Alcohol Use in Pregnancy and Neurocognitive Outcomes in a Contemporary New Zealand Birth Cohort

Analysis of the Growing Up in New Zealand Cohort at 8 Years

[March 2022]

MINISTRY OF SOCIAL DEVELOPMENT
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Authors

Dr Joanna Chu, National Institute for Health Innovation, School of Population Health, University of Auckland jt.chu@auckland.ac.nz

Dr Yannan Jiang, Department of Statistics, Faculty of Science, University of Auckland y.jiang@auckalnd.ac.nz

Dr Jessica McCormack, National Institute for Health Innovation, School of Population Health, University of Auckland j.mccormack@auckland.ac.nz

Dr Samantha Marsh, Social and Community Health, School of Population Health, University of Auckland sam.marsh@auckland.ac.nz

Dr Daniel Walsh, Statistical Consulting Centre, University of Auckland Daniel.walsh@auckland.ac.nz

Alesha Wells, Psychological Medicine, Faculty of Medical and Health Science, University of Auckland alesha.wells@auckland.ac.nz

Professor Chris Bullen, National Institute for Health Innovation, School of Population Health, University of Auckland c.bullen@auckland.ac.nz

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Executive summary

Surveys and population-based studies demonstrate that around one in five New Zealand women report drinking during pregnancy. Prenatal alcohol exposure (PAE) presents a direct risk to the developing fetus for neurocognitive and other harms, sometimes manifesting in childhood as Fetal Alcohol Spectrum Disorder (FASD). For this reason, New Zealand guidelines advise that there is no known safe level of maternal alcohol consumption during pregnancy.

There is limited research available in New Zealand about the extent, distribution and impacts of FASD. To estimate the prevalence in the population would require a large population-based prevalence study, such as is proposed by the World Health Organisation (WHO). The lack of data means that there is insufficient evidence on which policy makers can evaluate the full effects and costs of PAE.

In lieu of a population-based prevalence study, it has been considered that analysis of data from the *Growing Up in New Zealand* longitudinal cohort study (GUiNZ), a large, contemporary cohort study, may be useful in identifying patterns of alcohol exposure and their associations with neurocognitive outcomes in children.

Rationale

The GUiNZ study collected data on maternal alcohol exposure in pregnancy in its baseline wave, and on children at eight years of age. We conducted an analysis within the GUiNZ longitudinal cohort study dataset to explore the effect of PAE on neurocognitive development. There are two components to this analysis:

- The first part is a systematic review of the literature on the association between PAE and neurodevelopmental outcomes related to FASD (Developmental delay; Motor skills/function; Neurophysiology; Cognition; Cognitive development; Language; Academic achievement; IQ; Memory; Attention; Executive function; Affect regulation; Behaviour complications; Adaptive behaviour; Social skills; Communication).
- The second part of the research draws on the 8-year GUiNZ 8 dataset to do longitudinal analyses evaluating the impact of PAE on selected neurodevelopmental outcomes associated with FASD. We compared neurocognitive outcomes across three exposure categories: Non-drinkers, Abstainers during pregnancy, and Alcohol Exposed. The primary outcome was affect regulation (the mechanisms that modulate emotion and mood) at 8 years as measured by the Strengths and Difficulties Questionnaire (SDQ) administered to mothers in Wave 8 of the data collection. We also explored additional secondary neurocognitive outcomes collected in previous data waves between 9 months and 8 years (Wave 1, 2, 5, 6, and 8).

Part I: Systematic review

We identified 30 longitudinal cohort studies (N=299,572) meeting criteria that evaluated the impact of PAE on neurocognitive outcomes. Of those studies the most common domains evaluated were affect regulation and cognition (i.e., IQ).

Overall, the findings on the impact of PAE on neurocognitive outcomes were mixed across domains within the studies reviewed. None of the identified studies found evidence of the effect of PAE on executive function, but there were varied effects for motor skills (i.e., fine and gross motor movements), cognition, language, attention, affect regulation (i.e., expression of emotions), and adaptive behaviour (i.e., skills to function in everyday life).

The most consistent adverse effect of PAE on a specific domain was the domain of affect regulation. Seven out of eleven studies found adverse effects, in particular an adverse association between binge or heavy alcohol use during pregnancy and affect regulation.

Our analysis of moderators did not reveal any protective factor and we found few studies controlled for variables related to the postnatal environment.

Based on this comprehensive review of available large-scale cohort data, it is not possible to conclude that there is a safe level of alcohol consumption during pregnancy.

Part II: Growing Up in New Zealand Data analysis

To explore the relationship between PAE and neurocognitive development we analysed data from the GUiNZ study.

We classified women into three categories based on alcohol consumption before and/or during pregnancy. Women were classified as a "Non-drinker" if they did not consume alcohol before or during pregnancy. If a women consumed alcohol before pregnancy but not during pregnancy, they were classified as an "Abstainer". If a women consumed alcohol during pregnancy, they were classified as "Alcohol Exposed".

