed that 50% of the variability in alcoholism liability is linked with genetic predisposition (Verhulst et al., 2015), suggesting other risk factors may explain the remaining contribution. Although we were not able to measure genetic contributions, maternal pre-pregnancy and postnatal alcohol use were dealt out in our sequential models, but they did not appear to change the observed associations.

The effects of prenatal alcohol exposure during the first and third trimesters of pregnancy on the increased risk of harmful alcohol use in offspring have been consistently reported in animal studies. For instance, epidemiological data from animal studies suggest that prenatal exposure to alcohol may cause embryological changes resulting in neurobehavioral impairment and increase alcohol preference in exposed offspring (Shea et al., 2012). Further, evidence from a review of experimental studies suggested that the offspring of animals exposed to alcohol during the prenatal period demonstrated a greater propensity for alcohol and consumed much more alcohol than unexposed offspring (Spear and Molina, 2005). Complementing this view, a study administered 2.0 g/kg of ethanol (alcohol) to rats between 17 and 20 gestational days reported a two-fold increase in alcohol intake in offspring exposed to prenatal alcohol (Fabio et al., 2013). Most recently, a study from Italy found that the offspring of rats exposed to binge alcohol drinking during pregnancy were more susceptible to alcohol consumption during adolescence, further suggesting an epigenetic mechanism (Brancato et al., 2018). Replications of these findings in human studies could

Table 2
Association between prenatal alcohol exposure and the risk of harmful alcohol use in offspring at the age of 17 years.

Predictor and control variables		Risk ratios (RR) (95% CI) (harmful alcohol use)				
		Unadjusted	Model 1	Model 2	Model 3	Model 4
Alcohol use in the first trimester (exclusive)	Non-use	Reference	Reference	Reference	Reference	Reference
	≤ 3 standard drinks/week	1.24(1.06–1.45)	1.23(1.03–1.48)	1.19(0.98–1.43)	1.24(1.02–1.51)	1.21(0.98–1.48)
	≥ 4 standard drinks/week	1.50(1.21–1.86)	1.45(1.11–1.88)	1.40(1.07–1.83)	1.44(1.08–1.90)	1.45(1.08–1.93)
Alcohol use in the third trimester (exclusive)	Non-use	Reference	Reference	Reference	Reference	Reference
	≤ 3 standard drinks/week	1.31(1.11–1.54)	1.29(1.08–1.54)	1.22(1.01–1.47)	1.22(1.00–1.49)	1.19(0.97–1.45)
	≥ 4 standard drinks/week	1.41(1.14–1.74)	1.38(1.10–1.73)	1.37(1.09–1.73)	1.33(1.04–1.70)	1.34(1.05–1.72)
Alcohol use in the first and third trimesters	Non-use	Reference	Reference	Reference	Reference	Reference
	≤ 3 standard drinks/week	1.43(1.17–1.75)	1.49(1.15–1.93)	1.34(1.02–1.76)	1.39(1.04–1.84)	1.32(0.98–1.76)
	≥ 4 standard drinks/week	1.84(1.31–2.60)	1.95(1.27–3.01)	2.02(1.33–3.08)	1.86(1.17–2.96)	1.86(1.16–2.96)
Pre-pregnancy alcohol use	Non-use	Reference	Reference	Reference	Reference	Reference
	≤ 3 standard drinks/week	1.14(0.92–1.38)	1.13(0.91–1.38)	1.09(0.88–1.36)	1.10(0.88–1.37)	1.03(0.82–1.29)
	≥ 4 standard drinks/week	1.34(1.09–1.65)	1.28(1.03–1.59)	1.32(1.05–1.65)	1.18(0.92–1.50)	1.15(0.89–1.48)

Keys:
Model 1: adjusted for maternal age at conception, education, marital status, race, family income, and planned pregnancy, low birthweight, preterm birth, sex of child, maternal and paternal smoking during pregnancy.
Model 2: added maternal depressive, anxiety and stress symptoms at 13 years of follow-up, offspring aggressive behaviors at 10 years and anxious/depressed behaviors at 16 years of follow-up to Model 1.
Model 3: separately added maternal alcohol and tobacco use at 16 years of follow-up to Model 1.
Model 4: adjusted for all risk factors (all models).

provide additional evidence for the role of prenatal alcohol exposure in the development of harmful alcohol use in offspring.

An alternative hypothesis suggests that harmful alcohol use during adolescence may be largely influenced by parental alcohol drinking and other substance use (Richmond-Rakerd et al., 2014). This is also supported by findings from social learning theories that suggest children living with drinking parents may use alcohol because they observe frequent use by their parents over time (Eiden et al., 2009; Yule et al., 2013). For example, a prospective longitudinal study from Australia found that adolescents living with mothers drinking a much higher amount of alcohol occasionally and at irregular intervals were at the increased risks of developing problematic alcohol use in adolescence (Homel and Warren, 2019). This is also supported in our study, where further adjustment for postnatal maternal alcohol use slightly attenuated our observed risk estimates.

The strengths of this study include: the use of data from the large prospective cohort study, comprehensive assessment of prenatal environments and childhood psychopathology, relatively large sample size that enabled the generalizability of the results to other similar populations and reliable measures of the prenatal exposures and outcomes in offspring and adjusting for a wide range of potential confounders. Additionally, results from the negative control exposure of maternal pre-pregnancy alcohol use strengthen our analysis and give some support that the associations we found may be causal. We also conducted sensitivity analysis to identify risks in terms of gestational age. Evidence suggest that mothers who reported alcohol use during pregnancy are more likely to drink alcohol after childbirth. Indeed, we were able to control the effects of maternal postnatal alcohol and tobacco use at 16 years of follow up which further strengthen the robustness of our findings. Furthermore, we were able to include offspring mental health and behavioral problems separately in sequential models, but they did not affect our risk estimates.

This study also has some limitations. (1) The measure used to assess harmful alcohol use in offspring was questionnaires prepared specifically for the Raine study and thus not widely used measures. (2) The lack of a single well-accepted criterion to categorize maternal prenatal alcohol use may limit the ability to compare results between studies. (3) We did not have data on the second trimester prenatal alcohol exposure. (4) The quantity of alcohol consumed by pregnant mothers was measured using 'standard drink'. Although the World Health Organization (WHO) and Australian NHMRC guidelines set a similar criterion to define a 'standard drink', different countries have been using mixed methods to quantify alcohol consumption. Therefore, this should be taken into consideration while interpreting the findings of this study. (5) Due to the longitudinal nature of the study, there was relatively high attrition. Previous studies that used the Raine Study data reported selective attrition among socially disadvantaged families (Whitehouse et al., 2010). Selective attrition of socially disadvantaged families from the follow up may have resulted in less precise estimates. Nonetheless, epidemiological evidence from a similar prospective longitudinal study suggested that selective attrition did not appear to invalidate regression models to predict behavioral disorders (Wolke et al., 2009).

5. Conclusion

The results of this study suggest that maternal prenatal alcohol exposure of four or more standard drinks during the first and third trimesters of pregnancy is associated with an increased risk of harmful alcohol use in offspring at the age of 17 years. The findings of this study add to mounting evidence to guide primary prevention and intervention during the prenatal period. Therefore, adopting precautionary principles that suggest women to avoid or minimize alcohol consumption when they are trying to become pregnant may potentially alleviate such hazardous consequences later in their offspring.

Role of funding source

Nothing declared.

Contributors

BD conceived the hypothesis, designed the study, conducted longitudinal data analysis, interpretations of the results and wrote the first draft of the manuscript. GP, KB, RT, JN and RA contributed to the design of the study, reviewed the methodology, data analysis, interpretations of the results and contributed to critical revisions of the subsequent drafts of the manuscript for important intellectual content.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are extremely grateful to all of the study participants and families who took part in this study. The authors also acknowledge the Raine Study team for data collection and cohort coordination. The National Health and Medical Research Council for long term contribution to funding the Raine Study since initiation, </GS2>The University of Western Australia (UWA)</GS3>, Curtin University, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University, The University of Notre Dame Australia and The Raine Medical Research Foundation are acknowledged for providing funding for core management of the Raine Study. The 17 year follow-up of the Raine Cohort was supported by the National Health and Medical Research Council Program grant #353514, Project Grants #1099655 and #1173991. Bereket Duko is funded by Curtin University through Curtin International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. The funders had no role in the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2020.108305.

References

Achenbach, T.M., 1999. The child behavior checklist and related instruments. In: Maruish, M.E. (Ed.), The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, 2nd ed. Lawrence Erlbaum Associates, Mahwah, NJ.
Alati, R., Al Mamun, A., Williams, G.M., O'Callaghan, M., Najman, J.M., Bor, W., 2006. In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study. Arch. Gen. Psychiatry 63, 1009–1016.
Alati, R., Clavarino, A., Najman, J.M., O'Callaghan, M., Bor, W., Al. Mamun, A., Williams, G.M., 2008. The developmental origin of adolescent alcohol use: findings from the Mater University Study of Pregnancy and its outcomes. Drug Alcohol Depend. 98, 136–143.
Australian Institute of Health and Welfare (AIHW), 2017. National Drug Strategy and Household Survey 2016. Key Findings Online Data Tables. AIHW, Canberra.
Baer, J.S., Sampson, P.D., Barr, H.M., Connor, P.D., Streissguth, A.P., 2003. A 21-year longitudinal analysis of the effects of prenatal alcohol exposure on young adult drinking. Arch. Gen. Psychiatry 60, 377–385.
Bandiera, F.C., Loukas, A., Wilkinson, A.V., Perry, C.L., 2016. Associations between tobacco and nicotine product use and depressive symptoms among college students in Texas. Addict. Behav. 63, 19–22.
Barr, H.M., Bookstein, F.L., O'Malley, K.D., Connor, P.D., Huggins, J.E., Streissguth, A.P., 2006. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. Am. J. Psychiatry 163, 1061–1065.
Brancato, A., Castelli, V., Cavallaro, A., Lavanco, G., Plescia, F., Cannizzaro, C., 2018. Pre-conceptional and peri-gestational maternal binge alcohol drinking produces inheritance of mood disturbances and alcohol vulnerability in the adolescent offspring. Front. Psychiatry 9.
Brown, T.A., Chorpita, B.F., Korotitsch, W., Barlow, D.H., 1997. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behav. Res. Ther. 35, 79–89.
Chapman, S.L., Wu, L.T., 2013. Substance use among adolescent mothers: a review. Child Youth Serv. Rev. 35, 806–815.
Cornelius, M.D., Goldschmidt, L., Day, N.L., 2016. Gestational alcohol exposure and other factors associated with continued teenage drinking. Health Educ. Behav. 43, 428–433.
Dembo, R., Belenko, S., Childs, K., Wareham, J., 2009. Drug use and sexually transmitted diseases among female and male arrested youths. J. Behav. Med. 32, 129–141.
Drevets, W.C., Price, J.L., Furey, M.L., 2008. Brain structural and functional abnormalities in mood disorders: implications for neurocircuitry models of depression. Brain Struct. Funct. 213, 93–118.
Edenberg, H.J., Foroud, T., 2013. Genetics and alcoholism. Nat. Rev. Gastroenterol. Hepatol. 10, 487–494.
Eiden, R.D., Molnar, D.S., Colder, C., Edwards, E.P., Leonard, K.E., 2009. A conceptual model predicting internalizing problems in middle childhood among children of alcoholic and nonalcoholic fathers: the role of marital aggression. J. Stud. Alcohol Drugs 70, 741–750.
Fabio, M.C., March, S.M., Molina, J.C., Nizhnikov, M.E., Spear, N.E., Pautassi, R.M., 2013. Prenatal ethanol exposure increases ethanol intake and reduces c-Fos expression in infralimbic cortex of adolescent rats. Pharmacol. Biochem. Behav. 103, 842–852.
Fergusson, D.M., Horwood, L.J., Ridder, E.M., 2007. Conduct and attentional problems in childhood and adolescence and later substance use, abuse and dependence: results of a 25-year longitudinal study. Drug Alcohol Depend. 88, S14–26.
Gluckman, P.D., Hanson, M.A., Mitchell, M.D., 2010. Developmental origins of health and disease: reducing the burden of chronic disease in the next generation. Genome Med. 2, 14.
Goldschmidt, L., Richardson, G.A., De Genna, N.M., Cornelius, M.D., Day, N.L., 2019. Prenatal alcohol exposure and offspring alcohol use and misuse at 22years of age: a prospective longitudinal study. Neurotoxicol. Teratol. 71, 1–5.
Griswold, M.G., Fullman, N., Hawley, C., Arian, N., Zimsen, S.R.M., Tymeson, H.D., et al., 2018. Alcohol use and burden for 195 countries and territories, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet 392, 1015–1035.
Hadland, S.E., Xuan, Z., Sarda, V., Blanchette, J., Swahn, M.H., Heeren, T.C., Voas, R.B., Naimi, T.S., 2017. Alcohol policies and alcohol-related motor vehicle crash fatalities among young people in the US. Pediatrics 139, e20163037.
Homel, J., Warren, D., 2019. The relationship between parent drinking and adolescent drinking: differences for mothers and fathers and boys and girls. Subst. Use Misuse 54, 661–669.
Jacob, T., Waterman, B., Heath, A., True, W., Bucholz, K.K., Haber, R., Scherrer, J., Fu, Q., 2003. Genetic and environmental effects on offspring alcoholism: new insights using an offspring-of-twins design. Arch. Gen. Psychiatry 60, 1265–1272.
Kesmodel, U., 2001. Binge drinking in pregnancy-frequency and methodology. Am. J. Epidemiol. 154, 777–782.
Keyes, K.M., Brady, J.E., Li, G., 2015. Effects of minimum legal drinking age on alcohol and marijuana use: evidence from toxicological testing data for fatally injured drivers aged 16 to 25 years. Inj. Epidemiol. 2, 1.
Kim, D.R., Bale, T.L., Epperson, C.N., 2015. Prenatal programming of mental illness: current understanding of relationship and mechanisms. Curr. Psychiatry Rep. 17, 5.
Koob, G.F., Le Moal, M., 1997. Drug abuse: hedonic homeostatic dysregulation. Science 278, 52–58.
Lechner, W.V., Janssen, T., Kahler, C.W., Audrain-McGovern, J., Leventhal, A.M., 2017. Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents. Prev. Med. 96, 73–78.
Lee, J.Y., Brook, J.S., Nezia, N., Brook, D.W., 2016. Adolescent predictors of alcohol use in adulthood: a 22-year longitudinal study. Am. J. Addict. 25, 549–556.
Lovibond, P.F., Lovibond, S.H., 1995. The structure of negative emotional states: comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. Behav. Res. Ther. 33, 335–343.
Mangerud, W.L., Bjerkeset, O., Holmen, T.L., Lydersen, S., Indredavik, M.S., 2014. Smoking, alcohol consumption, and drug use among adolescents with psychiatric disorders compared with a population based sample. J. Adolesc. 37, 1189–1199.
Merikangas, K.R., Stolar, M., Stevens, D.E., Goulet, J., Preisig, M.A., Fenton, B., Zhang, H., O'Malley, S.S., Rounsaville, B.J., 1998. Familial transmission of substance use disorders. Arch. Gen. Psychiatry 55, 973–979.
Moore, S.E., Norman, R.E., Sly, P.D., Whitehouse, A.J., Zubrick, S.R., Scott, J., 2014. Adolescent peer aggression and its association with mental health and substance use in an Australian cohort. J. Adolesc. 37, 11–21.
Murray, K.W., Duggan, A., 2010. Understanding confounding in research. Pediatr. Rev. 31, 124.
Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342, 887–891.
NHMRC, 2009. Australian Guidelines to Reduce Health Risks From Drinking Alcohol. Available at. Commonwealth of Australia, pp. 2–3. http://www.nhmrc.gov.au/guidelines/publications/ds10.
NHMRC, 2020. Draft Australian Guidelines to Reduce Health Risks From Drinking Alcohol, 2020. https://www.nhmrc.gov.au/health-advice/alcohol.
O'Brien, J.W., Hill, S.Y., 2014. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. Alcohol Clin. Exp. Res. 38, 2952–2961.
Onrust, S.A., Otten, R., Lammers, J., Smit, F., 2016. School-based programmes to reduce and prevent substance use in different age groups: what works for whom? Systematic review and meta-regression analysis. Clin. Psychol. Rev. 44, 45–59.
Pedrelli, P., Shapero, B., Archibald, A., Dale, C., 2016. Alcohol use and depression during adolescence and young adulthood: a summary and interpretation of mixed findings. Curr. Addict. Rep. 3, 91–97.
Racz, S.J., Saha, S., Trent, M., Adger, H., Bradshaw, C.P., Goldweber, A., Cauffman, E., 2015. Polysubstance use among minority adolescent males incarcerated for serious offenses. Child Youth Care Forum 45, 205–220.
Richmond-Rakerd, L.S., Slutske, W.S., Heath, A.C., Martin, N.G., 2014. Genetic and environmental influences on the ages of drinking and gambling initiation: evidence for distinct aetiologies and sex differences. Addiction 109, 323–331.
Saban, A., Flisher, A.J., 2010. The association between psychopathology and substance use in young people: a review of the literature. J. Psychoactive Drugs 42, 37–47.
Shea, K.M., Hewitt, A.J., Olmstead, M.C., Brien, J.F., Reynolds, J.N., 2012. Maternal ethanol consumption by pregnant guinea pigs causes neurobehavioral deficits and increases ethanol preference in offspring. Behav. Pharmacol. 23, 105–112.
Spear, N.E., Molina, J.C., 2005. Fetal or infantile exposure to ethanol promotes ethanol ingestion in adolescence and adulthood: a theoretical review. Alcohol Clin. Exp. Res. 29, 909–929.
StataCorp, 2019. Stata Statistical Software: Release 16. StataCorp LLC, College Station, TX.
Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A. M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.

Stockings, E., Hall, W.D., Lynskey, M., Morley, K.I., Reavley, N., Strang, J., Patton, G., Degenhardt, L., 2016. Prevention, early intervention, harm reduction, and treatment of substance use in young people. Lancet Psychiatry 3, 280–296.
Straker, L., Mountain, J., Jacques, A., White, S., Smith, A., Landau, L., Stanley, F., Newnham, J., Pennell, C., Eastwood, P., 2017. Cohort profile: the western australian pregnancy cohort (Raine) study-generation 2. Int. J. Epidemiol. 46, 1384–1385j.
Tearne, J.E., Allen, K.L., Herbison, C.E., Lawrence, D., Whitehouse, A.J.O., Sawyer, M.G., Robinson, M., 2015. The association between prenatal environment and children's mental health trajectories from 2 to 14 years. Eur. Child Adolesc. Psychiatry 24, 1015–1024.
Verhulst, B., Neale, M.C., Kendler, K.S., 2015. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol. Med. 45, 1061–1072.
Whitehouse, A.J.O., Robinson, M., Zubrick, S.R., Ang, Q.W., Stanley, F.J., Pennell, C.E., 2010. Maternal life events during pregnancy and offspring language ability in middle childhood: the Western Australian Pregnancy Cohort Study. Early Hum. Dev. 86 (8), 487–492.
Wolke, D., Waylen, A., Samara, M., Steer, C., Goodman, R., Ford, T., Lamberts, K., 2009. Selective drop-out in longitudinal studies and non-biased prediction of behaviour disorders. Br. J. Psychiatry 195, 249–256.
Yule, A.M., Wilens, T.E., Martelon, M.K., Simon, A., Biederman, J., 2013. Does exposure to parental substance use disorders increase substance use disorder risk in offspring? A 5-year follow-up study. Am. J. Addict. 22, 460–465.
Zubrick, S.R., Silburn, S.R., Gurrin, L., Teoh, H., Shepherd, C., Carlton, J., Lawrence, D., 1997. Western Australian Child Health Survey: Education, Health and Competence, vol. 19. Australian Bureau of Statistics and the TVW Telethon Institute for Child Health Research, Perth.

Chapter 7: Prenatal tobacco exposure and offspring subsequent tobacco use

Chapter 7: Prenatal tobacco exposure and offspring subsequent tobacco use

This chapter incorporated two papers that examined the prospective association between prenatal tobacco exposure and offspring subsequent tobacco use. The first section of this chapter provided the first systematic review and meta-analysis on the prospective association between prenatal tobacco exposure and offspring subsequent tobacco smoking initiation or experimentation, lifetime, and current tobacco smoking as well as tobacco dependence during adolescence and young adulthood. The second study of this chapter has compared the effects of paternal and maternal prenatal tobacco exposures on offspring subsequent tobacco smoking during adolescence using a negative control analysis in progressive models. These studies addressed the following research objectives: to systematically review previous epidemiological research on the associations between prenatal tobacco exposure and offspring subsequent tobacco use; and examine the associations between maternal prenatal tobacco exposure and offspring subsequent tobacco smoking using population-based cohort study.

Paper 1: **Duko B**, Pereira G, Tait RJ, Nyadanu SD, Betts K, Alati R. Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-Analysis. Drug and Alcohol Dependence. 2021; 227:108993.

Paper 2: **Duko B,** Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence. Addictive Behaviours. 2021; 117:106871.

7.1 Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-analysis

Published manuscript and formal citation

Duko B, Pereira G, Tait RJ, Nyadanu SD, Betts K, Alati R. Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-Analysis. Drug and Alcohol Dependence. 2021; 227:108993.

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.drugalcdep.2021.108993.

Study purpose: Methodological variation in the ascertainment of prenatal tobacco smoking status and tobacco smoking/dependence in offspring as well as the level of adjustment for confounding may explain contrasting results reported by previous epidemiological studies. To fill this gap in literature, this systematic review and meta-analysis was conducted to identify the magnitude and consistency of associations reported between maternal prenatal tobacco smoking and subsequent tobacco smoking/dependence in offspring. Moreover, this is the first comprehensive systematic review and meta-analysis, that has examined the association between prenatal tobacco exposure and offspring subsequent tobacco smoking and dependence using twenty-six cohort and one case-control study.

Drug and Alcohol Dependence 227 (2021) 108993

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Prenatal Tobacco Exposure and the Risk of Tobacco Smoking and Dependence in Offspring: a Systematic Review and Meta-Analysis

Bereket Duko [a,b,*], Gavin Pereira [a,c], Robert J. Tait [d], Sylvester Dodzi Nyadanu [a], Kim Betts [a], Rosa Alati [a,e]

[a] Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Kent Street, Bentley, WA, 6102, Australia
[b] Faculty of Health Sciences, College of Medicine and Health Sciences, Hawassa University, Hawasaa, Ethiopia
[c] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA, 6102, Australia
[e] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, QLD, 4068, Australia

ARTICLE INFO

Keywords:
Tobacco
Smoking
Initiation
Dependence
Offspring
Prenatal
Systematic review
Meta-analysis

ABSTRACT

Background: There is some compelling, though not comprehensive, epidemiological evidence which suggests an association between prenatal tobacco exposure and tobacco smoking/dependence in offspring. We conducted a systematic review and meta-analysis to identify the magnitude and consistency of associations reported between prenatal tobacco exposure and subsequent tobacco smoking/dependence in offspring.

Methods: Using the PRISMA guideline, we systematically searched PubMed, SCOPUS, EMBASE and Psych-INFO to identify relevant studies. The methodological quality of all identified studies was checked by the Newcastle-Ottawa Scale. Inverse variance weighted random effects meta-analysis was used to estimate pooled risk ratio (RR) and 95 % confidence intervals (CI). We stratified outcomes by tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence. We further performed subgroup and leave-one-out sensitivity analyses. The protocol of this review was registered in the PROSPERO.

Results: Twenty-six cohort and one case-control study were included in the final meta-analysis. We found elevated pooled risks of tobacco smoking initiation [RR = 2.08, (95 % CI: 1.18–3.68)], ever tobacco smoking [RR = 1.21, (95 % CI: 1.05–1.38)], current tobacco smoking [RR = 1.70, (95 % CI: 1.48–1.95)] and tobacco dependence [RR = 1.50, (95 % CI: 1.31–1.73)] in offspring exposed to maternal prenatal tobacco use compared to non-exposed. We also noted higher risk estimate of current tobacco smoking in offspring exposed to heavy prenatal tobacco smoking [RR = 1.68, (95 % CI: 1.26–2.23)] when compared to prenatal exposure to lighter tobacco use [RR = 1.39, (95 % CI: 1.09–1.78)]. There was no association observed between paternal smoking during pregnancy and tobacco smoking in offspring.

Conclusion: Offspring exposed to maternal prenatal tobacco smoking are at an increased risk of tobacco smoking/dependence, indicating that tobacco smoking cessation during gestation may be imperative to reduce these risks in offspring.

1. Introduction

Tobacco smoking remains a major global public health concern. It is the second leading modifiable cause of morbidity and mortality and has claimed over 5 million lives every year since 1990 globally (GBD, 2016). Recent reports from the World Health Organization (WHO) in 2020 suggest that there are still 1.3 billion current tobacco smokers across 195 countries, and this figure is projected to rise to over 1.6 billion by the year 2025 (Organazation, 2020). Despite noticeable decline in trends of global tobacco smoking since 2000 (WHO, 2019), progress in meeting the worldwide goal set by countries and territories to cut tobacco smoking by 30 % by 2025 remains off track (WHO, 2011).

Although the precise underlying causes of tobacco smoking/dependence are not well understood, evidence from epidemiological studies suggests that a combination of individual socioeconomic factors such as age, education, occupation and income (Pust, Mohnen et al. 2008; Kim, Ko et al. 2012; Fernando, Wimaladasa et al. 2019), parents' and friends' tobacco smoking status (de Vries et al., 2003), adverse childhood

* Corresponding author at: Curtin School of Population Health, Faculty of Health Sciences, Curtin University, Kent Street, Bentley, WA, 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.drugalcdep.2021.108993
Received 21 June 2021; Received in revised form 14 July 2021; Accepted 15 July 2021
Available online 27 August 2021

experiences (Alcalá, von Ehrenstein et al. 2016) and environmental tobacco smoke exposure(Leonardi-Bee, Jere et al. 2011) can significantly contribute to tobacco smoking initiation/dependence. Further, it has been proposed that influences and parental behaviours during the prenatal period may also result in adverse outcomes in offspring via in-utero programming of the developing brain (Kim, Bale et al. 2015).

Maternal prenatal tobacco smoking is one such behaviour. It is widespread, with an estimated prevalence of 8.1 % in Europe, 5.9 % in the Americas and 1.2 % in Southeast Asia and 1.2 % in the Western Pacific region (Lange, Probst et al. 2018). A number of epidemiological studies have suggested that maternal prenatal tobacco smoking might prompt a predisposition in offspring to initiate tobacco smoking and even tobacco dependence later in life (Cornelius, Leech et al. 2000; Rydell, Cnattingius et al. 2012; Duko, Pereira et al. 2021). On the other hand, other studies have found no evidence of such associations (Buka, Shenassa et al. 2003; Porath and Fried, 2005; Menezes, Gonçalves et al. 2006; Menezes, Hallal et al. 2007; Monshouwer, Huizink et al. 2011; Rydell, Magnusson et al. 2014). For example, a retrospective cohort study of 1248 mothers from the US reported an association between tobacco dependence in offspring exposed to prenatal tobacco smoking but showed insufficient statistical evidence for current and lifetime tobacco smoking in offspring (Buka, Shenassa et al. 2003). Further, a large prospective longitudinal study of 4453 adolescents from the 1993 Pelotas cohort in Brazil reported an association with lifetime tobacco smoking (Menezes, Gonçalves et al. 2006). However, another prospective longitudinal study of the 1982 hospital-born children (N = 2718) in Pelotas in Brazil reported insufficient statistical evidence for association between maternal prenatal tobacco smoking and offspring current tobacco smoking (Menezes, Hallal et al. 2007). Methodological variation in the ascertainment of prenatal tobacco smoking status and tobacco smoking/dependence in offspring as well as the level of adjustment for confounding may explain these contrasting results. Nonetheless, the effect of prenatal tobacco smoking on the risk of tobacco smoking uptake in offspring has not be systematically reviewed and quantified to date. Therefore, we conducted a systematic review and meta-analysis to investigate the magnitude and consistency of associations reported between prenatal tobacco smoking and tobacco smoking initiation, lifetime and current tobacco smoking as well as tobacco dependence in offspring.

2. Methods

2.1. Research design

We followed the Preferred Reporting Items for Systematic review and Meta-analysis (PRISMA) guidelines to conduct this systematic review and meta-analysis (Moher, Shamseer et al. 2015). The literature search strategy, identification of the relevant studies, data extraction and analysis were compiled in accordance with a pre-defined protocol. The protocol of this review was prospectively registered in the International Prospective Register of Systematic Reviews (PROSPERO) with the registration number of CRD42020192555.

2.2. Data sources and literature searches

We systematically searched the following electronic databases: PubMed, EMBASE, SCOPUS and Psych-INFO to identify studies that reported the association between prenatal tobacco smoking and offspring tobacco smoking/dependence. Literature searches did not have language and date limits. The search terms and keywords were: "((cigarette use OR cigarette smoking OR cigarette exposure OR tobacco use OR tobacco exposure OR tobacco smoking) AND (prenatal OR antenatal OR pregnancy OR maternal OR gestational) AND (offspring OR adolescents OR youths OR young OR child OR childhood OR young adults OR adults) AND (nicotine experimentation OR nicotine initiation OR tobacco experimentation OR tobacco initiation OR lifetime tobacco use OR ever tobacco use OR daily tobacco use OR tobacco smoking OR current tobacco smoking OR tobacco consumption OR tobacco dependence OR nicotine dependence))".

2.3. Eligibility criteria

Studies were included in this systematic review and meta-analysis based on the following inclusion criteria: (1) studies conducted using observational study design (case-control, cohort design, case-cohort and nested case control), (2) the exposure of interest was prenatal tobacco smoking, (3) the outcome of interest was tobacco smoking initiation/experimentation, lifetime/ever tobacco smoking, current tobacco smoking and tobacco dependence, (4) measured outcomes using odds ratio (OR), risk ratio or relative risk (RR) estimates with 95 % confidence intervals (CIs) or reported data to calculate these. Studies conducted on animals, case reports, commentaries, editorials, letters, non-peer reviewed articles, abstracts of meeting or conferences were excluded from the review.

2.4. Data extraction

Two reviewers independently conducted data extraction based on the standardized data extraction form. The following data were extracted systematically from studies included in the final analysis: first author's name with year of publication, study design, country in which the study was carried out, fully adjusted confounders, odds ratios (OR) or risk ratio or relative risk (RR) with 95 % Confidence Intervals (CI), ascertainment of prenatal tobacco smoking and offspring tobacco smoking or dependence in accordance with the PRISMA guidelines (Moher, Shamseer et al. 2015). Any sources of tobacco smoking either self-report or clinical report was included in the review.

2.5. Study quality

The methodological quality of all selected studies was checked by two independent reviewers (BD and SDN) using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2017). This scale has been widely used for quality appraisal of case-control and cohort studies included in a systematic review and/or meta-analyses. It has three standard scoring categories such as high quality (scored 7–9), moderate quality (scored 4–6), and low quality (scored 0–3). These scoring categories were judged based on the following broad perspectives: (1) selection of the study groups (four items); (2) comparability between the groups (one item); (3) ascertainment of outcome and exposure variables (three items). As recommended by the scale, for each item in group selection, ascertainment of outcome and outcome categories, a maximum of one star could be given. However, a maximum of two stars could be given for comparability. Conflicting scores between two reviewers were resolved by via discussion.

2.6. Data synthesis and analysis

A meta-analysis was carried out using a Comprehensive Meta-Analysis (CMA) software version 3.0 (Borenstein et al., 2005). All studies that presented an effect size (OR/RR) or data to calculate these were included in the final meta-analysis. For the studies that produced multiple estimates, the estimate (RR/OR) with the most extensive adjustment were reported in this review. For the studies that reported multiple outcomes, each outcome was reported separately in this review. For seven studies that presented risk estimates in terms of gestational week (categorised as trimester 1, trimester 2 and trimester 3) but not for whole pregnancy period, the estimates for the first trimester (trimester 1) prenatal tobacco exposure were included in the final analysis. Further, only seven studies employed a separate analysis for the effects of light/moderate (< 1–9 cigarettes per day) and heavy tobacco smoking (≥10 cigarettes per day) during pregnancy on offspring

subsequent tobacco smoking. We, therefore, included the estimates of heavy tobacco smoking during pregnancy in our pooled analysis to ensure sufficient exposure contrast. To further explore which offspring outcomes were specifically linked to maternal prenatal tobacco exposure, we stratified meta-analyses by respective study outcomes such as tobacco smoking initiation (experimentation), lifetime (ever) tobacco smoking, current tobacco smoking and tobacco dependence. We used the inverse variance weighted random effect meta-analysis models to combine studies included in this review to estimate the link between exposure and outcome as well as to account for heterogeneity across the studies (Borenstein, Hedges et al. 2010). We also conducted a subgroup and sensitivity analysis to explore the potential source of heterogeneity. To identify studies that were highly influential on the pooled estimate, we employed a leave-one-out sensitivity analysis, whereby one study was removed at a time and meta-analysis repeated (Patsopoulos, Evangelou et al. 2008). Cochrane's Q-and I^2-test were used to detect the magnitude of statistical heterogeneity between studies (30). The scores of 25 %, 50 % and 75 % were considered to refer low, moderate and high heterogeneity between studies respectively (Higgins, Thompson et al. 2003). Potential publication bias was assessed by inspection of the funnel plot and Egger's test for regression asymmetry (Egger, Davey Smith et al. 1997).

3. Results

3.1. Study selection

Our systematic electronic literature search retrieved a total of 7705 articles initially, of which 6075 were excluded after title and abstract review as these articles were found not to be related to the subject. A total of 49 articles were screened at full-text review stage and of these, 27 articles met our pre-defined criteria were included in the final meta-analysis (Fig. 1).

3.2. Characteristics of included studies

Studies included in this systematic review and meta-analysis were published between 1994 (Kandel, Wu et al. 1994) and 2021 (Duko, Pereira et al. 2021; Shenassa, Rogers et al. 2021). These studies were conducted in nine countries: twelve studies were conducted in the US (Kandel, Wu et al. 1994; Cornelius, Leech et al. 2000; Buka, Shenassa et al. 2003; Cornelius, Leech et al. 2005; Agrawal, Scherrer et al. 2010; Cornelius, Goldschmidt et al. 2012; Weden and Miles, 2012; Shenassa, Papandonatos et al. 2015; Biederman, Martelon et al. 2017; De Genna, Goldschmidt et al. 2017; Ncube and Mueller, 2017; Shenassa, Rogers et al. 2021), two in the UK (Roberts, Munafò et al. 2005; Taylor, Howe et al. 2014), four in Australia (Al Mamun et al., 2006; O'Callaghan et al., 2006, 2009; Duko, Pereira et al. 2021), three in Sweden (Rydell,

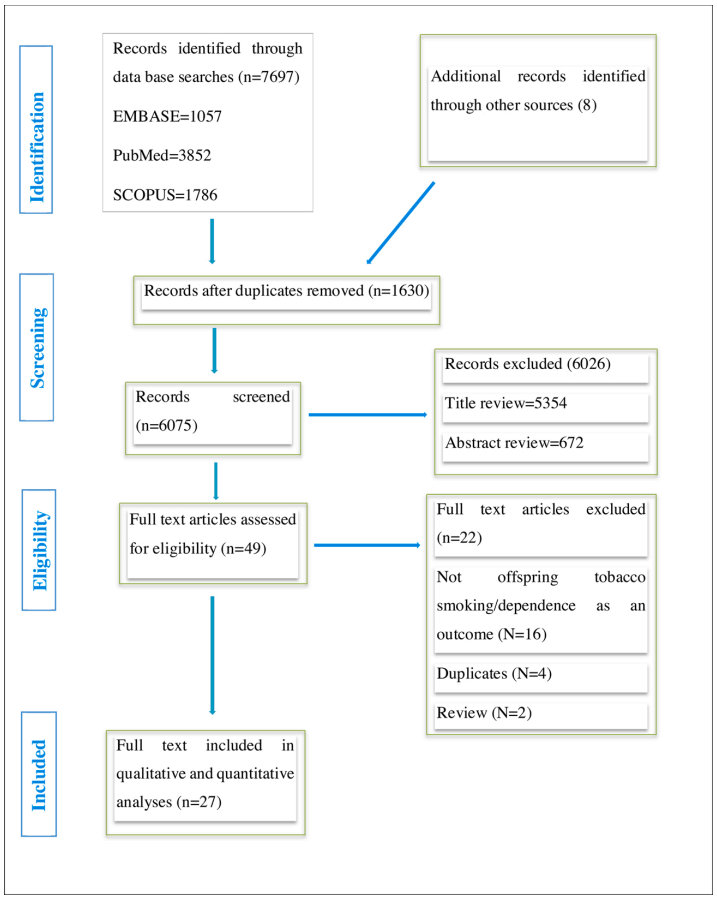


Fig. 1. PRISMA flowchart of review search.

Cnattingius et al. 2012; Rydell, Magnusson et al. 2014; Rydell, Granath et al. 2016), two in Brazil (Menezes, Gonçalves et al. 2006; Menezes, Hallal et al. 2007), one in Netherlands (Monshouwer, Huizink et al. 2011), one in Canada (Porath and Fried, 2005), one in Finland (Niemelä, Räisänen et al. 2017) and one in Germany (Lieb, Schreier et al. 2003). Twenty-six were cohort studies whereas one study was a case-control study. Out of these, eighteen studies investigated current tobacco smoking, eight investigated tobacco dependence, seven studies investigated lifetime (ever) tobacco smoking and four studies investigated tobacco smoking initiation/experimentation as outcomes in offspring. Five studies reported the association between paternal prenatal tobacco smoking and the risk of tobacco smoking in offspring (Menezes, Hallal et al. 2007; Rydell, Cnattingius et al. 2012; Taylor, Howe et al. 2014; Niemelä, Räisänen et al. 2017; Duko, Pereira et al. 2021) (Table 1). The sample size of the studies included in this systematic review and meta-analysis ranged from 152 to 64,112 study participants (Supplementary file 1).

3.3. Outcome measures

Of twenty-seven studies included in this systematic review, five studies used the third or the fourth revised version of the Diagnostic and Statistical Manual of Mental Disorders (DSM IV-TR), two studies used the Composite International Diagnostic Interview (CIDI), two studies used Fagerstrom Test for Nicotine Dependence (FTND), one study used Cigarette Dependence Scale (CDS-12), one study used Health Behaviour Questionnaire (HBQ), one study used the Drug History Questionnaire (DHQ) and sixteen studies used self-reported questionnaire to ascertain tobacco smoking/dependence as an outcome in offspring. The studies included in the review assessed tobacco smoking/dependence outcomes in offspring at different follow-up times (Table 1).

3.4. Quality assessment of included studies

Based on the revised Newcastle-Ottawa scale (NOS), nine studies scored 9, fourteen studies scored 8 and four studies scored 7. According to this scale rating, if a study or an article gets the NOS score of six or greater, it can be considered as a high-quality research output with low risk of bias (Supplementary file 2).

3.5. Prenatal tobacco smoking and risk of tobacco smoking and dependence

Maternal prenatal tobacco smoking was associated with the increased risk of current tobacco smoking in offspring with a pooled adjusted risk (RR) of 1.70, (95 % CI: 1.48–1.95)] (Fig. 2), risk of tobacco dependence [RR = 1.50, (95 % CI: 1.31–1.73)] (Fig. 3), lifetime (ever) tobacco smoking [RR = 1.21, (95 % CI: 1.05–1.38)] (Fig. 4), and tobacco smoking initiation (experimentation) [RR = 2.08, (95 % CI:1.18–3.68) (Fig. 5). We noted considerable heterogeneity between studies in associations with current tobacco smoking (I^2 = 75.24 %; Q = 68.66; P-value < 0.001), tobacco smoking initiation/experimentation (I^2 = 73.45 %; Q = 11.30; P-value = 0.01) and lifetime tobacco smoking (I^2 = 56.58 %; Q = 13.82; P-value = 0.03) and low heterogeneity between studies in association with tobacco dependence (I^2 = 29.44 %; Q = 9.92; P-value< 0.001), as offspring outcomes. However, we found insufficient statistical evidence for an association between paternal (partner) tobacco smoking during pregnancy and tobacco smoking in offspring [RR = 1.39, (95 % CI: 0.93–2.08)] (I^2 = 92.43 %; Q = 52.86; P-value< 0.001) (Fig. 6).

3.6. Confounding variables in multivariable models

Confounders may influence/change the association between prenatal tobacco exposure and offspring tobacco smoking/dependence behaviour. Studies included in this review fully or partially adjusted for different confounders. Maternal education, age and family income were commonly adjusted in most studies included in the review (Table 1). Eleven studies adjusted for maternal alcohol use during pregnancy. Nine studies controlled for paternal mental health problems whereas seven studies adjusted for existing child mental health and behavioural problems such as internalizing and externalizing behaviours. Further, maternal postnatal tobacco smoking was adjusted in fifteen studies (Supplementary file 3).

3.7. Publication bias

Epidemiological evidence suggests that any investigator should employ a suitable approach to evaluate publication bias such as Egger's regression or symmetry of funnel plots whenever there are at least 10 studies combined in a meta-analysis. These methods are not very reliable when combining less than 10 studies in a meta-analysis. Based on this, we have evaluated publication bias for studies that reported current tobacco smoking only (n = 18), as other outcomes were reported in less than 10 studies. Both visual inspection of the funnel plot (symmetric) and Egger's regression test indicated no evidence of potential publication bias (B=-0.30, SE = 0.58, P = 0.61, 2-tailed) (Fig. 7).

3.8. Subgroup and sensitivity analysis

Associations between maternal prenatal tobacco smoking and offspring current tobacco smoking or tobacco dependence did not substantially change by adjustment for mental health/behavioural problems in offspring, parental mental health problems, maternal alcohol or other drug use during pregnancy, socio-economic positions such as maternal age, educational level and family annual income, maternal postnatal tobacco smoking (Table 2).

Not surprisingly, effect estimates for current tobacco smoking in offspring were more elevated in studies that did not adjust for existing mental health or behavioural problems in offspring [RR = 1.82, (95 % CI: 1.26−2.61)] when compared to those that adjusted for these confounders [RR = 1.55, (95 % CI: 1.31−1.84)]. Similarly, the risk of tobacco dependence was slightly greater in the studies that did not control for the existing mental health or behavioural problems in offspring [RR = 1.61, (95 % CI: 1.35−1.91)] when compared to those adjusted for these risk factors [RR = 1.45, (95 % CI: 1.12−1.87)]. However, the risk of current tobacco smoking in offspring was not greater in the studies that did not adjust for any parental mental health problems that existed before the onset of offspring smoking behaviour [RR = 1.52, (95 % CI: 1.23−1.88)] compared to those adjusted [RR = 1.73, (95 % CI: 1.42−2.10)]. We also conducted a subgroup sensitivity analysis by limiting our analysis to the studies that included maternal alcohol and/or other drug use during pregnancy in the final model. The risk of developing current tobacco smoking behaviour in offspring were slightly higher in the studies that controlled for the effect of maternal alcohol and/or other drug use during pregnancy [RR = 1.83, (95 % CI: 1.51−2.23)] when compared to those studies that did not control for these risk factors [RR = 1.49, (95 % CI: 1.23−1.81)]. We also noted similar pattern in the studies that reported tobacco dependence as an outcome in offspring whereby the risk estimate substantially increased in the studies that adjusted for maternal alcohol and/or other drug use during pregnancy [RR = 1.92, (95 % CI: 1.29−2.86)].

The risk of current tobacco smoking and dependence in offspring did not substantially differ between those that did and did not adjust for maternal age, educational level and annual family income. For example, the risk of current tobacco smoking in offspring exposed to maternal tobacco smoking during pregnancy was RR = 1.52 (95 % CI: 1.25−1.85) and RR = 1.68 (95 % CI: 1.30−2.17) in the subgroup analysis of studies that adjusted and did not adjust for annual family income respectively. We further conducted a sensitivity analysis restricting the analysis to the studies that have adjusted for maternal postnatal tobacco smoking and we found that an increased risk of current tobacco smoking in offspring

Table 1
Summary of studies included in the current systematic review and meta-analysis.

First author, year	Country	Study design/ Characteristics	Outcome in offspring	Outcome ascertained by/Years	Sample size	Adjusted Risk Ratio (95 %CI)	Adjusted for
Kandel 1994	US	Retrospective cohort	Persistent tobacco smoking	Self-reported questionnaire/19 years	192	1.1(0.3−3.5) (boy) and 4.6 (1.2−17.2) (female)	Maternal age, education, prenatal alcohol exposure, maternal postnatal tobacco and other drug use.
Cornelius 2000	US	Retrospective cohort	Tobacco smoking experimentation	Self-reported questionnaire/10−14 years	589	5.50(1.96−14.40)	Prenatal alcohol and marijuana use, current tobacco and other substance use, demographic characteristics, SES and psychological status, child characteristics including measures of behaviour, IQ, achievement, temperament and alcohol use
Buka 2003	US	Retrospective cohort (National Collaborative Perinatal Project)	Tobacco dependence Current tobacco smoking Ever tobacco smoking	DSM-III criteria/29 years (mean age)	1248	1.6 (1.2–2.1) (PTE > 20 cigs/ day) 1.2 (0.9–1.6) (PTE > 20 cigs/ day) 0.8 (0.5–1.3) (PTE > 20 cigs/ day)	Maternal age at pregnancy, family socioeconomic status at time of pregnancy, maternal race/ethnicity, offspring gender, and offspring age at time of interview
Lieb 2003	Germany	Prospective cohort	Tobacco dependence Current tobacco smoking	DSM IV Self-reported questionnaire/14−24 year	938	2.71 (1.46–5.03) 2.08 (1.37–3.15)	Sex and age of children.
Porath 2005	Canada	Prospective cohort (Ottawa Prenatal Prospective Study Cohort)	Tobacco smoking initiation Daily tobacco use	Drug History Questionnaire/16−21 years	152	2.16 (1.06−4.39) 1.41(0.65−3.06)	Maternal alcohol use during pregnancy, maternal age at time of pregnancy, and family income and average parental education
Roberts 2005	UK	Retrospective Cohort (National Child Development Study and the 1970 British Birth Survey Cohorts)	Current tobacco smoking	Self-reported questionnaire/ 16 and 30/33 years	6714	0.97(0.85−1.12) at 16 years 1.05(0.90−1.24) at 30/33 years	Offspring sex, birth cohort, maternal age at offspring birth, paternal social class at offspring birth, maternal smoking at 16-year follow-up, and paternal smoking at 16-year follow-up
Cornelius 2005	US	Retrospective cohort	Ever tobacco use	Health Behaviour Questionnaire/14 years	567	1.02(1.00−1.03)	Sociodemographic factors, prenatal alcohol and marijuana exposures, maternal and child psychological characteristics, mother's tobacco, alcohol and marijuana use at the 14-year, peers tobacco smoking
Mamun 2006	Australia	Prospective cohort (MUSP)	Late onset and smoked regularly Early onset and smoked regularly	Self-reported questionnaire/ 21 years	2984	2.00 (1.57−2.53) 2.46 (1.78−3.40)	Age, sex, SES (family income, maternal education), depression, dyadic adjustment, alcohol consumption, number of children in the family at 5-years follow-up, breastfeeding, child internalizing, externalizing behaviours and social attention and thought problems
Menezes 2006	Brazil	Retrospective Cohort	Lifetime tobacco use	Self-reported questionnaire/10−12 years	4453	1.79(1.27−2.53)	Adolescents sex, living with/without the biological father, relationship with mother, being beaten by the parents, family conflict, maternal postnatal smoking, bad influences on the adolescent, participation in fights, history of attempting to run away from home and experience with alcoholic beverages.
O'Callaghan 2006	Australia	Prospective cohort (MUSP)	Current tobacco smoking	Self-reported questionnaire/14 years	4541	0.8(0.5−1.2) for 1st and 1.5 (0.97-3.5) for 3rd trimester PTE	Maternal education, marital status, gross family income, mother and partner ever arrested, No. of children in household, maternal depression, maternal and tobacco use, child internalizing behaviour, child aggression
Menezes 2007	Brazil	Retrospective cohort	Current tobacco use (male) Current tobacco use (female)	Self-reported questionnaire/15 years	2718	1.14(0.86−1.50) (PTE < 15 cigs/day) 1.25(0.81−1.91) (PTE > 15 cigs/day) 1.73(0.90−3.33) (PTE < 15 cigs/day) 2.53(0.99−6.48) (PTE > 15 cigs/day)	Maternal skin colour, marital status, family income, maternal and paternal education, maternal age, paternal alcohol related problems, postnatal maternal smoking and paternal tobacco smoking in child's infancy
O'Callaghan 2009	Australia	Prospective cohort (MUSP)	Tobacco dependence	Lifetime version of CIDI-Auto/ 21 years	2546	1.45 (1.12−1.87)	Age, maternal education, breastfeeding, parent-child communication, behavioural and internalizing problems
Agrawal 2010	US	Retrospective cohort (study offspring-of-twins)	Regular tobacco smoking		1342	1.74(1.18−2.58)	Birth weight, Preterm birth, Remediation, Conduct problems, ADHD, Low scholastic achievement, Maternal

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Study design/ Characteristics	Outcome in offspring	Outcome ascertained by/Years	Sample size	Adjusted Risk Ratio (95 %CI)	Adjusted for
Weden 2010	US	Population-based longitudinal study (Children and Young Adults of the National Longitudinal Survey of Youth 1979 cohort (NLSY79-CYA))	Early onset current smokers Late onset current smokers Early experimenters	Self-reported questionnaire/12–32 years Self-reported questionnaire/14–25 years	5809	2.75 (2.03–3.73) 1.66 (1.28–2.16) 2.12 (1.14–3.94)	drinking during pregnancy, Maternal Heavy Smoking, Maternal Current smoking, Maternal Drug Use, Maternal Alcohol Dependence; Maternal ADHD and Maternal CD problems, Paternal Lifetime Nicotine Dependence, Paternal Current Smoking (PCUR) and Paternal conduct disorder Age at baseline, age at first smoking assessment, gender, and race/ethnicity), maternal age at child's birth, and educational attainment and marital status when the child was aged 14 years, and breastfed, prenatal care, and a score of the mother's endorsement in 1980 of 12 adolescent delinquency behaviours from the NLSY79-modified Self-Reported Delinquency Interview
Monshouwer 2011	Netherlands	Population-based prospective cohort (TRIALS study)	Current tobacco smoking	Self-reported questionnaire/ 11.5 years (average age)	2230	1.46(0.95–2.25) (prenatal tobacco use of 1−10 cigarettes/ day) 1.56 (0.88–2.78) (prenatal tobacco use of 10+ cigarettes/ day)	Maternal alcohol use during pregnancy, age mother at childbirth and socioeconomic status, parental history of internalizing and externalizing problems and paternal smoking
Cornelius 2012	US	Retrospective cohort	Current tobacco smoking Tobacco dependence	Self-reported questionnaire/22 years Fagerstrom Test for Nicotine Dependence/ 22 years	608	1.70(1.10−2.63) for 1st TRIM 2.22(1.39−3.55) for 2nd TRIM 1.68(1.16−2.63) for 3rd TRIM (PTE > 10 cigs/day) 2.05(1.16−3.65) for 3rd TRIM (PTE > 10 cigs/day)	Gender, race, age at the time of the assessment, prenatal exposure to alcohol and marijuana, and maternal variables including education, SES, depression and hostility.
Rydell 2012	Sweden	Prospective cohort (BROMS (Children's Smoking and Environment in Stockholm County) cohort)	Lifetime experience of symptoms of nicotine dependence Tobacco consumption	Self-reported questionnaire/17 years	897 902	1.45(1.05−2.01) 1.61(1.23−2.12)	Parental postnatal tobacco use during the index child's age of 11–14 years (any v. none) and for parents with college education (none, one or both)
Rydell 2013	Sweden	Retrospective cohort (Population-based medical birth registries)	Daily tobacco use Lifetime tobacco use	Self-reported questionnaire/ 18−27 years	983	1.22 (0.80−1.86) 1.16 (0.79−1.70)	Parents psychiatric morbidity, parents' postnatal tobacco use, socioeconomic characteristics and characteristics of upbringing
Taylor 2014	UK	Prospective cohort (ALSPAC)	late-onset-regular smoker late-onset-regular smoker Tobacco initiation	Self-reported questionnaire/14−16 years	6484	1.49(1.17−1.90) 2.27(1.64−3.15) 1.23 (0.97, 1.57)	Sex, maternal age, parity, maternal educational attainment, crowding and housing tenure, partner smoking
Niemela 2015	Finland	Prospective cohort (Northern Finland Birth Cohort 1986 (NFBC86)	Daily tobacco smoking	Self-reported questionnaire/15−16 years	4462	1.8(1.3−2.5)	Gender, family structure, parental educational level, dwelling, family structure, paternal smoking during pregnancy, maternal and paternal smoking at offspring age 15−16 years
Shenassa 2015	US	The Providence and Boston sites of the Collaborative Perinatal Project (1959–1966)	Tobacco dependence Ever tobacco smoking	CIDI/40 years Self-reported questionnaire	1783	1.25 (1.07−1.46) 1.07 (0.91−1.26)	Race/ethnicity, offspring sex and age, mother's age at pregnancy, gravida and family socioeconomic index.
Ncube 2016	US	Population-based cohort study	Prenatal tobacco smoking	Self-reported questionnaire	64,112	1.78 (1.72−1.84)	The year the daughter delivered, her marital status and educational attainment, and the mothers' race/ethnicity
Rydell 2016	Sweden	Prospective cohort (Swedish Sibling Health Cohort)	Tobacco dependence	Cigarette Dependence Scale (CDS-12)	193	1.55 (0.92−2.60)	Birth order, sibling order and birth year, previous quit attempts or time to relapses
Biederman 2017	US	Case control	Lifetime tobacco use	DSM-III criteria/18 years and above	496	1.16 (1.1−2.3)	Maternal age, race/ethnicity, Attention deficit hyperactivity disorder in offspring, parental antisocial personality, maladaptive parenting, mental health problem in offspring
De Genna 2018	US	Prospective cohort	Tobacco dependence	Fagerstrom Test for Nicotine Dependence/ 16 years	784	1.81(1.02–3.19) for 1st trimester exposure 1.81 (1.04–3.16) for 3rd (PTE > 10 cigs/day)	Race, prenatal exposure to alcohol and marijuana, maternal education, child age, maternal postnatal nicotine dependence and sex

(*continued on next page*)

Table 1 (*continued*)

First author, year	Country	Study design/ Characteristics	Outcome in offspring	Outcome ascertained by/Years	Sample size	Adjusted Risk Ratio (95 %CI)	Adjusted for
Duko 2021	Australia	Prospective cohort study (the Raine Study)	Current tobacco smoking	Self-reported questionnaire/ 17 years	1210	1.50(1.13–1.97) for 1st trimester	Maternal age at conception, marital status, race, family income, low birthweight, preterm birth, maternal and paternal education, sex of child, and maternal alcohol use during pregnancy, maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioural problems, postnatal maternal tobacco use at 13 years
Shenassa 2021	US	Prospective cohort study	Ever tobacco smoking	Life Interview of Smoking Trajectories Questionnaire	1692	1.15(0.91–1.44)	Gravida, age, gender, marital status, education, household income, and depression

Key: ALSPAC: Avon Longitudinal Study of Parents and Children.
CIDI: COMPOSITE INTERNATIONAL DIAGNOSTIC INTERVIEW.
DSM: Diagnostic and Statistical Manual of Mental Disorders.
MUSP: Mater-University of Queensland Study of Pregnancy.
TRIALS: Tracking Adolescents' Individual Lives Survey.

in the studies that did not include this risk factor in their final model [RR = 1.84, (95 % CI: 1.41−2.39)]. However, no substantial difference was detected in the studies that reported tobacco dependence as an outcome.

Further, to identify dose-related effects of prenatal tobacco smoking on offspring current tobacco smoking behaviour, we also conducted a sensitivity analysis restricting analysis to studies that reported a dose-effect relationship. Risk estimates were elevated for current tobacco smoking in offspring exposed to heavy prenatal tobacco smoking ($\geq$ 10 cigarettes/day during pregnancy) [RR = 1.68, (95 % CI: 1.26–2.23)] when compared to light or moderate prenatal tobacco smoking (1–9 cigarettes/day during pregnancy) [RR = 1.39, (95 % CI: 1.09–1.78)]. Moreover, the pooled estimated risk ratio for current tobacco smoking in offspring varied between 1.64 (95 % CI: 1.43–1.88) and 1.78 (95 % CI: 1.60–1.98) and for tobacco dependence in offspring varied between 1.42 (95 % CI: 1.26–1.56) and 1.59 (95 % CI: 1.39–1.84) in our leave-one-out sensitivity analysis, suggesting estimates were not substantially affected by individual studies (Supplementary file 4 and 5).

4. Discussion

This systematic review and meta-analysis examined the risk of tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence in offspring exposed to maternal tobacco smoking during pregnancy reported in twenty-six cohort studies and one case control study. We found evidence of associations with all relevant outcomes. Further, there were suggestions of dose-response associations as risk estimates were more elevated amongst offspring exposed to heavy maternal prenatal tobacco smoking when compared to offspring exposed to lessen amounts of tobacco in pregnancy. We found insufficient evidence for an association between paternal/partner tobacco smoking during pregnancy and tobacco smoking in offspring. Associations reported in this study did not substantially change by adjustment for mental health/behavioural problems in offspring, parental mental health problems, maternal alcohol or other drug use during pregnancy, maternal postnatal tobacco smoking and socio-economic positions such as maternal age, educational level, and family annual income. These findings indicate that cessation of tobacco use during prenatal period may have potential benefit to the mothers and their offspring.

While a precise mechanism explaining the reported associations between prenatal tobacco exposure and tobacco smoking/dependence in offspring is not well understood, a number of direct and indirect mechanisms have been suggested (Ernst, Moolchan et al. 2001). One proposed direct mechanism linking prenatal tobacco exposure and tobacco smoking/dependence in offspring is that the addictive and neurotoxic effects of the hazardous compounds found in tobacco smoke that can readily cross the placenta (Hyman, 2005). These chemicals, most importantly nicotine, in turn bind to nicotinic cholinergic receptors and result in irreversible deficits in cholinergic activity by pre-empting the natural roles of these receptors (Slotkin, 2008). These may facilitate the release of a number of neurotransmitters in the mesolimbic area, the corpus striatum, the frontal cortex and in the shell of the nucleus accumbens of the brain (Benowitz, 2009). The nucleus accumbens, a primary site mediating reward behaviour, found in the rostral and ventral forebrain, is believed to be directly involved in drug-induced reward (Salgado and Kaplitt, 2015). The aforementioned release of neurotransmitters, most importantly dopamine, in these parts of the brain signal a pleasurable experience (Nestler, 2005). Further, epidemiological evidence from a review of *in vivo* studies has suggested that prenatal exposure to tobacco was linked with morphological and neurochemical alternations of the parts of the brain regulating the reward system and reward-driven behaviours in offspring (Malanga and Kosofsky, 2003), supporting the elements of hypothesis that relate prenatal tobacco smoking with offspring subsequent brain vulnerability to nicotine addiction that endures into adulthood (Slotkin, 2008).

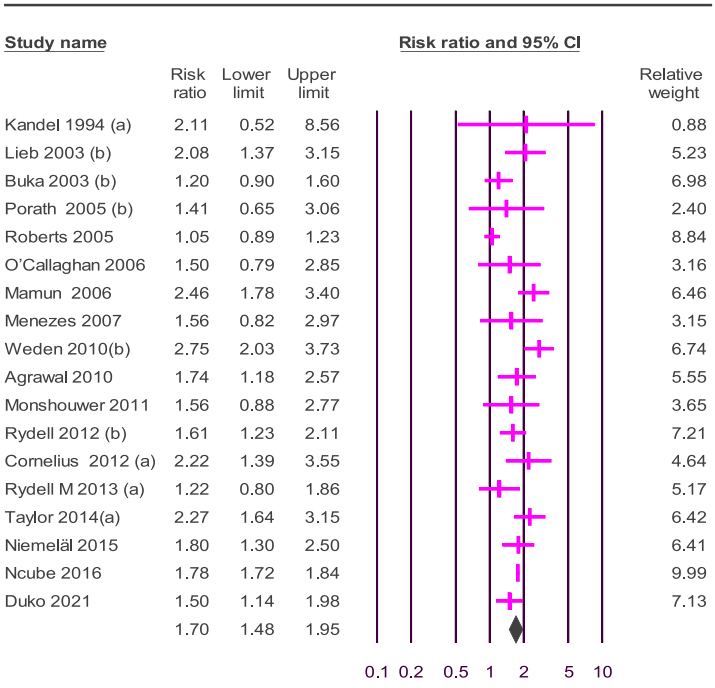


Fig. 2. The risk of current tobacco smoking in offspring exposed to maternal prenatal tobacco smoking.

Alternatively, a proposed indirect mechanism is that maternal tobacco smoking during pregnancy may restrict placental blood flow and placing the fetus at the increased risks for low birthweight, preterm birth and small for gestational age (Shah and Bracken, 2000; Ko, Tsai et al. 2014), which in turn may lead to mental health and behavioural problems in offspring via mediating the effects of prenatal tobacco smoking (Ernst, Moolchan et al. 2001; Herrmann, King et al. 2008). This pathway is corroborated by observation from a longitudinal study from the US (N = 1342) that suggested maternal prenatal tobacco smoking was linked with decreasing birthweight and also with the increased risk of Attention Deficit Hyperactivity Disorder (ADHD) and regular tobacco smoking in offspring (Agrawal, Scherrer et al. 2010). Furthermore, reports from additional epidemiological studies also revealed increased rates of mental health and behavioural problems among preterm (Johnson and Marlow, 2011; Nosarti, Reichenberg et al. 2012) and low birthweight children (Mathewson, Chow et al. 2017).

Epidemiological evidence also suggests that prenatal exposure to maternal tobacco smoking may be linked with epigenetic changes of DNA methylation in offspring (Gao, Jia et al. 2015; Joehanes, Just Allan et al. 2016; Richmond, Suderman et al. 2018; Rauschert, Melton et al. 2019; Wiklund, Karhunen et al. 2019). To support this explanation, a meta-analysis synthesized the results of 16 cohort studies that reported genome-wide DNA methylation in offspring exposed to prenatal tobacco smoking identified more than 6000 differentially methylated CpGs sites in the cord blood of newborns (Joehanes, Just Allan et al. 2016). Furthermore, emerging evidence suggesting that some of such changes in DNA methylation may persist from childhood to adulthood (Richmond, Simpkin et al. 2015; Richmond, Suderman et al. 2018; Wiklund, Karhunen et al. 2019). The corresponding changes in DNA methylation profiles of the genome are believed to be responsible for the alterations in hypothalamus–pituitary–adrenal axis (HPA-axis) (Bick, Naumova et al. 2012). Moreover, in a population-based longitudinal study from Sweden, cortisol concentration, a biomarker for the activation of HPA axis, was prospectively linked with tobacco smoking in adolescents (Raffetti, Landgren et al. 2021).

Further epidemiological evidence has suggested that offspring born to mothers smoking tobacco during pregnancy are more likely to be exposed to postnatal tobacco smoke in childhood if their mothers continued to smoke after the pregnancy (De Genna, Goldschmidt et al. 2016) and may initiate tobacco smoking later in life by emulating their parents' smoking behaviour. This is further strengthened by evidence from a systematic review and meta-analysis that synthesized the results of 56 studies linking environmental tobacco exposure to tobacco smoking uptake in childhood and adolescence (Leonardi-Bee, Jere et al. 2011). In that study, the odds of tobacco smoking increased two-fold in children and adolescents exposed to maternal postnatal tobacco smoking. In our subgroup meta-analysis, the risk of current tobacco smoking was 84 % and 44 % higher for offspring exposed to prenatal tobacco smoking compared to non-exposed before and after adjusting for postnatal maternal tobacco smoking respectively, suggesting that the 40 % additional increase in risk of tobacco smoking in offspring may be due to exposure to maternal postnatal tobacco smoking.

Offspring existing mental health and, behavioural problems and parental mental health difficulties may predispose individuals to smoke

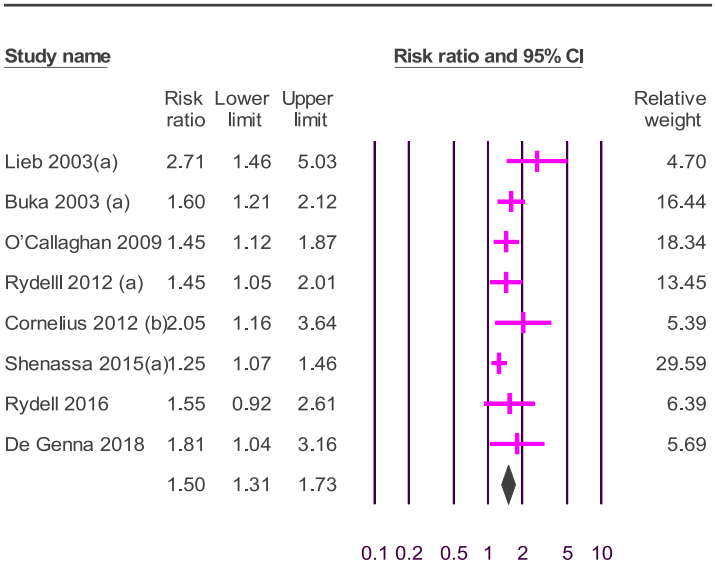


Fig. 3. The risk of tobacco dependence in offspring exposed to maternal prenatal tobacco smoking.

tobacco (Bilgi, Aksoy et al. 2017; Fluharty, Taylor et al. 2017; Kerr, Dalrymple et al. 2018; Duko, Ayano et al. 2020). For example, a school-based randomized controlled intervention trial (N = 477) of children at age 10 and 11 years reported a mediating role of Attention Deficit Hyperactivity Disorder (ADHD) symptoms on early-onset experimentation with smoking in late childhood (Huizink, van Lier et al. 2009). A large population-based longitudinal study using data from the US Children and Young Adults of the National Longitudinal Survey of Youth 1979 cohort (N = 5027) tested whether the association between maternal tobacco smoking before, during and after pregnancy and offspring tobacco smoking behaviour was mediated by child behavioural problems in middle childhood (Miles and Weden, 2012). In that study, although the odds of tobacco smoking in offspring exposed to prenatal tobacco smoking increased irrespective of whether mothers quit tobacco smoking after birth, child behavioural problems that occurred before the onset of offspring tobacco smoking appeared to partially mediate the association. Further, evidence from a systematic review that examined the results of 148 studies that investigated the associations of mental health problems between tobacco smoking reported that baseline depression/anxiety was linked with later tobacco smoking behaviour in more than half of the included studies (Fluharty, Taylor et al. 2017). Similarly, in our meta-analysis, the risk of tobacco smoking/dependence was slightly greater in the studies that did not adjust for the existing mental health or behavioural problems in offspring and any parental mental health problems.

Another possibility is that the association between prenatal tobacco smoking and subsequent tobacco smoking/dependence in offspring may be confounded by maternal and family socio-economic positions (Brion, Victora et al. 2010). Some of socio-demographic and economic factors that may affect the association between prenatal tobacco smoking and tobacco smoking/dependence in offspring such as maternal education, age and family income were commonly adjusted in the majority of studies included in the review. Epidemiological evidence has suggested that mothers who smoked tobacco during pregnancy were more likely to have lower educational attainment and family income compared to non-smoking pregnant mothers (Muhajarine, D'Arcy et al. 1997; Heaman and Chalmers, 2005; Nagahawatte and Goldenberg, 2008). These have been found to be linked with offspring tobacco smoking behaviour (Porath and Fried, 2005; Taylor, Howe et al. 2014). For example, in Ottawa Prenatal Prospective cohort Study, prenatal tobacco smoking and daily tobacco smoking in offspring were associated with maternal age, lower annual family income and lower educational attainment (Porath and Fried, 2005). Similarly, in our meta-analysis, the risk of current tobacco smoking and dependence in offspring slightly attenuated in the studies that included maternal age, educational level and annual family income in the final model, suggesting maternal socio-economic positions may have some role in the observed associations.

Moreover, comparison of paternal prenatal tobacco smoking on offspring smoking behaviour can be used to examine whether observed associations are due to confounding by heritable predisposition to addictive behaviours or likely to be casual. To explore this, we have conducted a sensitive analysis by restricting our analysis to those studies that reported estimates for paternal (partner) tobacco smoking in pregnancy (N = 5 studies) and observed insufficient statistical evidence for an association, suggesting some support for the possibility that the observations we have observed for maternal prenatal tobacco smoking may be causal.

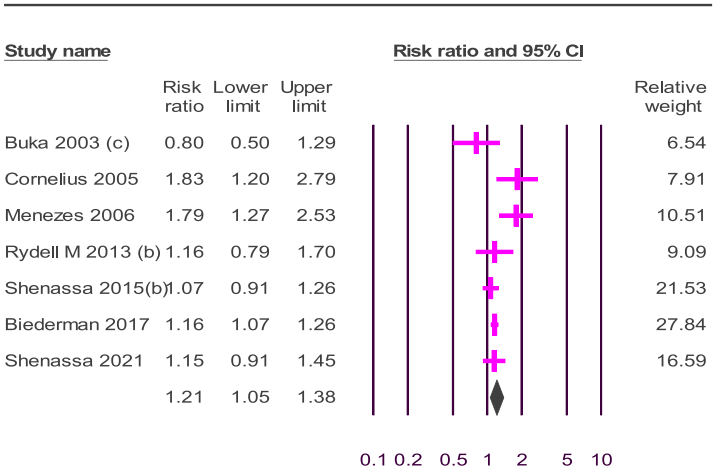


Fig. 4. The risk of lifetime (ever) tobacco smoking in offspring exposed to maternal prenatal tobacco smoking.

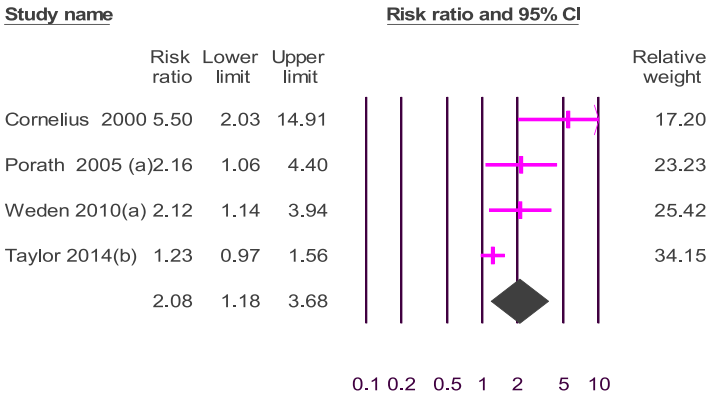


Fig. 5. The risk of tobacco smoking initiation/experimentation in offspring exposed to maternal prenatal tobacco smoking.

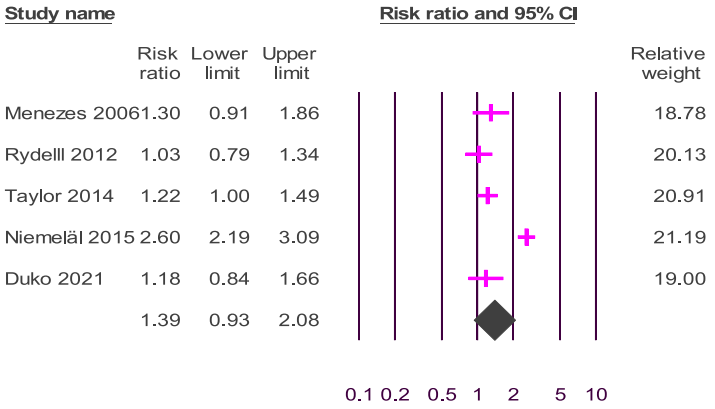


Fig. 6. The risk of tobacco smoking in offspring exposed to paternal tobacco smoking during pregnancy.

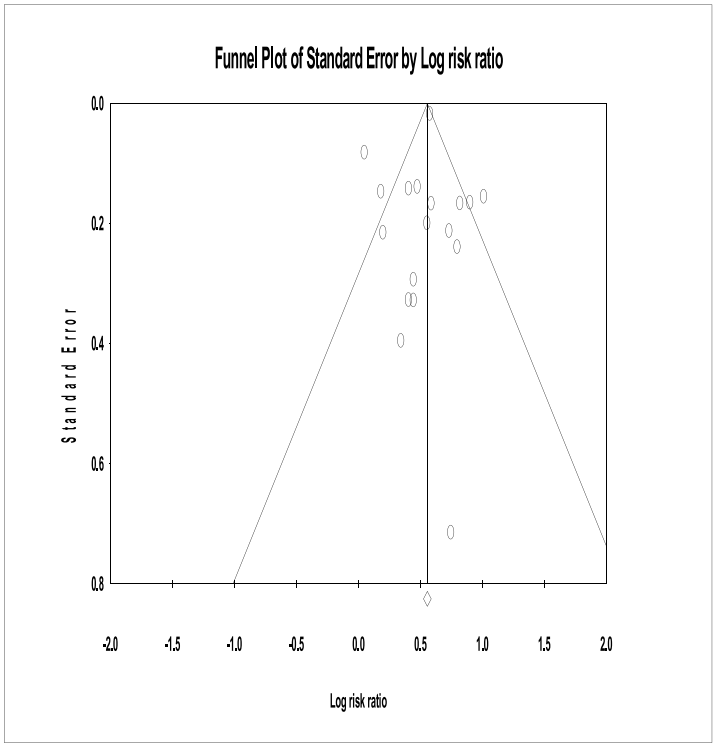


Fig. 7. Funnel plot showing no evidence of publication bias of studies that reported current tobacco smoking (n = 18).

Table 2
Subgroup and sensitivity analysis of studies included in the current meta-analysis (current tobacco smoking and tobacco dependence in offspring).

Covariate Control	Types of outcome in offspring	Covariate Adjustment	Number of studies that reported (n)	Pooled Risk Ratio (RR)	95 % Confidence Interval
Mental health/ Behavioural problems in offspring	Current tobacco smoking	Yes	5	1.55	1.31−1.84
		No	13	1.82	1.26−2.61
	Tobacco dependence	Yes	3	1.45	1.12−1.87
		No	5	1.61	1.35−1.91
Parental mental health problems	Current tobacco smoking	Yes	8	1.73	1.42−2.10
		No	10	1.52	1.23−1.88
Maternal alcohol and other drug use during pregnancy	Current tobacco smoking	Yes	8	1.83	1.51−2.23
		No	10	1.49	1.23−1.81
	Tobacco dependence	Yes	4	1.92	1.29−2.86
		No	4	1.50	1.28−1.76
Maternal age and educational level	Current tobacco smoking	Yes	11	1.67	1.39−2.01
		No	7	1.48	1.13−1.93
	Tobacco dependence	Yes	5	1.56	1.31−1.87
		No	3	1.54	1.20−1.97
Family income	Current tobacco smoking	Yes	9	1.52	1.25−1.85
		No	9	1.68	1.30−2.17
	Tobacco dependence	Yes	3	1.60	1.21−2.12
		No	5	1.54	1.29−1.82
Maternal postnatal tobacco smoking	Current tobacco smoking	Yes	7	1.44	1.22−1.70
		No	11	1.84	1.41−2.39
	Tobacco dependence	Yes	3	1.53	1.16−2.03
		No	5	1.56	1.32−1.85

The strengths of this study include: the inclusion of multiple adverse outcomes to further explore which offspring outcomes were specifically linked to maternal prenatal smoking; the assessment of outcomes in offspring were based on standard and well-accepted screening tools; comparison of maternal and paternal prenatal tobacco smoking and, the methodological quality of studies included in the review was checked by two independent reviewers using NOS. By doing so, we have reduced possible reviewer bias. We further conducted an additional sensitivity analysis to test dose-response associations. However, several caveats should be considered when interpreting and generalizing the findings of this study. As expected, when synthesizing data from observational studies with varying samples and methodologies, we observed considerable heterogeneity between studies in associations with all adverse outcomes. However, we employed subgroup and leave-one-out-sensitivity analysis to further explore source of heterogeneity and identify highly influential studies on the pooled estimate, respectively. Moreover, results were robust to both subgroup and leave-one-out sensitivity analyses. Further, some important studies may have been excluded if the studies did not report the required estimates (e.g. OR/ RR, or data to calculate these) for this meta-analysis. We also noted that the level of adjustment for confounders was inconsistent in the studies included in the review. Nevertheless, we found associations in the studies that comprehensively adjusted for confounders as well as for studies that did not fully adjust. Whilst we observed associations between prenatal tobacco smoking and subsequent tobacco smoking/ dependence in offspring, the possibilities of unmeasured or residual confounding need to be considered. Although self-report of tobacco smoking status has been found to be a valid assessment measure(Patrick, Cheadle et al. 1994), prenatal tobacco smoking is likely to be under-reported by pregnant mothers (Shipton, Tappin et al. 2009). This in turn would serve to attenuate any associations with offspring tobacco smoking/dependence. Further, whether associations observed in this study are casual remains unclear as the analysis of this review was merely on observational studies that may be subject to reverse causality and would likely result in less precise estimates of associations. We did not analyse gender and age specific effect estimates due to a lack of sufficient and consistent data from the included studies. Lastly, of 27 studies included in the review, only seven studies reported the dose-response associations for current tobacco smoking, and this might have reduced the precision of the estimate.