The primary outcome focused on the SDQ Total Difficulties score in children at age 8 years as a measure of affect regulation. The SDQ is an emotional and behavioural screening questionnaire based on parent-rating. We calculated the Total Difficulties score and subscale scores and categorized scores as normal and borderline/abnormal. Secondary outcomes included birth outcomes, academic achievement, language, attention, and motor control.

We summarized all outcomes overall and by exposure category. Regression analysis was conducted on selected outcomes including SDQ at age 2, non-verbal communication, joint and sustained attention, early literacy, vocabulary, oral language, and social information processing. Three regression models were considered on each outcome, including an unadjusted model, fully adjusted model including all pre-specified confounding variables, and an adjusted model with stepwise selection.

Additional analyses were conducted for the primary outcome using level and timing of exposure. We conducted separate subgroup analyses for Māori and Pacific mothers.

Key Findings

Of the 6,822 women enrolled in the GUiNZ study, information about prenatal alcohol exposure and child outcomes were available for 6,732 mothers. Exposure groups differed significantly at baseline according to maternal demographic, socioeconomic and health status variables.

- We found no significant differences in affect regulation at 8 years between exposure categories after controlling for prenatal tobacco exposure and neighbourhood deprivation, maternal mental health, and household chaos at 8 years.
- We did not detect a significant difference in affect regulation at 8 years when we compared different levels and timing of exposure.
- We found no significant differences for any birth outcomes or our other secondary variables, except for parent-rated oral language, for which PAE was associated with significantly higher scores.
- Among Māori mothers we found an association of prenatal alcohol exposure with significantly increased risk of abnormal scores on two of the SDQ subscales.
- We did not detect any significant differences among Pacific mothers.

Due to limitations in the available exposure variable and outcome variables it was not possible to infer the prevalence of FASD in the GUiNZ cohort; this would only be possible with a case ascertainment study.

Although the analysis did not find an association between alcohol use in pregnancy and affect regulation this is a finding more likely to reflect imprecision in the measures of exposure and outcome available to us, rather than absence of an association. Our study sits within a large body of evidence that has demonstrated the risks associated with alcohol use in pregnancy and the long-term adverse outcomes for individuals exposed to alcohol in pregnancy. The weight of evidence indicates there is no safe level of alcohol use in pregnancy.

Recommendations

- Continued promotion of health messages about the risk of alcohol use in pregnancy using clear, consistent, and unambiguous messaging, is required.
- Monitor the prevalence of alcohol use in pregnancy to evaluate the effectiveness of messaging and resources:
    - All women should be asked about their alcohol use when pregnant by a lead maternity carer and this should be recorded in their health records;

    - National survey of alcohol and drug use in the New Zealand population including of alcohol and other drugs during pregnancy.
- Investigate the potential stigma associated with alcohol consumption during pregnancy and barriers to reporting alcohol use in pregnancy.
- Establish a cohort study that specifically examines alcohol use in pregnancy.
- Conduct a case-ascertainment study based on the WHO protocol in order to estimate the prevalence of FASD. This information is essential for health, justice, and education systems to plan for and respond to the needs of individuals living with FASD.

Introduction

NZ guidelines for alcohol use in pregnancy advise that there is no known safe level of alcohol consumption during pregnancy(1). Consumption of alcohol is high in NZ, with 79% of adults reporting consuming alcohol during the last 12 months according to the New Zealand Health Survey 2020/2021 (N=9,709)(2). Three quarters of NZ women (75%) report drinking alcohol in the last year, with the highest prevalence of alcohol use in European women (83%) and Māori women (82%), and women aged 45-54 years (80%)(2). An analysis of data collected in Wave 0 of the *Growing Up in New Zealand* longitudinal cohort study (GUiNZ) (N=6822) in 2009 found that around 1 in 5 women reported consuming alcohol after becoming aware of pregnancy, and 71% reported consuming alcohol before becoming pregnant or before pregnancy awareness (3). The study found 23% of women reported drinking alcohol during pregnancy, 13% after the first trimester. The odds of consuming any alcohol during pregnancy were significantly higher for women who were European or Māori (adjusted Odds Ratio [OR] 1.3, 95% Confidence Interval [CI]1.1-1.5, women with no secondary school qualifications (aOR 1.4, 95% CI 1.1-1.9), women in their first pregnancy (aOR 1.2, 95% CI 1.9-2.5), and women with unplanned pregnancies (aOR 2.2, 95% CI 1.9-2.5).

Similar findings have been reported outside of NZ: global estimates suggest that alcohol is consumed in 9.8% of pregnancies (95% CI 8.9-11.1%) (4). Australian research highlighted the high rates of alcohol intake between conception and recognition of pregnancy, with rates as high as 60.6%, decreasing to 18.3% after pregnancy recognition (5).

Alcohol is a known teratogen that passes freely through the placenta and can have adverse effects on fetal development, including changes in brain development associated with cognitive and behavioural changes in children(4-6). Prenatal alcohol exposure (PAE) may result in neurodevelopmental impairments, ranging from domain specific deficits to global impairments with lifelong effects.

Fetal alcohol spectrum disorder (FASD) is the diagnostic term used to describe the neurological and physical effects or consequences of PAE (9). Diagnosis of FASD requires comprehensive assessment by a multi-disciplinary team of 10 neurocognitive domains, with significant impairment shown in at least three neurocognitive domains (as per the Canadian guidelines) (10). Due to the complexity of the assessments involved, most diagnosis occurs around 8yeras of age. Without proper support, individuals living with FASD face many challenges across multiple life domains, with adverse long-term health, education, and social outcomes for the individuals, their families/whānau, and society (11, 12) The overall annual cost to society in NZ is estimated at NZ$690 million (13), although this is likely an underestimate given the prevalence of FASD in NZ is unknown and substantial costs (such as incarceration and mental health service use) are excluded(14). Furthermore, without diagnosis, individuals living with FASD are

unlikely to receive adequate or individualised care to match their needs, or may be misdiagnosed (e.g., with autism or unrelated neurodevelopmental disorders), resulting in inadequate support (15). The burden of alcohol harm in New Zealand falls disproportionately on Māori and Pacific families due to the political, socio-economic and health conditions that contribute to inequitable health outcomes and the failure to implement policies that would address alcohol related harm(16).

No data are available on the prevalence of FASD in NZ. However, based on international studies, the Ministry of Health estimates that 30 in every 1000 births may be affected by alcohol (17). On that basis, FASD is likely to be a significant public health problem in NZ. Global prevalence of FASD is estimated at 7.7 per 1000 children (95% CI 4.9-11.7). However, the prevalence of FASD varies by country, with high estimates in countries with pervasive drinking populations (e.g., South Africa: 111.1 per 1000 [95% CI, 71.1-158.4]; Ireland: 47.5 per 1000 [95% CI, 28.0-73.6)(18).

These findings suggest that FASD and PAE is a major public health concern in many Western countries, including NZ.

Rationale

Due to the limited research available in NZ about FASD, and the lack of data from large scale, prospective cohort studies, there is insufficient evidence for policy makers in NZ to evaluate the full effect of PAE. The report builds on previous research on the impact of PAE on behaviour and affect regulation and adds to the evidence base by evaluating the impact on the domains of communication and cognition.

The first part of the report is a systematic review of the literature on the association between PAE and neurodevelopmental outcomes related to FASD. The second part of the report uses data collected in the eight-year data collection wave (DCW8) of the GUiNZ study data to undertake longitudinal analyses evaluating the impact of PAE on neurodevelopmental outcomes associated with FASD. In the third part of the report, we discuss the findings in the context of available literature and make recommendations for future research in this area.

Part I: Systematic Review

Aim

The aim of this systematic review is to provide a comprehensive review of large cohort-based studies, which are sufficiently powered to detect the impact of different levels of alcohol consumption across neurodevelopmental domains. The review also aims to understand how environmental and maternal factors moderate the impact of PAE on offspring.

Methods

We conducted a systematic narrative review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) standard (19). The protocol was registered in PROSPERO 2021 (CRD42021256407). A detailed description of the search strategy and methodology can be found in Appendix 1.

Findings

Our search strategy identified 30 (N=299,572) relevant articles from birth cohorts recruited between 1981 and 2015 (see Figure 1). Twelve studies were from Denmark, seven were from the UK, five were from Australia, two each from Norway and New Zealand, and one each from Brazil and South Africa.