5. Conclusion

Our findings demonstrated that offspring born to mothers smoking tobacco during pregnancy are at increased risk for tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence independently of maternal postnatal tobacco smoking, paternal tobacco smoking during pregnancy and sociodemographic confounders. Therefore, tobacco smoking cessation during prenatal period is imperative and may potentially reduce such outcomes in offspring. Further genetically sensitive designs may be warranted to gain more insight into the true effect of associations reported by this study.

Role of funding source

No external funding obtained for this systematic review and meta-analysis.

Contributors

BD conceived the hypothesis, developed the methodology, identified all potential studies, extracted the data, assessed quality, conducted a meta-analysis, and wrote the first draft of the manuscript. SND reviewed abstracts and assessed the methodological quality of the included studies. GP, RT, KB and RA reviewed the protocol, reviewed data extraction, data analysis and contributed to subsequent drafts of the manuscript. All authors read and approved the final manuscript.

Declaration of Competing Interest

All authors have no conflicts of interest to disclose.

Acknowledgments

We are so grateful to the Curtin University for providing us a wide range of available online databases. Bereket Duko is a recipient of Curtin University International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. Gavin Pereira was funded by NHMRC grants# 1099655 and 1173991, and the Research Council of Norway through Centre of Excellence, grant #262700. The funders had no role in the data extraction, study design, the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2021.108993.

References

Agrawal, A., Scherrer, J.F., Grant, J.D., Sartor, C.E., Pergadia, M.L., Duncan, A.E., Madden, P.A.F., Haber, J.R., Jacob, T., Bucholz, K.K., Xian, H., 2010. The effects of maternal smoking during pregnancy on offspring outcomes. Prev. Med. 50 (1–2), 13–18.

Al Mamun, A., O'Callaghan, F.V., Alati, R., O'Callaghan, M., Najman, J.M., Williams, G. M., Bor, W., 2006. Does maternal smoking during pregnancy predict the smoking patterns of young adult offspring? A birth cohort study. Tob. Control 15 (6), 452–457.

Alcalá, H.E., von Ehrenstein, O.S., Tomiyama, A.J., 2016. Adverse childhood experiences and use of cigarettes and smokeless tobacco products. J. Community Health 41 (5), 969–976.

Benowitz, N.L., 2009. Pharmacology of nicotine: addiction, smoking-induced disease, and therapeutics. Annu. Rev. Pharmacol. Toxicol. 49, 57–71.

Bick, J., Naumova, O., Hunter, S., Barbot, B., Lee, M., Luthar, S.S., Raefski, A., Grigorenko, E.L., 2012. Childhood adversity and DNA methylation of genes involved in the hypothalamus-pituitary-adrenal axis and immune system: whole-genome and candidate-gene associations. Dev. Psychopathol. 24 (4), 1417–1425.

Biederman, J., Martelon, M., Woodworth, K.Y., Spencer, T.J., Faraone, S.V., 2017. Is maternal smoking during pregnancy a risk factor for cigarette smoking in offspring? A longitudinal controlled study of adhd children grown up. J. Atten. Disord. 21 (12), 975–985.

Bilgi, B., Aksoy, U.M., Şahmelikoğlu Onur, Ö., Maner, A.F., 2017. Attention-Deficit/Hyperactivity disorder and nicotine dependence in adults. Noro Psikiyatr. Ars. 54 (4), 322–327.

Borenstein, M., Hedges, L., Higgins, J., Rothstein, H., 2005. Comprehensive Meta-Analysis Version 2. Biostat, Englewood, NJ, pp. 104.

Borenstein, M., Hedges, L.V., Higgins, J.P., Rothstein, H.R., 2010. A basic introduction to fixed-effect and random-effects models for meta-analysis. Res. Synth. Methods 1 (2), 97–111.

Brion, M.J., Victora, C., Matijasevich, A., Horta, B., Anselmi, L., Steer, C., Menezes, A.M., Lawlor, D.A., Davey Smith, G., 2010. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics 126 (1), e57–65.

Buka, S.L., Shenassa, E.D., Niaura, R., 2003. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. Am. J. Psychiatry 160 (11), 1978–1984.

Cornelius, M.D., Leech, S.L., Goldschmidt, L., Day, N.L., 2000. Prenatal tobacco exposure: is it a risk factor for early tobacco experimentation? Nicotine Tob. Res. 2 (1), 45–52.

Cornelius, M.D., Leech, S.L., Goldschmidt, L., Day, N.L., 2005. Is prenatal tobacco exposure a risk factor for early adolescent smoking? A follow-up study. Neurotoxicol. Teratol. 27 (4), 667–676.

Cornelius, M.D., Goldschmidt, L., Day, N.L., 2012. Prenatal cigarette smoking: long-term effects on young adult behavior problems and smoking behavior. Neurotoxicol. Teratol. 34 (6), 554–559.

De Genna, N.M., Goldschmidt, L., Day, N.L., Cornelius, M.D., 2016. Prenatal and postnatal maternal trajectories of cigarette use predict adolescent cigarette use. Nicotine Tob. Res. 18 (5), 988–992.

De Genna, N.M., Goldschmidt, L., Day, N.L., Cornelius, M.D., 2017. Prenatal tobacco exposure, maternal postnatal nicotine dependence and adolescent risk for nicotine dependence: birth cohort study. Neurotoxicol. Teratol. 61, 128–132.

de Vries, H., Engels, R., Kremers, S., Wetzels, J., Mudde, A., 2003. Parents' and friends' smoking status as predictors of smoking onset: findings from six European countries. Health Educ. Res. 18 (5), 627–636.

Duko, B., Ayano, G., Pereira, G., Betts, K., Alati, R., 2020. Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis. Soc. Psychiatry Psychiatr. Epidemiol. 55 (12), 1549–1562.

Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2021. Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence. Addict. Behav. 117, 106871.

Egger, M., Davey Smith, G., Schneider, M., Minder, C., 1997. Bias in meta-analysis detected by a simple, graphical test. Bmj 315 (7109), 629–634.

Ernst, M., Moolchan, E.T., Robinson, M.L., 2001. Behavioral and neural consequences of prenatal exposure to nicotine. J. Am. Acad. Child Adolesc. Psychiatry 40 (6), 630–641.

Fernando, H.N., Wimaladasa, I.T.P., Sathkoralage, A.N., Ariyadasa, A.N., Udeni, C., Galgamuwa, L.S., Herath, P., Kumarasinghe, N., 2019. Socioeconomic factors associated with tobacco smoking among adult males in Sri Lanka. BMC Public Health 19 (1), 778.

Fluharty, M., Taylor, A.E., Grabski, M., Munafò, M.R., 2017. The association of cigarette smoking with depression and anxiety: a systematic review. Nicotine Tob. Res. 19 (1), 3–13.

Gao, X., Jia, M., Zhang, Y., Breitling, L.P., Brenner, H., 2015. DNA methylation changes of whole blood cells in response to active smoking exposure in adults: a systematic review of DNA methylation studies. Clin. Epigenetics 7 (1), 113.

GBD, 2016. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 388 (10053), 1659–1724.

Heaman, M.I., Chalmers, K., 2005. Prevalence and correlates of smoking during pregnancy: a comparison of aboriginal and non-aboriginal women in manitoba. Birth 32 (4), 299–305.

Herrmann, M., King, K., Weitzman, M., 2008. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. Curr. Opin. Pediatr. 20 (2), 184–190.

Higgins, J.P., Thompson, S.G., Deeks, J.J., Altman, D.G., 2003. Measuring inconsistency in meta-analyses. Bmj 327 (7414), 557–560.

Huizink, A.C., van Lier, P.A., Crijnen, A.A., 2009. Attention deficit hyperactivity disorder symptoms mediate early-onset smoking. Eur. Addict. Res. 15 (1), 1–9.

Hyman, S.E., 2005. Addiction: a disease of learning and memory. Am. J. Psychiatry 162 (8), 1414–1422.

Joehanes, R., Just Allan, C., Marioni Riccardo, E., Pilling Luke, C., Reynolds Lindsay, M., Mandaviya Pooja, R., Guan, W., Xu, T., Elks Cathy, E., Aslibekyan, S., Moreno-Macias, H., Smith Jennifer, A., Brody Jennifer, A., Dhingra, R., Yousefi, P., Pankow James, S., Kunze, S., Shah Sonia, H., McRae Allan, F., Lohman, K., Sha, J., Absher Devin, M., Ferrucci, L., Zhao, W., Demerath Ellen, W., Bressler, J., Grove Megan, L., Huan, T., Liu, C., Mendelson Michael, M., Yao, C., Kiel Douglas, P., Peters, A., Wang-Sattler, R., Visscher Peter, M., Wray Naomi, R., Starr John, M., Ding, J., Rodriguez Carlos, J., Wareham Nicholas, J., Irvin Marguerite, R., Zhi, D., Barrdahl, M., Vineis, P., Ambatipudi, S., Uitterlinden André, G., Hofman, A., Schwartz, J., Colicino, E., Hou, L., Vokonas Pantel, S., Hernandez Dena, G., Singleton Andrew, B., Bandinelli, S., Turner Stephen, T., Ware Erin, B., Smith Alicia, K., Klengel, T., Binder Elisabeth, B., Psaty Bruce, M., Taylor Kent, D., Gharib Sina, A., Swenson Brenton, R., Liang, L., DeMeo Dawn, L., O'Connor George, T., Herceg, Z., Ressler Kerry, J., Conneely Karen, N., Sotoodehnia, N., Kardia Sharon, L.R., Melzer, D., Baccarelli Andrea, A., van Meurs Joyce, B.J., Romieu, I., Arnett Donna, K., Ong Ken, K., Liu, Y., Waldenberger, M., Deary Ian, J., Fornage, M., Levy, D., London Stephanie, J., 2016. Epigenetic signatures of cigarette smoking. Circ. Cardiovasc. Genet. 9 (5), 436–447.

Johnson, S., Marlow, N., 2011. Preterm birth and childhood psychiatric disorders. Pediatr. Res. 69 (8), 11–18.

Kandel, D.B., Wu, P., Davies, M., 1994. Maternal smoking during pregnancy and smoking by adolescent daughters. Am. J. Public Health 84 (9), 1407–1413.

Kerr, S., Dalrymple, K., Chelminski, I., Zimmerman, M., 2018. Depression and substance use disorders in the offspring of depressed parents as a function of the parent's borderline personality disorder symptomatology. Ann. Clin. Psychiatry 30 (2), 207–214.

Kim, Y.S., Ko, H., Yoon, C., Lee, D.-H., Sung, J., 2012. Social determinants of smoking behavior: the Healthy Twin Study, Korea. J. Prev. Med. Public Health 45 (1), 29–36.

Kim, D.R., Bale, T.L., Epperson, C.N., 2015. Prenatal programming of mental illness: current understanding of relationship and mechanisms. Curr. Psychiatry Rep. 17 (2), 5.

Ko, T.-J., Tsai, L.-Y., Chu, L.-C., Yeh, S.-J., Leung, C., Chen, C.-Y., Chou, H.-C., Tsao, P.-N., Chen, P.-C., Hsieh, W.-S., 2014. Parental smoking during pregnancy and its association with low birth weight, small for gestational age, and preterm birth offspring: a birth cohort study. Pediatr. Neonatol. 55 (1), 20–27.

Lange, S., Probst, C., Rehm, J., Popova, S., 2018. National, regional, and global prevalence of smoking during pregnancy in the general population: a systematic review and meta-analysis. Lancet Glob. Health 6 (7), e769–e776.

Leonardi-Bee, J., Jere, M.L., Britton, J., 2011. Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: a systematic review and meta-analysis. Thorax 66 (10), 847.

Lieb, R., Schreier, A., Pfister, H., Wittchen, H.U., 2003. Maternal smoking and smoking in adolescents: a prospective community study of adolescents and their mothers. Eur. Addict. Res. 9 (3), 120–130.

Malanga, C.J., Kosofsky, B.E., 2003. Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. Dev. Brain Res. 147 (1), 47–57.

Mathewson, K.J., Chow, C.H., Dobson, K.G., Pope, E.I., Schmidt, L.A., Van Lieshout, R.J., 2017. Mental health of extremely low birth weight survivors: a systematic review and meta-analysis. Psychol. Bull. 143 (4), 347–383.

Menezes, A.M., Gonçalves, H., Anselmi, L., Hallal, P.C., Araújo, C.L., 2006. Smoking in early adolescence: evidence from the 1993 Pelotas (Brazil) Birth Cohort Study. J. Adolesc. Health 39 (5), 669–677.

Menezes, A.M., Hallal, P.C., Horta, B.L., 2007. Early determinants of smoking in adolescence: a prospective birth cohort study. Cad. Saude Publica 23 (2), 347–354.

Miles, J.N.V., Weden, M.M., 2012. Is the intergenerational transmission of smoking from mother to child mediated by children's behavior problems? Nicotine & Tob. Res.: Off. J. Soc. Res. Nicotine and Tob. 14 (9), 1012–1018.

Moher, D., Shamseer, L., Clarke, M., Ghersi, D., Liberati, A., Petticrew, M., Shekelle, P., Stewart, L.A., 2015. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. Syst. Rev. 4, 1.

Monshouwer, K., Huizink, A.C., Harakeh, Z., Raaijmakers, Q.A., Reijneveld, S.A., Oldehinkel, A.J., Verhulst, F.C., Vollebergh, W.A., 2011. Prenatal smoking exposure and the risk of behavioral problems and substance use in adolescence: the TRAILS study. Eur. Addict. Res. 17 (6), 342–350.

Muhajarine, N., D'Arcy, C., Edouard, L., 1997. Prevalence and predictors of health risk behaviours during early pregnancy: saskatoon pregnancy and health study. Can. J. Public Health 88 (6), 375–379.

Nagahawatte, N.T., Goldenberg, R.L., 2008. Poverty, maternal health, and adverse pregnancy outcomes. Ann. N. Y. Acad. Sci. 1136, 80–85.

Ncube, C.N., Mueller, B.A., 2017. Daughters of mothers who smoke: a population-based cohort study of maternal prenatal tobacco use and subsequent prenatal smoking in offspring. Paediatr. Perinat. Epidemiol. 31 (1), 14–20.

Nestler, E.J., 2005. Is there a common molecular pathway for addiction? Nat. Neurosci. 8 (11), 1445–1449.
Niemelä, S., Räisänen, A., Koskela, J., Taanila, A., Miettunen, J., Ramsay, H., Veijola, J., 2017. The effect of prenatal smoking exposure on daily smoking among teenage offspring. Addiction 112 (1), 134–143.
Nosarti, C., Reichenberg, A., Murray, R.M., Cnattingius, S., Lambe, M.P., Yin, L., MacCabe, J., Rifkin, L., Hultman, C.M., 2012. Preterm birth and psychiatric disorders in young adult life. Arch. Gen. Psychiatry 69 (6), E1–8.
O'Callaghan, F.V., O'Callaghan, M., Najman, J.M., Williams, G.M., Bor, W., Alati, R., 2006. Prediction of adolescent smoking from family and social risk factors at 5 years, and maternal smoking in pregnancy and at 5 and 14 years. Addiction 101 (2), 282–290.
O'Callaghan, F.V., Al Mamun, A., O'Callaghan, M., Alati, R., Najman, J.M., Williams, G. M., Bor, W., 2009. Maternal smoking during pregnancy predicts nicotine disorder (dependence or withdrawal) in young adults - a birth cohort study. Aust. N. Z. J. Public Health 33 (4), 371–377.
Organazation, W.H., 2020. Tobacco.
Patrick, D.L., Cheadle, A., Thompson, D.C., Diehr, P., Koepsell, T., Kinne, S., 1994. The validity of self-reported smoking: a review and meta-analysis. Am. J. Public Health 84 (7), 1086–1093.
Patsopoulos, N.A., Evangelou, E., Ioannidis, J.P., 2008. Sensitivity of between-study heterogeneity in meta-analysis: proposed metrics and empirical evaluation. Int. J. Epidemiol. 37 (5), 1148–1157.
Porath, A.J., Fried, P.A., 2005. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicol. Teratol. 27 (2), 267–277.
Pust, S., Mohnen, S.M., Schneider, S., 2008. Individual and social environment influences on smoking in children and adolescents. Public Health 122 (12), 1324–1330.
Raffetti, E., Landgren, A.J., Andersson, F., Donato, F., Lavebratt, C., Forsell, Y., Galanti, M.R., 2021. Cortisol Concentration as Predictor of Tobacco Initiation in Adolescents: Results From a Population-Based Swedish Cohort. J. Adolesc. Health 68 (4), 758–764.
Rauschert, S., Melton, P.E., Burdge, G., Craig, J.M., Godfrey, K.M., Holbrook, J.D., Lillycrop, K., Mori, T.A., Beilin, L.J., Oddy, W.H., Pennell, C., Huang, R.-C., 2019. Maternal smoking during pregnancy induces persistent epigenetic changes into adolescence, independent of postnatal smoke exposure and is associated with cardiometabolic risk. Front. Genet. 10 (770).
Richmond, R.C., Simpkin, A.J., Woodward, G., Gaunt, T.R., Lyttleton, O., McArdle, W.L., Ring, S.M., Smith, A.D.A.C., Timpson, N.J., Tilling, K., Davey Smith, G., Relton, C.L., 2015. Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). Hum. Mol. Genet. 24 (8), 2201–2217.
Richmond, R.C., Suderman, M., Langdon, R., Relton, C.L., Davey Smith, G., 2018. DNA methylation as a marker for prenatal smoke exposure in adults. Int. J. Epidemiol. 47 (4), 1120–1130.
Roberts, K.H., Munafò, M.R., Rodriguez, D., Drury, M., Murphy, M.F., Neale, R.E., Nettle, D., 2005. Longitudinal analysis of the effect of prenatal nicotine exposure on subsequent smoking behavior of offspring. Nicotine Tob. Res. 7 (5), 801–808.
Rydell, M., Cnattingius, S., Granath, F., Magnusson, C., Galanti, M.R., 2012. Prenatal exposure to tobacco and future nicotine dependence: population-based cohort study. Br. J. Psychiatry 200 (3), 202–209.
Rydell, M., Magnusson, C., Cnattingius, S., Granath, F., Svensson, A.C., Galanti, M.R., 2014. Exposure to maternal smoking during pregnancy as a risk factor for tobacco use in adult offspring. Am. J. Epidemiol. 179 (12), 1409–1417.
Rydell, M., Granath, F., Cnattingius, S., Svensson, A.C., Magnusson, C., Galanti, M.R., 2016. Maternal smoking during pregnancy and offspring's tobacco dependence. A study of exposure-discordant sibling pairs. Drug Alcohol Depend. 167, 23–28.
Salgado, S., Kaplitt, M.G., 2015. The nucleus accumbens: a comprehensive review. Stereotact. Funct. Neurosurg. 93 (2), 75–93.
Shah, N.R., Bracken, M.B., 2000. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am. J. Obstet. Gynecol. 182 (2), 465–472.
Shenassa, E.D., Papandonatos, G.D., Rogers, M.L., Buka, S.L., 2015. Elevated risk of nicotine dependence among sib-pairs discordant for maternal smoking during pregnancy: evidence from a 40-year longitudinal study. Epidemiology 26 (3), 441–447.
Shenassa, E.D., Rogers, M.L., Buka, S.L., 2021. Maternal smoking during pregnancy, offspring smoking, adverse childhood events, and risk of major depression: a sibling design study. Psychol. Med. 1–11.
Shipton, D., Tappin, D.M., Vadiveloo, T., Crossley, J.A., Aitken, D.A., Chalmers, J., 2009. Reliability of self reported smoking status by pregnant women for estimating smoking prevalence: a retrospective, cross sectional study. BMJ 339, b4347.
Slotkin, T.A., 2008. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicol. Teratol. 30 (1), 1–19.
Taylor, A.E., Howe, L.D., Heron, J.E., Ware, J.J., Hickman, M., Munafò, M.R., 2014. Maternal smoking during pregnancy and offspring smoking initiation: assessing the role of intrauterine exposure. Addiction 109 (6), 1013–1021.
Weden, M.M., Miles, J.N., 2012. Intergenerational relationships between the smoking patterns of a population-representative sample of US mothers and the smoking trajectories of their children. Am. J. Public Health 102 (4), 723–731.
Wells, G.A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M., T. P, 2017. The Newcastle-ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-analyses. The Ottawa Hospital Research Institute. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
WHO, 2011. WHO Report on the Global Tobacco Epidemic.
WHO, 2019. WHO Global Report on Trends in Prevalence of Tobacco Use 2000-2025, Third Edition.
Wiklund, P., Karhunen, V., Richmond, R.C., Parmar, P., Rodriguez, A., De Silva, M., Wielscher, M., Rezwan, F.I., Richardson, T.G., Veijola, J., Herzig, K.-H., Holloway, J. W., Relton, C.L., Sebert, S., Järvelin, M.-R., 2019. DNA methylation links prenatal smoking exposure to later life health outcomes in offspring. Clin. Epigenetics 11 (1), 97.

7.2 Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence.

Published manuscript and formal citation

Duko B, Pereira G, Betts K, Tait RJ, Newnham J, Alati R. Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence. Addictive Behaviours. 2021; 117:106871.

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.addbeh.2021.10687.

Study purpose: Evidence suggests that offspring born to mothers using tobacco during pregnancy may have increased risk of tobacco use when compared to mothers who did not. However, it is uncertain whether the association is due to the intrauterine or shared environmental exposures. In this case, comparing the association between maternal and paternal prenatal tobacco exposure with offspring tobacco smoking may give us some evidence to clarify the etiological basis for adolescent tobacco smoking. Maternal and paternal prenatal tobacco exposures are more likely affected by similar socio-economic confounders, suggesting that if prenatal factors are involved in the causal pathway to adolescent smoking, then the association will be more strongly seen with maternal prenatal tobacco use and not with paternal use at the time of the pregnancy. Therefore, the aim of this study was to examine the association between maternal prenatal tobacco exposure and tobacco smoking in offspring using paternal prenatal tobacco exposure as a negative control for intrauterine exposure comparison.

Addictive Behaviors 117 (2021) 106871

Contents lists available at ScienceDirect

Addictive Behaviors

journal homepage: www.elsevier.com/locate/addictbeh

Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence

Bereket Duko [a,*], Gavin Pereira [a,b,c], Kim Betts [a], Robert J. Tait [d], John Newnham [e], Rosa Alati [a,f]

[a] School of Population Health, Curtin University, Kent Street, Bentley, WA 6102, Australia
[b] Telethon Kids Institute, Northern Entrance, Perth Children's Hospital, 15 Hospital Ave, Nedlands, WA 6009, Australia
[c] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[d] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA 6102, Australia
[e] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands WA 6009, Australia
[f] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland 4068, Australia

ARTICLE INFO

Keywords:
Tobacco
Pregnancy
Adolescents
Offspring
Smoking
The Raine Study

ABSTRACT

Background: Mounting epidemiological evidence suggests an association between prenatal tobacco exposure and an increased risk of tobacco smoking in offspring. However, it is uncertain whether the association is due to the intrauterine or shared environmental exposures.
Methods: Study participants were from the Raine Study, a prospective birth cohort study based in Perth, Western Australia (N = 2730). Tobacco smoking in adolescents, at age 17 years, was measured using a self-reported questionnaire. Log-binomial regression was used to estimate the relative risks (RRs) of tobacco smoking in offspring exposed to maternal prenatal tobacco use during the first and third trimesters of pregnancy. We have also calculated the E-values to investigate the potential effect of unmeasured confounding. Paternal smoking during pregnancy was used as a negative control for comparison.
Results: A total of 1210 mothers-offspring pairs were included in the final analysis. After controlling for potential confounders, we found increased risks of tobacco smoking in offspring exposed to maternal prenatal tobacco use during the first trimester [RR 1.50 (95% CI: 1.13–1.97)] (E-value for point estimate = 2.37) and during both trimesters of pregnancy [RR 1.41 (95% CI: 1.03–1.89)] (E-value for point estimate = 2.17). However, we found insufficient statistical evidence for an association between paternal smoking during pregnancy and risk of tobacco smoking in offspring [RR 1.18 (95% CI: 0.84–1.67)].
Conclusion: Maternal prenatal tobacco exposure was associated with an increased risk of tobacco smoking in offspring at the age of 17 years. Tobacco smoking cessation at the early stages of gestation may reduce the risk of tobacco smoking in the next generation.

1. Introduction

Tobacco smoking is a public health challenge that is often initiated before the age of 18 years. Reports from the Australian Institute of Health and Welfare (AIHW) in 2015 showed that tobacco smoking contributed 13.3% to deaths and illnesses in Australia (AIHW, 2019), suggesting more than one in every seven deaths is due to tobacco use. Further, estimates from the Australian Secondary Students' Alcohol and Drug (ASSAD) survey of 2017 (Guerin & White, 2018) indicated that from 33% of adolescents who reported current tobacco smoking approximately 22% smoked tobacco daily. Thus, efforts aimed at identifying potential risk factors of adolescent tobacco smoking have public health and clinical significance.

The precursors of adolescent tobacco smoking are multifactorial (Thorgeirsson et al., 2010; Mays et al., 2014; Lochbuehler et al., 2016; Terracciano and Costa, 2004; Fluharty et al., 2017; Hitchman et al., 2014; Balfour, 2004). Epidemiological studies postulate that a combination of genetic (Thorgeirsson et al., 2010), family and nonfamily environmental factors (Mays et al., 2014; Lochbuehler et al., 2016; Iakunchykova et al., 2015), personality traits (Terracciano & Costa, 2004), existing mental health problems (Fluharty, Taylor, Grabski, & Munafò, 2017) and low socioeconomic positions (Hitchman et al., 2014) may play a significant role in their progression. Most importantly, in utero exposure to tobacco smoking may modify dopaminergic

* Corresponding author at: Kent Street, Bentley, Perth, Western Australia 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.addbeh.2021.106871
Received 10 November 2020; Received in revised form 1 February 2021; Accepted 2 February 2021
Available online 10 February 2021

projections in the brain and change the response of this system to the effects of tobacco later in life (Balfour, 2004).

Whether determinants of adolescent tobacco smoking can be traced back to the prenatal period is less understood. Epidemiological data from existing longitudinal studies suggest that offspring exposed to prenatal tobacco may have an increased risk of tobacco smoking compared to non-exposed (Cornelius et al., 2012; Al Mamun et al., 2006; O'Callaghan et al., 2009; Biederman et al., 2017). For example, a study of data from 4462 mother-offspring pairs in the Northern Finland Birth Cohort (NFBC) indicated that the risk of tobacco smoking in offspring exposed to maternal prenatal tobacco use increases approximately by two folds (Niemelä et al., 2017). Further, evidence from the Ottawa Prenatal Prospective Study (OPPS) also suggested that tobacco smoking in offspring was significantly associated with prenatal tobacco use (Porath & Fried, 2005). Nonetheless, additional studies have reported no associations for maternal prenatal tobacco exposure (Buka et al., 2003; Roberts et al., 2005), while others suggested gender specific associations (Kandel et al., 1994; Oncken et al., 2004). For instance, a retrospective cohort study from the US that included two separate cohorts has shown gender specific risk associations, such that prenatal tobacco exposure was associated with tobacco smoking in girls only (Kandel, Wu, & Davies, 1994).

Methodological variations in handling potential confounders are more likely to delineate these conflicting results. For instance; maternal educational attainment, low socio-economic positions, maternal mental health problems, prenatal alcohol and postnatal tobacco use, and existing mental health problems in offspring (Cnattingius, 2004; Huizink, 2009; Wakschlag et al., 2002; Cornelius et al., 1995, 2007; O'Brien and Hill, 2014), have also been associated with offspring tobacco smoking. Incomplete statistical adjustment of these variables and retrospective recalls of prenatal tobacco exposure, prone to bias, may produce less precise estimates.

Alternative methods such as negative control analysis may produce evidence to support inference as to whether an effect of the prenatal exposure on the outcome is present (Sanderson et al., 2018; Lipsitch et al., 2010). In this case, this can be done by comparing the association between maternal and paternal prenatal tobacco use with offspring tobacco smoking. Maternal and paternal prenatal tobacco exposures are more likely affected by similar socio-economic confounders, suggesting that if prenatal factors are involved in the causal pathway to adolescent smoking, then the association will be more strongly seen with maternal prenatal tobacco use and not with paternal use at the time of the pregnancy. This method of using a negative control has been used to test the association between prenatal tobacco exposure and the risk of tobacco smoking in adolescent offspring (Niemelä et al., 2017). However, replications of these findings could provide additional evidence for the role of prenatal tobacco exposure in the development of subsequent tobacco smoking in the next generation. Furthermore, most previous studies did not differentiate trimester-specific effects, which is critically important to propose appropriate intervention strategies (Miller, 2006). Therefore, the aim of this study was to examine the association between maternal prenatal tobacco exposure (Raine Study Generation 1) and tobacco smoking in offspring (Raine Study Generation 2) using paternal prenatal tobacco exposure as a negative control for intrauterine exposure comparison.

2. Methods and data

2.1. Study design and participants

The current study is based on the data of the first and second generations of the Raine Study, a prospective multigenerational observational study of 2730 pregnant mothers (Generation 1) and their offspring (Generation 2). The Raine Study participant's recruitment, data collection and follow up strategies have been described in detail elsewhere (Straker et al.,0000 ; Newnham et al., 1993). Pregnant mothers who received antenatal care at King Edward Memorial Hospital (KEMH) and a nearby private clinic in Perth between 1989 and 1991 were recruited to the study. Out of 2,868 live births, 138 mothers with multiple gestation were excluded. The final study cohort (generation 2) consisted of those who completed substance use assessment at age of 17 years (n = 1210). Ethical approval for this study was gained from the Human Research Ethics Committees (HREC) of the University of Western Australia (RA/4/20/5722). At each follow-up assessment, written informed consent was gained from each study participant after the details of the procedures had been fully described.

3. Measures

3.1. Ascertainment of exposure: Prenatal tobacco use (Generation 1)

At 18 and 34 weeks of gestations, pregnant mothers reported the number of cigarettes smoked per day during the first three months of pregnancy (first trimester) and they were currently (third trimester) smoking, respectively. We used this data to categorize pregnant mothers as either non-smoker or smoker. At 18 weeks of gestations, cotinine (a biomarker for exposure to tobacco smoke) was measured in serum from 238 pregnant mothers to validate self-reported maternal prenatal tobacco exposure because serum cotinine concentrations in body fluids could accurately demonstrate nicotine consumption (Sharma, Sane, Anand, Marimutthu, & Benegal, 2019). Evidence from a validation study showed good agreement between self-reported prenatal tobacco exposure and measured serum cotinine concentration (Stick, Burton, Gurrin, Sly, & LeSouëf, 1996). To further explore the timing of maternal prenatal tobacco exposure, we have produced the following categories; no exposure throughout pregnancy, first trimester (Trim-1) exposure, third trimester (Trim-3) exposure and, both first and third trimesters (Trim-1 and 3) exposures. The study did not have data on prenatal tobacco exposure during the second trimester of pregnancy. At the same time point in pregnancy (at 18 weeks of gestation), pregnant mothers also reported the smoking status of their partners (fathers of the study participants) during their pregnancy. We used these data to categorize fathers of the study child as either non-smoker or smoker. We used paternal prenatal tobacco exposure as a negative control for intrauterine exposure, in that we assumed that paternal prenatal tobacco exposure is likely to be affected by similar measured and unmeasured risk factors of maternal prenatal tobacco use but not expected to have direct prenatal causal effect on offspring tobacco smoking.

3.2. Ascertainment of outcome: Tobacco smoking at the age of 17 years (Generation 2)

Tobacco smoking at the age of 17 years was assessed by using a self-reported questionnaire to measure adolescents' smoking habits in the past four weeks. Adolescents were asked to report whether or not they had smoked tobacco in the past four weeks. We grouped adolescents who replied "yes" to above question as 'current tobacco users' whereas those reported "no" or "never smoked" were used as a reference control group. This categorization has been used in a previous study that used the same cohort data (Moore et al., 2014). Current tobacco use was reported as tobacco smoking in this study.

3.3. Assessment of confounders

Confounders may explain observed associations between prenatal tobacco exposure and offspring tobacco smoking (Murray & Duggan, 2010). Maternal, paternal and children's potential confounders included; marital status, maternal and paternal educational level, age at child birth, ethnicity (race), family income at conception, maternal prenatal alcohol use and sex of child. We also included immediate adverse pregnancy outcomes such as preterm birth and low birthweight. At 13 years of follow-up, mothers rated their symptoms of depression

and anxiety using a short form of the Depression Anxiety Stress Scales (DASS) (Lovibond & Lovibond, 1995). We used these data to categorize pregnant mothers as depressed/non-depressed and anxious/non-anxious using the recommended cut-off scores of ≥ 10 and ≥ 8 respectively (Lovibond & Lovibond, 1995). Tobacco smoking in adolescents has been associated with parental postnatal tobacco smoking (Wellman et al., 2016) and mental health problems in adolescents (Bandiera et al., 2016; Lechner et al., 2017). Mothers reported their postnatal smoking status (yes/no) at 13 years of follow-up. Adolescent internalizing behavioural problems such as withdrawn, somatic complaints, anxious/depressed were assessed at 16 years of follow-up using Youth Self Report (YSR/11–18) with cut-off of T-score ≥ 60 (Achenbach, 1999).

3.4. Statistical analysis

We used log-binomial regression models to examine the prospective associations between prenatal tobacco exposure and the risk of tobacco smoking in offspring at the age of 17 years with STATA 16.0 (StataCorp., 2019). These models estimated relative risks (RRs) as a measure of association. To investigate whether the associations between prenatal tobacco exposure and offspring tobacco smoking persist when different risk factors are taken into consideration, we used progressive models to separately predict changes in estimated effects. Model 1 was adjusted by maternal and child covariates; marital status, maternal age at conception, race, family income, low birthweight, preterm birth, sex of child, maternal and paternal education, and maternal alcohol use during pregnancy. Then we added maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioural problems to Model 1(Model 2). Adolescents may learn tobacco smoking from their parents through normalizing the behaviour of tobacco smoking irrespective of whether tobacco use occurred during or after pregnancy. To explore this, we separately added postnatal maternal tobacco smoking at 13 years of follow-up to model 1(Model 3). Model 4 was adjusted for all covariates. We repeated analysis excluding early prenatal tobacco exposure from the models and adding late pregnancy exposure to tobacco (at 34 weeks) to investigate whether early and late prenatal exposures had significant impact on the overall analysis and identify risks in terms of gestational age. We then used paternal tobacco smoking during partner's pregnancy as a negative control for intrauterine exposure. Next, we estimated the difference in estimates after fitting the models with all variables including the control variables. We also conducted an additional sensitivity analysis to calculate the E-value, is a continues measure of an association, to investigate the potential effect of unmeasured confounding (Haneuse, VanderWeele, & Arterburn, 2019). Its lowest possible value is 1 (E-value = 1), suggesting no unmeasured confounding is needed to explain away the observed association whereas the higher E-value suggests the stronger the confounder associations must to be explain away the effect (Haneuse et al., 2019; VanderWeele TJ, Ding P, M M. Technical Considerations in the Use of the E-value" Harvard University Biostatistics Working Paper Series Working Paper 215., 2018). Moreover, for the purpose of accounting for the possibilities of bias due to study participants attrition, we employed multiple imputations by chained equation using the "mice" STATA command (Sterne et al., 2009; Royston, 2005). We used 50 cycles of regression switching and generated 50 imputed datasets and repeated all analyses using the imputed datasets.

4. Results

4.1. Characteristics of study participants

Mothers of offspring with tobacco smoking at the age of 17 years were more likely to be younger, report low family income per annum, alcohol and tobacco use during pregnancy when compared to mothers of offspring who did not smoke tobacco. Out of 254 (21%) offspring who reported tobacco smoking, 45.6% were males, 7.3% were of low birthweight, and 28% were born to mothers smoking tobacco during the first trimester of pregnancy whereas 25.7% were exposed to third trimester prenatal tobacco use only. Further, 25.6% were exposed to postnatal tobacco smoke at 13 years of follow-up (Table 1).

4.2. Association between prenatal tobacco exposure and tobacco smoking in offspring

We found an increased risk of tobacco smoking in the unadjusted model among offspring exposed to maternal prenatal tobacco use during the first trimester [RR 1.58 (95% CI: 1.25–2.00)], third trimester [RR 1.56 (95% CI: 1.22–2.00)] and during both trimesters of pregnancy [RR 1.65 (95% CI: 1.28–2.13)]. Similarly, paternal tobacco use during partner's pregnancy was associated with an increased risk of tobacco use in offspring at the age of 17 years [RR 1.38 (95% CI: 1.10–1.72)] (Table 2). When we adjusted for Model 1, the estimates for the first trimester, third trimester and both trimesters were slightly attenuated. However, we found insufficient statistical evidence for an association between paternal tobacco use during partner's pregnancy and risk of tobacco smoking in offspring [RR 1.21 (95% CI: 0.96–1.53)] (P-value > 0.05). In the fully adjusted model (Model 4), the estimates did not substantially change for the first trimester maternal prenatal tobacco exposure [RR 1.50 (95% CI: 1.13–1.97)] but slight attenuation for both trimesters exposure [RR 1.41 (95% CI: 1.03–1.89)]. Statistical evidence from our sensitivity analysis (E-value) suggested that the relative risk of the association between an unmeasured confounder and (i) maternal prenatal tobacco exposure and (ii) tobacco smoking in offspring would need to be at least 2.37 for each association to explain away or nullify the associations observed in our study (Model 4) (Table 3). In contrast, we found insufficient statistical evidence for an association between third trimester maternal prenatal tobacco exposure and offspring tobacco smoking [RR 1.20 (95% CI: 0.93–1.51)]. Moreover, we did not find any statistical evidence suggesting substantial difference in estimates when we included or removed a control variable in/from all sequential models (Table 3). We observed similar results when we repeated analysis using the imputed data (Table 2 and Supplementary file 2).