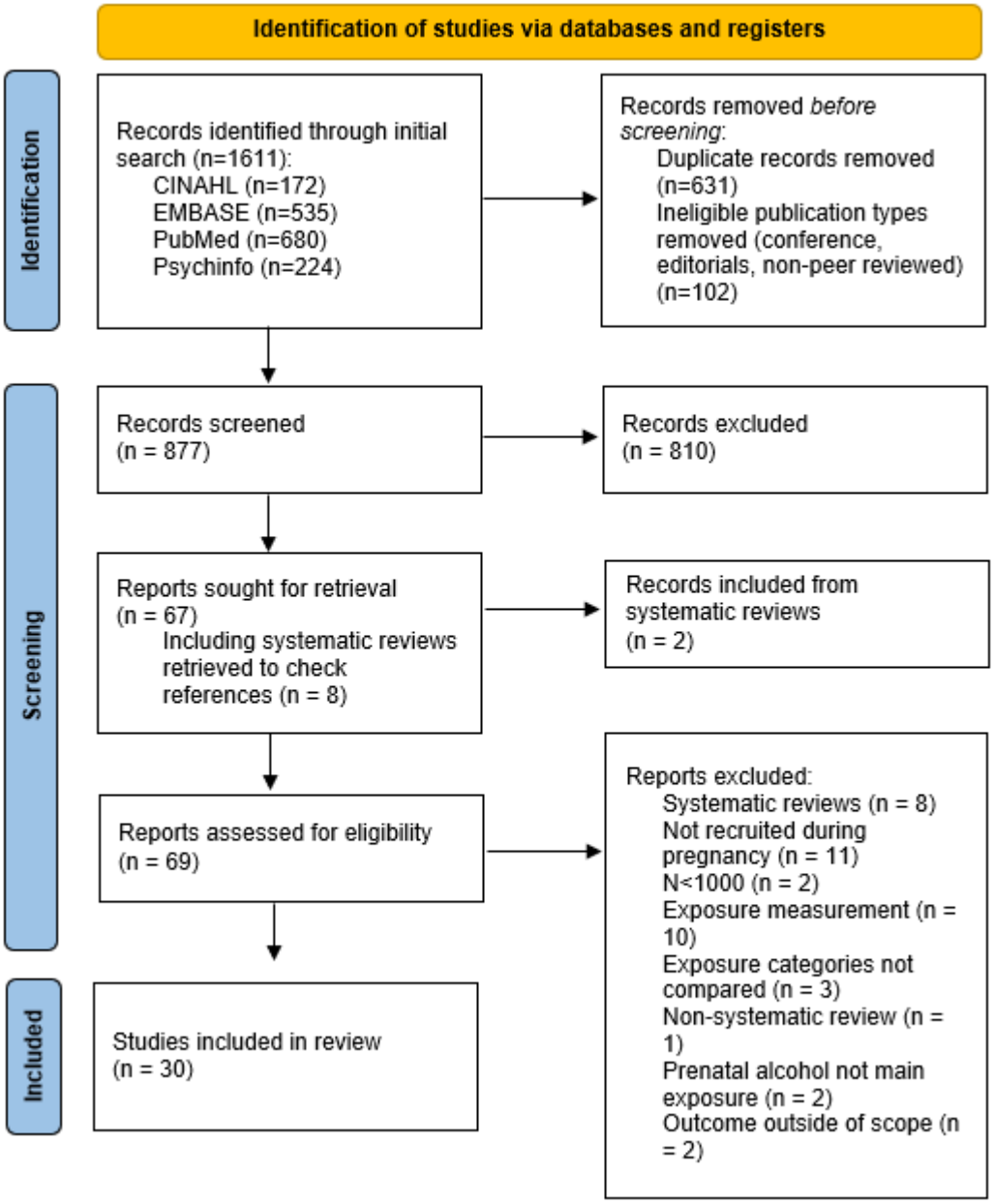

Figure 1: PRISMA flow chart of included studies

Most studies interviewed women around about their alcohol use around 16-20 weeks' gestation (n=24). Self-reported retrospective recall was used in all studies.

Of the 10 neurocognitive domains identified in the Canadian Guidelines by Cook, Green (10) the main domains evaluated in these studies were affect regulation (43.3%) (20-32), cognition (36.7%) (23, 33-36), and attention (26.7%) (24, 28, 29, 37-41); no studies evaluated memory or neurophysiology. An overview of study outcomes is provided in Table 1. Outcomes were assessed in offspring between 6 months and 19 years of age. Most of the studies evaluated children before 6 years (n=21), which is before FASD is generally diagnosed in NZ.

Most studies included in our analysis were deemed high quality after being assessed against the Newcastle-Ottawa Scale (42), scoring between 7-9 (66.7%) and none of the studies were deemed very high risk. Results of the study quality assessment can be found in Appendix 2.

Table 1: Summary of study outcome characteristics.

Characteristic	Number of studies	%
Neurodevelopmental Domains Assessed		
Neurophysiology	0	0
Motor Skills	5	16.7
Cognition	11	36.7
Language	3	10.0
Academic Achievement	5	16.7
Memory	0	0
Attention	8	26.7
Executive Function	3	10.0
Affect Regulation	13	43.3
Adaptive behaviour, social skills, or communication	1	3.3
Age at outcome assessment		
< 2 years of age	9	30.0
3 – 5 years of age	12	40.0
6 – 12 years of age	9	30.0
13 – 18 years of age	3	10.0
Up to 19 years of age	1	3.3

Note: Studies reported on multiple outcomes, therefore the percentages displayed above do not add to 100.

Overall, evidence of the effects of PAE on neurodevelopmental outcomes were mixed for most of the outcomes evaluated in this review. None of the studies found evidence of effects of PAE on executive function or cognition, but there were varied effects for motor skills, cognition, language, attention, affect regulation, and adaptive behaviour and social skills. The presence or absence of adverse effects of PAE depended in part on the timing of exposure (e.g., early versus late

pregnancy) and amount of exposure (e.g., binge versus daily drinking), although effects were not consistent across or within outcomes.

The most consistent effect found across studies was the impact of PAE on affect regulation (studies described in Table 2), which refers to the mechanisms that control or modulate emotions, moods, and feelings. Nine out of thirteen studies evaluating affect regulation found adverse effects of PAE on affect regulation, particularly for heavy alcohol consumption or binge drinking during pregnancy (20, 21, 24, 25, 27-31). Some studies found that low levels of PAE might be protective against adverse neurodevelopmental outcomes (22, 26). However, this finding is likely to reflect unmeasured confounding variables in the non-drinking population than a real effect (43).