5. Discussion

This study examined prospectively the association between maternal prenatal tobacco exposure and the risk of tobacco smoking in offspring at the age of 17 years using paternal tobacco smoking during partner's pregnancy as a negative control exposure. We observed that offspring exposed to maternal prenatal tobacco exposure during the first trimester and during both trimesters of pregnancy had the increased risks of tobacco smoking at the age of 17 years. However, we noted insufficient statistical evidence for an increased risk of tobacco smoking in offspring exposed to third trimester trimester maternal tobacco use only. Varying level of statistical adjustment for potential confounders including a negative control did not alter the observed associations, suggesting the robustness of our findings.

The results of this study support the findings of the existing studies that reported the increased risk of tobacco smoking or dependence in offspring exposed to maternal prenatal tobacco use (De Genna et al., 2017; Al Mamun et al., 2006; O'Callaghan et al., 2009; Biederman et al., 2017; Niemelä et al., 2017). A study of data from 2984 mother-offspring pairs in the 'Mater-University of Queensland Study of Pregnancy' indicated that offspring exposed to maternal prenatal tobacco use were 2.11 times more likely to start tobacco smoking after 14 years of age when compared to non-exposed (RR 2.11 (95% CI 1.68–2.66) (12). Likewise, in a prospective longitudinal study from the Northern Finland prenatal exposure to maternal tobacco predicted the risk of tobacco smoking in offspring at age 15–16 years (Niemelä et al., 2017). The estimates of this study did not substantially change after adjusting for other paternal and parental smoking behaviours. Nonetheless, a few previous studies have

Table 1
Characteristics of mothers and children included in the final analysis based on offspring tobacco smoking at the age 17 years of follow-up.

Variables included in the model		Tobacco smoking at 17 years (n = 1210)				*P-value*
		Use		Non-use		
		n	%	n	%	
Marital status	Married	168	66.1	707	74.0	0.04
	Never married	41	16.1	83	8.6	
	Defacto	39	15.4	139	14.6	
	Separate/divorce/ widow	6	2.4	27	2.8	
Maternal Educational level	Schooling Up to 12 years	116	45.7	409	42.8	0.05
	Trade certificate/ apprenticeship	52	20.5	178	18.6	
	Professional registration/ College Diploma	52	20.5	168	17.6	
	University degree	34	13.4	201	21.0	
Paternal Educational level	Schooling Up to 12 years	57	27.1	238	28.3	0.60
	Trade certificate/ apprenticeship	60	28.6	230	27.3	
	Professional registration/ College Diploma	44	21.0	149	17.7	
	University degree	49	23.3	225	26.7	
Mothers' age at child birth	<20 years	20	7.7	56	5.7	0.45
	20–24.99 years	47	18.2	171	17.5	
	25–29.99 years	76	29.3	285	29.3	
	30–34.99 years	81	31.3	289	29.7	
	>35 years	35	13.5	173	17.8	
Mothers' Ethnicity (race)	Caucasian	234	92	855	89.4	0.20
	Non-Caucasian	20	8.0	101	10.6	
Family income during pregnancy	≤24,000 AUD	119	46.7	333	34.8	<0.01
	>24,000 AUD	135	53.3	623	65.2	
Maternal alcohol use during 1st trimester	Non-use	111	43.7	500	52.3	0.03
	1–3 Standard drinks/week	110	43.3	368	38.5	
	≥4 Standard drinks/week	33	13.0	88	9.2	
Maternal alcohol use during 3rd trimester	Non-use	138	57.0	544	60.3	0.56
	1–3 Standard drinks/week	78	32.2	259	28.7	
	≥4 Standard drinks/week	26	10.8	98	11.0	
Preterm birth (<37 weeks)	No	243	9.6	887	93.0	0.11
	Yes	11	4.4	68	7.0	
Birthweight	Low birth weight (<2.5 K.G)	19	7.3	72	7.4	0.97
	Normal birthweight (≥2.5 K.G)	240	93.3	901	92.6	
Sex of child	Male	118	45.6	495	50.8	0.13
	Female	141	54.4	479	49.2	
Maternal tobacco use (1st trimester)	Non-smoker	183	72.0	789	82.5	<0.01
	Smoker	71	28.0	167	17.5	
Maternal tobacco use (3rd trimester)	Non-smoker	180	74.3	757	92.4	<0.01
	Smoker	62	25.7	62	7.6	
Paternal tobacco use (During partner's pregnancy)	Non-smoker	154	60.6	669	70.0	0.04
	Smoker	100	39.4	287	30.0	
Maternal depression at 13 years of follow-up	Non-depressed	210	89.0	812	89.7	0.74
	Depressed	26	11.0	93	10.3	
Maternal anxiety at 13 years of follow-up	No-anxiety symptoms	228	96.6	855	94.5	0.18
	Anxiety symptoms	8	3.4	50	5.5	
Offspring Internalizing behaviors at 16 years of follow-up	Non-internalizing behaviors	193	75.4	835	86.3	0.03
	Internalizing behaviors	63	24.6	133	13.7	
Maternal postnatal tobacco use at 13 years of follow-up	Non-smoker	177	74.4	764	84	0.02
	Smoker	61	25.6	144	16	

presented contrasting results. For example, a retrospective cohort study from the USA reported that prenatal tobacco exposure was associated with tobacco smoking in girls only (Kandel et al., 1994). However, the findings of that study were based on a relatively a small sample size (N = 797) and were likely to suffer from recall bias. In contrast, we did not find evidence for gender differences in the association between prenatal tobacco exposure and tobacco smoking in offspring.

The mechanisms underlying the association between maternal prenatal tobacco exposure and tobacco smoking in offspring are not well understood. However, several putative mechanisms have been suggested. One proposed mechanism includes the neurotoxic and addictive effects of the chemical ingredients present in tobacco smoke (Hyman, 2005). These chemicals can cross the placenta and consequently act on nicotinic acetylcholine receptors (nAChR), 'a membrane protein that binds to the acetylcholine (Ach) neurotransmitter' and starts to exist in the brain of fetus as early as the first trimester (Pauly and Slotkin, 2008). The corresponding stimulation of these receptors at early stages of development could lead to apoptotic or mitotic abnormalities (Wickström, 2007). This in turn may affect the natural reward system of the brain (Balfour, 2004) and increase the propensity of the exposed adolescents for tobacco smoking. Similarly, an increased level of plasma testosterone has been reported in the offspring of mice and sheep exposed to maternal prenatal tobacco use and this alteration has been suggested to elevate offspring preference to smoke tobacco (Smith, Cloak, Poland, Torday, & Ross, 2003).

Epidemiological evidence also suggests that existing mental health problems may predispose adolescents to smoke tobacco (Fluharty et al., 2017; Slomp et al., 2019). A systematic review conducted in 2015 examined the longitudinal association between tobacco smoking and mental health problems in 148 studies from different countries (Fluharty et al., 2017). For the majority of studies included in the review, depressive and anxiety disorders predicted later smoking behavior. In contrast, results from a study conducted in the USA suggested that the association between prenatal tobacco exposure and electronic cigarette use in offspring was not mediated by adolescents' current mental health problems (De Genna, Richardson, Goldschmidt, Day, & Cornelius, 2018). Consistent with the findings of that study, the association that we observed between maternal prenatal tobacco exposure and subsequent tobacco smoking in offspring remained consistent and statistically significant when we further adjusted for these disorders.

An alternative hypothesis suggests that adolescents may smoke tobacco by emulating the behaviour of their parents smoking behaviour (Wellman et al., 2016; Leonardi-Bee et al., 2011). For example, a systematic review and *meta*-analysis conducted in 2010 to synthesize the results of 58 studies linking parental smoking to child subsequent tobacco smoking reported that the odds of adolescents' tobacco smoking increase approximately by two-fold if at least one parent or family member smoke tobacco (Leonardi-Bee, Jere, & Britton, 2011). In contrast, a result of a longitudinal study in the USA (N = 784) did not suggest an association between maternal postnatal tobacco dependence and offspring tobacco dependence after adjusting for prenatal tobacco exposure (De Genna, Goldschmidt, Day, & Cornelius, 2017).

Table 2
Association between maternal and paternal prenatal tobacco exposure and risk of tobacco smoking in offspring at the age of 17 years.

Predictor and control variables	Relative risks (RRs) (95% CI) (tobacco smoking)				
	Unadjusted	Model 1	Model 2	Model 3	Model 4
Maternal prenatal tobacco use (1st trimester)	1.58 (1.25–2.00)	1.34 (1.05–1.73)	1.50 (1.16–1.93)	1.42 (1.07–1.88)	1.50 (1.13–1.97)
Maternal prenatal tobacco use (3rd trimester)	1.56 (1.22–2.00)	1.31 (1.01–1.72)	1.26 (0.94–1.69)	1.28 (0.90–1.26)	1.20 (0.93–1.51)
Maternal prenatal tobacco use (both trimesters)	1.65 (1.28–2.13)	1.38 (1.04–1.82)	1.41 (1.04–1.89)	1.44 (1.04–1.98)	1.41 (1.03–1.89)
Paternal smoking during pregnancy	1.38 (1.10–1.72)	1.21 (0.96–1.53)	1.20 (0.95–1.52)	1.21 (0.94–1.55)	1.18 (0.84–1.67)

Keys: Non-smoker was used as a reference group in all models.
Model 1: maternal age at conception, marital status, race, family income, low birthweight, preterm birth, maternal and paternal education, sex of child, and maternal alcohol use during pregnancy.
Model 2: added maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioral problems to Model 1.
Model 3: separately added postnatal maternal tobacco use at 13 years of follow-up to model 1.
Model 4: adjusted for all risk factors.

Table 3
The risk of tobacco smoking in offspring exposed to maternal prenatal tobacco use (First trimester) when a control variable included along with E-value.

Models	Relative risks (RRs) (95% CI)	*P*-value for difference between maternal and paternal associations	E-value	
			For Point Estimate	For Confidence Interval
Model 1	1.34 (1.05–1.73)	0.023	2.01	1.28
Model 2	1.50 (1.16–1.93)	0.001	2.37	1.56
Model 3	1.42 (1.07–1.88)	0.016	2.19	1.34
Model 4	1.50 (1.13–1.97)	0.005	2.37	1.51

Keys: Model 1: included maternal age at conception, marital status, race, family income, low birthweight, preterm birth, maternal and paternal education, sex of child, and maternal alcohol use during pregnancy.
Model 2: added maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioural problems to Model 1.
Model 3: separately added postnatal maternal tobacco use at 13 years of follow-up to model 1.
Model 4: adjusted for all risk factors.

Complementing this view, further statistical adjustment for postnatal maternal tobacco use at 13 years of follow-up in our sequential models did not change the observed risk estimates.

The strengths of this study include: the use of a prospective cohort dataset with a relatively larger sample size that enabled the generalizability of the results to other similar populations; comprehensive adjustment of potential maternal and child confounders; and an additional analysis to identify risks in terms of gestational age, sensitivity analysis to calculate the E-values and validation of self-reported maternal smoking status with biological markers of tobacco smoking (e.g. serum cotinine levels). The findings from the negative control exposure of paternal smoking during pregnancy strengthen our analysis and provide some support that the associations we found may be causal. Further, we were able to control for the effects of maternal postnatal tobacco use at 13 years of follow up which further strengthen the robustness of our findings. Moreover, we were also able to adjust for offspring mental health problems in sequential models but they did not appear to change the observed association.

A limitation of this study was the lack of a standard measure/scale to assess tobacco smoking in offspring. However, our results are comparable to the majority of previous studies which have used similar measures. Although we were able to control for the effects of maternal postnatal tobacco exposure, we did not have data on non familial environmental risk factors including peer influence. Therefore, this should be taken into consideration while interpreting the findings of this study. Similar to other longitudinal studies, selective attrition rates, most notably reports of selective attrition among socially disadvantaged parents may have resulted in less precise estimates. However, a previous study that evaluated the potential bias due to recruitment and loss of participants suggested that the Raine Study had no evidence of significant perinatal selection bias (Whitehouse et al., 2010).

6. Conclusion

The findings of this study suggest that offspring exposed to maternal prenatal tobacco exposure during the first trimester and during both trimesters of pregnancy had the increased risks of tobacco smoking at 17 years of age using a negative control analysis. Tobacco smoking cessation at the early stages of gestation may reduce the risk of tobacco smoking in the next generation.

Author agreement

All authors have seen and approved the final version of the manuscript being submitted. Authors warrant that the article is the authors' original work, hasn't received prior publication and isn't under consideration for publication elsewhere.

CRediT authorship contribution statement

Bereket Duko: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Software, Visualization, Writing - original draft. **Gavin Pereira:** Conceptualization, Data curation, Methodology, Resources, Supervision, Validation, Visualization. **Kim Betts:** Conceptualization, Data curation, Methodology, Resources, Supervision, Validation, Visualization. **Robert J. Tait:** Conceptualization, Methodology, Resources, Visualization. **John Newnham:** Conceptualization, Methodology, Resources, Visualization. **Rosa Alati:** Conceptualization, Data curation, Methodology, Resources, Supervision, Validation, Visualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgements

We are so grateful for all the families who took part in this study. Authors also acknowledge the Raine Study team such as data collectors, cohort managers, data managers, data officers, clerical staff and research scientists for longitudinal data collection and cohort coordination. The National Health and Medical Research Council (NHMRC) for long term contribution to funding the Raine Study since initiation; the Raine Medical Research Foundation; The University of Western Australia (UWA), Curtin University, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University and The University of Notre Dame Australia are

acknowledged for providing funding for core management of the Raine Study. The 17 year follow-up of the Raine Cohort was supported by the National Health and Medical Research Council Program Project Grants #1099655 and #1173991. Bereket Duko is funded by Curtin University International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. The funders had no role in the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.addbeh.2021.106871.

References

Achenbach TM. The Child Behavior Checklist and related instruments M.E. Maruish (Ed.), The use of psychological testing for treatment planning and outcomes assessment (2nd ed.), Lawrence Erlbaum Associates, Mahwah, NJ 1999.

AIHW. Australian institute health and welfare (AIHW), Alcohol, tobacco & other drugs in Australia, accessed March 28, 2019, . 2018.

Al Mamun, A., O'Callaghan, F. V., Alati, R., O'Callaghan, M., Najman, J. M., Williams, G. M., et al. (2006). Does maternal smoking during pregnancy predict the smoking patterns of young adult offspring? A birth cohort study. *Tobacco Control., 15*(6), 452–457.

Balfour, D. (2004). The neurobiology of tobacco dependence: A preclinical perspective on the role of the dopamine projections to the nucleus accumbens [corrected]. *Nicotine & Tobacco Research, 6*(6), 899–912.

Bandiera, F. C., Loukas, A., Wilkinson, A. V., & Perry, C. L. (2016). Associations between tobacco and nicotine product use and depressive symptoms among college students in Texas. *Addictive Behaviors, 63*, 19–22.

Biederman, J., Martelon, M. K., Woodworth, K. Y., Spencer, T. J., & Faraone, S. V. (2017). Is maternal smoking during pregnancy a Risk Factor for Cigarette Smoking in Offspring? A Longitudinal Controlled Study of ADHD Children Grown Up. *Journal of attention disorders., 21*(12), 975–985.

Buka, S. L., Shenassa, E. D., & Niaura, R. (2003). Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: A 30-year prospective study. *American Journal of Psychiatry, 160*(11), 1978–1984.

Cnattingius, S. (2004). The epidemiology of smoking during pregnancy: Smoking prevalence, maternal characteristics, and pregnancy outcomes. *Nicotine & Tobacco Research, 6*(Suppl 2), S125–S140.

Cornelius, M. D., Goldschmidt, L., & Day, N. L. (2012). Prenatal cigarette smoking: Long-term effects on young adult behavior problems and smoking behavior. *Neurotoxicology and Teratology, 34*(6), 554–559.

Cornelius, M., Goldschmidt, L., DeGenna, N., & Day, N. (2007). Smoking during teenage pregnancies: Effects on behavioral problems in offspring. *Nicotine & Tobacco Research, 9*(7), 739–750.

Cornelius, M. D., Taylor, P. M., Geva, D., & Day, N. L. (1995). Prenatal tobacco and marijuana use among adolescents: Effects on offspring gestational age, growth, and morphology. *Pediatrics, 95*(5), 738–743.

De Genna, N. M., Goldschmidt, L., Day, N. L., & Cornelius, M. D. (2017). Prenatal tobacco exposure, maternal postnatal nicotine dependence and adolescent risk for nicotine dependence: Birth cohort study. *Neurotoxicology and Teratology., 61*, 128–132.

De Genna, N. M., Richardson, G. A., Goldschmidt, L., Day, N. L., & Cornelius, M. D. (2018). Prenatal exposures to tobacco and cannabis: Associations with adult electronic cigarette use. *Drug and Alcohol Dependence, 188*, 209–215.

Fluharty, M., Taylor, A. E., Grabski, M., & Munafò, M. R. (2017). The association of cigarette smoking with depression and anxiety: A Systematic Review. *Nicotine & Tobacco Research, 19*(1), 3–13.

Guerin, N., & White, V. (2018). *Australian secondary school students' use of tobacco, alcohol, and over-the-counter and illicit substances in 2017*. Victoria: Centre for Behavioural Research in Cancer.

Haneuse, S., VanderWeele, T. J., & Arterburn, D. (2019). Using the E-Value to assess the potential effect of unmeasured confounding in observational studies. *JAMA, 321*(6), 602–603.

Hitchman, S. C., Fong, G. T., Zanna, M. P., Thrasher, J. F., Chung-Hall, J., & Siahpush, M. (2014). Socioeconomic status and smokers' number of smoking friends: Findings from the International Tobacco Control (ITC) Four Country Survey. *Drug and alcohol dependence., 143*, 158–166.

Huizink, A. C. (2009). Moderate use of alcohol, tobacco and cannabis during pregnancy: New approaches and update on research findings. *Reproductive Toxicology, 28*(2), 143–151.

Hyman, S. E. (2005). Addiction: A Disease of Learning and Memory. *American Journal of Psychiatry., 162*(8), 1414–1422.

Iakunchykova, O. P., Andreeva, T. I., Nordstrom, D. L., Shkiryak-Nizhnyk, Z. A., Antipkin, Y. G., Hryhorczuk, D. O., et al. (2015). The impact of early life stress on risk of tobacco smoking initiation by adolescents. *Addictive behaviors., 50*, 222–228.

Kandel, D. B., Wu, P., & Davies, M. (1994). Maternal smoking during pregnancy and smoking by adolescent daughters. *American Journal of Public Health, 84*(9), 1407–1413.

Lechner, W. V., Janssen, T., Kahler, C. W., Audrain-McGovern, J., & Leventhal, A. M. (2017). Bi-directional associations of electronic and combustible cigarette use onset patterns with depressive symptoms in adolescents. *Preventive Medicine, 96*, 73–78.

Leonardi-Bee, J., Jere, M. L., & Britton, J. (2011). Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: A systematic review and meta-analysis. *Thorax, 66*(10), 847–855.

Lipsitch, M., Tchetgen Tchetgen, E., & Cohen, T. (2010). Negative controls: A tool for detecting confounding and bias in observational studies. *Epidemiology, 21*(3), 383–388.

Lochbuehler, K., Schuck, K., Otten, R., Ringlever, L., & Hiemstra, M. (2016). Parental Smoking and Smoking Cognitions among Youth: A Systematic Review of the Literature. *European Addiction Research., 22*(4), 215–232.

Lovibond, P. F., & Lovibond, S. H. (1995). The structure of negative emotional states: Comparison of the Depression Anxiety Stress Scales (DASS) with the Beck Depression and Anxiety Inventories. *Behaviour Research and Therapy., 33*(3), 335–343.

Mays, D., Gilman, S. E., Rende, R., Luta, G., Tercyak, K. P., & Niaura, R. S. (2014). Parental smoking exposure and adolescent smoking trajectories. *Pediatrics, 133*(6), 983–991.

Miller, M. (2006). *Normal processes and the effects of alcohol and nicotine*. Oxford University Press.

Moore, S. E., Norman, R. E., Sly, P. D., Whitehouse, A. J. O., Zubrick, S. R., & Scott, J. (2014). Adolescent peer aggression and its association with mental health and substance use in an Australian cohort. *Journal of Adolescence., 37*(1), 11–21.

Murray, K. W., & Duggan, A. (2010). Understanding Confounding in Research. *Pediatrics in Review., 31*(3), 124–126.

Newnham, J. P., Evans, S. F., Michael, C. A., Stanley, F. J., & Landau, L. I. (1993). Effects of frequent ultrasound during pregnancy: A randomised controlled trial. *Lancet (London, England)., 342*(8876), 887–891.

Niemelä, S., Räisänen, A., Koskela, J., Taanila, A., Miettunen, J., Ramsay, H., et al. (2017). The effect of prenatal smoking exposure on daily smoking among teenage offspring. *Addiction, 112*(1), 134–143.

O'Brien, J. W., & Hill, S. Y. (2014). Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. *Alcoholism, Clinical and Experimental Research, 38*(12), 2952–2961.

O'Callaghan FV, Al Mamun A, O'Callaghan M, Alati R, Najman JM, Williams GM, et al. Maternal smoking during pregnancy predicts nicotine disorder (dependence or withdrawal) in young adults - a birth cohort study. Aust N Z J Public Health. 2009;33(4):371-7.

Oncken, C., McKee, S., Krishnan-Sarin, S., O'Malley, S., & Mazure, C. (2004). Gender effects of reported in utero tobacco exposure on smoking initiation, progression and nicotine dependence in adult offspring. *Nicotine & Tobacco Research, 6*(5), 829–833.

Pauly, J. R., & Slotkin, T. A. (2008). Maternal tobacco smoking, nicotine replacement and neurobehavioural development. *Acta Paediatrica, 97*(10), 1331–1337.

Porath, A., & Fried, P. (2005). Effects of prenatal cigarette and marijuana exposure on drug use among offspring. *Neurotoxicology and Teratology, 27*(2), 267–277.

Roberts, K., Munafò, M., Rodriguez, D., Drury, M., Murphy, M., Neale, R., et al. (2005). Longitudinal analysis of the effect of prenatal nicotine exposure on subsequent smoking behavior of offspring. *Nicotine & Tobacco Research, 7*(5), 801–808.

Royston, P. (2005). Multiple imputation of missing values: Update of ice. *The Stata Journal., 5*(4), 527–536.

Sanderson, E., Macdonald-Wallis, C., & Davey, S. G. (2018). Negative control exposure studies in the presence of measurement error: Implications for attempted effect estimate calibration. *International Journal of Epidemiology, 47*(2), 587–596.

Sharma, P., Sane, N., Anand, S. D., Marimutthu, P., & Benegal, V. (2019). Assessment of cotinine in urine and saliva of smokers, passive smokers, and nonsmokers: Method validation using liquid chromatography and mass spectrometry. *Indian Journal of Psychiatry., 61*(3), 270–276.

Slomp, F. M., Bara, T. S., Picharski, G. L., & Cordeiro, M. L. (2019). Association of cigarette smoking with anxiety, depression, and suicidal ideation among brazilian adolescents. *Neuropsychiatric Disease and Treatment, 15*, 2799–2808.

Slotkin, T. A. (2008). If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? *Neurotoxicology and Teratology., 30*(1), 1–19.

Smith, L., Cloak, C., Poland, R., Torday, J., & Ross, M. (2003). Prenatal nicotine increases testosterone levels in the fetus and female offspring. *Nicotine & Tobacco Research., 5*(3), 369–374.

StataCorp. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC. 2019.

Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ. 2009; 338:b2393.

Stick, S. M., Burton, P. R., Gurrin, L., Sly, P. D., & LeSouëf, P. N. (1996). Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. *The Lancet., 348*(9034), 1060–1064.

Straker L, Mountain J, Jacques A, White S, Smith A, Landau L, et al. Cohort Profile: The Western Australian Pregnancy Cohort (Raine) Study-Generation 2. International journal of epidemiology. 2017;46(5):1384-5j.

Terracciano, A., & Costa, P. T., Jr. (2004). Smoking and the Five-Factor Model of personality. *Addiction (Abingdon, England)., 99*(4), 472–481.

Thorgeirsson, T. E., Gudbjartsson, D. F., Surakka, I., Vink, J. M., Amin, N., Geller, F., et al. (2010). Sequence variants at CHRNB3-CHRNA6 and CYP2A6 affect smoking behavior. *Nature Genetics, 42*(5), 448–453.

VanderWeele TJ, Ding P, M M. Technical Considerations in the Use of the E-value" Harvard University Biostatistics Working Paper Series Working Paper 215. 2018.

Wakschlag, L. S., Pickett, K. E., Cook, E., Benowitz, N. L., & Leventhal, B. L. (2002). Maternal smoking during pregnancy and severe antisocial behavior in offspring: A review. *American Journal of Public Health, 92*(6), 966–974.

Wellman, R. J., Dugas, E. N., Dutczak, H., O'Loughlin, E. K., Datta, G. D., Lauzon, B., et al. (2016). Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth. *American Journal of Preventive Medicine, 51*(5), 767–778.

Whitehouse, A. J. O., Robinson, M., Zubrick, S. R., Ang, Q. W., Stanley, F. J., & Pennell, C. E. (2010). Maternal life events during pregnancy and offspring language ability in middle childhood: The Western Australian Pregnancy Cohort Study. *Early Human Development, 86*(8), 487–492.

Wickström, R. (2007). Effects of nicotine during pregnancy: Human and experimental evidence. *Current Neuropharmacology, 5*(3), 213–222.

Chapter 8: Prenatal alcohol and tobacco exposures and offspring cannabis use

Chapter 8: Prenatal alcohol and tobacco exposures and offspring cannabis use

Published manuscript and formal citation

Duko B, Pereira G, Tait RJ, Betts K, Newnham J, Alati R. Prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring: Findings from a population-based cohort study. Neurotoxicology and Teratology. 2022; 90:107064

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ntt.2022.107064.

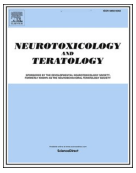
Study purpose: Existing epidemiological studies examining the association between prenatal and offspring addictive substances have been limited to alcohol and tobacco although the same biological pathways potentially apply to offspring cannabis use. Therefore, using the Western Australian prospective cohorts of pregnancy, childhood, adolescence, and adulthood (the Raine Study) data were used to address the following research objective: to examine the associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring in late adolescence.

Neurotoxicology and Teratology 90 (2022) 107064

Contents lists available at ScienceDirect

Neurotoxicology and Teratology

journal homepage: www.elsevier.com/locate/neutera



Prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring: Findings from a population-based cohort study

Bereket Duko [a,*], Gavin Pereira [a,b], Robert J. Tait [c], Kim Betts [a], John Newnham [d], Rosa Alati [a,e]

[a] Curtin School of Population Health, Curtin University, Kent Street, Bentley, WA 6102, Australia
[b] Centre for Fertility and Health (CeFH), Norwegian Institute of Public Health, Oslo, Norway
[c] National Drug Research Institute, Faculty of Health Sciences, Curtin University, 7 Parker Place Building 609, Level 2 Technology Park, Bentley, WA 6102, Australia
[d] Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, 17 Monash Ave, Nedlands, WA 6009, Australia
[e] Institute for Social Sciences Research, The University of Queensland, 80 Meier's Rd, Indooroopilly, Queensland 4068, Australia

ARTICLE INFO

Keywords:
Alcohol
Tobacco
Pregnancy
Adolescents
cannabis use
Raine study

ABSTRACT

Background: There is a paucity of prospective longitudinal studies examining the associations between maternal use of alcohol and tobacco during pregnancy and the risk of cannabis use in offspring. The aim of this study was to examine the association between prenatal alcohol and tobacco exposures and offspring cannabis use.
Methods: Data were from the Raine Study, a longitudinal prospective birth cohort based in Western Australia. Cannabis use at 17 years of age was measured with a self-reported questionnaire developed to capture risky behaviors in adolescents. Associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring were examined using log-binomial regression models, computing relative risk (RR). We also computed the *E*-values (E) to estimate the extent of unmeasured confounding.
Results: After adjusting for potential confounders, we observed increased risks of cannabis use in offspring exposed to first trimester prenatal alcohol use (RR = 1.38, 95% CI: 1.09–1.75; E = 2.10, CI:1.40) and tobacco use (RR = 1.42, 95% CI: 1.08–1.86; E = 2.19, CI:1.37) as well as third trimester prenatal alcohol use (RR = 1.39, 95% CI: 1.09–1.79; E = 2.13, CI:1.40) and tobacco use (RR = 1.39, 95% CI: 1.09–1.79; E = 2.21, CI:1.34]. We also noted dose-response associations in which risk estimates in offspring increased with the level of exposures to prenatal alcohol and tobacco use.
Conclusion: These findings provide epidemiological evidence for effects of prenatal alcohol and tobacco exposures on offspring cannabis use. Although these results should be confirmed by other studies, the present study adds to the mounting evidence suggesting that women should be encouraged to abstain from alcohol and tobacco during pregnancy.

1. Background

Cannabis is one of the most commonly consumed illicit drugs in Australia. Estimates from the Australian Secondary School Students' Alcohol and Drug survey of 2017 indicated that 8% of adolescents aged 12–17 years reported current cannabis use, making cannabis the most commonly consumed illicit drug in this age group (Guerin and White, 2018). Cannabis use during adolescence has been linked to poor physical health (Herbeck et al., 2013), impairments in neurocognitive performance (Jacobus and Tapert, 2014), poor academic performance and increased school dropout (Volkow et al., 2014; Meier et al., 2015), mental health problems (Meier et al., 2015; Gobbi et al., 2019), lower life satisfaction (Lew et al., 2019) and even suicide (Gobbi et al., 2019; Bolanis et al., 2020). Further, several epidemiological studies have also demonstrated that cannabis use is an antecedent to the aforementioned outcomes (Bagot et al., 2015; Meier et al., 2015; Gobbi et al., 2019; Schmidt et al., 2020). Measures should therefore be taken to rigorously identify early-life presumptive risk factors of cannabis use in adolescence.

The precise causes for cannabis use are multifactorial (Hayatbakhsh et al., 2009; Verweij et al., 2010; Tarter et al., 2014; Bogdan et al., 2016; Courtney et al., 2017). Epidemiological studies hypothesize that the interactions between biological (Agrawal and Lynskey, 2006; Verweij et al., 2010), psychological, social, and environmental factors (Hayatbakhsh et al., 2009; Verweij et al., 2010; Bogdan et al., 2016) may contribute to habitual use. Most importantly, early-life adversities

* Corresponding author at: Curtin School of Population Health, Curtin University, Australia, Kent Street, Bentley, Perth, WA 6102, Australia.
E-mail address: b.adema@postgrad.curtin.edu.au (B. Duko).

https://doi.org/10.1016/j.ntt.2022.107064
Received 8 October 2021; Received in revised form 5 January 2022; Accepted 5 January 2022
Available online 7 January 2022

originating during fetal development such as low socioeconomic positions, parental substance use and mental health problems may increase the risk of mental health and behavioural problems in offspring later in life (Tarter et al., 2014; Smith et al., 2016; Koponen et al., 2020). Maternal prenatal alcohol and tobacco exposures are amongst such adversities. Reports from the Australian Institute of Health and Welfare (AIHW) in 2017 showed that 35% of women drink alcohol during pregnancy and 9.2% of women who gave birth smoked tobacco during the first 20 weeks of pregnancy (AIHW, 2017).

There is a paucity of prospective longitudinal studies testing the associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring (Barr et al., 2006; O'Brien and Hill, 2014; Bennett and Lewis, 2020). Epidemiological evidence from the few available longitudinal studies showed that offspring exposed to prenatal alcohol use may have an increased risk of illicit drug use compared to those non-exposed (Barr et al., 2006; O'Brien and Hill, 2014). A prospective cohort study from the US suggested a 2.56-fold increased risk of drug use disorders in offspring exposed to prenatal alcohol use (Barr et al., 2006). Further, a retrospective cohort study of 5922 mother-offspring pairs from the German Health Interview and Examination Survey for Children and Adolescents (the KiGGS study) suggested gender-specific associations, such that low to moderate maternal prenatal alcohol use was associated with illicit drug use in adolescent females only (Pfinder et al., 2014). Moreover, the aforementioned studies have only reported illicit drug use as a single outcome (combining all illicit drug use) in offspring exposed to maternal alcohol use during pregnancy.

Although the association between prenatal tobacco exposure and offspring tobacco smoking has been documented in numerous studies (De Genna et al., 2017; Duko et al., 2021a), there is a paucity of studies examining the association between prenatal tobacco exposure and risk of cannabis use in offspring (Porath and Fried, 2005; Day et al., 2006; Goldschmidt et al., 2012; De Genna et al., 2021). A study of data from the Maternal Health Practices and Child Development Project (MHPCD) observed an association between prenatal tobacco exposure and cannabis use in offspring at the age of 16 years after controlling for sociodemographic, environmental, prenatal alcohol and cannabis exposures, child and maternal psychological factors (Goldschmidt et al., 2012). Nonetheless, another study from the MHPCD project did not observe such an association for offspring at the age of 14 years (Day et al., 2006). Similarly, the Ottawa Prenatal Prospective Study (OPPS) presented insufficient statistical evidence for an association between prenatal tobacco exposure and offspring regular cannabis use (Porath and Fried, 2005). The lack of association in that study may be due to lack of statistical power due to the small sample size ($N = 152$), with fewer cases in the critical analysis, suggesting the necessity of population-based prospective studies with larger sample sizes, which are warranted to produce more precise estimates and improve the generalizability of results. The aim of our study was to estimate the associations between prenatal alcohol and tobacco exposures (Gen1), and the risk of cannabis use in offspring (Gen2). We hypothesized that such associations can be observed in offspring in late adolescence.

2. Methods

2.1. Study design and participants

Study participants were offspring of mothers enrolled in the Raine Study between 1989 and 1992. The Raine Study is a multigenerational ongoing population-based prospective cohort, which recruited a total of 2730 pregnant women (Gen1) visiting King Edward Memorial Hospital (KEMH) and nearby private clinics in Perth, Western Australia, between 16 and 20 weeks of pregnancy. These pregnancies resulted in a total of 2868 live-born offspring (Gen2). Complete data were available for 1065 mother-offspring pairs. Full details of the Raine Study participants' recruitment and methodology have been published elsewhere (Newnham et al., 1993; Straker et al., 2017). This study was approved by the Human Research Ethics Committees (HREC) of the University of Western Australia. Written informed consent was obtained from each study participant at enrollment and at each follow-up assessment after the details of the procedures had been fully explained.

2.2. Exposures: prenatal alcohol and tobacco exposures (Gen1)

At 18 weeks of pregnancy, mothers of the study adolescents reported the average of the total number of standard drinks of alcohol consumed per week during the first three months of pregnancy. They also provided an average of the total number of standard drinks of alcohol they were currently drinking at 34 weeks of pregnancy. According to the National Health and Medical Research Council (NHMRC) guidelines of 2009 (NHMRC, 2009), one standard drink in Australia constitutes 10 g of absolute alcohol, which is approximately equal to 285 mL of full strength beer (4.8% alcohol), 425 mL of low strength beer (2.7% alcohol), 375 mL of mid strength beer (3.5% alcohol), 100 mL of champagne (12% alcohol), 330 mL of spirits (40% alcohol), 275 mL bottle of ready-to-drink beverage (5% alcohol) and 100 mL of wine (red - 13% alcohol, and white – 11.5% alcohol). We used these data to categorize pregnant mothers as either non-drinkers (non-exposed) or drinkers (exposed). To further examine dose-response associations, we defined prenatal alcohol exposure as: non-drinker (category 1), up to three standard drinks of alcohol per week (category 2); and four or more standard drinks of alcohol per week (category 3) during the first and third trimesters of pregnancy. The same categorization was applied in our previous study that examined the association between prenatal alcohol exposure and harmful alcohol use in offspring (Duko et al., 2020). At the same time point, pregnant mothers also self-reported the average number of cigarettes they had smoked per day during the first and the third trimesters of pregnancy. In order to validate these self-reported responses on tobacco-smoke exposure, a validation study was conducted by Stick et al. (1996). From that study, cotinine, a metabolite of nicotine (Moran, 2012), was measured in serum from 238 pregnant mothers who reported tobacco smoking during the first three months of pregnancy. Evidence from that validation study suggested good agreement between self-reported maternal tobacco smoking during pregnancy and measured serum cotinine concentration (Stick et al., 1996). To ensure consistency with a previous study on this cohort (Duko et al., 2021b), we recoded this variable into three categories: no prenatal tobacco exposure (Category 1), less than 10 cigarettes/day (Category 2) and 10 or more cigarettes per day (Category 3) during the first and third trimesters of pregnancy.

2.3. Outcome: Cannabis use in offspring (Gen2)

Cannabis use at 17 years of age (Gen2) was measured by using a self-reported questionnaire developed to capture risky behaviors in adolescents. Adolescents were asked, "How often do you use cannabis (marijuana) for non-medical purposes?" We grouped adolescents who responded daily, weekly and monthly use to the above question as 'current cannabis users' whereas those reported 'never' and 'once over one year ago' were categorized as non-current cannabis users/abstainers. A previous study from the same cohort has used a similar classification to categorize cannabis use in adolescents at age 17 years (Moore et al., 2014). Current cannabis use was reported as cannabis use in this study.