Table 2. Epidemiological studies evaluating the impact of PAE on behaviour and affect regulation.

Author, year	Country	Number of participants (offspring)	Years Recruited	Outcome Measure	Offspring Age	Result
Alvik, 2011 (21)	Norway	1330	2000-2001	Infant Characteristics Questionnaire	6 months	Binge drinking predicted difficult temperament
Alvik, 2013 (20)	Norway	1116	2000-2001	Strengths and Difficulties Questionnaire (SDQ)	5.5 years	Binge drinking predicted abnormal/borderline SDQ scores
D'Souza, 2019(22)	New Zealand	5768	2009-2010	SDQ	2 years	No significant association
Halliday, 2017 (23)	Australia	554	2011-2012	Brief Infant Toddler Social Emotional Assessment	2 years	No significant association
Niclasen, 2014 (24)	Denmark	37152	1996-2002	SDQ	7 years	Binge drinking associated with significantly higher externalizing scores
Niclasen, 2014 (25)	Denmark	37152	1996-2002	SDQ	7 years	Binge drinking associated with significantly higher externalizing and internalizing scores in male offspring. No significant association in female offspring
Robinson et al., 2010 (26)	Australia	1860	1989-1991	Child Behaviour Checklist	2, 5, 8, 10, and 14 years	Light and moderate drinking associated with positive behaviour and reduction in behavioural problems

Sayal, 2007 (30)	UK	[range]	1991-1992	SDQ	47, 81, 93, and 108 months	Consumption of <1 drink per week associated with clinically significant problems in female offspring. No significant association in male offspring
Sayal, 2009 (29)	UK	8240	1991-1992	SDQ	47 months	Binge drinking associated with increased risk of clinically significant problems
Sayal, 2013 (27)	UK	10558	1991-1992	SDQ	11 years	No effect of light drinking on teacher-rated SDQ. Significant association between light drinking and worse outcomes for parent-rated SDQ scores in girls compared to abstainers
Sayal, 2014 (28)	UK	7965	1991-1992	SDQ	10-11 years	Binge drinking associated with increased problems in girls based on parent-rated SDQ. Binge drinking without daily drinking associated with increased problems in both genders on teacher-rated SDQ
Schoeps, 2018 (31)	New Zealand	60156	2009-2010	Infant Behaviour Questionnaire; SDQ	9 months and 2 years	Alcohol consumption during pregnancy associate with lower positive affect, affiliation/regulation, and orienting capacity temperament scores.
Skogerbø,	Denmark	1628	1997-2003	Behaviour/mental health (SDQ parent and teacher)	5 years	No significant association between low to moderate drinking and SDQ scores

Moderators

Parental socio-economic characteristics was the only confounder consistent across 30 studies. Socio-economic characteristics included one or multiple of the following variables: socioeconomic position, education, social class, house ownership, crowding, income, civil status (e.g., married, divorced), area-level deprivation, employment status, marital status, and family structure (e.g., single-parent, two-parents, living with kin). Maternal age and maternal smoking during pregnancy were also commonly controlled for in most analyses (maternal age; n=27 studies; maternal smoking: n=26 studies) (see Appendix 3 for additional moderators).

Our analysis of moderators did not reveal any protective factors. Long-term neurodevelopmental outcomes of PAE are susceptible to exposures in the environment between *in utero* exposure and the time of outcome measurement. While all studies controlled for measurable maternal baseline variables and other exposures *in utero*, few studies included variables relating to the postnatal environment that could be important, such as parenting styles, quality of the caregiving environment, neighbourhood deprivation at time of outcome measure and domestic relationships.

Conclusions

Based on this comprehensive review of available large-scale cohort data, there is no evidence of a safe level of alcohol consumption during pregnancy. The longitudinal cohort studies produced mixed findings in most of the ten neurodevelopmental domains considered in this review and there are limitations in the quality and consistency in which PAE is studied, as well as limitations in the timing and utility of outcome measures. Finally, further exploration of residual confounding variables is vital, including measuring the characteristics of the environment after birth and using a separate classification for women who abstain from alcohol during pregnancy and those who do not drink at all.

Part II: Data Analysis

Aim

To explore the relationship between PAE and neurocognitive development outcomes at 8-years using data from the Growing Up in New Zealand (GUiNZ) study cohort.

Method

We analysed data from the Growing Up in New Zealand study. We incorporated potential moderators identified in the systematic review into the analyses.

Aim

To explore the relationship between PAE and neurocognitive development outcomes at 8-years using data from the Growing Up in New Zealand (GUiNZ) study cohort.

Study Population

The GUiNZ cohort is a longitudinal study of children whose mothers were recruited prospectively in 2008-2010 from Auckland and Waikato regions of New Zealand. The methods of the GUiNZ study are described on the study website (http://www.growingup.co.nz/en/about-the-study.html). Information was collected from participating pregnant mothers and their partners beginning prior to birth and continuing up to the most recent wave of data collection when the children in the cohort were 8 years of age. Pregnant women were eligible to participate in the study if they had an expected delivery date between 25th April 2009 and 25th March 2010. The sample is representative of all NZ births in 2007-2010 (44). In total, 6,822 pregnant women enrolled (44). Due to the small number of multiple births in the study cohort, we excluded all multiple birth babies from the analysis cohort. Thus, the cohort consists of 6,853 children, of which 6,643 were singleton births.

Measurement of Alcohol Intake

Antenatal interviews took place during the last trimester of pregnancy (n=5668) or postnatally (n=1154). Women were asked to recall their alcohol use at three time periods:

- before becoming pregnant or before pregnancy awareness (T1).
- first three months of pregnancy (T2).
- after the first three months of pregnancy (T3).

Women were asked to estimate the average number of alcoholic drinks consumed per week. In New Zealand standard drinks are defined a 10g of pure alcohol. Responses were given in drinks per week and coded to the following categories in the dataset provided: (0) Did not drink; (1) Less than 1 drink; (2) 1-3 drinks; (3) 4-19 drinks; and (4) 20+ drinks.

We classified women according to three categories:

- Non-drinker: Women that did not consume alcohol before pregnancy or before pregnancy awareness and did not consume alcohol during pregnancy.
- Abstainer: Women who did not consume alcohol in pregnancy, but did consume alcohol before pregnancy or before pregnancy awareness
- Alcohol Exposed: Any women that reported consuming alcohol during pregnancy (i.e., T2 and/or T3).

The classification of the unexposed cohort into Abstainer and Non-drinker was done due to significant differences between Abstainers and Non-drinkers in previous studies (see Alvik, Aalen (38)).

Timing of exposure was classified as

- Early exposure (>0 drinks at T2, 0 at T3)
- Late exposure (0 drinks at T2, >0 drinks at T3)
- Both early and late exposure (>0 drinks at both T2 and T3)
- No exposure (0 drinks at T2 and T3).

The level of exposure was classified as

- Very low (less than 1 drink)
- Low (1-3 drinks)
- High (4-19 drinks)
- Very high (20+ drinks)
- None (0 drinks).

If a mother consumed alcohol in both time periods, the level of exposure was coded according to the higher of the two exposures.

Primary Outcome

The primary outcome was the Strengths and Difficulties Questionnaire (SDQ) Total Difficulties score at age 8 years. The SDQ is an emotional and behavioural screening questionnaire based on parent-rating. It has been used in other longitudinal cohort studies as a measure of affect regulation (20, 22, 24, 25, 27-32), which is one of the ten neurocognitive domains of FASD (10). The SDQ (45) is a self-report questionnaire that was administered to mothers at DCW2, DCW 5, and DCW 8. The Total Difficulties scores is generated by summing all 25 items (excluding the prosocial items) and can range from 0 to 40, with more extreme scores indicating more difficulties.

Along with the summed scores, we also analysed SDQ as a dichotomised variable, with scores categorised as either normal (0-13) or borderline/abnormal (14-40) on the basis of cut-offs taken from Australian norms (46)[1]. Analyses were also conducted on each of the five subscales: Emotional problems (e.g., seeming worried unhappy, or easily scared), Conduct problems (e.g., often loses temper, argumentative, fights with other children), Hyperactivity (e.g., restless, easily distracted), Peer problems (e.g., solitary, not liked by other children), and Prosocial (e.g., considerate, shares with others) (47).

Secondary Outcomes

We were also interested in other neurocognitive outcomes measured at follow-up assessments between 9 months and 8 years. These included the following measures related to the neurocognitive domains impacted by FASD:

- Affect Regulation
    - SDQ (DCW2)(45).
    - Child Behaviour Questionnaire (Very Short Form; CBQ VSF), a measure of temperament administered to parents (DCW)(48).
- Language
    - MacArthur-Bates Communication Development Inventory (MacArthur CDI II) – First communication Gestures Scale (12-items), a measure of non-verbal communication administered to parents (DCW1)(49).
    - Adapted Peabody Picture Vocabulary Test (PPVT), a test of receptive vocabulary administered by child observation (DCW5)(50). A derived variable – latent receptive language – was generated from the core 20 items.
- Executive Function
    - Stack and topple, an observation of different types of attention administered in the child observation (DCW2)(51).
    - Hand Clap task, a test of response inhibition consisting of 16 trials administered in the child observation (DCW5).
- Academic Achievement
    - Dynamic Indicators Basic Early Literacy Skills (DIBELS), a measure of reading an early literacy skill administered to children (DCW5) (52).

[1] No New Zealand norms of the SDQ have been published although the Ministry of Health guidance for the B4 School check includes thresholds for secondary assessment and referral.

    - Name and Number Task, a measure of academic skill taken form the Who Am I? Developmental Assessment (LSAC) administered to children (DCW5) (53).
    - Parent Rating of Oral Language and Literacy (PROLL), a measure of oral language administered to parents (DCW5)(54).
    - B4 school check, self-reported areas of concern from parents (DCW6).
- Adaptive behaviour, social skills, and communication
    - Social Information Processing, a measure adapted from the Peer Provocation Inventory (DWC8)(55).