2.4. Confounders

We controlled for confounders available in this study and which have been previously reported to have associations between prenatal alcohol and tobacco exposures and the risk of cannabis (illicit drug) use in offspring. The following early-life parental and child factors were assessed at baseline: maternal educational level (schooling up to 12

years, trade certificate / apprenticeship, professional registration/ college diploma and university degree), maternal age during pregnancy (< 20 years, 20–25 years, 25–30 years, 30–35 years and > 35 years), ethnicity (Caucasian and non-Caucasian), marital status (married, never married, de-facto and widowed/divorced/separated), annual family income (low income < AUD $24,000 and moderate to high income > AUD $24,000), paternal tobacco smoking during partner's pregnancy (yes/no), sex of child (male/female), preterm birth(<37 weeks of gestation) (yes/no), birth weight (low-birth weight (< 2.5 kg), normal birth-weight (2.5–3.99 kg) and high-birth weight (>4.0 kg)) and maternal history of psychiatric disorder during pregnancy (yes/no). Further, Depression Anxiety Stress Scale (DASS) was used to measure maternal depressive symptoms at 14 years of follow-up (Akin and Citin, 2007). At 14 years of follow-up, mothers also self-reported their postnatal tobacco smoking status (yes/no). The total depressive symptoms score of DASS was dichotomized as depressed (≤ 9) or not depressed (normal ≥10) based on the recommended severity thresholds. A systematic review and meta-analysis conducted in 2014 suggested an association between comorbid anxiety and depression and cannabis use (Kedzior and Laeber, 2014). Similarly, during the middle and high school years, aggressive behavior and cannabis use have been associated with each other although a causal association has not been established yet (Liu and Petras, 2017). Therefore, we have included existing anxious/depressed and aggressive behavioural problems of adolescents at the age of 14 years. These behaviors were ascertained by using parent completed Child Behavior Checklist (CBCL4–18), the *Diagnostic and Statistical Manual of Mental Disorders, fourth edition, text revision* (DSM IV) oriented screening tool (Achenbach, 1999). In this study, the subscales were dichotomized as anxious/depressed and aggressive behaviors using the CBCL t-scores ≥70 (Achenbach, 1999).

2.5. Statistical analysis

Associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring were examined using log-binomial regression models, computing relative risks (RRs) as measure of association with STATA 16.1. We added different risk factors as adjustment variables in sequential models to better examine the role of potential confounders. Firstly, we produced unadjusted estimates for both exposures. Next, we mutually-adjusted these two models of prenatal alcohol and tobacco exposures for one another (Model 1). Model 2 was adjusted by maternal age at conception, education, marital status, annual family income, ethnicity (race), paternal tobacco smoking during partner's pregnancy and sex of child, preterm birth, and low birthweight. Then, we added maternal psychiatric disorder during pregnancy and maternal depressive symptoms and postnatal tobacco smoking at 14 years of follow-up and offspring anxious, depressed and aggressive behaviors at 14 years (Model 3). We repeated a similar analysis by removing the first trimester prenatal alcohol and tobacco exposures from these models and replacing them with the third trimester prenatal alcohol and tobacco exposures to further estimate risks in terms of gestational age. Moreover, as a sensitivity analysis, we conducted *multiple imputations by chained equations* to account for missing data (Royston, 2005; Sterne et al., 2009) and produced 50 imputed datasets. We also conducted an additional sensitivity analysis to compute *E*-values (Haneuse et al., 2019). The E-value is defined as the minimum strength of association on the risk-ratio scale (VanderWeele and Ding, 2017; Linden et al., 2020) that an unmeasured confounder possibly will require to have with prenatal alcohol and tobacco exposures and offspring cannabis use to explain away or nullify the reported associations based on measured confounders (VanderWeele and Ding, 2017, Linden et al., 2020). The lowest possible E-value is one. High values suggest considerable unmeasured confounding would be required to explain or nullify away the reported association whereas lower values indicate little unmeasured confounding would be required to explain or nullify away the reported association (VanderWeele and Ding, 2017, Linden et al., 2020). Finally, we also conducted an additional sensitivity analysis after re-categorizing offspring cannabis use as non-users/abstainers, lifetime users (cannabis use once over one year ago) and current users (daily/weekly/monthly use) to examine whether the associations between prenatal alcohol and tobacco exposures and offspring cannabis use differ when the way cannabis use was defined varies using multinomial logit models.

3. Results

3.1. Characteristics of study participants

Mothers whose offspring reported cannabis use at the age of 17 years were more likely to be younger and unmarried, report low annual family income, alcohol and tobacco use during the first and third trimesters of pregnancy, divorce or separation and lower educational level when compared to mothers of offspring that did not report cannabis use **(**Table 1**).** Of the total offspring included in this study; 22.7% reported cannabis use, 48.5% were exposed to prenatal alcohol use (39.1% in 3rd trimester) and 18.7% were exposed to prenatal tobacco use during the first trimester (17.0% in 3rd trimester), 4.2% reported elevated rates of anxious/depressive symptoms whereas 3.5% reported elevated rates of aggressive behavior at the age of 14 years.

3.2. Associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring

Univariate analysis showed that offspring born to mothers drinking any alcohol during the first trimester of pregnancy were 1.40 times more likely to report cannabis use at the age of 17 years when compared to offspring born to non-alcohol drinking mothers during pregnancy [RR = 1.40; 95% CI (1.12–1.75)]**.** Similarly, offspring exposed to prenatal tobacco during the first trimester were 1.58 times more likely to report cannabis use at age of 17 years when compared to those unexposed [RR = 1.58; 95% CI (1.24–2.01)].)]. We also observed similar patterns for third trimester pregnancy alcohol [RR = 1.39; 95% CI (1.09–1.79)] and tobacco [RR = 1.40; 95% CI (1.07–1.93)] exposures **(**Table 2**).** When we mutually adjusted for prenatal alcohol and tobacco exposures, the estimates for the first and third trimesters were slightly attenuated (Model 1). Further adjustment of Model 1 by maternal age at conception, education, marital status, annual family income, ethnicity (race), and paternal tobacco smoking during partner's pregnancy and sex of child, preterm birth and low birthweight did not substantially change the estimate for the first trimester [RR = 1.37; 95% CI (1.10–1.71)] but slightly strengthened the estimate for the third trimester prenatal alcohol exposure [RR = 1.42; 95% CI (1.12–1.79)]. However, the risk estimates were slightly attenuated for the first trimester [RR = 1.33; 95% (1.03–1.74)] and third trimester [RR = 1.41; 95% CI (1.07–1.86)] prenatal tobacco exposure **(Model 2).** In the fully adjusted model **(Model 3),** the estimates did not substantially change for the first [RR = 1.38; 95% CI (1.09–1.75)] and third trimesters [RR = 1.39; 95% CI (1.09–1.75)] prenatal alcohol exposure but there was slight strengthening in the estimates for the first [RR = 1.42; 95% CI (1.08–1.86)] and third trimesters [RR = 1.43; 95% CI (1.07–1.93)] prenatal tobacco exposure. Further, we have examined for sex-specific differences in associations between prenatal alcohol and tobacco exposures and offspring cannabis use in our preliminary analysis (χ^2 test) and we did not find sufficient evidence for sex-specific differences (p-value = 0.12).

The risk estimates for cannabis use in offspring increased in magnitude and precision with increasing exposure to prenatal alcohol and tobacco use **(**Table 2**).** We observed relative risks (RR) of 1.36 (95% CI: 1.06–1.74) and 1.46 (95% CI: 1.03–2.08) for offspring born to mothers drinking up to three standard drinks of alcohol/week and four or more standard drinks of alcohol per week during the first trimester of pregnancy respectively. Similarly, there were also suggestions of dose-response relationships as estimates were slightly greater in offspring exposed to prenatal tobacco use of ≥10 cigarettes/day [RR = 1.43; 95%

Table 1
Characteristics of mothers and offspring for comparing the major covariates amongst offspring using and not using cannabis at the age of 17 years.

Variables included in the model		Cannabis use (n = 1065)				P-value
		Non-user		User		
		n	%	*n*	%	
Maternal age at conception	< 20 years	41	4.9	20	8.1	0.186
	20–25 years	141	16.8	49	20.0	
	25–30 years	257	30.7	67	27.2	
	30–35 years	245	29.3	72	29.3	
	≥ 35 years	153	18.3	38	15.4	
Mothers' Education status at conception	Schooling Up to 12 years	323	39.2	112	46.1	0.243
	Trade certificate/ apprenticeship	167	20.4	44	18.1	
	Professional registration/ College Diploma	152	18.5	44	18.1	
	University degree	180	21.9	43	17.7	
Annual family income at conception	≤ 24,000 AUD	274	33.3	111	45.7	<
	> 24,000 AUD	548	66.7	132	54.3	0.001
Marital status	Married	622	75.7	165	68.0	0.100
	Never married	72	8.8	31	12.7	
	Defacto	109	13.3	40	16.3	
	Separate/divorce/ widow	19	2.3	7	3.0	
Ethnicity/race	Caucasian	727	88.4	224	92.2	0.098
	Non-Caucasian	95	11.6	19	7.8	
Preterm birth	No	759	92.4	234	96.3	0.035
	Yes	62	7.6	9	3.7	
Child's sex	Male	416	49.7	136	55.3	0.124
	Female	421	50.3	110	44.7	
Birthweight	Low birth weight (< 2.5 K.G)	62	7.4	14	5.7	0.631
	Normal birthweight (2.5–3.99 K.G)	696	83.2	209	85.3	
	High birthweight (> 4.0 K.G)	79	9.4	22	9.0	
Maternal prenatal tobacco use (1st trimester)	Non-smoker	687	83.6	178	73.3	<
	Smoker	135	16.4	65	26.7	0.001
Maternal prenatal tobacco use (3rd trimester)	Non-smoker	663	85.4	174	75.0	<
	Smoker	113	14.6	58	25.0	0.001
Maternal prenatal alcohol use (1st trimester)	Non-drinker	444	54.0	105	43.2	0.003
	Drinker	378	46.0	138	56.8	
Maternal prenatal alcohol use (3rd trimester)	Non-drinker	471	63.7	121	54.3	0.01
	Drinker	268	36.3	102	45.7	
Maternal history of psychiatric disorder during pregnancy	No psychiatric disorder	802	97.6	236	97.1	0.697
	Psychiatric disorder	20	2.4	7	2.9	
Maternal depression at 13 years of follow-up	Non-depressed	701	90.0	206	90.7	0.768
	Depressed	79	10.0	21	9.3	
Offspring anxious and depressed behavior at 14 years of follow-up	Non-anxious/ depressed	806	95.6	231	94.0	0.102
	Anxious/ depressed	31	4.4	15	6.0	
Offspring aggressive behavior at 14 years of follow-up	Non-aggressive	697	92.6	185	81.1	0.01
	Aggressive	56	7.4	43	18.9	

Key: p-value refers to chi-square test of association between offspring cannabis use and other covariates.

Table 2
Association between maternal prenatal alcohol and tobacco exposure and the risk of cannabis use in offspring at the age of 17 years.

Prenatal Exposures (Predictor variables)	Relative risk (95%CI)			
	Unadjusted	Model 1	Model 2	Model 3
Prenatal alcohol exposure at first trimester				
Prenatal alcohol exposure	1.40 (1.12–1.75)	1.36 (1.09–1.70)	1.37 (1.10–1.71)	1.38 (1.09–1.75)
Up to 3 standard drinks/week	1.37 (1.08–1.73)	1.34 (1.06–1.70)	1.33 (1.05–1.68)	1.36 (1.06–1.74)
4 or more standard drinks/week	1.53 (1.08–2.18)	1.43 (1.03–2.04)	1.49 (1.06–2.11)	1.46 (1.03–2.08)
Prenatal alcohol exposure at third trimester				
Prenatal alcohol exposure	1.35 (1.07–1.70)	1.33 (1.05–1.66)	1.42 (1.12–1.79)	1.39 (1.09–1.79)
Up to 3 standard drinks/week	1.16 (0.70–1.91)	1.10 (0.67–1.82)	1.24 (0.75–2.07)	1.28 (0.70–2.12)
4 or more standard drinks/week	1.39 (1.10–1.75)	1.37 (1.08–1.72)	1.48 (1.17–1.87)	1.43 (1.11–1.84)
Prenatal tobacco exposure at first trimester				
Prenatal tobacco exposure	1.58 (1.24–2.01)	1.50 (1.21–1.95)	1.33 (1.03–1.74)	1.42 (1.08–1.86)
1–9 Cigs/day	1.52 (1.12–2.06)	1.49 (1.10–2.02)	1.37 (1.01–1.88)	1.38 (1.01–1.94)
≥ 10 Cigs/day	1.67 (1.20–2.28)	1.58 (1.15–2.18)	1.41 (1.01–1.95)	1.43 (1.02–2.01)
Prenatal tobacco exposure at third trimester				
Prenatal tobacco exposure	1.63 (1.27–2.09)	1.58 (1.23–2.03)	1.41 (1.07–1.86)	1.43 (1.07–1.93)
1–9 Cigs/day	1.52 (1.06–2.17)	1.49 (1.04–2.13)	1.27 (0.89–1.84)	1.32 (0.90–1.95)
≥ 10 Cigs/day	1.72 (1.28–2.32)	1.70 (1.26–2.30)	1.57 (1.16–2.14)	1.46 (1.03–2.07)

Foot note: none-users were used as a reference control for all above categories.
NB: Analyses were run separately by trimester but reported together for ease of presentation.
Key:
Model 1: Mutually adjusted for prenatal tobacco and alcohol exposure.
Model 2: Adjusted for maternal age at conception, education, marital status, annual family income, ethnicity (race), paternal tobacco smoking during pregnancy and sex of child, preterm birth and low birthweight.
Model 3: Fully adjusted for maternal age at conception, education, marital status, annual family income, ethnicity (race), paternal tobacco smoking during pregnancy, sex of child, preterm birth, low birthweight, maternal psychiatric disorder during pregnancy, and maternal depression and postnatal tobacco smoking at 14 years of follow-up and offspring anxious, depressed and aggressive behavior at 14 years.

CI (1.02–2.01)] when compared to offspring exposed to <10 cigarettes/day [RR = 1.38; 95% CI (1.01–1.94)] during the first trimester of pregnancy. Further, the results from the sensitivity analysis after re-categorizing adolescent cannabis use were similar to those from the main analysis **(Supplementary file 1).** Moreover, analyses repeated using the imputed dataset resulted in negligible difference with the original estimates **(Supplementary file 2).**

3.3. Sensitivity analysis (E-values)

We computed an additional sensitivity analysis to produce the E-values to examine the extent of confounding required to explain associations. E-values for the associations we observed in this study and their lower confidence interval closest to the null are: first trimester prenatal alcohol exposure [E-value = 2.10 (CI = 1.40)], third trimester prenatal alcohol exposure [E-value =2.13 (CI = 1.40)], first trimester prenatal tobacco exposure [E-value =2.19 (CI = 1.37)], and third trimester prenatal tobacco exposure [E-value = 2.21 (CI = 1.34)] **(**Table 3**).** The evidence from the E-values suggested that the association between an unmeasured confounder (e.g. prenatal cannabis use, substance use

Table 3
Sensitivity analysis (*E*-values) for the association between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring for fully adjusted Model (Model 3).

Maternal Prenatal exposures		Relative Risks (RR) (95% CI)	E-values	
			For Point Estimate	For Confidence Interval
Prenatal alcohol exposure at first trimester	Any use (any amount)	1.38 (1.09–1.75)	2.10	1.40
	Up to 3 standard drinks/week	1.36 (1.06–1.74)	2.06	1.31
	4 or more standard drinks/week	1.46 (1.03–2.08)	2.28	1.21
Prenatal alcohol exposure at third trimester	Any use (any amount)	1.39 (1.09–1.79)	2.13	1.40
	Up to 3 standard drinks/week	1.28 (0.70–2.12)	1.88	1.00
	4 or more standard drinks/week	1.43 (1.11–1.84)	2.21	1.46
Prenatal tobacco exposure at first trimester	Smoker (any)	1.42 (1.08–1.86)	2.19	1.37
	1–9 Cigs/day	1.38 (1.01–1.94)	2.10	1.11
	≥ 10 Cigs/day	1.43 (1.02–2.01)	2.21	1.16
Prenatal tobacco exposure at third trimester	Smoker (any)	1.43 (1.07–1.93)	2.21	1.34
	1–9 Cigs/day	1.32 (0.90–1.95)	1.97	100
	≥ 10 Cigs/day	1.46 (1.03–2.07)	2.28	1.28

NB: Analyses were run separately by trimester but reported together for ease of presentation.

disorders and other) and first trimester prenatal alcohol exposure and risk of cannabis use in offspring would require a relative risk of at least 2.10 to nullify the observed association i.e. weaker confounding could not do so. Similarly, an unmeasured confounder (e.g., prenatal cannabis use, substance use disorders and other) for the association between first trimester prenatal tobacco exposure and risk of cannabis use in offspring would require a relative risk of at least 2.19 to nullify the observed association (Fig. 1). Again, weaker confounding could not do so. Therefore, moderate unmeasured confounders are needed to nullify the reported link between exposure and outcome.

4. Discussion

4.1. Main findings

We examined the association between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring at the end of adolescence using a prospective multigenerational birth cohort in Western Australia. To the best of our knowledge, this is the first prospective cohort study to investigate the association between prenatal alcohol exposure and offspring cannabis use in late adolescence. We found statistical evidence for the associations between prenatal alcohol and tobacco exposures and cannabis use in offspring at the age of 17 years after adjusting for a wide range of potential confounders. We also observed dose-response associations, based on risk estimates that were slightly elevated amongst offspring exposed to higher levels of prenatal alcohol and tobacco use when compared to lower levels of prenatal exposure. Therefore, these findings further increase the reasons for avoiding alcohol (Bower et al., 2017) and tobacco during pregnancy to reduce adverse outcomes in offspring.

4.2. Prenatal alcohol exposure and risk of cannabis use in offspring

The findings of this study are consistent with the results of the few available epidemiological studies that reported an association between prenatal alcohol exposure and risk of illicit drug use in offspring (Barr et al., 2006; O'Brien and Hill, 2014; Pfinder et al., 2014). A prospective cohort study of young adults ($N = 500$) born to mothers who reported prenatal alcohol use in the US observed an increased odds of substance use disorders (alcohol and illicit drugs) [Adjusted odds ratio (AOR) =2.56; 95% CI (1.45–4.32)] at the age of 25 years (Barr et al., 2006). Similarly, a study of data from 5922 mother-offspring pairs in the KiGGS study revealed that offspring exposed to prenatal alcohol use were 1.62 times more likely to report any illicit drug use at the age between 11 and 17 years [AOR = 1.62; 95% CI (1.23–2.14)] (Pfinder et al., 2014). This is also corroborated by another prospective cohort study from the US that reported an increased risk of illicit drug use disorder in offspring exposed to prenatal alcohol use even after adjusting for familial history of alcohol dependence (O'Brien and Hill, 2014).

The precise mechanism detailing the association between prenatal alcohol exposure and the risk of cannabis use in offspring remains unclear. However, a number of putative mechanisms have been suggested. One possible explanation linking prenatal alcohol exposure and offspring cannabis use may be related to the theory of developmental origins of adult diseases that suggests a wide range of adult diseases including mental and behavioural problems have their origins in prenatal exposures (Barker et al., 2002; Alati et al., 2007). Evidence from a non-human primate model suggests that prenatal alcohol exposure may enhance arterial stiffness and alters vasodilator function in offspring (Parkington et al., 2014) and this in turn results in poor placental perfusion and oxygen supply (Lo et al., 2017). The corresponding poor in utero conditions such as these may result in reprogramming of the hypothalamic–pituitary–adrenal (HPA) axis that endures into adulthood (Newby et al., 2015). This is also supported by the results from a study based in the US that observed significantly higher cortisol concentrations, a biomarker for the activation of HPA axis, in children and adolescents exposed to prenatal alcohol use (McLachlan et al., 2016). The dysregulation of the HPA axis may lead to altered neuroendocrine functions such as hyper-responsiveness to stress (Weinberg et al., 2008) and this in turn may increase the propensity of offspring to use substance or illicit drugs (Kreek et al., 2005).

4.3. Prenatal tobacco exposure and risk of cannabis use in offspring

The results of this study add to a converging body of evidence on the role of prenatal tobacco exposure as an early-life presumptive risk factor for offspring cannabis use at the end of adolescence, even after adjusting for other maternal and child covariates. Our finding is consistent with the US based prospective cohort study on the 16-year follow-up of children enrolled in the Maternal Health Practices and Child Development Project (MHPCD) that reported a prospective association between prenatal tobacco exposure and the risk of cannabis use in offspring after controlling for sociodemographic, environmental, prenatal alcohol and cannabis exposures, child and maternal mental health problems (Goldschmidt et al., 2012). Nonetheless, some studies have produced conflicting results (Buka et al., 2003; Porath and Fried, 2005; Day et al., 2006). For instance, another study from the MHPCD project did not observe an association between prenatal tobacco exposure and cannabis use in offspring at the age of 14 years after adjusting for home environment (Day et al., 2006). The discrepant findings may be due to variability in offspring ages of assessment, such that cannabis use is more pronounced as the age of adolescents increases and this may hinder the statistical capacity of that study to observe similar behaviors in younger adolescents. Further, the Ottawa Prenatal Prospective Study (OPPS) did not find evidence for an association between prenatal tobacco exposure and risk of cannabis use in offspring at ages of 16–21 years (Porath and Fried, 2005). The lack of evidence for an association in

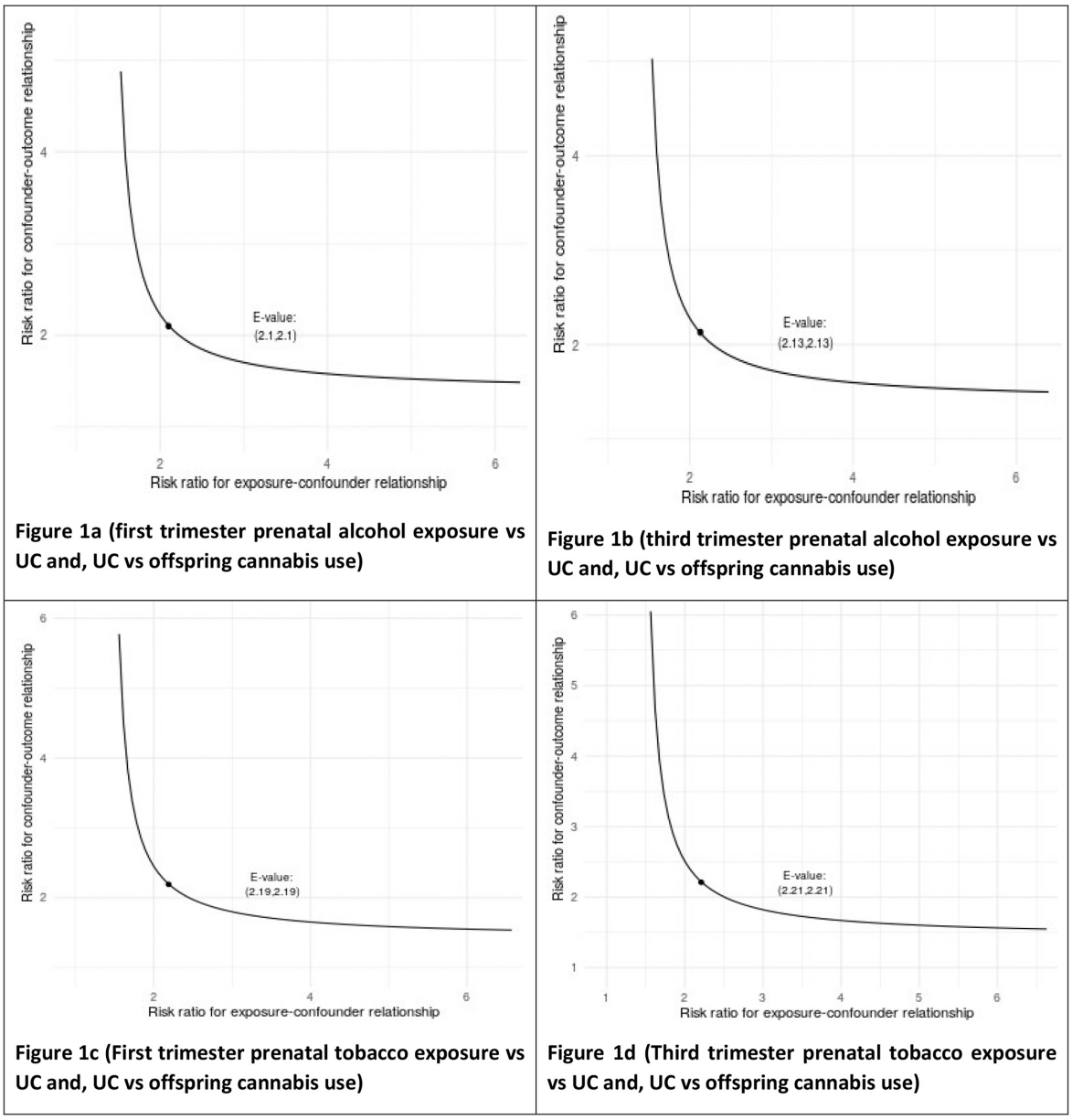


Figure 1a (first trimester prenatal alcohol exposure vs UC and, UC vs offspring cannabis use)

Figure 1b (third trimester prenatal alcohol exposure vs UC and, UC vs offspring cannabis use)

Figure 1c (First trimester prenatal tobacco exposure vs UC and, UC vs offspring cannabis use)

Figure 1d (Third trimester prenatal tobacco exposure vs UC and, UC vs offspring cannabis use)

Fig. 1. (a-d): Plot showing the level of unmeasured confounding needed to nullify exposure –confounder and confounder-outcome association.
Each point along the curve defines a joint association between the two sensitivity parameters that could potentially explain away the estimated effect. (UC = unmeasured confounder).

that study may be due to lack of statistical power as a result of very small sample size ($N = 152$).

Prenatal exposure to tobacco may increase the risk of offspring cannabis use via different proposed biological mechanisms (Ernst et al., 2001). One proposed mechanism linking prenatal tobacco exposure to offspring substance use is that the addictive, neurotoxic and carcinogenic effects of the thousands of hazardous chemicals found in tobacco smoke that readily pass through the placenta to the fetus (Hyman, 2005). One of these chemicals, most importantly nicotine, disrupts the function of the nicotinic acetylcholine receptor (nAChR), which is believed to express in the fetal brain in the first trimester of pregnancy in humans (Dwyer et al., 2009). The corresponding nicotine-induced alternation of nAChR may result in a profound impact on the function of the brain reward circuitries, thereby contributing to substance dependence or addiction in offspring (Fowler et al., 2008). This is also corroborated by evidence from in vivo study in which exposure to prenatal nicotine induced modifications in the reward pathways in adolescent male rats (Franke et al., 2008). This pathway is further

strengthened by observation from a two-generational study of adolescents and their parents in Canada (Saguenay Youth Study) that suggested prenatal tobacco exposure appeared to interact with the α6 subunit of nAChR gene, which in turn influence substance/drug use in adolescence (Lotfipour et al., 2010).

4.4. The role of genetic, environmental, and confounding factors

The observations we observed in this study may be due to several genetic factors shared by the parents and child (Degenhardt et al., 2001; Lynskey et al., 2002). For example, a preponderance of epidemiological studies reported that elevated risk of cannabis use disorder was observed in close relatives of probands with cannabis use disorders when compared to healthy controls (Merikangas et al., 2009; Johnson et al., 2020). Evidence from a controlled family study from the US showed that 47% of the male spouses and 25% of the female spouses of probands with cannabis use disorders reported cannabis use disorders (Merikangas et al., 2009). Nonetheless, a large prospective longitudinal study of 3176 young adults from the 'Mater-University of Queensland Study of Pregnancy' (MUSP) found weak evidence to support this hypothesis (Hayatbakhsh et al., 2007). The findings of that study suggest that maternal tobacco smoking at 14 years of follow-up was associated with an increased risk of offspring cannabis use at 21 years, independent of maternal tobacco smoking at 5 years of follow-up, suggesting social learning and environmental factors may explain some part of the observed association rather than genetics. Although our study had no capacity to examine the aforementioned genetic factors, maternal postnatal tobacco smoking at 14 years of follow-up was included in our progressive models, but it did not appear to change the associations reported in this study.

The associations that we found between prenatal alcohol and tobacco exposures and risk of cannabis use in offspring may be explained by several confounders such as maternal and child mental health problems. A study of 792 adolescents from the Raising Healthy Children (RHC) project in the US ($N = 792$) suggested that offspring of parents with clinically confirmed depressive disorder were five times more likely to report illicit drug abuse and dependence when compared to offspring of parents without depressive disorder (Cortes et al., 2009). Similarly, emerging evidence suggests that during the middle and high school years, aggressive behavioural problems and cannabis use are associated with each other (Liu and Petras, 2017). This observation was further strengthened by evidence from a systematic review and meta-analysis of 31 primary studies that reported associations between cannabis use and comorbid anxiety and depression (Kedzior and Laeber, 2014). Most recently, in a prospective cohort study of 500 adolescents who were exposed to prenatal tobacco and cannabis use, adolescents' cannabis use and externalizing behavioural problems at 14 years of follow-up have predicted combined use of cannabis and cigarettes at the age of 22 years after adjusting for child sex, race and early tobacco use as well as prenatal tobacco and cannabis exposures (De Genna et al., 2021). We also observed slight attenuation in the risk estimates after including existing anxious and depressed as well as aggressive behavioural problems of adolescents measured at the age of 14 years in our sequential models. Nonetheless, none of them appear to change the direction of association, suggesting the direct effects of prenatal tobacco exposure on offspring cannabis use.

Moreover, based on the evidence from the *E*-values, moderate unmeasured confounders are needed to nullify the reported link between exposures and outcome. However, we cannot rule out the possibility of unmeasured confounding. To completely explain away the associations observed in this study, such an unmeasured confounder would need to be associated with prenatal alcohol and tobacco exposures and offspring cannabis use at the level of the calculated *E*-values. More specifically, this would require relative risks of at least 2.10 for the observed associations between the first trimester prenatal alcohol exposure and offspring cannabis use; and 2.21 for the observed associations between the first trimester prenatal tobacco exposure and offspring cannabis use. In our opinion, unmeasured and residual confounding may explain some, but not all of the reported association.

4.5. The strengths and limitations

This study has a number of strengths: the prospective measures of prenatal alcohol and tobacco exposures, outcomes and other covariates included in this study; the use of population-based study design with a relatively large sample size and the use of validated data on prenatal tobacco exposure. Further, comprehensive statistical adjustment of multiple covariates using sequential models, running multiple imputations to test the impact of missing data on overall estimates, conducting additional analysis to estimate the risks in terms of trimesters of pregnancy (e.g. for 1st and 3rd trimester) and computing E-values to examine the extent of unmeasured confounding required to explain associations were the other strengths of our study. However, several caveats should be considered when interpreting and generalizing the results of this study. This study did not collect data on second trimester prenatal alcohol and tobacco exposures, and these would have allowed us to estimate the risks for the whole of pregnancy exposure. We were not able to control for adolescents' early cannabis use, which would have enabled a test for the indirect pathway of prenatal alcohol and tobacco exposures on offspring cannabis use at the age of 17 years as suggested by some previous studies (De Genna et al., 2021). Although we were able to control for paternal tobacco smoking during pregnancy and maternal postnatal tobacco smoking, this study did not have data on prenatal drug exposures such as cannabis, cocaine, heroin and others. Given this limitation, more mechanistic studies are warranted to elucidate specific causal links. Further, we were not able to control for maternal mental health problems during pregnancy. However, we did adjust for self-reported history of maternal psychiatric disorder during conception and maternal depressive symptoms at 14-year follow-up as proxies for adolescents' predisposition to mental health and behavioural problems.

5. Conclusion

The findings of this study suggest that offspring exposed to prenatal alcohol and tobacco use during the first and third trimesters were at increased risk of cannabis use at the age of 17 years when compared to unexposed offspring. Although a number of studies of offspring exposed to prenatal alcohol and tobacco exposures have focused mainly on subsequent offspring alcohol and tobacco use, the results of this study add to the converging body of evidence that such adolescents should also be monitored for the risk of cannabis use at the end of adolescence. We identified that moderate amounts of unmeasured confounding would need to explain away the observed associations. Therefore, our findings need to be confirmed by other studies such as genetic sensitive studies that can elucidate specific causal pathways independent of social determinants. Nonetheless, this is additional strong evidence to support the recommendation that women should be encouraged to abstain from alcohol and tobacco during pregnancy.

Authors' contributions

BD conceived the hypothesis, designed the study, conducted longitudinal data analysis, interpretations of the results and wrote the first draft of the manuscript. GP, RT, KB, JN and RA contributed to the design of the study, reviewed the methodology, data analysis, interpretations of the results and contributed to critical revisions of the subsequent drafts of the manuscript for important intellectual content.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence

the work reported in this paper.

Acknowledgements

We are sincerely grateful for for all the Raine Study participants and their family who took part in this study and the Raine study team such as data collectors, data officers, clerical staff, data and cohort managers, research scientists and volunteers for data collection and cohort coordination for such long period of time. The National Health and Medical Research Council (NHMRC) for long term contribution to funding the Raine Study since initiation, the Raine Medical Research Foundation, The University of Western Australia (UWA), Curtin University, Women and Infants Research Foundation, Telethon Kids Institute, Edith Cowan University, Murdoch University and The University of Notre Dame Australia are acknowledged for providing funding for core management of the Raine Study. The 17-year follow-up of the Raine study was supported by the NHMRC Program grant #353514, Project Grants #1099655, and #1173991. Bereket Duko is a recipient of Curtin University International Postgraduate Research Scholarship (CIPRS) and the Raine Study PhD Top-Up Scholarship. Gavin Pereira was funded by NHMRC grants# 1099655 and 1173991, and the Research Council of Norway through Centre of Excellence, grant #262700. The funders had no role in the data collection, study design, the analysis, interpretations of the results, writing the reports and the decision to submit the paper for possible publication.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ntt.2022.107064.