As well as neurocognitive outcomes the following outcomes at birth and up to 9 months were of interest:

- Delivery type
- Fetal count (i.e., singletons, multiples)
- Gestational age in term
- Baby's gender
- Birth weight and birth length
- Days in hospital
- Baby's weight at 6 weeks and 9 months
- Baby's sleeping and feeding patterns
- Mother's feeling within self at 6 weeks
- Baby's health status at 9 months
- Baby's health or developmental problems at 9 months (including illnesses, immunisation, medication)

Potential Confounders

The following maternal baseline characteristics (DCW0) were considered as potential confounding variables in the analysis based on findings from the systematic review:

- Age (years) at antenatal interview
- Self-prioritised maternal ethnicity (Statistics New Zealand Level 1 classification)
- Pre-pregnancy weight (kg), height (m) and BMI (kg/m2)
- Highest completed qualification
- Labour force status (i.e., employed, unemployed, student, not in workforce)
- Current smoking status (i.e., current smoker or non-smoker)

- Medication uses during pregnancy
- General health status, disability, and clinical diagnoses
- Edinburgh postnatal depression scale (Normal [0-11], Abnormal [12 or above])(56)
- Perceived stress scale (0-40)(57)
- Interparental relationship (15-105)(58)
- Household structure (i.e., parent alone, two parents, parent(s) with extended family, parent(s) living with non-kin
- Total annual household income (≤$20K - >$150K)
- NZ Deprivation Index 2006
- Paternal alcohol and tobacco use

We also considered birth outcomes and outcomes up to 9 months, as well as the following variables collected in the contemporaneous data waves:

- Current NZ Deprivation Index 2006 or 2013
- Maternal drug use at 9 months
- Maternal mental Health (PHQ) (59)
- Home environment (CHAOS) (60)

Statistical Analysis

Data analysis was performed via remote access to the secure e-platform hosted by the Growing Up NZ data team. All study results exported from the platform were reviewed by the data team who would then release the files via emails upon approval. Statistical analysis was performed using R (the R project for statistical computing, https://www.r-project.org/). Statistical tests were two-sided at 5% significance level.

Maternal and paternal characteristics

Maternal and paternal characteristics collected during pregnancy (DCW0) were summarised overall and by maternal alcohol exposure level. Those mothers who didn't provide information on their alcohol use in pregnancy were excluded from the main study cohort.

Continuous variables were summarised as the numbers observed and missing, mean, standard deviation (SD), median (Q2) and interquartile range (Q1 and Q3). Categorical variables were summarised as frequencies (n) and percentages (%). Missing data were reported but excluded from the analysis. The difference between groups were tested using the analysis of variance (ANOVA) on continuous variables, and the chi-square test on categorical variables.

Child outcomes at birth

All registered babies born alive to the mothers in the main study cohort were included in the childbirth cohort, including both single and multiple births (DCW1). Birth outcomes were summarised overall and by maternal alcohol exposure levels using descriptive statistics, and similar statistical tests were used to compare the variables between alcohol exposure levels.

Regression analysis was conducted on selected child outcomes at birth up to 9 months. The outcomes were pre-specified based on the literature (e.g., birthweight and birth term), or those that showed significant differences between alcohol exposure levels. Linear regression was used on continuous outcomes, and logistic regression on binary outcomes (categorical variables with more than two categories were grouped using a pre-determined cut-off).

Three regression models were considered on each outcome, including an unadjusted model, fully adjusted model including all pre-specified maternal and paternal confounding variables and child gender, and an adjusted model with stepwise selection including only significant independent variables in the final model to avoid multicollinearity in selected confounders and test the robustness of the full model. Where appropriate, this final model was used to interpret the results on the association between maternal alcohol exposure and childbirth outcomes.

The following variables were considered in the full models:

- Maternal age
- Maternal ethnicity
- Maternal education
- Maternal labour status
- Maternal smoking status
- Household structure
- Household income
- NZDep 2006
- Maternal health pre-pregnancy
- Maternal health status: depression
- Maternal health status: anxiety
- Maternal perceived stress
- Inter-parental relationship
- Postnatal marijuana and other drug use
- Paternal alcohol and tobacco use

Due to the small number of multiple births in the study cohort, we decided to exclude all multiple birth babies from the analysis cohort. Therefore, no cluster effect is expected. Where appropriate, categorical variables with a large amount of missing data were coded Unknown as a separate category when the data were missing.

For continuous outcomes, unadjusted and adjusted mean differences between alcohol exposure levels were reported with 95% confidence intervals and p-values. For binary outcomes, unadjusted and adjusted odds ratios (ORs) were reported with 95% confidence intervals and p-values.

Primary and secondary outcomes at follow-up

We conducted regression analysis on primary and secondary outcomes from 9 months to 8 years, using a similar modelling approach to that described above. For each variable we considered three regression models: unadjusted, fully adjusted including all pre-specified confounding variables (see Appendix 4), and stepwise selection model.