References

Achenbach, T.M., 1999. The child behavior checklist and related instruments. In: Maruish, M.E. (Ed.), The Use of Psychological Testing for Treatment Planning and Outcomes Assessment, 2nd ed. Lawrence Erlbaum Associates, Mahwah, NJ.
Agrawal, A., Lynskey, M.T., 2006. The genetic epidemiology of cannabis use, abuse and dependence. Addiction 101 (6), 801–812.
AIHW, 2017. "National Drug Strategy and Household Survey 2016." Key Findings Online Data Tables. AIHW, Canberra.
Akin, A., Citin, B., 2007. The depression anxiety and StressScale (DASS): the study of validity and reliability. Educational Sci.: Theory Practice 7 (1), 260–268.
Alati, R., Lawlor, D.A., Mamun, A.A., Williams, G.M., Najman, J.M., O'Callaghan, M., Bor, W., 2007. Is there a fetal origin of depression? Evidence from the mater university study of pregnancy and its outcomes. Am. J. Epidemiol. 165 (5), 575–582.
Bagot, K.S., Milin, R., Kaminer, Y., 2015. Adolescent initiation of cannabis use and early-onset psychosis. Subst. Abus. 36 (4), 524–533.
Barker, D.J., Eriksson, J.G., Forsén, T., Osmond, C., 2002. Fetal origins of adult disease: strength of effects and biological basis. Int. J. Epidemiol. 31 (6), 1235–1239.
Barr, H.M., Bookstein, F.L., O'Malley, K.D., Connor, P.D., Huggins, J.E., Streissguth, A.P., 2006. Binge drinking during pregnancy as a predictor of psychiatric disorders on the structured clinical interview for DSM-IV in young adult offspring. Am. J. Psychiatry 163 (6), 1061–1065.
Bennett, D.S., Lewis, M., 2020. Does prenatal cocaine exposure predict adolescent substance use? Neurotoxicol. Teratol. 81, 106906.
Bogdan, R., Winstone, J.M.A., Agrawal, A., 2016. Genetic and environmental factors associated with cannabis involvement. Curr. Addict. Rep. 3 (2), 199–213.
Bolanis, D., Orri, M., Castellanos-Ryan, N., Renaud, J., Montreuil, T., Boivin, M., Vitaro, F., Tremblay, R.E., Turecki, G., Côté, S.M., Séguin, J.R., Geoffroy, M.-C., 2020. Cannabis use, depression and suicidal ideation in adolescence: direction of associations in a population based cohort. J. Affect. Disord. 274, 1076–1083.
Bower, C., Elliott, E.J., Zimmet, M., Doorey, J., Wilkins, A., Russell, V., Shelton, D., Fitzpatrick, J., Watkins, R., 2017. Australian guide to the diagnosis of foetal alcohol spectrum disorder: a summary. J. Paediatr. Child Health 53 (10), 1021–1023.
Buka, S.L., Shenassa, E.D., Niaura, R., 2003. Elevated risk of tobacco dependence among offspring of mothers who smoked during pregnancy: a 30-year prospective study. Am. J. Psychiatry 160 (11), 1978–1984.
Cortes, R.C., Fleming, C.B., Mason, W.A., Catalano, R.F., 2009. Risk factors linking maternal depressed mood to growth in adolescent substance use. J. Emot. Behav. Disord. 17 (1), 49–64.
Courtney, K.E., Mejia, M.H., Jacobus, J., 2017. Longitudinal studies on the etiology of cannabis use disorder: a review. Curr. Addict. Rep. 4 (2), 43–52.
Day, N.L., Goldschmidt, L., Thomas, C.A., 2006. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. Addiction 101 (9), 1313–1322.
De Genna, N.M., Goldschmidt, L., Day, N.L., Cornelius, M.D., 2017. Prenatal tobacco exposure, maternal postnatal nicotine dependence and adolescent risk for nicotine dependence: birth cohort study. Neurotoxicol. Teratol. 61, 128–132.
De Genna, N.M., Goldschmidt, L., Richardson, G.A., Cornelius, M.D., Day, N.L., 2021. Prenatal exposure to tobacco and cannabis, early cannabis initiation, and daily dual use of combustible cigarettes and cannabis during young adulthood. Addict. Behav. 116, 106820.
Degenhardt, L., Hall, W., Lynskey, M., 2001. The relationship between cannabis use, depression and anxiety among Australian adults: findings from the National Survey of Mental Health and Well-Being. Soc. Psychiatry Psychiatr. Epidemiol. 36 (5), 219–227.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2020. Associations of prenatal alcohol exposure and offspring harmful alcohol use: findings from the Raine Study. Drug Alcohol Depend. 217, 108305.
Duko, B., Pereira, G., Betts, K., Tait, R.J., Newnham, J., Alati, R., 2021a. Prenatal exposure to maternal, but not paternal, tobacco smoking is associated with smoking in adolescence. Addict. Behav. 117, 106871.
Duko, B., Pereira, G., Tait, R.J., Newnham, J., Betts, K., Alati, R., 2021b. Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: findings from the Raine study. J. Psychiatr. Res. 142, 1–8.
Dwyer, J.B., McQuown, S.C., Leslie, F.M., 2009. The dynamic effects of nicotine on the developing brain. Pharmacol. Ther. 122 (2), 125–139.
Ernst, M., Moolchan, E.T., Robinson, M.L., 2001. Behavioral and neural consequences of prenatal exposure to nicotine. J. Am. Acad. Child Adolesc. Psychiatry 40 (6), 630–641.
Fowler, C.D., Arends, M.A., Kenny, P.J., 2008. Subtypes of nicotinic acetylcholine receptors in nicotine reward, dependence, and withdrawal: evidence from genetically modified mice. Behav. Pharmacol. 19 (5–6), 461–484.
Franke, R.M., Park, M., Belluzzi, J.D., Leslie, F.M., 2008. Prenatal nicotine exposure changes natural and drug-induced reinforcement in adolescent male rats. Eur. J. Neurosci. 27 (11), 2952–2961.
Gobbi, G., Atkin, T., Zytynski, T., Wang, S., Askari, S., Boruff, J., Ware, M., Marmorstein, N., Cipriani, A., Dendukuri, N., Mayo, N., 2019. Association of cannabis use in adolescence and risk of depression, anxiety, and suicidality in young adulthood: a systematic review and Meta-analysis. JAMA Psychiatry 76 (4), 426–434.
Goldschmidt, L., Cornelius, M.D., Day, N.L., 2012. Prenatal cigarette smoke exposure and early initiation of multiple substance use. Nicot. Tobacco Res.: Off. J. Soc. Res. Nicotine Tobacco 14 (6), 694–702.
Guerin, N., White, V., 2018. Australian Secondary School Students' Use of Tobacco, Alcohol, and Over-The-Counter and Illicit Substances in 2017. Centre for Behavioural Research in Cancer, Victoria.
Haneuse, S., VanderWeele, T.J., Arterburn, D., 2019. Using the E-value to assess the potential effect of unmeasured confounding in observational studies. JAMA 321 (6), 602–603.
Hayatbakhsh, M.R., Alati, R., Hutchinson, D.M., Jamrozik, K., Najman, J.M., Mamun, A. A., O'Callaghan, M., Bor, W., 2007. Association of maternal smoking and alcohol consumption with young adults' cannabis use: a prospective study. Am. J. Epidemiol. 166 (5), 592–598.
Hayatbakhsh, M.R., Najman, J.M., Bor, W., O'Callaghan, M.J., Williams, G.M., 2009. Multiple risk factor model predicting cannabis use and use disorders: a longitudinal study. Am. J. Drug Alcohol Abuse 35 (6), 399–407.
Herbeck, D.M., Brecht, M.L., Lovinger, K., Raihan, A., Christou, D., Sheaff, P., 2013. Poly-drug and marijuana use among adults who primarily used methamphetamine. J. Psychoactive Drugs 45 (2), 132–140.
Hyman, S.E., 2005. Addiction: a disease of learning and memory. Am. J. Psychiatry 162 (8), 1414–1422.
Jacobus, J., Tapert, S.F., 2014. Effects of cannabis on the adolescent brain. Curr. Pharm. Des. 20 (13), 2186–2193.
Johnson, E.C., Demontis, D., Thorgeirsson, T.E., Walters, R.K., Polimanti, R., Hatoum, A. S., Sanchez-Roige, S., Paul, S.E., Wendt, F.R., Clarke, T.-K., Lai, D., Reginsson, G.W., Zhou, H., He, J., Baranger, D.A.A., Gudbjartsson, D.F., Wedow, R., Adkins, D.E., Adkins, A.E., Alexander, J., Bacanu, S.-A., Bigdeli, T.B., Boden, J., Brown, S.A., Bucholz, K.K., Bybjerg-Grauholm, J., Corley, R.P., Degenhardt, L., Dick, D.M., Domingue, B.W., Fox, L., Goate, A.M., Gordon, S.D., Hack, L.M., Hancock, D.B., Hartz, S.M., Hickie, I.B., Hougaard, D.M., Krauter, K., Lind, P.A., McClintick, J.N., McQueen, M.B., Meyers, J.L., Montgomery, G.W., Mors, O., Mortensen, P.B., Nordentoft, M., Pearson, J.F., Peterson, R.E., Reynolds, M.D., Rice, J.P., Runarsdottir, V., Saccone, N.L., Sherva, R., Silberg, J.L., Tarter, R.E., Tyrfingsson, T., Wall, T.L., Webb, B.T., Werge, T., Wetherill, L., Wright, M.J., Zellers, S., Adams, M. J., Bierut, L.J., Boardman, J.D., Copeland, W.E., Farrer, L.A., Foroud, T.M., Gillespie, N.A., Grucza, R.A., Harris, K.M., Heath, A.C., Hesselbrock, V., Hewitt, J.K., Hopfer, C.J., Horwood, J., Iacono, W.G., Johnson, E.O., Kendler, K.S., Kennedy, M. A., Kranzler, H.R., Madden, P.A.F., Maes, H.H., Maher, B.S., Martin, N.G., McGue, M., McIntosh, A.M., Medland, S.E., Nelson, E.C., Porjesz, B., Riley, B.P., Stallings, M.C., Vanyukov, M.M., Vrieze, S., Walters, R., Polimanti, R., Johnson, E., McClintick, J., Hatoum, A., He, J., Wendt, F., Zhou, H., Adams, M., Adkins, A., Aliev, F., Bacanu, S.-A., Batzler, A., Bertelsen, S., Biernacka, J., Bigdeli, T., Chen, L.-S., Clarke, T.-K., Chou, Y.-L., Degenhardt, F., Docherty, A., Edwards, A., Fontanillas, P., Foo, J., Fox, L., Frank, J., Giegling, I., Gordon, S., Hack, L., Hartmann, A., Hartz, S., Heilmann-Heimbach, S., Herms, S., Hodgkinson, C., Hoffman, P., Hottenga, J., Kennedy, M., Alanne-Kinnunen, M., Konte, B., Lahti, J., Lahti-Pulkkinen, M., Lai, D., Ligthart, L., Loukola, A., Maher, B., Mbarek, H., McIntosh, A., McQueen, M., Meyers, J., Milaneschi, Y., Palviainen, T., Pearson, J., Peterson, R., Ripatti, S., Ryu, E., Saccone, N., Salvatore, J., Sanchez-Roige, S., Schwandt, M., Sherva, R., Streit, F., Strohmaier, J., Thomas, N., Wang, J.-C.,

Webb, B., Wedow, R., Wetherill, L., Wills, A., Boardman, J., Chen, D., Choi, D.-S., Copeland, W., Culverhouse, R., Dahmen, N., Degenhardt, L., Domingue, B., Elson, S., Frye, M., Gäbel, W., Hayward, C., Ising, M., Keyes, M., Kiefer, F., Kramer, J., Kuperman, S., Lucae, S., Lynskey, M., Maier, W., Mannisto, S., Müller-Myhsok, B., Murray, A., Nurnberger, J., Palotie, A., Preuss, U., Räikkönen, K., Reynolds, M., Ridinger, M., Scherbaum, N., Schuckit, M., Soyka, M., Treutlein, J., Witt, S., Wodarz, N., Zill, P., Adkins, D., Boden, J., Boomsma, D., Bierut, L., Brown, S., Bucholz, K., Cichon, S., Costello, E.J., de Wit, H., Diazgranados, N., Dick, D., Eriksson, J., Farrer, L., Foroud, T., Gillespie, N., Goate, A., Goldman, D., Grucza, R., Hancock, D., Harris, K.M., Heath, A., Hesselbrock, V., Hewitt, J., Hopfer, C., Horwood, J., Iacono, W., Johnson, E., Kaprio, J., Karpyak, V., Kendler, K., Kranzler, H., Krauter, K., Lichtenstein, P., Lind, P., McGue, M., MacKillop, J., Madden, P., Maes, H., Magnusson, P., Martin, N., Medland, S., Montgomery, G., Nelson, E., Nöthen, M., Palmer, A., Pederson, N., Penninx, B., Porjesz, B., Rice, J., Rietschel, M., Riley, B., Rose, R., Rujescu, D., Shen, P.-H., Silberg, J., Stallings, M., Tarter, R., Vanyukov, M., Vrieze, S., Wall, T., Whitfield, J., Zhao, H., Neale, B., Gelernter, J., Edenberg, H., Agrawal, A., Davis, L.K., Bogdan, R., Gelernter, J., Edenberg, H.J., Stefansson, K., Børglum, A.D., Agrawal, A., 2020. A large-scale genome-wide association study meta-analysis of cannabis use disorder. Lancet Psychiatry 7 (12), 1032–1045.

Kedzior, K.K., Laeber, L.T., 2014. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population- a meta-analysis of 31 studies. BMC Psychiatry 14 (1), 136.

Koponen, A.M., Nissinen, N.-M., Gissler, M., Autti-Rämö, I., Sarkola, T., Kahila, H., 2020. Prenatal substance exposure, adverse childhood experiences and diagnosed mental and behavioral disorders – a longitudinal register-based matched cohort study in Finland. SSM - Population Health 11, 100625.

Kreek, M.J., Nielsen, D.A., Butelman, E.R., LaForge, K.S., 2005. Genetic influences on impulsivity, risk taking, stress responsivity and vulnerability to drug abuse and addiction. Nat. Neurosci. 8 (11), 1450–1457.

Lew, D., Xian, H., Qian, Z., Vaughn, M.G., 2019. Examining the relationships between life satisfaction and alcohol, tobacco and marijuana use among school-aged children. J. Public Health (Oxf) 41 (2), 346–353.

Linden, A., Mathur, M.B., VanderWeele, T.J., 2020. Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: the evalue package. Stata J. 20 (1), 162–175.

Liu, W., Petras, H., 2017. Chapter e3 - Aggressive behavior and cannabis use. In: Handbook of Cannabis and Related Pathologies. V. R. Preedy. Academic Press, San Diego, pp. e19–e28.

Lo, J.O., Schabel, M.C., Roberts, V.H.J., Wang, X., Lewandowski, K.S., Grant, K.A., Frias, A.E., Kroenke, C.D., 2017. First trimester alcohol exposure alters placental perfusion and fetal oxygen availability affecting fetal growth and development in a non-human primate model. Am. J. Obstet. Gynecol. 216 (3), 302.e301–302.e308.

Lotfipour, S., Leonard, G., Perron, M., Pike, B., Richer, L., Séguin, J.R., Toro, R., Veillette, S., Pausova, Z., Paus, T., 2010. Prenatal exposure to maternal cigarette smoking interacts with a polymorphism in the α6 nicotinic acetylcholine receptor gene to influence drug use and striatum volume in adolescence. Mol. Psychiatry 15 (1), 6–8.

Lynskey, M.T., Heath, A.C., Nelson, E.C., Bucholz, K.K., Madden, P.A., Slutske, W.S., Statham, D.J., Martin, N.G., 2002. Genetic and environmental contributions to cannabis dependence in a national young adult twin sample. Psychol. Med. 32 (2), 195–207.

McLachlan, K., Rasmussen, C., Oberlander, T.F., Loock, C., Pei, J., Andrew, G., Reynolds, J., Weinberg, J., 2016. Dysregulation of the cortisol diurnal rhythm following prenatal alcohol exposure and early life adversity. Alcohol (Fayetteville, NY) 53, 9–18.

Meier, M.H., Hill, M.L., Small, P.J., Luthar, S.S., 2015. Associations of adolescent cannabis use with academic performance and mental health: a longitudinal study of upper middle class youth. Drug Alcohol Depend. 156, 207–212.

Merikangas, K.R., Li, J.J., Stipelman, B., Yu, K., Fucito, L., Swendsen, J., Zhang, H., 2009. The familial aggregation of cannabis use disorders. Addiction 104 (4), 622–629.

Moore, S.E., Norman, R.E., Sly, P.D., Whitehouse, A.J.O., Zubrick, S.R., Scott, J., 2014. Adolescent peer aggression and its association with mental health and substance use in an Australian cohort. J. Adolesc. 37 (1), 11–21.

Moran, V.E., 2012. Cotinine: beyond that expected, more than a biomarker of tobacco consumption. Front. Pharmacol. 3, 173.

Newby, E.A., Myers, D.A., Ducsay, C.A., 2015. Fetal endocrine and metabolic adaptations to hypoxia: the role of the hypothalamic-pituitary-adrenal axis. Am. J. Physiol. Endocrinol. Metab. 309 (5), E429–E439.

Newnham, J.P., Evans, S.F., Michael, C.A., Stanley, F.J., Landau, L.I., 1993. Effects of frequent ultrasound during pregnancy: a randomised controlled trial. Lancet 342 (8876), 887–891.

NHMRC, 2009. Australian guidelines to reduce health risks from drinking alcohol. Commonwealth of Australia.: Pages 2, 3.

O'Brien, J.W., Hill, S.Y., 2014. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. Alcohol. Clin. Exp. Res. 38 (12), 2952–2961.

Parkington, H.C., Kenna, K.R., Sozo, F., Coleman, H.A., Bocking, A., Brien, J.F., Harding, R., Walker, D.W., Morley, R., Tare, M., 2014. Maternal alcohol consumption in pregnancy enhances arterial stiffness and alters vasodilator function that varies between vascular beds in fetal sheep. J. Physiol. 592 (12), 2591–2603.

Pfinder, M., Liebig, S., Feldmann, R., 2014. Adolescents' use of alcohol, tobacco and illicit drugs in relation to prenatal alcohol exposure: modifications by gender and ethnicity. Alcohol Alcohol. 49 (2), 143–153.

Porath, A.J., Fried, P.A., 2005. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicol. Teratol. 27 (2), 267–277.

Royston, P., 2005. Multiple imputation of missing values: update of ice. Stata J. 5 (4), 527–536.

Schmidt, K., Tseng, I., Phan, A., Fong, T., Tsuang, J., 2020. A systematic review: adolescent Cannabis use and suicide. Addict. Disord. Treat. 19 (3).

Smith, M.V., Gotman, N., Yonkers, K.A., 2016. Early childhood adversity and pregnancy outcomes. Matern. Child Health J. 20 (4), 790–798.

Sterne, J.A.C., White, I.R., Carlin, J.B., Spratt, M., Royston, P., Kenward, M.G., Wood, A. M., Carpenter, J.R., 2009. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. BMJ 338, b2393.

Stick, S.M., Burton, P.R., Gurrin, L., Sly, P.D., LeSouëf, P.N., 1996. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. Lancet 348 (9034), 1060–1064.

Straker, L., Mountain, J., Jacques, A., White, S., Smith, A., Landau, L., Stanley, F., Newnham, J., Pennell, C., Eastwood, P., 2017. Cohort profile: the Western Australian Pregnancy Cohort (Raine) study-generation 2. Int. J. Epidemiol. 46 (5), 1384–1385j.

Tarter, R., Kirisci, L., Reynolds, M., 2014. A new approach to researching the etiology of cannabis use disorder: integrating transmissible and nontransmissible risk within a developmental framework. Subst. Abus. 35 (4), 336–343.

VanderWeele, T.J., Ding, P., 2017. Sensitivity analysis in observational research: introducing the E-value. Ann. Intern. Med. 167 (4), 268–274.

Verweij, K.J.H., Zietsch, B.P., Lynskey, M.T., Medland, S.E., Neale, M.C., Martin, N.G., Boomsma, D.I., Vink, J.M., 2010. Genetic and environmental influences on cannabis use initiation and problematic use: a meta-analysis of twin studies. Addiction 105 (3), 417–430.

Volkow, N.D., Baler, R.D., Compton, W.M., Weiss, S.R.B., 2014. Adverse health effects of marijuana use. N. Engl. J. Med. 370 (23), 2219–2227.

Weinberg, J., Sliwowska, J.H., Lan, N., Hellemans, K.G., 2008. Prenatal alcohol exposure: foetal programming, the hypothalamic-pituitary-adrenal axis and sex differences in outcome. J. Neuroendocrinol. 20 (4), 470–488.

Chapter 9: General discussion and conclusion

Chapter 9: General discussion and conclusion

9.1 Chapter overview

The prenatal period is a critical time of great vulnerability for the developing brain that can be influenced by several health hazardous. Prenatal alcohol and tobacco exposures are some of such modifiable risk factors, and have been suggested to impact on offspring adverse mental health and substance use outcomes later in life (1-4). However, the findings of those few available epidemiological studies are inconclusive and suggested the need for further examinations. To address the gaps identified in the literature, various data sources and statistical modelling approaches were followed. Data sources included several electronic databases and the use of birth cohort data to attempt causal inference. Statistical modelling included meta-analysis, log-binomial regression, negative-binomial regression, multinomial logistic regression, negative control analysis and computing E-values. More comprehensive discussion, conclusions, strengths, and limitations of the nine papers were incorporated into the respective chapters of this thesis (chapter 4-8). Therefore, this chapter provides a brief summary of the main findings, discussion, public health implications, strengths and limitations, directions for future research and conclusion.

9.2 Main findings

9.2.1 Findings from the three systematic reviews and meta-analyses (three papers)

The first two systematic reviews and meta-analyses (SRMAs) included in this thesis examined the associations between prenatal tobacco exposure and offspring mental health and substance use outcomes. To my knowledge, these SRMAs are the first to examine the magnitude and consistency of associations reported by previous epidemiological studies on the topics. The results of these SRMAs showed increased pooled relative risks of depressive and bipolar disorders, tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence in offspring exposed to prenatal tobacco use compared to non-exposed offspring. More specifically, there were suggestions of dose-response associations as risk estimates were more elevated amongst offspring exposed to heavy maternal prenatal tobacco smoking when compared to offspring exposed to lower levels of tobacco smoking in pregnancy. Estimates did not substantially change after adjustment for a wide range of potential confounders including previous mental health problems in offspring and parents, and postnatal exposure to substance use and socio-economic position. Taken together, these results suggest

that avoiding tobacco smoking during pregnancy should be a greater priority for intervention to avoid adverse consequences that can be observed in adolescence and young adulthood.

A previous epidemiological study has indicated that more specific associations between prenatal alcohol and tobacco exposures on offspring substance use during adolescence, suggesting that prenatal alcohol exposure was associated with offspring alcohol use and similarly prenatal tobacco exposure was linked with offspring tobacco smoking (5). Therefore, an additional systematic review was also conducted to examine the association between prenatal alcohol exposure and offspring alcohol use. This was also the first systematic review on the topic. Existing studies on the topic are few and geographically limited to developed countries. More than 90% of the studies included in this review reported an increased risk of alcohol use disorder or increased level of alcohol drinking in offspring exposed to prenatal alcohol use. The large variability across studies in the definitions of low, moderate, heavy or *binge-level* prenatal alcohol exposure and the timepoint at which prenatal alcohol exposure occurred (first, second or/and third trimester or all) may limit more conclusive inference, and also limited the ability to undertake a meta-analysis.

9.2.2 Findings from the Raine Study (six papers)

This PhD project further examined the associations between prenatal alcohol and tobacco exposures and the risk of conduct disorder, depressive and anxiety symptoms in adolescent and young adult offspring using longitudinal prospective birth cohort data from the Raine Study. Associations between prenatal alcohol and tobacco exposures and offspring subsequent alcohol, tobacco and cannabis use in late adolescence were also examined. The risk of depressive symptoms in adolescents exposed to maternal alcohol use of six or more standard drinks of alcohol per week and any amount of tobacco smoking per day during the first three months of pregnancy was approximately 50% higher when compared to those non-exposed. We found insufficient statistical evidence for an increased risk of depressive symptoms in offspring exposed to lower amount of maternal alcohol consumption during the first three months of pregnancy. Similarly, while young adults exposed to prenatal tobacco use tend to experience more symptoms of anxiety (as much as 50% greater than their non-exposed counterparts), such outcomes were not observed for offspring exposed to prenatal alcohol use. It is important to note that this finding could be either reflect the existence of no harmful effect, or possibly more likely, that a harmful effect exists but was not observable within this particular cohort. Consequently, this finding should be confirmed by additional studies as this is the first prospective cohort study to investigate the association between prenatal alcohol exposure and offspring anxiety symptoms in young adulthood (Chapter 4). Further, slightly increased risk

estimates in offspring exposed to higher levels of maternal alcohol consumption during pregnancy, limit us from concluding that there is a safe level of alcohol consumption during the prenatal period in relation to future anxiety symptoms in offspring. Associations reported in this thesis were independent of sociodemographic variation, predisposition to maternal and paternal mental health problems and paternal smoking during pregnancy. Moreover, associations did not appear to be mediated by the effects of prenatal alcohol and tobacco use on adverse pregnancy and birth outcomes.

Previous longitudinal studies linking maternal prenatal tobacco smoking to offspring conduct disorder symptoms have produced inconsistent findings. Therefore, investigating maternal and paternal tobacco smoking during pregnancy may provide additional clarity as to the etiological basis for conduct disorder symptoms. Such design would distinguish between shared or socioeconomic status or environmental influences which are difficult to disentangle using conventional statistical adjustment. If maternal tobacco smoking during pregnancy but not paternal tobacco smoking is linked with an increased risk of conduct disorder symptoms in offspring, this may provide more support for a pathway via in *utero* exposure. Such a study was also included in this thesis. Specifically, the prospective association between maternal prenatal tobacco smoking and conduct disorder symptoms in offspring was compared with effects of paternal prenatal tobacco smoking on offspring outcome. The risk of conduct disorder symptoms (CD) was 52% greater for adolescents exposed to prenatal tobacco use when compared to those non-exposed. The higher rates of CD symptoms observed with increasing levels of prenatal tobacco exposure pointed to a dose-response relationship, such that those adolescents born to mothers smoking more than 10 cigarettes per day during pregnancy had much higher point estimates of risk (RR) compared to those smoking fewer cigarettes. Estimates were robust to controlling for potential confounders. Paternal tobacco smoking during partner's pregnancy had no notable effect on CD symptoms in offspring, suggesting a biological effect of maternal tobacco smoking during pregnancy on offspring CD symptoms (Chapter 5). These findings make a significant contribution to strengthening the evidence base for an effect of maternal prenatal tobacco smoking on the risk of conduct disorder symptoms in young adolescence.

In chapters 6-8, associations between prenatal alcohol and tobacco exposures and offspring subsequent alcohol use, tobacco smoking and cannabis use at the age of 17 years were also examined. Adolescents exposed to four or more standard drinks of alcohol per week during the first and third trimesters of pregnancy had a 1.86-fold increased risk of consuming alcohol at harmful levels when compared to those non-exposed. The risk of harmful alcohol use in

offspring increased in magnitude with increasing exposure to maternal alcohol use during pregnancy. No associations were observed between maternal pre-pregnancy and postnatal alcohol use and offspring harmful alcohol use, indicating specificity to prenatal timing of exposure. Similarly, adolescents exposed to prenatal tobacco use had an increased risk of tobacco smoking at the age of 17 years when compared to those non-exposed offspring (Chapter 7). Adjustment for potential confounders including a negative control exposure did not alter the findings, while a non-significant association was observed between paternal tobacco smoking during partner's pregnancy and offspring tobacco smoking during adolescence. These findings indicate that again, the associations are more likely to reflect true effects of exposure via mothers' tobacco smoking during pregnancy.

The risk of cannabis use was 38% and 42% higher for offspring exposed to prenatal alcohol and tobacco use, respectively after adjusting for a wide range of potential confounders. Dose-response associations were also observed, based on risk estimates that were slightly elevated amongst offspring exposed to higher levels of prenatal alcohol and tobacco use when compared to lower levels of prenatal exposure. Again, as this was the first study using prospectively collected data to investigate the association between prenatal alcohol exposure and offspring cannabis use in late adolescence, the findings of this thesis should be replicated in future studies with better capacity to account for confounding and timing of the exposure (Chapter 8).

9.3 Discussion of main findings

A few available epidemiological studies have shown significant associations between prenatal alcohol and tobacco exposures and a number of mental health and substance use outcomes in offspring. This thesis has further strengthened such evidence by testing prospective associations between maternal prenatal alcohol and tobacco exposures and the risk of mood disorders, depressive, anxiety and conduct disorder symptoms, as well as substance use in offspring using meta-analytical approaches and a population-based birth cohort study. Evidence from these analyses suggested increased risks of developing adverse mental health and substance use outcomes in offspring exposed to prenatal alcohol and tobacco use. The following sections separately discuss associations between prenatal alcohol and tobacco exposures and specific mental health and substance use outcomes in offspring.

9.3.1 Prenatal alcohol exposure and offspring mental health and substance use outcomes

Adolescents exposed to prenatal alcohol use had an increased risk of developing depressive symptoms when compared to those non-exposed (Chapter 4). This is in line with the findings of those few available epidemiological studies that reported similar observations (1, 6). For

instance, Easey et al. tested the association between prenatal alcohol exposure and offspring depression using the longitudinal data from 14,062 mother-offspring pairs in the Avon Longitudinal Study of Children and Parents (ALSPAC) (6). In that study and, in line with our findings, offspring exposed to prenatal alcohol use during the first trimester were more likely to report depressive symptoms compared to those non-exposed. Other studies have produced conflicting results (7, 8). A prospective cohort study examined the association between prenatal alcohol use and the risk of internalizing behaviors in offspring suggested that offspring exposed to maternal alcohol use of six or more standard drinks during the first three months of pregnancy were less likely to develop internalizing behaviors including depression when compared to those non-exposed and exposed to occasional alcohol use (8). However, that study combined 'abstainers' with 'occasional prenatal alcohol use' as a reference control group as well as using parent report from the Child Behavior Checklist (CBCL) to measure outcomes in offspring, parental report of CBCL has been found to be a weak report, while child ratings from the CBCL outweigh parental ratings in identifying childhood internalizing behaviors (9). Moreover, multi-informant approaches have been recommended in the assessment of young children's CBCL syndromes (10). At the same time, however, non-significant association was observed between prenatal alcohol exposure and the risk of experiencing symptoms of anxiety in young adults, which is consistent with the results from several previous studies (11-14). In support of these findings, a large prospective longitudinal study of more than thirty thousand offspring from the Danish National Birth Cohort found that children exposed to prenatal alcohol consumption of five or more alcohol units during the first and third trimesters were less likely to report emotional/anxiety symptoms (11). An additional study also reported similar findings (12). It is also plausible that the effects of prenatal alcohol exposure have longer latency, thereby requiring further follow-up to observe associations.

The findings from this thesis also advance the existing body of evidence with regard to the risk of harmful alcohol use in offspring exposed to prenatal alcohol use (Chapter 6). As mentioned in the earlier section, after controlling for several confounders including paternal and maternal prenatal tobacco exposures, adolescents exposed to four or more standard drinks of alcohol per week during the first and third trimesters of pregnancy had a 1.86-fold increased risk (86%) of consuming alcohol at harmful levels. These results are consistent with other epidemiological studies (15-18). In addition to harmful alcohol use, the results of this thesis also suggested that offspring exposed to prenatal alcohol use had an increased risk of cannabis use in late adolescence. This finding is in line with the results of the few available epidemiological studies that observed an association between prenatal alcohol exposure and risk of illicit drug use in

offspring (5, 7, 19). Most notably, a US based prospective cohort study reported an increased risk of illicit drug use in offspring exposed to prenatal alcohol use even after adjusting for familial history of alcohol dependence (5). Therefore, avoiding alcohol consumption during prenatal period is the safest option for mothers and children and this should be promoted via public health interventions.

9.3.2 Prenatal tobacco exposure and offspring mental health and substance use outcomes

The risk of depressive symptoms in offspring exposed to prenatal tobacco use was approximately 50% higher when compared to those non-exposed. This association persisted after adjusting for available confounders. These findings were consistent with evidence from some previous studies (20-23), but not all (24-26). For instance, a US based prospective cohort study found small associations in the opposite direction, suggesting male offspring born to mothers smoking 10 or more cigarettes/day during pregnancy are protected from mood disorders or are less likely to develop mood disorders (24). However, that study had a very small sample size (n=238) and may therefore be sensitive to even small amounts of bias.

Increased risk of experiencing anxiety symptoms (as much as 50% greater) was also observed in young adults of mothers who reported tobacco smoking during the first and third trimesters of pregnancy compared to those non-exposed. A dose-response association was also observed between prenatal tobacco exposure and the risk of experiencing symptoms of anxiety in young adults. These findings are consistent with the results of a few studies that reported significant associations between prenatal tobacco exposure and risk of internalizing behaviors such as anxiety and emotional symptoms in children and adolescents (21, 22, 27-29). Nonetheless, other studies found null associations (30, 31). For instance, a prospective study that combined the data of two birth cohorts namely the Avon Longitudinal Study of Parents and Children and Brazilian Pelotas study reported insufficient statistical evidence for association between prenatal tobacco smoking and internalizing problems in preschool children at 4 years of age after adjusting for maternal socioeconomic status, parental psychopathology and alcohol consumption (31). This was an informative study, as it had both a very large sample size and utilised two different birth cohorts conducted in two different parts of the world. However, the children in both studies were very young. The lack of evidence for an association may reflect varying offspring ages of assessment and variations in the included confounders. Most notably, evidence from few available epidemiological studies demonstrated that anxiety symptoms are more observable as the age of children and adolescent increases (32) and this may potentially

limit the capacity of that study to observe associations among younger children with follow-up ending prior to young adulthood.

The results presented in this thesis further advance the existing evidence by testing the prospective association between maternal prenatal tobacco smoking and CD symptoms in offspring using paternal prenatal tobacco smoking as a proxy for environmental tobacco smoke exposure. The risk of developing conduct disorder symptoms was 52% higher for adolescents exposed to maternal prenatal tobacco use. Paternal prenatal tobacco smoking had no notable effect on CD symptoms in offspring, supporting the view that maternal prenatal tobacco use may have in utero effects on offspring CD symptoms. The findings were consistent with some studies (31, 33-35) but not all (36-39). For instance, a US based study observed insufficient evidence for an increased risk of CD symptoms in offspring exposed to maternal tobacco smoking during pregnancy (36). However, that study examined prenatal tobacco exposure using a retrospective method, which could have introduced exposure misclassification due to recall bias, thereby contributing to less precise estimates.

Similarly, we have also examined the prospective association between maternal prenatal tobacco exposure and the risk of tobacco smoking in offspring using paternal tobacco smoking during partner's pregnancy as a negative control exposure. We noted that offspring born to mothers who reported tobacco smoking during pregnancy had increased risks of tobacco smoking at the age of 17 years. Varying level of statistical adjustment for potential confounders including a negative control did not alter the observed associations. This observation supports the findings of the existing epidemiological studies that suggested an increased risk of tobacco smoking or dependence in offspring exposed to prenatal tobacco use (40-44). Nonetheless, a few previous studies have produced conflicting results. For instance, a retrospective cohort study from the US reported that prenatal tobacco exposure was associated with tobacco smoking in girls only (45). However, the findings of that study were based on a relatively small sample size (N=797). In contrast, we did not find statistical evidence for gender differences in the association between prenatal tobacco exposure and tobacco smoking in offspring.

Similarly, the findings of this study revealed that adolescents exposed to prenatal tobacco use had an increased risk of cannabis use when compared to those non-exposed. This finding was consistent with findings from a US based cohort study that reported a prospective association between prenatal tobacco exposure and the risk of cannabis use in offspring after controlling for sociodemographic, environmental, prenatal alcohol and cannabis exposures, and child and maternal mental health problems (46). Nonetheless, some studies have produced conflicting results (47-49). For instance, a US based longitudinal study observed non-significant

association between prenatal tobacco exposure and cannabis use in offspring at the age of 14 years (47). The Ottawa Prenatal Prospective Study (OPPS) has also found a similar finding (48). These seemingly conflicting findings may be due to variability in offspring ages of assessment, such that cannabis use is more prevalent as the age of adolescents increases and this may hinder the statistical capacity of specific studies to observe similar behaviours in younger adolescents.

9.4 Potential mechanisms

The precise mechanisms explaining long-term effects of prenatal alcohol and tobacco exposures on offspring mental health and substance use outcomes are difficult to ascertain due to the confounding effects of several familial, epigenetic, genetic, developmental, and environmental risk factors (50-52). Several mechanisms that may explain the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes have been explained in this thesis. Notable mechanisms are discussed below.

Epidemiological studies suggest that prenatal exposure to alcohol may result in dose-responsive constriction of blood vessels in the placenta which in turn may elevate blood pressure and decrease placenta weight (53, 54). A recent systematic review has also highlighted that prenatal tobacco exposure was associated with impaired placental vascularization (55), which in turn influences birth weight (56). The placental vasoconstriction may result in placental and fetal hypoxia (57). Epidemiological evidence suggests that prenatal hypoxia may result in long-term impairments of the dopaminergic systems which can endures into adulthood (58). The corresponding physiological alterations may significantly affect the function of dopamine neurotransmitter (59) and contribute to the development of mental health and substance use outcomes in offspring.

An indirect proposed mechanism detailing the associations reported in this thesis is that prenatal alcohol and tobacco exposures may affect placental blood circulation, putting the fetus at increased risk of preterm birth, low birthweight and small for gestational age (60-62); which in turn may result in mental health and behavioural problems in offspring via such mediation (63, 64). However, we did not find evidence of mediation via preeclampsia, preterm birth and low birthweight.

One of the proposed direct mechanisms linking prenatal tobacco exposure and offspring mental health and substance use outcomes is that the neurotoxic components that have an addictive effect, and consists of thousands of hazardous compounds present in tobacco smoke that are able to cross the placenta (65). This in turn can minimize the neuronal area in several regions of the hippocampus, ‘a complex brain structure with main role of learning and memory’, and

prompt irreversible modifications to the brain cell structure, which persists into young adulthood and even beyond (66). Further, evidence from *in vivo* studies indicates that exposure to prenatal tobacco smoking may impact the role of dopamine and serotonin (67-69), which are neurotransmitters that have been linked to several mental health problems in humans. Further, maternal prenatal tobacco exposure was linked with morphological and neurochemical alternations of the parts of the brain regulating the reward system and reward-driven behaviours in offspring (70), supporting the elements of the hypothesis that link maternal prenatal substance exposures with offspring subsequent brain vulnerability to substance addiction that endures into adulthood (71).

Evidence from *in vivo* studies suggested that prenatal exposure to alcohol (ethanol) and tobacco (nicotine) may be associated with mood disturbance and depression-like behavior in rat offspring (72-74). Additional *in vivo* studies have also reported that such exposures during prenatal period may increase the propensity of exposed offspring to consume much alcohol and nicotine compared to non- exposed (75, 76). For instance, a study that administered 5.8 g/kg of ethanol (alcohol) to pregnant mice during preimplantation phase reported significant growth retardation and physical malformations in nearly all viable embryos (77), suggesting teratogenic effects of alcohol exposure during the preimplantation period. Similarly, offspring of mice exposed to maternal prenatal nicotine demonstrated an increased nicotine preference during adolescence compared to those non-exposed (76). In human studies such experimentation would be unethical, however, our findings could provide additional evidence for the role of prenatal alcohol and tobacco exposures in the development of mental health substance use outcomes in offspring.

Genetic predisposition to maternal and paternal mental health problems may also play a significant role in the development of mental health and substance use outcomes in offspring. Several epidemiological studies have documented that the risks of developing mental health and substance use problems are substantially higher in the close relatives of affected probands when compared to health controls (78-81). To support this explanation, a meta-analysis synthesized the results of six studies with a total of more than fifteen thousand mother-child dyads found that the odds of developing depression in offspring of mothers with perinatal depression increased approximately by 2-fold (80), which may be a predictor for offspring alcohol use (81).Further, close relatives of probands with anxiety disorders are at four to six-fold increased risk for anxiety disorders when compared to healthy controls (78). Nonetheless, the genetic liability to anxiety disorders ranged from 30–40% (78), suggesting that other presumptive risk factors such as prenatal alcohol drinking and tobacco smoking may explain

the remaining proportion. Such a hypothesis is compatible with findings from our study, where further adjustment for previous maternal mental health problems during pregnancy, maternal depressive and anxiety symptoms at 14-year follow-up as proxies for offspring predisposition to psychiatric conditions slightly attenuated the risk estimates. Furthermore, estimates from twin and adoption studies also suggested that 50% of the variability in alcoholism liability is linked with genetic predisposition (82), suggesting other risk factors may explain the remaining contribution. Although we were not able to measure genetic contributions, maternal pre-pregnancy and postnatal alcohol use were dealt out in our sequential models, but they did not appear to change associations reported in this thesis.

Maternal prenatal alcohol and tobacco exposures have also been linked with dysregulated expression of microRNA and altered DNA methylation in the offspring (83, 84). Differential methylation of CpG-sites in related genes has been associated with the dysregulation of hypothalamic-pituitary-adrenocortical (HPA) axis (85). The corresponding dysregulation of HPA axis may result in various of form of psychiatric disorders such as mood disorders (86), major depressive disorder (87), anxiety disorders (88), addiction (89) and others (90, 91) and could be via epigenetic mechanisms. These observations are further supported by evidence from *in vivo* studies, which reported that alcohol and nicotine exposures during gestation can induce HPA axis-hypersensitivity in the exposed offspring of rodents (92, 93).

An alternative speculation may suggest substance use during adolescence may be largely affected by parental behaviors (94, 95). This interpretation is supported by social learning theories that propose adolescents living in an environment where alcohol is consumed may drink alcohol because drinking by their parents or care givers that is sustained over a period of time normalizes the behavior (96, 97). Most notably, a longitudinal study from Australia reported that adolescents living with mothers consuming a higher amount of alcohol occasionally and in irregular intervals were at increased odds of developing problematic alcohol use in adolescence than mothers consumed no alcohol (98). Similarly, adolescents may initiate tobacco smoking by *emulating* the behaviour of their parents' smoking (99, 100). A systematic review and meta-analysis that synthesized the results of 58 observational studies linking parental tobacco smoking to child subsequent tobacco smoking observed that the odds of adolescents' tobacco smoking increase approximately by two-fold if at least one parent or family member smoke tobacco (100). In our study, further adjustment for postnatal maternal alcohol and tobacco use attenuated the strength of the association between prenatal alcohol and tobacco exposures and offspring harmful alcohol use and tobacco smoking, respectively.

Epidemiological evidence may also suggests that children exposed to parental tobacco smoking when they were young children may develop adverse mental health problems later in life (101, 102). A study based in the US observed that postnatal tobacco smoke exposure was significantly linked with mental health problems in offspring after adjusting for a number of confounders (103). This is also supported by findings from a French study that examined the effects of pre-and postnatal tobacco exposures on offspring mental health and behavioural problems (104). In that study, the odds of developing internalizing behaviours was 72% and 38% greater for children exposed to pre- and postnatal maternal tobacco smoking, suggesting that postnatal tobacco smoking results in a 34 percentage point elevation in odds of developing internalizing behaviours compared to prenatal tobacco smoking. Similarly, a slight attenuation in the risk estimates was also observed in all studies included in this thesis after adjusting for postnatal maternal tobacco smoking.

Isolating whether prenatal alcohol and tobacco exposure contributes as a causes of offspring mental health and substance use outcomes is difficult. Associations reported in this thesis may be due to confounders such as maternal and familial socio-economic positions and parenting style which are associated with prenatal tobacco smoking and alcohol drinking (105, 106). For instance, maternal alcohol drinking and tobacco smoking during pregnancy may be associated with certain parenting style (107). Such parenting styles could include relatively harsh parenting that involves physical punishment, child maltreatment, rejection and over-protection (107, 108), which in turn may result in mental health and behavioural problems in adolescents (109), possibly by lowering self-esteem. Further, epidemiological studies have also suggested that women smoking tobacco during pregnancy were more likely to report lower academic level, income and social class (110-112). These in turn have been associated with mental health and substance use problems in offspring (113, 114). This is also supported by a Dutch population-based cohort study examining prospective associations between prenatal tobacco smoking and offspring mental health problems where a significant association was found in unadjusted analysis; whereas, insufficient statistical evidence was reported after adjustment for parental educational attainment and family income (OR 1.22, 95% CI 0.90–1.63) (115), suggesting parental socioeconomic positions accounted for the greater risk of mental health problems in offspring (116). Several socio-economic factors that may influence the association between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes such as maternal age, education, marital status, parity, and family income were included as covariates in the analysis in the papers within this thesis, but such confounding did not appear to fully explain the findings reported in this thesis.

9.5 Public health implications of the findings

With the growing burden of mental health and substance use problems in adolescents and young adults, the findings of this thesis have a number of public health implications. The findings of this thesis demonstrate that prenatal alcohol and tobacco exposures were associated with increased risks of mental health and substance use problems in the adolescent and young adult cohorts investigated. The relative risks for most outcomes investigated, where higher in magnitude in adolescents and young adults exposed to higher amounts of maternal prenatal alcohol and tobacco use when compared to those with lower levels of prenatal exposure, suggesting dose-response associations. The primary implications are presented in this section, and mainly provide further empirical evidence to avoid alcohol and tobacco consumption during pregnancy. These may help reduce the risk of adverse mental health and substance use outcomes in subsequent generations. To mitigate the effects of prenatal alcohol and tobacco exposures on adverse offspring outcomes, the interventions efforts need to target individuals early, possibly from adolescence through young adulthood. Strengthening the existing school-based prevention programs for alcohol and tobacco use (e.g. social influence approach), which are critically important to reduce such substance use later in young adulthood, when young women become pregnant (117). It has been proposed that such intervention could potentially increase knowledge about specific substances and also improve attitudes towards substance use (118). Misinformation is also of concern. A study that retrieved information on consumption of alcohol in relation to pregnancy and breastfeeding from the websites of 23 alcohol industry–funded bodies reported that these bodies contributed to misinformation and thereby increase the rates of maternal alcohol consumption during pregnancy (119). Consistency in policy advice related to alcohol consumption in pregnancy is also warranted. Although several countries, including Australia, have revised policies detailing alcohol use in the last few years, there is substantial variability in policy advice on alcohol consumption during pregnancy (120, 121). Most notably, the WHO recommendation on alcohol use states that ‘pregnant women should not drink’(121) while some countries state ‘not drinking alcohol during pregnancy is the safest option’. Maternal alcohol consumption and tobacco smoking (including exposure to passive smoke) should be frequently monitored during pregnancy with additional social support provided to promote abstinence of alcohol and tobacco from the time of pregnancy attempt for planned pregnancies, or from the time at which pregnancy is recognised for other pregnancies. In Australia, approximately 56% of pregnant women reported consuming alcohol while not knowing their pregnancy status (122). Nonetheless, a relatively

large number of pregnant women (26%) continued consuming alcohol once they knew they were pregnant. Similarly, the rates of tobacco smoking were slightly greater in the first 20 weeks of gestation (11%) compared to after 20 weeks of pregnancy (8%) (122). Strengthening the accessibility and availability of nicotine replacement therapy (NRT) may help reduce cravings and withdrawal symptoms when women quit tobacco smoking. Most notably, evidence from the available epidemiological studies suggests that all forms of commercially available NRTs could potentially increase the rate of quitting tobacco smoking by 50 to 70% (123). Obstetric and public health programs could place greater emphasis on psychological and educational interventions. For instance, evidence from several systematic reviews suggests that psychological and educational interventions may decrease the propensity of pregnant women to drink alcohol or increase abstinence from alcohol during pregnancy (124, 125). Further, smoking cessation interventions are also recommended to avoid or reduce the rates of tobacco smoking during pregnancy. In a Cochrane review that included a total of 102 randomised controlled and 9 cluster-randomised trials; counselling, regular feedback and incentives are found to be effective to assist pregnant women to quit tobacco smoking (126, 127). Moreover, strengthening the efforts on early detection and interventions of mental health and substance use problems in adolescents and young adults is also imperative. Most notably, well-designed and technology-sensitive peer support prevention strategies such as 'The Mind Your Mate Study' that can be easily available to individuals across different settings are also important (128). Such peer support prevention strategy could potentially facilitate discussion around mental health and reduce the impact of mental health and substance use problems in adolescents and young adults (128).

9.6 General strengths and limitations

The three systematic reviews and meta-analyses incorporated into this thesis were the first to provide up to date and summarised evidence on the magnitude and consistency of associations reported between prenatal alcohol and tobacco exposures and the risk of subsequent alcohol and tobacco use as well as mood disorders in offspring. As per the Preferred Reporting Items for Systematic review and Meta-Analysis guidelines, all SRMAs included in this thesis were prospectively registered in the international prospective register of systematic reviews (PROSPERO). To minimize possible reviewer bias, predefined search strategies, data extraction protocols and the methodological quality appraisal of studies included in those SRMAs were performed by two independent reviewers. Further, subgroup and sensitivity analyses including leave-one-out-sensitivity analysis were conducted to identify sources of

heterogeneity. Offspring adverse outcomes such as depression, bipolar disorder, alcohol, and tobacco subsequent use were ascertained using the standard and validated screening and diagnostic tools including those using ICD 9/10 and DSM IV criteria. Moreover, our literature searches did not have language and date limits.

The wide range of prenatal and postnatal measures and relatively large sample of the Raine Study allowed the examination of specific directional hypotheses across an extended period of follow-up. We were able to measure and adjust for a wide range of sociodemographic, child and familial characteristics that could potentially confound the effects of prenatal alcohol and tobacco exposures on offspring mental health and substance use outcomes. Prenatal alcohol and tobacco exposures were prospectively measured during the first and third trimesters of pregnancy, which confirm that ascertainment of exposure status was unaffected by retrospective recall bias. Validation of self-reported maternal smoking status with biological markers of tobacco smoking (e.g. serum cotinine levels) is also a study strength. Cotinine is considered as gold standard biomarker of tobacco smoke exposure (129). The results from that validation study revealed a strong agreement between reported and biological measured smoking status (130). Similarly, offspring adverse outcomes such as conduct disorder, depressive and anxiety symptoms as well as alcohol, tobacco and cannabis use during adolescence and in young adulthood were prospectively collected and ascertained using well-accepted standardized, validated and recommended screening tools (131-133). Adjustments for the effects of paternal smoking during pregnancy, pre-pregnancy maternal alcohol use and postnatal maternal alcohol and tobacco consumption on offspring adverse outcomes, further strengthen the robustness of our findings and provide some support that the associations observed may be causal. The examination of the role of mediators, the application of sequential models, performing additional sensitivity analysis and including multiple imputations to examine the impact of missing data on overall estimates are also strengths of this thesis. Trimester-specific analyses to identify risks in terms of gestational age was also performed. Moreover, one practicable quantitative approach to identifying the potential of whether the results are attributable to confounding is by computing E-values, which was also applied in this thesis (134, 135).

The following limitations should be considered when interpreting the findings of this thesis. In the two meta-analyses, we did not analyse gender, age and study design specific effect estimates due to lack of sufficient and consistent data from the included studies. In some of the studies included in the meta-analysis on the association between prenatal tobacco exposure and offspring mood disorders, the follow up period may have been too short to observe validated

and diagnosed mood disorders. Epidemiological studies included in the systematic review of the association between prenatal alcohol exposure and offspring subsequent alcohol use used varying definitions of low, moderate, heavy or *binge* prenatal alcohol use, which limited the ability to undertake a meta-analysis.

The primary studies based on the Raine cohort data did not include variables on paternal alcohol consumption during partners' pregnancy and second trimester prenatal alcohol and tobacco exposures, these would have allowed for inclusion of another negative control exposure and to produce estimates for whole pregnancy exposures, respectively. Loss to follow-up in this thesis was relatively high, although can be expected for such a long period of follow-up of the cohort and this may have introduced bias. However, the patterns of prenatal alcohol and tobacco use did not differ between those lost to follow-up and those retained in the study. This suggests that attrition is unlikely to have introduced substantial bias and it is unlikely that the bias is directional. Further, a previous epidemiological study that examined the potential bias that may come and go due to recruitment, selection, and loss of study participants demonstrated that the Raine Study had no evidence of significant perinatal selection bias namely recruitment and attrition bias (136). Similarly, we observed negligible variation in the final estimates after repeating sensitivity analyses with multivariate imputation. It is also important to note that due to the large number of statistical tests conducted, some statistically significant associations will occur due to chance. This study was not able to adjust for parental mental health diagnosis and parental externalizing behavioural problems as they were not measured during follow periods. We tried to minimize this by adjusting for maternal history of mental health problems during pregnancy, maternal postnatal depressive, anxiety and stress symptoms as well as paternal emotional problems at 14 years of follow-up. Although not all women who drink alcohol and smoke tobacco during pregnancy engage in consuming illegal drugs, such use may be correlated with prenatal alcohol and tobacco consumption, but we did not have these data to include in the adjusted models. Epidemiological studies suggest that familial alcohol dependence (51), stressful life events during pregnancy (137), family conflict, criminal behavior, child-rearing practice, neighborhood characteristics, adolescents' peer influence and early substance initiation or experimentation may indirectly increase the risk of mental health and substance use problems in adolescents and young adults (138-141). However, the Raine Study did not include such data, which would have enabled a test for the indirect pathway of prenatal alcohol and tobacco exposures on offspring adverse outcomes. Although self-report of alcohol consumption has been widely accepted, maternal prenatal alcohol exposure is likely to be under-reported by pregnant mothers due to perceived stigma

associated with drinking during pregnancy or if women were not aware of their pregnancy status until later stages of pregnancy. This may in turn have attenuated associations with offspring mental health and substance use outcomes (6).

9.7 Direction for future research

This thesis addresses the paucity of research on the associations between prenatal alcohol and tobacco exposures and offspring mental health and substance use outcomes by synthesizing the results of existing studies (meta-analyses) and using longitudinal data from the Raine Study. However, the associations observed in this thesis may not necessarily reflect the true effects of prenatal alcohol and tobacco exposures on offspring adverse outcomes. Based on the research conducted in this thesis, recommendations for future studies include: (1) the need to report maternal and paternal alcohol consumption levels in grams per week (g/week) to improve the synthesis of evidence and minimize the heterogeneity of prenatal alcohol definition; (2) measurement of maternal prenatal alcohol and tobacco exposures for all trimesters as this helps understand at which stage of pregnancy maternal alcohol and tobacco use has the greatest effect on offspring subsequent mental health and substance use outcomes; (3) the need to consider the mediating role of immediate pregnancy and birth outcomes such as preeclampsia, preterm birth and low birthweight in the associations between prenatal alcohol and tobacco exposures and offspring outcomes as this may help estimate the indirect effects of those prenatal exposures on offspring adverse outcomes; (4) the need to consider laboratory tests (e.g. ethyl glucuronide test) to identify and quantify prenatal alcohol consumption. These could potentially minimize the need for pregnant women to recall the amount and frequency of their alcohol drinking and tobacco smoking as well as perceived stigma linked with drinking alcohol and smoking tobacco during prenatal the period (129, 142); (5) consideration of non-familial environmental risk factors, peer pressure and other factors which can affect adolescents' decision to initiate substance use; (6) the need to consider prenatal drug use such as cannabis and others when estimating the effects of prenatal alcohol and tobacco exposures on offspring adverse mental health and substance use outcomes; (7) consideration of statistical adjustment for parental mental health problems, maternal stressful life events during pregnancy and familial alcohol dependence as proxies for offspring predisposition to mental health and substance use problems; and (8) consideration of pre-conception exposure, and genetic predisposition to alcohol drinking and smoking possibly using Mendellian Randomization.

9.8 Conclusion

The work presented in this thesis contributes a number of substantive findings to the existing body of evidence associated to early life determinants of mental health and substance use outcomes for adolescents and young adults. Findings from the systematic review suggested that maternal prenatal alcohol exposure was associated with offspring subsequent alcohol use. The findings from the two meta-analyses also suggested that offspring exposed to maternal prenatal tobacco smoking are at increased risk of depressive and bipolar disorders, tobacco smoking initiation, lifetime tobacco smoking, current tobacco smoking and tobacco dependence and independently of maternal postnatal tobacco smoking, paternal tobacco smoking during pregnancy and sociodemographic confounders. The findings from the primary studies indicated that maternal prenatal alcohol and tobacco exposures were associated with increased risks of different forms of mental health problems such as depressive, anxiety and conduct disorder symptoms in adolescents and young adults. Further, the results also demonstrated prospective associations between prenatal alcohol and tobacco exposures and offspring subsequent substance use such as alcohol, tobacco and cannabis use during late adolescence. Moreover, dose-response associations were also observed. However, there was negligible evidence for associations between prenatal alcohol exposure and the risk of anxiety symptoms in young adulthood; and paternal prenatal tobacco smoking and offspring conduct disorder symptoms and tobacco smoking. The associations found in this thesis may not necessarily reflect the true magnitude of effects of prenatal alcohol and tobacco exposures on offspring adverse outcomes. However, taken together with the current body of knowledge, it is clear that there is sufficient evidence of harm observed in this thesis to warrant the precautionary principle, that there is no known safe level of exposure to alcohol and tobacco during pregnancy and that such exposure should be minimized, if not eliminated.

References

1. Easey KE, Dyer ML, Timpson NJ, Munafò MR. Prenatal alcohol exposure and offspring mental health: A systematic review. Drug and Alcohol Dependence. 2019;197:344-53.
2. Dodge NC, Jacobson JL, Jacobson SW. Effects of Fetal Substance Exposure on Offspring Substance Use. Pediatr Clin North Am. 2019;66(6):1149-61.
3. Alati R, Lawlor DA, Mamun AA, Williams GM, Najman JM, O'Callaghan M, et al. Is There a Fetal Origin of Depression? Evidence from the Mater University Study of Pregnancy and Its Outcomes. American Journal of Epidemiology. 2007;165(5):575-82.
4. Taylor AE, Carslake D, de Mola CL, Rydell M, Nilsen TIL, Bjørngaard JH, et al. Maternal Smoking in Pregnancy and Offspring Depression: a cross cohort and negative control study. Sci Rep. 2017;7(1):12579.
5. O'Brien JW, Hill SY. Effects of prenatal alcohol and cigarette exposure on offspring substance use in multiplex, alcohol-dependent families. Alcohol Clin Exp Res. 2014;38(12):2952-61.
6. Easey KE, Timpson NJ, Munafò MR. Association of Prenatal Alcohol Exposure and Offspring Depression: A Negative Control Analysis of Maternal and Partner Consumption. Alcohol Clin Exp Res. 2020;44(5):1132-40.
7. Barr HM, Bookstein FL, O'Malley KD, Connor PD, Huggins JE, Streissguth AP. Binge drinking during pregnancy as a predictor of psychiatric disorders on the Structured Clinical Interview for DSM-IV in young adult offspring. Am J Psychiatry. 2006;163(6):1061-5.
8. Robinson M, Oddy WH, McLean NJ, Jacoby P, Pennell CE, de Klerk NH, et al. Low-moderate prenatal alcohol exposure and risk to child behavioural development: a prospective cohort study. Bjog. 2010;117(9):1139-50.
9. Konold TR, Walthall JC, Pianta RC. The Behavior of Child Behavior Ratings: Measurement Structure of the Child Behavior Checklist Across Time, Informants, and Child Gender. Behavioral Disorders. 2004;29(4):372-83.
10. Derks EM, Hudziak JJ, van Beijsterveldt CE, Dolan CV, Boomsma DI. A study of genetic and environmental influences on maternal and paternal CBCL syndrome scores in a large sample of 3-year-old Dutch twins. Behav Genet. 2004;34(6):571-83.
11. Niclasen J, Andersen A-MN, Strandberg-Larsen K, Teasdale TW. Is alcohol binge drinking in early and late pregnancy associated with behavioural and emotional development at age 7 years? European child & adolescent psychiatry. 2014;23(12):1175-80.
12. Lund IO, Moen Eilertsen E, Gjerde LC, Røysamb E, Wood M, Reichborn-Kjennerud T, et al. Is the association between maternal alcohol consumption in pregnancy and pre-school child behavioural and emotional problems causal? Multiple approaches for controlling unmeasured confounding. Addiction. 2019;114(6):1004-14.
13. Skogerbø Å, Kesmodel US, Denny CH, Kjaersgaard MIS, Wimberley T, Landrø NI, et al. The effects of low to moderate alcohol consumption and binge drinking in early pregnancy on behaviour in 5-year-old children: a prospective cohort study on 1628 children. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(9):1042-50.
14. Kelly Y, Iacovou M, Quigley MA, Gray R, Wolke D, Kelly J, et al. Light drinking versus abstinence in pregnancy – behavioural and cognitive outcomes in 7-year-old children: a longitudinal cohort study. BJOG: An International Journal of Obstetrics & Gynaecology. 2013;120(11):1340-7.
15. Goldschmidt L, Richardson GA, De Genna NM, Cornelius MD, Day NL. Prenatal alcohol exposure and offspring alcohol use and misuse at 22years of age: A prospective longitudinal study. Neurotoxicol Teratol. 2019;71:1-5.
16. Alati R, Al Mamun A, Williams GM, O'Callaghan M, Najman JM, Bor W. In utero alcohol exposure and prediction of alcohol disorders in early adulthood: a birth cohort study. Arch Gen Psychiatry. 2006;63(9):1009-16.
17. Alati R, Clavarino A, Najman JM, O'Callaghan M, Bor W, Mamun AA, et al. The developmental origin of adolescent alcohol use: findings from the Mater University Study of Pregnancy and its outcomes. Drug Alcohol Depend. 2008;98(1-2):136-43.

18. Baer JS, Sampson PD, Barr HM, Connor PD, Streissguth AP. A 21-Year Longitudinal Analysis of the Effects of Prenatal Alcohol Exposure on Young Adult Drinking. Archives of General Psychiatry. 2003;60(4):377-85.
19. Pfinder M, Liebig S, Feldmann R. Adolescents' Use of Alcohol, Tobacco and Illicit Drugs in Relation to Prenatal Alcohol Exposure: Modifications by Gender and Ethnicity. Alcohol and Alcoholism. 2014;49(2):143-53.
20. Biederman J, Martelon M, Woodworth K, Spencer TJ, Faraone SV. Is maternal smoking during pregnancy a risk factor for cigarette smoking in offspring? A longitudinal controlled study of ADHD children grown up. Journal of Attention Disorders. 2017;21(12):975-85.
21. Ashford J, van Lier PA, Timmermans M, Cuijpers P, Koot HM. Prenatal smoking and internalizing and externalizing problems in children studied from childhood to late adolescence. J Am Acad Child Adolesc Psychiatry. 2008;47(7):779-87.
22. Robinson M, McLean NJ, Oddy WH, Mattes E, Bulsara M, Li J, et al. Smoking cessation in pregnancy and the risk of child behavioural problems: a longitudinal prospective cohort study. J Epidemiol Community Health. 2010;64(7):622-9.
23. Moylan S, Gustavson K, Øverland S, Karevold EB, Jacka FN, Pasco JA, et al. The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: The Norwegian mother and child cohort study. BMC Medicine. 2015;13(1).
24. Talati A, Wickramaratne PJ, Wesselhoeft R, Weissman MM. Prenatal tobacco exposure, birthweight, and offspring psychopathology. Psychiatry Res. 2017;252:346-52.
25. Chudal R, Brown AS, Gissler M, Suominen A, Sourander A. Is maternal smoking during pregnancy associated with bipolar disorder in offspring? Journal of Affective Disorders. 2015;171:132-6.
26. Batstra L, Hadders-Algra M, Neeleman J. Effect of antenatal exposure to maternal smoking on behavioural problems and academic achievement in childhood: prospective evidence from a Dutch birth cohort. Early Human Development. 2003;75(1):21-33.
27. Moylan S, Gustavson K, Øverland S, Karevold EB, Jacka FN, Pasco JA, et al. The impact of maternal smoking during pregnancy on depressive and anxiety behaviors in children: the Norwegian Mother and Child Cohort Study. BMC medicine. 2015;13:24-.
28. Indredavik MS, Brubakk A-M, Romundstad P, Vik T. Prenatal smoking exposure and psychiatric symptoms in adolescence. Acta paediatrica (Oslo, Norway : 1992). 2007;96(3):377-82.
29. Ekblad M, Gissler M, Lehtonen L, Korkeila J. Prenatal smoking exposure and the risk of psychiatric morbidity into young adulthood. Arch Gen Psychiatry. 2010;67(8):841-9.
30. Höök B, Cederblad M, Berg R. Prenatal and postnatal maternal smoking as risk factors for preschool children's mental health. Acta Paediatr. 2006;95(6):671-7.
31. Brion MJ, Victora C, Matijasevich A, Horta B, Anselmi L, Steer C, et al. Maternal smoking and child psychological problems: disentangling causal and noncausal effects. Pediatrics. 2010;126(1):e57-65.
32. Zahn-Waxler C, Klimes-Dougan B, Slattery MJ. Internalizing problems of childhood and adolescence: prospects, pitfalls, and progress in understanding the development of anxiety and depression. Development and psychopathology. 2000;12(3):443-66.
33. Palmer RHC, Bidwell LC, Heath AC, Brick LA, Madden PAF, Knopik VS. Effects of Maternal Smoking during Pregnancy on Offspring Externalizing Problems: Contextual Effects in a Sample of Female Twins. Behavior genetics. 2016;46(3):403-15.
34. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal Smoking and Early Childhood Conduct Problems: Testing Genetic and Environmental Explanations of the Association. Archives of General Psychiatry. 2004;61(8):836-43.
35. Ruisch IH, Dietrich A, Glennon JC, Buitelaar JK, Hoekstra PJ. Maternal substance use during pregnancy and offspring conduct problems: A meta-analysis. Neuroscience & Biobehavioral Reviews. 2018;84:325-36.
36. Agrawal A, Scherrer JF, Grant JD, Sartor CE, Pergadia ML, Duncan AE, et al. The effects of maternal smoking during pregnancy on offspring outcomes. Preventive medicine. 2010;50(1-2):13-8.

37. D'Onofrio BM, Van Hulle CA, Waldman ID, Rodgers JL, Harden KP, Rathouz PJ, et al. Smoking during pregnancy and offspring externalizing problems: an exploration of genetic and environmental confounds. Development and psychopathology. 2008;20(1):139-64.
38. Maughan B, Taylor A, Caspi A, Moffitt TE. Prenatal smoking and early childhood conduct problems: testing genetic and environmental explanations of the association. Arch Gen Psychiatry. 2004;61(8):836-43.
39. Silberg JL, Parr T, Neale MC, Rutter M, Angold A, Eaves LJ. Maternal smoking during pregnancy and risk to boys' conduct disturbance: an examination of the causal hypothesis. Biol Psychiatry. 2003;53(2):130-5.
40. O'Callaghan FV, Al Mamun A, O'Callaghan M, Alati R, Najman JM, Williams GM, et al. Maternal smoking during pregnancy predicts nicotine disorder (dependence or withdrawal) in young adults - a birth cohort study. Aust N Z J Public Health. 2009;33(4):371-7.
41. Al Mamun A, O'Callaghan FV, Alati R, O'Callaghan M, Najman JM, Williams GM, et al. Does maternal smoking during pregnancy predict the smoking patterns of young adult offspring? A birth cohort study. Tobacco control. 2006;15(6):452-7.
42. Biederman J, Martelon M, Woodworth KY, Spencer TJ, Faraone SV. Is Maternal Smoking During Pregnancy a Risk Factor for Cigarette Smoking in Offspring? A Longitudinal Controlled Study of ADHD Children Grown Up. J Atten Disord. 2017;21(12):975-85.
43. Niemelä S, Räisänen A, Koskela J, Taanila A, Miettunen J, Ramsay H, et al. The effect of prenatal smoking exposure on daily smoking among teenage offspring. Addiction. 2017;112(1):134-43.
44. De Genna NM, Goldschmidt L, Day NL, Cornelius MD. Prenatal tobacco exposure, maternal postnatal nicotine dependence and adolescent risk for nicotine dependence: Birth cohort study. Neurotoxicology and Teratology. 2017;61:128-32.
45. Kandel DB, Wu P, Davies M. Maternal smoking during pregnancy and smoking by adolescent daughters. American journal of public health. 1994;84(9):1407-13.
46. Goldschmidt L, Cornelius MD, Day NL. Prenatal cigarette smoke exposure and early initiation of multiple substance use. Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco. 2012;14(6):694-702.
47. Day NL, Goldschmidt L, Thomas CA. Prenatal marijuana exposure contributes to the prediction of marijuana use at age 14. Addiction. 2006;101(9):1313-22.
48. Porath AJ, Fried PA. Effects of prenatal cigarette and marijuana exposure on drug use among offspring. Neurotoxicology and teratology. 2005;27(2):267-77.
49. 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.
50. Baler RD, Volkow ND, Fowler JS, Benveniste H. Is fetal brain monoamine oxidase inhibition the missing link between maternal smoking and conduct disorders? J Psychiatry Neurosci. 2008;33(3):187-95.
51. Hill SY, Lowers L, Locke-Wellman J, Shen SA. Maternal smoking and drinking during pregnancy and the risk for child and adolescent psychiatric disorders. J Stud Alcohol. 2000;61(5):661-8.
52. Murray J, Burgess S, Zuccolo L, Hickman M, Gray R, Lewis SJ. Moderate alcohol drinking in pregnancy increases risk for children's persistent conduct problems: causal effects in a Mendelian randomisation study. J Child Psychol Psychiatry. 2016;57(5):575-84.
53. Steane SE, Young SL, Clifton VL, Gallo LA, Akison LK, Moritz KM. Prenatal alcohol consumption and placental outcomes: a systematic review and meta-analysis of clinical studies. Am J Obstet Gynecol. 2021;225(6):607.e1-.e22.
54. Lo JO, Schabel MC, Roberts VHJ, Wang X, Lewandowski KS, Grant KA, et al. First trimester alcohol exposure alters placental perfusion and fetal oxygen availability affecting fetal growth and development in a non-human primate model. American journal of obstetrics and gynecology. 2017;216(3):302.e1-.e8.

55. Pintican D, Poienar AA, Strilciuc S, Mihu D. Effects of maternal smoking on human placental vascularization: A systematic review. Taiwanese Journal of Obstetrics and Gynecology. 2019;58(4):454-9.
56. Salafia CM, Misra DP, Yampolsky M, Charles AK, Miller RK. Allometric Metabolic Scaling and Fetal and Placental Weight. Placenta. 2009;30(4):355-60.
57. Shamshirsaz AA, Paidas M, Krikun G. Preeclampsia, hypoxia, thrombosis, and inflammation. J Pregnancy. 2012;2012:374047.
58. Giannopoulou I, Pagida MA, Briana DD, Panayotacopoulou MT. Perinatal hypoxia as a risk factor for psychopathology later in life: the role of dopamine and neurotrophins. Hormones (Athens). 2018;17(1):25-32.
59. Dunlop BW, Nemeroff CB. The Role of Dopamine in the Pathophysiology of Depression. Archives of General Psychiatry. 2007;64(3):327-37.
60. Ko T-J, Tsai L-Y, Chu L-C, Yeh S-J, Leung C, Chen C-Y, et al. Parental Smoking During Pregnancy and Its Association with Low Birth Weight, Small for Gestational Age, and Preterm Birth Offspring: A Birth Cohort Study. Pediatrics & Neonatology. 2014;55(1):20-7.
61. Shah NR, Bracken MB. A systematic review and meta-analysis of prospective studies on the association between maternal cigarette smoking and preterm delivery. Am J Obstet Gynecol. 2000;182(2):465-72.
62. Nykjaer C, Alwan NA, Greenwood DC, Simpson NAB, Hay AWM, White KLM, et al. Maternal alcohol intake prior to and during pregnancy and risk of adverse birth outcomes: evidence from a British cohort. Journal of Epidemiology and Community Health. 2014;68(6):542.
63. Ernst M, Moolchan ET, Robinson ML. Behavioral and neural consequences of prenatal exposure to nicotine. J Am Acad Child Adolesc Psychiatry. 2001;40(6):630-41.
64. Herrmann M, King K, Weitzman M. Prenatal tobacco smoke and postnatal secondhand smoke exposure and child neurodevelopment. Curr Opin Pediatr. 2008;20(2):184-90.
65. Hyman SE. Addiction: a disease of learning and memory. Am J Psychiatry. 2005;162(8):1414-22.
66. Roy TS, Sabherwal U. Effects of gestational nicotine exposure on hippocampal morphology. Neurotoxicol Teratol. 1998;20(4):465-73.
67. Cowen PJ, Browning M. What has serotonin to do with depression? World Psychiatry. 2015;14(2):158-60.
68. Muneoka K, Ogawa T, Kamei K, Mimura Y, Kato H, Takigawa M. Nicotine exposure during pregnancy is a factor which influences serotonin transporter density in the rat brain. Eur J Pharmacol. 2001;411(3):279-82.
69. Muneoka K, Ogawa T, Kamei K, Muraoka S, Tomiyoshi R, Mimura Y, et al. Prenatal nicotine exposure affects the development of the central serotonergic system as well as the dopaminergic system in rat offspring: involvement of route of drug administrations. Brain Res Dev Brain Res. 1997;102(1):117-26.
70. Malanga CJ, Kosofsky BE. Does drug abuse beget drug abuse? Behavioral analysis of addiction liability in animal models of prenatal drug exposure. Developmental Brain Research. 2003;147(1):47-57.
71. Slotkin TA. If nicotine is a developmental neurotoxicant in animal studies, dare we recommend nicotine replacement therapy in pregnant women and adolescents? Neurotoxicology and Teratology. 2008;30(1):1-19.
72. Brancato A, Castelli V, Cavallaro A, Lavanco G, Plescia F, Cannizzaro C. Pre-conceptional and Peri-Gestational Maternal Binge Alcohol Drinking Produces Inheritance of Mood Disturbances and Alcohol Vulnerability in the Adolescent Offspring. Front Psychiatry. 2018;9:150-.
73. O'Connor MJ. Mental Health Outcomes Associated with Prenatal Alcohol Exposure: Genetic and Environmental Factors. Current Developmental Disorders Reports. 2014;1(3):181-8.
74. Zhang C, Fan S-J, Sun A-B, Liu Z-Z, Liu L. Prenatal nicotine exposure induces depression-like behavior in adolescent female rats via modulating neurosteroid in the hippocampus. Mol Med Rep. 2019;19(5):4185-94.

75. Shea KM, Hewitt AJ, Olmstead MC, Brien JF, Reynolds JN. Maternal ethanol consumption by pregnant guinea pigs causes neurobehavioral deficits and increases ethanol preference in offspring. Behav Pharmacol. 2012;23(1):105-12.
76. Klein LC, Stine MM, Pfaff DW, Vandenbergh DJ. Maternal nicotine exposure increases nicotine preference in periadolescent male but not female C57B1/6J mice. Nicotine & Tobacco Research. 2003;5(1):117-24.
77. Padmanabhan R, Hameed MS. Effects of acute doses of ethanol administered at pre-implantation stages on fetal development in the mouse. Drug Alcohol Depend. 1988;22(1-2):91-100.
78. Hettema JM, Prescott CA, Myers JM, Neale MC, Kendler KS. The Structure of Genetic and Environmental Risk Factors for Anxiety Disorders in Men and Women. Archives of General Psychiatry. 2005;62(2):182-9.
79. Gottschalk MG, Domschke K. Genetics of generalized anxiety disorder and related traits. Dialogues in clinical neuroscience. 2022.
80. Tirumalaraju V, Suchting R, Evans J, Goetzl L, Refuerzo J, Neumann A, et al. Risk of Depression in the Adolescent and Adult Offspring of Mothers With Perinatal Depression: A Systematic Review and Meta-analysis. JAMA Network Open. 2020;3(6):e208783-e.
81. Lamis DA, Malone PS, Lansford JE, Lochman JE. Maternal depressive symptoms as a predictor of alcohol use onset and heavy episodic drinking in youths. J Consult Clin Psychol. 2012;80(5):887-96.
82. Verhulst B, Neale MC, Kendler KS. The heritability of alcohol use disorders: a meta-analysis of twin and adoption studies. Psychol Med. 2015;45(5):1061-72.
83. Knopik VS, Maccani MA, Francazio S, McGeary JE. The epigenetics of maternal cigarette smoking during pregnancy and effects on child development. Dev Psychopathol. 2012;24(4):1377-90.
84. Lussier AA, Bodnar TS, Mingay M, Morin AM, Hirst M, Kobor MS, et al. Prenatal Alcohol Exposure: Profiling Developmental DNA Methylation Patterns in Central and Peripheral Tissues. Frontiers in Genetics. 2018;9.
85. Chatzittofis A, Boström ADE, Ciuculete DM, Öberg KG, Arver S, Schiöth HB, et al. HPA axis dysregulation is associated with differential methylation of CpG-sites in related genes. Scientific Reports. 2021;11(1):20134.
86. Varghese FP, Brown ES. The Hypothalamic-Pituitary-Adrenal Axis in Major Depressive Disorder: A Brief Primer for Primary Care Physicians. Primary care companion to the Journal of clinical psychiatry. 2001;3(4):151-5.
87. Pariante CM, Lightman SL. The HPA axis in major depression: classical theories and new developments. Trends Neurosci. 2008;31(9):464-8.
88. Faravelli C, Lo Sauro C, Godini L, Lelli L, Benni L, Pietrini F, et al. Childhood stressful events, HPA axis and anxiety disorders. World J Psychiatry. 2012;2(1):13-25.
89. Lovallo WR. The hypothalamic-pituitary-adrenocortical axis in addiction. Int J Psychophysiol. 2006;59(3):193-4.
90. Chatzittofis A, Arver S, Öberg K, Hallberg J, Nordström P, Jokinen J. HPA axis dysregulation in men with hypersexual disorder. Psychoneuroendocrinology. 2016;63:247-53.
91. Speer KE, Semple S, Naumovski N, D'Cunha NM, McKune AJ. HPA axis function and diurnal cortisol in post-traumatic stress disorder: A systematic review. Neurobiol Stress. 2019;11:100180.
92. He X, Lu J, Dong W, Jiao Z, Zhang C, Yu Y, et al. Prenatal nicotine exposure induces HPA axis-hypersensitivity in offspring rats via the intrauterine programming of up-regulation of hippocampal GAD67. Archives of toxicology. 2017;91(12):3927-43.
93. Wieczorek L, Fish EW, O'Leary-Moore SK, Parnell SE, Sulik KK. Hypothalamic-pituitary-adrenal axis and behavioral dysfunction following early binge-like prenatal alcohol exposure in mice. Alcohol. 2015;49(3):207-17.
94. Richmond-Rakerd LS, Slutske WS, Heath AC, Martin NG. Genetic and environmental influences on the ages of drinking and gambling initiation: evidence for distinct aetiologies and sex differences. Addiction (Abingdon, England). 2014;109(2):323-31.

95. Hoffmann JP, Cerbone FG. Parental substance use disorder and the risk of adolescent drug abuse: an event history analysis. Drug Alcohol Depend. 2002;66(3):255-64.
96. Eiden RD, Molnar DS, Colder C, Edwards EP, Leonard KE. A Conceptual Model Predicting Internalizing Problems in Middle Childhood Among Children of Alcoholic and Nonalcoholic Fathers: The Role of Marital Aggression. Journal of Studies on Alcohol and Drugs. 2009;70(5):741-50.
97. Yule AM, Wilens TE, Martelon MK, Simon A, Biederman J. Does exposure to parental substance use disorders increase substance use disorder risk in offspring? A 5-year follow-up study. The American Journal on Addictions. 2013;22(5):460-5.
98. Homel J, Warren D. The Relationship Between Parent Drinking and Adolescent Drinking: Differences for Mothers and Fathers and Boys and Girls. Subst Use Misuse. 2019;54(4):661-9.
99. Wellman RJ, Dugas EN, Dutczak H, O'Loughlin EK, Datta GD, Lauzon B, et al. Predictors of the Onset of Cigarette Smoking: A Systematic Review of Longitudinal Population-Based Studies in Youth. Am J Prev Med. 2016;51(5):767-78.
100. Leonardi-Bee J, Jere ML, Britton J. Exposure to parental and sibling smoking and the risk of smoking uptake in childhood and adolescence: a systematic review and meta-analysis. Thorax. 2011;66(10):847.
101. Knopik VS. Maternal smoking during pregnancy and child outcomes: real or spurious effect? Developmental neuropsychology. 2009;34(1):1-36.
102. Kabir Z, Connolly GN, Alpert HR. Secondhand smoke exposure and neurobehavioral disorders among children in the United States. Pediatrics. 2011;128(2):263-70.
103. Gatzke-Kopp L, Willoughby MT, Warkentien S, Petrie D, Mills-Koonce R, Blair C. Association between environmental tobacco smoke exposure across the first four years of life and manifestation of externalizing behavior problems in school-aged children. Journal of Child Psychology and Psychiatry. 2020;61(11):1243-52.
104. Chastang J, Baïz N, Cadwallader JS, Robert S, Dywer JL, Charpin DA, et al. Postnatal Environmental Tobacco Smoke Exposure Related to Behavioral Problems in Children. PLoS One. 2015;10(8):e0133604-e.
105. Peng B, Hu N, Yu H, Xiao H, Luo J. Parenting Style and Adolescent Mental Health: The Chain Mediating Effects of Self-Esteem and Psychological Inflexibility. Frontiers in Psychology. 2021;12.
106. Hakulinen C, Mok PLH, Horsdal HT, Pedersen CB, Mortensen PB, Agerbo E, et al. Parental income as a marker for socioeconomic position during childhood and later risk of developing a secondary care-diagnosed mental disorder examined across the full diagnostic spectrum: a national cohort study. BMC Medicine. 2020;18(1):323.
107. Bi X, Yang Y, Li H, Wang M, Zhang W, Deater-Deckard K. Parenting Styles and Parent–Adolescent Relationships: The Mediating Roles of Behavioral Autonomy and Parental Authority. Frontiers in Psychology. 2018;9.
108. Lansford JE, Miller-Johnson S, Berlin LJ, Dodge KA, Bates JE, Pettit GS. Early physical abuse and later violent delinquency: a prospective longitudinal study. Child Maltreat. 2007;12(3):233-45.
109. Kingsbury M, Sucha E, Manion I, Gilman SE, Colman I. Adolescent Mental Health Following Exposure to Positive and Harsh Parenting in Childhood. Can J Psychiatry. 2020;65(6):392-400.
110. Tanya Nagahawatte N, Goldenberg RL. Poverty, Maternal Health, and Adverse Pregnancy Outcomes. Annals of the New York Academy of Sciences. 2008;1136(1):80-5.
111. Villalbí JR, Salvador J, Cano-Serral G, Rodríguez-Sanz MC, Borrell C. Maternal smoking, social class and outcomes of pregnancy. Paediatr Perinat Epidemiol. 2007;21(5):441-7.
112. de Wolff MG, Backhausen MG, Iversen ML, Bendix JM, Rom AL, Hegaard HK. Prevalence and predictors of maternal smoking prior to and during pregnancy in a regional Danish population: a cross-sectional study. Reproductive Health. 2019;16(1):82.
113. Kinge JM, Øverland S, Flatø M, Dieleman J, Røgeberg O, Magnus MC, et al. Parental income and mental disorders in children and adolescents: prospective register-based study. International Journal of Epidemiology. 2021;50(5):1615-27.

114. Manhica H, Straatmann VS, Lundin A, Agardh E, Danielsson A-K. Association between poverty exposure during childhood and adolescence, and drug use disorders and drug-related crimes later in life. Addiction. 2021;116(7):1747-56.
115. Roza SJ, Verhulst FC, Jaddoe VWV, Steegers EAP, Mackenbach JP, Hofman A, et al. Maternal smoking during pregnancy and child behaviour problems: the Generation R Study. International Journal of Epidemiology. 2009;38(3):680-9.
116. Dolan CV, Geels L, Vink JM, van Beijsterveldt CEM, Neale MC, Bartels M, et al. Testing Causal Effects of Maternal Smoking During Pregnancy on Offspring's Externalizing and Internalizing Behavior. Behavior genetics. 2016;46(3):378-88.
117. Teesson M, Newton NC, Barrett EL. Australian school-based prevention programs for alcohol and other drugs: A systematic review. Drug and Alcohol Review. 2012;31(6):731-6.
118. Newton NC, Conrod P, Teesson M, Faggiano F. School-based Alcohol and Other Drug Prevention. In: Verster JC, Brady K, Galanter M, Conrod P, editors. Drug Abuse and Addiction in Medical Illness: Causes, Consequences and Treatment. New York, NY: Springer New York; 2012. p. 545-60.
119. Lim AWY, Van Schalkwyk MCI, Maani Hessari N, Petticrew MP. Pregnancy, Fertility, Breastfeeding, and Alcohol Consumption: An Analysis of Framing and Completeness of Information Disseminated by Alcohol Industry–Funded Organizations. Journal of Studies on Alcohol and Drugs. 2019;80(5):524-33.
120. McBride N, Carruthers S, Hutchinson D. Reducing alcohol use during pregnancy: listening to women who drink as an intervention starting point. Global Health Promotion. 2012;19(2):6-18.
121. WHO. Guidelines for identification and management of substance use and substance use disorders in pregnancy, . In: Organization WH, editor. 2014.
122. AIHW. National Drug Strategy and Household Survey 2016. key findings online data tables Canberra: AIHW. 2017.
123. Stead L, Perera R, Bullen C, Mant D, Lancaster T. Nicotine replacement therapy for smoking cessation. Cochrane Database Syst Rev. 2012;11(CD000146).
124. Stade BC, Bailey C, Dzendoletas D, Sgro M, Dowswell T, Bennett D. Psychological and/or educational interventions for reducing alcohol consumption in pregnant women and women planning pregnancy. Cochrane Database of Systematic Reviews. 2009(2).
125. Gilinsky A, Swanson V, Power K. Interventions delivered during antenatal care to reduce alcohol consumption during pregnancy: A systematic review. Addiction Research & Theory. 2011;19(3):235-50.
126. Chamberlain C, O'Mara-Eves A, Oliver S, Caird JR, Perlen SM, Eades SJ, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev. 2013;10(10):Cd001055.
127. Chamberlain C, O'Mara-Eves A, Porter J, Coleman T, Perlen SM, Thomas J, et al. Psychosocial interventions for supporting women to stop smoking in pregnancy. Cochrane Database Syst Rev. 2017;2(2):Cd001055.
128. Birrell L, Furneaux-Bate A, Chapman C, Newton NC. A Mobile Peer Intervention for Preventing Mental Health and Substance Use Problems in Adolescents: Protocol for a Randomized Controlled Trial (The Mind Your Mate Study). JMIR Res Protoc. 2021;10(7):e26796.
129. Benowitz NL, Bernert JT, Caraballo RS, Holiday DB, Wang J. Optimal Serum Cotinine Levels for Distinguishing Cigarette Smokers and Nonsmokers Within Different Racial/Ethnic Groups in the United States Between 1999 and 2004. American Journal of Epidemiology. 2009;169(2):236-48.
130. Stick SM, Burton PR, Gurrin L, Sly PD, LeSouëf PN. Effects of maternal smoking during pregnancy and a family history of asthma on respiratory function in newborn infants. The Lancet. 1996;348(9034):1060-4.
131. Beck JS, Beck AT, Jolly BJ. Beck youth inventories of emotional and social impairment." The Psychological Corporation, San Atonio , TX (2001). 2001.
132. Brown TA, Chorpita BF, Korotitsch W, Barlow DH. Psychometric properties of the Depression Anxiety Stress Scales (DASS) in clinical samples. Behav Res Ther. 1997;35(1):79-89.

133. Achenbach TM, Dumenci L, Rescorla LA. DSM-oriented and empirically based approaches to constructing scales from the same item pools. J Clin Child Adolesc Psychol. 2003;32(3):328-40.
134. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.
135. Linden A, Mathur MB, VanderWeele TJ. Conducting sensitivity analysis for unmeasured confounding in observational studies using E-values: The evalue package. The Stata Journal. 2020;20(1):162-75.
136. White SW, Eastwood PR, Straker LM, Adams LA, Newnham JP, Lye SJ, et al. The Raine study had no evidence of significant perinatal selection bias after two decades of follow up: a longitudinal pregnancy cohort study. BMC Pregnancy and Childbirth. 2017;17(1):207.
137. Kingsbury M, Weeks M, MacKinnon N, Evans J, Mahedy L, Dykxhoorn J, et al. Stressful Life Events During Pregnancy and Offspring Depression: Evidence From a Prospective Cohort Study. J Am Acad Child Adolesc Psychiatry. 2016;55(8):709-16.e2.
138. Alati R, Najman JM, Kinner SA, Mamun AA, Williams GM, O'Callaghan M, et al. Early predictors of adult drinking: a birth cohort study. Am J Epidemiol. 2005;162(11):1098-107.
139. Fergusson DM, Boden JM, Horwood LJ. The developmental antecedents of illicit drug use: evidence from a 25-year longitudinal study. Drug Alcohol Depend. 2008;96(1-2):165-77.
140. Herrenkohl TI, Lee JO, Kosterman R, Hawkins JD. Family influences related to adult substance use and mental health problems: a developmental analysis of child and adolescent predictors. J Adolesc Health. 2012;51(2):129-35.
141. Salom CL, Williams GM, Najman JM, Alati R. Familial factors associated with development of alcohol and mental health comorbidity. Addiction. 2015;110(2):248-57.
142. Bearer CF, Stoler JM, Cook JD, Carpenter SJ. Biomarkers of alcohol use in pregnancy. Alcohol Res Health. 2004;28(1):38-43.

Appendices

Appendix A

Supplementary Files

Supplementary file for chapter 4.1 (a): Quality assessment of the included studies based on the Newcastle-Ottawa-Scale

Study Name	Selection				Comparability	Outcome			Total (9⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	Demonstration that outcome of interest was not present at start of study (⋆)	Comparability (⋆⋆)	Assessment of outcome (⋆)	Follow-up long enough for outcomes to occur (⋆)	Adequacy of follow-up of cohorts (⋆)	
Quinn et al, 2017	⋆	⋆	⋆	⋆	⋆	⋆	⋆	⋆	8
Talati et al, 2013	⋆	⋆	⋆	⋆	⋆	⋆	⋆	⋆	8
Chudal et al, 2015	-	⋆	⋆	⋆	⋆⋆	⋆	⋆	⋆	7
Talati et al, 2017	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	⋆	8
Ekblad et al, 2010	⋆	⋆	⋆	⋆	⋆	⋆	⋆	⋆	7
Hill et al, 2000	-	⋆	⋆	⋆	⋆	⋆	⋆	⋆	7
Menezes et al, 2013	⋆	⋆	-	⋆	⋆⋆	⋆	⋆	⋆	8
Taylor et al, 2017	⋆	⋆	⋆	⋆	⋆⋆	⋆	⋆	⋆	9
Meier et al, 2017	⋆	⋆	-	⋆	⋆⋆	⋆	⋆	⋆	8
Biederman et al, 2017	-	⋆	-	⋆	⋆⋆	⋆	⋆	⋆	7

Supplementary file for chapter 4. 1 (b): Sensitivity analysis of relative risk for each study being removed at a time (relative risk (RR) and 95% confidence interval) for prenatal tobacco exposure and risk of mood disorders in offspring (leave-one-out sensitivity analysis)

Study excluded	RR	95%CI
Quinn et al, 2017	1.46	1.25-1.70
Talati et al, 2013	1.38	1.23-1.54
Chudal et al, 2015	1.46	1.29-1.64
Talati et al, 2017	1.43	1.27-1.61
Ekblad et al, 2010	1.33	1.22-1.43
Hill et al, 2000	1.42	1.26-1.59
Menezes et al, 2013	1.43	1.26-1.61
Taylor et al, 2017	1.47	1.29-1.67
Meier et al, 2017	1.47	1.27-1.70
Biederman et al, 2017	1.42	1.26-1.59

Key. The analysis is based on random effect model of meta-analysis

Supplementary file 1 for chapter 4.2 (a): Characteristics of mothers and children for comparing the major covariates between children with and without depressive symptoms at the age of 17 years

Variables included in the model		Depression at age 17 years (n=1,168)				P-value
		Depressed		Non-depressed		
		n	*%*	*n*	*%*	
Maternal age at conception	< 20 years	15	5.5	55	6.0	0.489
	20-25 years	51	18.8	158	17.6	
	25-30 years	69	25.3	272	30.4	
	30-35 years	85	31.2	268	30.0	
	≥ 35 years	52	19.2	143	16.0	
Marital status	Married	192	70.8	641	73.3	0.361
	Never married	31	11.4	83	9.5	
	Defacto	37	13.7	130	14.9	
	Separate/divorce/widow	11	4.1	21	2.4	
Ethnicity	Caucasian	243	90.0	791	90.4	0.723
	Non-Caucasian	28	10.0	84	9.6	
Family income at conception	≤ 24,000 AUD	111	41.0	316	36.1	0.149
	> 24,000 AUD	160	59.0	559	63.9	
Parity	Nulliparous	119	44.0	442	50.5	0.057
	Multiparous	152	56.0	433	49.5	
Current pregnancy	Not planned	132	48.7	370	42.3	0.063
	Planned	139	51.3	505	57.7	
Previous history of maternal mental illness	No	261	96.3	857	98.0	0.128
	Yes	10	3.7	18	2.0	
Preterm birth	No	252	93.0	819	93.7	0.674
	Yes	19	7.0	55	6.3	
Birthweight	Low birth weight (< 2.5K.G)	20	7.4	66	7.4	0.462
	Normal birthweight (2.5 -3. 99K.G)	232	85.3	741	82.8	
	High birthweight (> 4.0K.G)	20	7.3	88	9.8	
Child's sex	Male	87	32.0	493	55.0	0.08
	Female	185	68.0	403	45.0	
Maternal depression at 13 years of follow-up	Non-depressed	214	87.3	753	89.9	0.264
	Depressed	31	12.7	85	10.1	
Prenatal tobacco use (first trimester)	Non-smoker	202	74.5	716	81.8	0.009
	< 15 cigarettes/day	37	13.7	95	10.9	
	> 15 cigarettes/day	32	11.8	64	7.3	
Paternal smoking during pregnancy	Smoker	99	36.5	268	30.6	0.069
	Non-smoker	172	63.5	607	69.4	

Maternal prenatal alcohol use (first trimester)	Non-use	132	48.7	448	51.2	0.045
	1-2 standard drinks/week	94	34.7	314	35.9	
	3-5 standard drinks/week	27	10.0	76	8.7	
	≥ 6 standard drinks/week	18	6.6	37	4.2	

Key: P-value refers a chi-square test of association between offspring depressive symptoms and categorical variables.

	Non-use	< 2 standard drinks/week	3-5 standard drinks/ week	> 6 standard drinks/week	Non-smoker	Smoker (any)	< 15 cigs/day	> 15 cigs/day
	Prenatal alcohol use				Prenatal tobacco use			
Unadjusted	1	1.01	1.15	1.43	1	1.38	1.27	1.51
Model 1	1	1.04	1.1	1.56	1	1.38	1.33	1.46
Model 2	1	1.02	1.12	1.55	1	1.4	1.52	1.62
Model 3	1	1.03	1.14	1.59	1	1.4	1.5	1.6
Model 4	1	1.03	1.11	1.46	1	1.37	1.33	1.45
Model 5	1	1.04	1.16	1.59	1	1.36	1.43	1.5

Supplementary file 2 for chapter 4.2 (b): depicting risks of depressive symptoms in offspring increased in magnitude and precision with increasing exposure to prenatal tobacco use in progressive models.

Supplementary file 3 for chapter 4.2 (c): Association between prenatal alcohol and tobacco use and depressive symptoms in offspring at age of 17 years using imputed data set.

Categorical Variables		**Unadjusted**	**Adjusted**
		RR (95%CI)	RR (95% CI)
Prenatal tobacco use (1st trimester)	Smoker	1.37(1.09–1.73)	1.37(1.04-1.79)
	Non-smoker	Reference	Reference
Prenatal alcohol use (1st trimester)	Non-use	Reference	Reference
	≤ 2 standard drinks/week	1.02(0.81-1.29)	1.04(0.81-1.33)
	3-5 standard drinks/week	1.15(0.81-1.65)	1.17(0.79-1.70)
	≥ 6 standard drinks/week	1.43(1.02-2.15)	1.46(1.01-2.19)

Key: final model included; maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception, maternal depression and smoking at 13 years of follow-up, preterm birth, birth weight, and paternal smoking status during pregnancy.

Supplementary file 3 for chapter 4.2 (d). Association between prenatal alcohol and tobacco use (at 34 weeks) and depressive symptoms in offspring at the age of 17 years

Predictor Variables		Risk Ratio (95%CI)	
		Unadjusted	**Fully adjusted**
Prenatal alcohol use (third trimester)	Non-use	Reference	Reference
	≤ 2 standard drinks/week	1.02(0.65-1.10)	1.01(0.65-1.12)
	3-5 standard drinks/ week	1.02(0.53-1.82)	1.01(0.60-1.50)
	≥ 6 standard drinks/week	1.15(0.75-1.75)	1.07(0.57-2.01)
Prenatal tobacco use (third trimester)	Non-smoker	Reference	Reference
	Smoker (any)	1.13 (0.88–1.47)	1.02(0.72-1.44)
	< 15 cigs/day	1.01(0.69-1.32)	1.01(0.59-1.33)
	≥ 15 cigs/day	1.70(1.17-2.45)	1.41(0.88-2.28)

Fully adjusted for: maternal age at conception, education, marital status, ethnicity (race), family income at conception, parity, planned pregnancy, sex of child, history of maternal psychiatric disorder during conception, maternal depression and smoking at 13 years of follow-up, preterm birth, birth weight, and paternal smoking status during pregnancy.

Supplementary file 1 for chapter 4.3. Associations between prenatal tobacco and alcohol exposures and the risk of experiencing symptoms of anxiety in young adults at the age of 20 years using *imputed datasets* (relative risks with 95% confidence intervals)

Predictor Variables	RR (95% CI)	
	Unadjusted	Fully adjusted
Non-use	Reference	Reference
Prenatal tobacco exposure at first trimester	1.49 (1.24-1.80)	1.44 (1.14-1.82)
Prenatal tobacco exposure at third trimester	1.52 (1.25-1.85)	1.44 (1.12-1.87)
Prenatal alcohol exposure at first trimester	1.12 (0.81-1.53)	1.03 (0.67-1.57)
Prenatal alcohol exposure at third trimester	1.11 (0.91-1.36)	1.09 (0.89-1.35)

NB: Analyses were run separately by trimester but reported together for ease of presentation**.**

Fully adjusted model: included maternal age at conception, education, marital status, family income, maternal race, paternal prenatal tobacco smoking, pre-eclampsia, preterm birth, birthweight and maternal postnatal tobacco smoking at 14 years follow-up and anxiety symptoms at 16 years of follow-up

Supplementary file for chapter 5. Association between maternal and paternal prenatal tobacco smoking and risk of CD symptoms in offspring at the age of 14 years using *imputed datasets* (rate ratios with 95% confidence intervals)

Predictor Variables		RR (95% CI)		
		Unadjusted	Adjusted for Each other	Adjusted for all covariates
Maternal prenatal tobacco smoking at 1st trimester	Non-smoker	Reference	Reference	Reference
	1-9 Cigs/day	1.73(1.36-2.18)	1.58(1.23-2.01)	1.37(1.08-1.73)
	≥ 10 Cigs/day	1.95(1.48-2.55)	1.79(1.32-2.33)	1.47(1.12-1.93)
Maternal prenatal tobacco smoking at 3rd trimester	1-9 Cigs/day	1.43(1.10-1.87)	1.27(1.01-1.68)	1.18(1.01-1.50)
	≥ 10 Cigs/day	1.95(1.50-2.53)	1.72(1.31-2.27)	1.47(1.14-1.93)
Maternal prenatal tobacco smoking during both trimesters of pregnancy	1-9 Cigs/day	1.66(1.26-2.20)	1.45(1.09-1.94)	1.28(1.01-1.69)
	≥ 10 Cigs/day	2.22(1.50-3.31)	2.06(1.38-3.09)	1.76(1.20-2.59)
Paternal prenatal tobacco smoking	Non-smoker	Reference	Reference	Reference
	Smoker	1.58(1.34-1.87)	1.33(1.10-1.62)	1.07(0.69-1.44)

Supplementary file 1 for chapter 6.1: Quality assessment of the included studies based on the Newcastle-Ottawa-Scale (N=11)

Study Name	Selection				Comparability	Outcome			Total (9⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	Demonstration that outcome of interest was not present at start of study (⋆)	Comparability (⋆⋆)	Assessment of outcome (⋆)	Follow-up long enough for outcomes to occur (⋆)	Adequacy of follow-up of cohorts (⋆)	
Duko 2020	*	*	*	*	*	*	*	*	8
Goldschmidt 2019	*	*	*	*	*	*	*	*	8
Alati 2006	*	*	*	*	**	*	*	*	9
Alati 2008	*	*	*	*	**	*	*	*	9
Baer 1998	*	*	*	*	*	*	*	*	8
Baer 2003	*	*	*	*	*	*	*	*	8
Cornelius 2016	*	*	*	*	**	*	*	*	9
Lees 2020	*	*	*	*	*	*		*	7
Zaso 2020	*	*	*	*	**	*	*	*	9
Pfinder 2013	*	*	*	*	*	*	*	*	7
O'Brien 2014		*	*	*	*	*	*	*	7

Supplementary file 2 for chapter 6.2: Association between prenatal alcohol exposure and the risk of harmful alcohol use in offspring at the age of 17 years using imputed datasets.

Predictor and control Variables		Risk ratios (RR) (95% CI)	
		Unadjusted	Adjusted for all covariates
Prenatal alcohol use	Non-use	Reference	Reference
	≤ 3 standard drinks/week	1.24(1.21-1.27)	1.18(0.98-1.38)
	≥ 4 standard drinks/ week	1.51(1.21-1.86)	1.44(1.17-1.79)

Key: fully adjusted models included; maternal age at conception, education, marital status, race, family income, and planned pregnancy, low birthweight, preterm birth, sex of child, maternal and paternal smoking during pregnancy, maternal depressive, anxiety and stress symptoms at 13 years of follow-up, offspring aggressive behaviours at 10 years and anxious/depressed behaviours at 16 years of follow-up, maternal alcohol and tobacco use at 16 years of follow-up.**Supplementary file for**

Chapter 7.1: Showing the most comprehensive numbers of key confounders simultaneously measured and adjusted in the studies included in this review (descending order).

First author, year	Country	Study design/ Characteristics	Measured and Adjusted (covariates)
Duko 2021	Australia	Prospective cohort study (the Raine Study)	Maternal age at conception, marital status, race, family income, low birthweight, preterm birth, maternal and paternal education, sex of child, and maternal alcohol use during pregnancy, maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioral problems, postnatal maternal tobacco use at 13 years
Agrawal 2010	US	Retrospective cohort (study offspring-of-twins)	Birth weight, Preterm birth, Remediation, Conduct problems, ADHD, Low scholastic achievement, Maternal drinking during pregnancy, Maternal Heavy Smoking, Maternal Current smoking, Maternal Drug Use, Maternal Alcohol Dependence; Maternal ADHD and Maternal CD problems, Paternal Lifetime Nicotine Dependence, Paternal Current Smoking (PCUR) and Paternal conduct disorder
Cornelius 2000	US	Retrospective cohort	Prenatal alcohol and marijuana use, current tobacco and other substance use, demographic characteristics, SES and psychological status, child characteristics including measures of behavior, IQ, achievement, temperament and alcohol use
Mamun 2006	Australia	Prospective cohort (MUSP)	Age, sex, SES (family income, maternal education), depression, dyadic adjustment, alcohol consumption, number of children in the family at 5-years follow-up, breastfeeding, child internalizing, externalizing behaviors and social attention and thought problems
Menezes 2006	Brazil	Retrospective Cohort	Adolescents sex, living with/without the biological father, relationship with mother, being beaten by the parents, family conflict, maternal postnatal smoking, bad influences on the adolescent, participation in fights, history of attempting to run away from home and experience with alcoholic beverages.
O'Callaghan 2006	Australia	Prospective cohort (MUSP)	Maternal education, marital status, gross family income, mother and partner ever arrested, No. of children in household, maternal depression, maternal and tobacco use, child internalizing behavior, child aggression
Weden 2010	US	Population-based longitudinal study	Age at baseline, age at first smoking assessment, gender, and race/ethnicity),

		(Children and Young Adults of the National Longitudinal Survey of Youth 1979 cohort (NLSY79-CYA))	maternal age at child's birth, and educational attainment and marital status when the child was aged 14 years, and breastfed, prenatal care, and a score of the mother's endorsement in 1980 of 12 adolescent delinquency behaviors from the NLSY79-modified Self-Reported Delinquency Interview
Biederman 2017	US	Case control	Maternal age, race/ethnicity, Attention deficit hyperactivity disorder in offspring, parental antisocial personality, maladaptive parenting, mental health problem in offspring
Cornelius 2005	US	Retrospective cohort	Sociodemographic factors, prenatal alcohol and marijuana exposures, maternal and child psychological characteristics, mother's tobacco, alcohol and marijuana use at the 14-year, peers tobacco smoking
Cornelius 2012	US	Retrospective cohort	Gender, race, age at the time of the assessment, prenatal exposure to alcohol and marijuana, and maternal variables including education, SES, depression and hostility.
Niemela 2015	Finland	Prospective cohort (Northern Finland Birth Cohort 1986 (NFBC86)	Gender, family structure, parental educational level, dwelling, family structure, paternal smoking during pregnancy, maternal and paternal smoking at offspring age 15-16 years
Monshouwer 2011	Netherlands	Population-based prospective cohort (TRIALS study)	Maternal alcohol use during pregnancy, age mother at childbirth and socioeconomic status, parental history of internalizing and externalizing problems and paternal smoking
Buka 2003	US	Retrospective cohort (National Collaborative Perinatal Project)	Maternal age at pregnancy, family socioeconomic status at time of pregnancy, maternal race/ethnicity, offspring gender, and offspring age at time of interview
Roberts 2005	UK	Retrospective Cohort (National Child Development Study and the 1970 British Birth Survey Cohorts)	Offspring sex, birth cohort, maternal age at offspring birth, paternal social class at offspring birth, maternal smoking at 16-year follow-up, and paternal smoking at 16-year follow-up
Rydell 2013	Sweden	Retrospective cohort (Population-based medical birth registries)	Parents psychiatric morbidity, parents' postnatal tobacco use, socioeconomic characteristics, and characteristics of upbringing
Porath 2005	Canada	Prospective cohort (Ottawa Prenatal Prospective Study Cohort)	Maternal alcohol use during pregnancy, maternal age at time of pregnancy, and family income and average parental education
Rydell 2012	Sweden	Prospective cohort (BROMS (Children's Smoking and Environment in	Parental postnatal tobacco use during the index child's age of 11–14 years (any v. none) and for parents with college education (none, one or both)

		Stockholm County) cohort)	
O'Callaghan 2009	Australia	Prospective cohort (MUSP)	Age, maternal education, breastfeeding, parent-child communication, behavioral and internalizing problems
De Genna 2018	US	Prospective cohort	Race, prenatal exposure to alcohol and marijuana, maternal education, child age, maternal postnatal nicotine dependence and sex
Shenassa 2015	US	The Providence and Boston sites of the Collaborative Perinatal Project (1959–1966)	Race/ethnicity, offspring sex and age, mother's age at pregnancy, gravida and family socioeconomic index.
Kandel 1994	US	Retrospective cohort	Maternal age, education, prenatal alcohol exposure, maternal postnatal tobacco and other drug use.
Taylor 2014	UK	Prospective cohort (ALSPAC)	Sex, maternal age, parity, maternal educational attainment, crowding and housing tenure, partner smoking
Ncube 2016	US	Population-based cohort study	The year the daughter delivered, her marital status and educational attainment, and the mothers' race/ethnicity
Shenassa 2021	US	Prospective cohort study	Gravida, age, gender, marital status, education, household income, and depression
Rydell 2016	Sweden	Prospective cohort (Swedish Sibling Health Cohort)	Birth order, sibling order and birth year, previous quit attempts or time to relapses
Lieb 2003	Germany	Prospective cohort	Sex and age of children.

Supplementary file 2 for Chapter 7.1: Quality assessment of the included studies based on the Newcastle-Ottawa-Scale (N=27)

Study Name	Selection				Comparability	Outcome			Total (9⋆)
	Representativeness of exposed cohort (⋆)	Selection of non-exposed cohort (⋆)	Ascertainment of exposure (⋆)	Demonstration that outcome of interest was not present at start of study (⋆)	Comparability (⋆⋆)	Assessment of outcome (⋆)	Follow-up long enough for outcomes to occur (⋆)	Adequacy of follow-up of cohorts (⋆)	
O'Callaghan 2009	*	*	*	*	*	*	*	*	8
Monshouwer 2011	*	*	*	*	**	*	*	*	9
Rydell 2013	*	*	*	*	*	*		*	7
Porath 2005	*	*	*	*	**	*	*	*	9
De Genna 2018	*	*	*	*	*	*	*	*	8
Duko 2021	*	*	*	*	**	*	*		8
Mamun 2006	*	*	*	*	**	*	*	*	9
Cornelius 2005	*	*	*	*	**	*	*	*	9
Buka 2003	*	*	*	*	*	*	*	*	8
Biederman 2017***	*	*	*	*	*		*	*	7
Cornelius 2000	*	*	*	*	**	*	*	*	9
Cornelius 2012	*	*	*	*	**	*	*	*	9
Menezes 2007	*	*	*	*	*	*	*	*	8
Menezes 2006	*	*	*	*	*	*	*	*	8
Taylor 2014	*	*	*	*	**	*	*	*	9
O'Callaghan 2006	*	*	*	*	**	*	*		8
Kandel 1994	*	*	*	*	*	*	*		7
Agrawal 2010	*	*	*	*	**	*	*		8
Lieb R 2003	*	*	*	*	*	*	*	*	8
Rydell 2016	*	*	*	*	*		*	*	7
Niemela 2015	*	*	*	*	**	*	*		8
Roberts 2005	*	*	*	*	**	*	*	*	9
Rydell 2012	*	*	*	*	**	*	*	*	9
Shenassa 2015	*	*	*	*	*	*	*	*	8
Weden 2010	*	*	*	*	*	*	*	*	8

Ncube 2016	*	*	*	*	*	*	*	*	8
Shenassa 2021	*	*	*	*	*	*	*	*	8

*** - we used case control study quality assessment part of NOS for this specific study.

Supplementary file 3 for Chapter 7.1: Leave-one-out sensitivity analysis. Pooled risk ratio (95% confidence interval) for the association between prenatal tobacco exposure and risk of current tobacco smoking in offspring after removal of each study one at a time.

Study excluded	Pooled Risk Ratio (RR)	95%CI
Kandel 1994	1.69	1.47-1.95
Buka 2003	1.68	1.45-1.94
Lieb 2003 (b)	1.74	1.51-2.01
Porath 2005	1.71	1.48-1.96
Roberts 2005	1.78	1.60-1.98
O'Callaghan 2006	1.70	1.48-1.96
Mamun 2006	1.65	1.44-1.91
Menezes 2007	1.70	1.48-1.96
Agrawal 2010	1.70	1.47-1.96
Weden 2010	1.64	1.43-1.88
Monshouwer 2011	1.70	1.48-1.96
Cornelius 2012	1.68	1.45-1.93
Rydell 2012 (b)	1.70	1.48-1.95
Rydell M 2013	1.73	1.50-1.99
Taylor 2014(a)	1.66	1.44-1.92
Niemeläl 2015	1.69	1.46-1.96
Ncube 2016	1.70	1.42-2.02
Duko 2021	1.71	1.48-1.98

Key. The analysis is based on random effect model of meta-analysis

Supplementary file 4 for Chapter 7.1: Leave-one-out sensitivity analysis. Pooled risk ratio (95% confidence interval) for the association between prenatal tobacco exposure and risk of tobacco dependence in offspring after removal of each study one at a time.

Study excluded	Pooled Risk Ratio (RR)	95%CI
Buka 2003 (a)	1.51	1.28-1.78
Lieb 2003(a)	1.42	1.26-1.56
O'Callaghan 2009	1.55	1.30-1.85
Cornelius 2012 (b)	1.48	1.28-1.70
Rydelll 2012 (a)	1.54	1.30-1.82
Shenassa 2015(a)	1.59	1.39-1.84
Rydell 2016	1.52	1.30-1.78
De Genna 2018	1.50	1.29-1.74

Key. The analysis is based on random effect model of meta-analysis

Supplementary file 1 for Chapter 7.2: The risk of tobacco smoking in offspring exposed to maternal prenatal tobacco use compared with paternal prenatal tobacco use.

Models	**Relative risks (RRs) (95% CI)**		***P*-value for difference between maternal and paternal associations**	
	Maternal prenatal tobacco exposure (Trim 1 exposure)	Paternal prenatal tobacco exposure (control variable)	When a control variable included in the model	When a control variable removed from the model
Unadjusted	1.58 (1.25-2.00)	1.38 (1.10-1.72)	0.003	0.001
Model 1	1.34 (1.05-1.73)	1.21 (0.96-1.53)	0.023	0.006
Model 2	1.50 (1.16-1.93)	1.20 (0.95-1.52)	0.001	0.001
Model 3	1.42 (1.07-1.88)	1.21 (0.94-1.55)	0.016	0.005
Model 4	1.50 (1.13-1.97)	1.18 (0.84-1.67)	0.005	0.020

Note:

Model 1: maternal age at conception, education, marital status, race, family income, low birthweight, preterm birth, sex of child, and maternal alcohol use during pregnancy

Model 2: added maternal depressive and anxiety symptoms at 13 years of follow-up and offspring co-existing internalizing behavioural problems to Model 1

Model 3: separately added postnatal maternal tobacco use at 13 years of follow-up to model 1.

Model 4: adjusted for all risk factors

Supplementary file 1 for Chapter 8. Sensitivity analysis of association between maternal prenatal alcohol and tobacco exposure and the risk of current and lifetime cannabis use in offspring at the age of 17 years.

Reference category: non-exposed to prenatal alcohol and tobacco

Prenatal Exposures (Predictor variables)	Relative Risk Ratio (RR)			
	Lifetime cannabis use		Current cannabis use	
	Unadjusted	Fully adjusted	Unadjusted	Fully adjusted
Prenatal alcohol exposure at first trimester	1.22(1.03-1.45)	1.16(0.96-1.41)	1.23(1.06-1.42)	1.24(1.06-1.46)
Prenatal alcohol exposure at third trimester	1.49(1.03-2.15)	1.17(0.80-2.58)	1.58(1.12-2.25)	1.46(1.08-1.98)
Prenatal tobacco exposure at first trimester	1.70(1.17-2.61)	1.06(0.65-1.73)	1.85(1.32-2.61)	1.52(1.02-2.29)
Prenatal tobacco exposure at third trimester	2.01(1.31-3.09)	1.35(0.85-2.14)	2.01(1.32-3.05)	1.56(1.02-2.43)

Fully adjusted model included: unadjusted model and maternal age at conception, education, marital status, annual family income, ethnicity (race), paternal tobacco smoking during pregnancy, sex of child, preterm birth, low birthweight, maternal psychiatric disorder during pregnancy, and maternal depression and postnatal tobacco smoking at 14 years of follow-up and offspring anxious, depressed and aggressive behavior at 14 years.

Supplementary file 2 for Chapter 8. Associations between prenatal alcohol and tobacco exposures and the risk of cannabis use in offspring at the age of 17 years using *imputed datasets* (relative risks with 95% confidence intervals)

Predictor Variables	**RR (95% CI)**		
	Unadjusted	Model 1	Model 2
Non-use	Reference	Reference	Reference
Prenatal alcohol exposure at first trimester	1.38 (1.05-1.32)	1.36 (1.09-1.70)	1.39 (1.07-1.83)
Prenatal alcohol exposure at third trimester	1.33 (1.06-1.68)	1.32 (1.05-1.66)	1.38 (1.08-1.77)
Prenatal tobacco exposure at first trimester	1.58 (1.24-2.01)	1.54 (1.21-1.95)	1.40 (1.11-1.77)
Prenatal tobacco exposure at third trimester	1.63 (1.27-2.09)	1.60 (1.25-2.05)	1.45 (1.08-1.93)

NB: Analyses were run separately by trimester but reported together for ease of presentation.

Key:

Model 1: Mutually adjusted for prenatal tobacco and alcohol exposure.

Model 2: Fully adjusted for maternal age at conception, education, marital status, annual family income, ethnicity (race), paternal tobacco smoking during pregnancy, sex of child, preterm birth, low birthweight, maternal psychiatric disorder during conception, and maternal depression and postnatal tobacco smoking at 14 years of follow-up and offspring anxious, depressed and aggressive behavior at 14 years.

Appendix B

Copyright Information

SPRINGER NATURE LICENSE
TERMS AND CONDITIONS
Feb 04, 2022

This Agreement between Mr. Bereket Duko ("You") and Springer Nature ("Springer Nature") consists of your license details and the terms and conditions provided by Springer Nature and Copyright Clearance Center.

License Number	5241750668351
License date	Feb 04, 2022
Licensed Content Publisher	Springer Nature
Licensed Content Publication	Social Psychiatry and Psychiatric Epidemiology
Licensed Content Title	Prenatal tobacco use and the risk of mood disorders in offspring: a systematic review and meta-analysis
Licensed Content Author	Bereket Duko et al
Licensed Content Date	Sep 7, 2020
Type of Use	Thesis/Dissertation
Requestor type	non-commercial (non-profit)
Format	electronic
Portion	full article/chapter
Will you be translating?	no
Circulation/distribution	1 - 29
Author of this Springer Nature content	yes
Title	PhD candidate
Institution name	Curtin University
Expected presentation date	Mar 2022
Requestor Location	Mr. Bereket Duko 33A Dumond Street, Bentley Perth, Western Australia 6102 Australia Attn: Mr. Bereket Duko
Total	0.00 USD

Terms and Conditions

Licensed Content Title	Prenatal tobacco exposure and the risk of conduct disorder symptoms in offspring at the age of 14 years: Findings from the Raine Study
Licensed Content Author	Bereket Duko,Gavin Pereira,Robert J. Tait,John Newnham,Kim Betts,Rosa Alati
Licensed Content Date	Oct 1, 2021
Licensed Content Volume	142
Licensed Content Issue	n/a
Licensed Content Pages	8
Start Page	1
End Page	8
Type of Use	reuse in a thesis/dissertation
Portion	full article
Circulation	1