The fully adjusted model for outcomes collected in DCW8 included all the following variables:

- Offspring gender
- Self-identified ethnicity
- Weight at birth
- Maternal smoking status during pregnancy
- Maternal mental health at 8 years
- Neighbourhood deprivation at 8 years
- Household chaos at 8 years

Linear regression was used on continuous outcomes and reported as unadjusted and adjusted mean differences between maternal alcohol exposure levels. Logistic regression was used on binary outcomes (categorical variables with more than two categories were grouped using a pre-determined cut-off) and reported as unadjusted and adjusted odds ratios (ORs). All model estimates were reported with 95% confidence intervals and p-values.

Timing and Level of Exposure

Additional analyses were conducted for the primary outcome – SDQ Total Difficulties Score – on the association with the timing and level of maternal alcohol exposure.

Subgroup Analysis

Separate analyses were conducted for the Māori and Pacific mothers and their children. Analysis was conducted as described for the main analysis with the data restricted to each of the subgroups based on self-reported maternal ethnicity.

Results

Baseline maternal characteristics

Of the 6,822 women enrolled in the study, information about prenatal alcohol use was unavailable for 25 women. Once we excluded those with no child data, we were left with a sample of 6,732 mothers at baseline.

The characteristics of the sample by exposure group are described in Table 3. Twenty-nine percent of women consumed alcohol during some point in their pregnancy. We found significant difference in the baseline maternal characteristics of the exposure groups for demographic, socioeconomic and health status variables. The Non-drinker group had a higher proportion of Asian and Pacific women and a higher proportion of women from the most deprived neighbourhoods compared to the Abstainer and Drinker groups. A smaller proportion of women in the Abstainer group reported health problems such as asthma, anaemia, and anxiety and depression, however a greater proportion diabetes in pregnancy. Compared to the Non-Drinker group, a greater proportion of the Drinker group were under 25 years, were Māori, had no formal qualifications, from most deprived neighbourhoods. Current smoking status varied between exposure group; 5.3% of the Non-drinker group reported currently smoking, 9.2% of the Abstainer group, and 17.8% of the Alcohol Exposed group.

Table 3. Maternal baseline characteristics by exposure group

Variable	Overall		Alcohol Exposed		Abstainer		Non-drinker		P value
	N	%	N	%	N	%	N	%	
Total	6,732		1,905	(28.3)	2,900	(43.1)	1,927	(28.6)	
Age Mean (SD)	30.05	(5.9)	29.96	(6.3)	30.27	(5.7)	29.82	(5.6)	0.024
Maternal Ethnicity									<0.001
NZE	3,814	(56.8)	1,248	(65.7)	1,936	(66.9)	630	(32.7)	
Māori	931	(13.9)	387	(20.4)	351	(12.1)	193	(10.0)	
Pacific	983	(14.6)	191	(10.1)	325	(11.2)	467	(24.3)	
Asian	991	(14.8)	73	(3.8)	282	(9.7)	636	(33.0)	
Education									<0.001
None	475	(7.1)	195	(10.3)	155	(5.4)	125	(6.5)	
Secondary School	1,604	(23.9)	424	(22.3)	623	(21.5)	557	(29.0)	
Diploma	2,059	(30.6)	565	(29.8)	899	(31.0)	595	(30.9)	
Bachelor's Degree	1,525	(22.7)	411	(21.6)	703	(24.3)	411	(21.4)	

Higher Degree	1,056	(15.7)	304	(16.0)	516	(17.8)	236	(12.3)	
Labour Status									<0.001
Employed	3,630	(56.5)	1,072	(58.2)	1,726	(62.2)	832	(45.9)	
Unemployed	535	(8.3)	160	(8.7)	168	(6.1)	207	(11.4)	
Student	460	(7.2)	139	(7.6)	201	(7.3)	120	(6.6)	
Not in Workforce	1,800	(28.0)	470	(25.5)	678	(24.5)	652	(36.0)	
Current Smoker									<0.001
Yes	644	(10.6)	311	(17.8)	243	(9.2)	90	(5.3)	
No	5455	(89.4)	1441	(82.8)	2400	(90.8)	1614	(94.7)	
Household Structure									<0.001
Parent Alone	229	(3.4)	89	(4.7)	80	(2.8)	60	(3.1)	
Two Parents	4,423	(65.7)	1,192	(62.6)	2,065	(71.2)	1,166	(60.5)	
Parent(s) with extended or non-kin	2,080	(30.9)	624	(32.8)	755	(26.0)	701	(36.4)	
Household Income									<0.001
<=$30K	506	(9.8)	136	(9.3)	157	(6.8)	213	(15.4)	
$30-50K	724	(14.0)	177	(12.1)	247	(10.7)	300	(21.7)	
$50-70K	849	(16.5)	185	(12.6)	355	(15.4)	309	(22.3)	
$70-100K	1,190	(23.1)	319	(21.8)	569	(24.7)	302	(21.8)	
>$100-150K	1,886	(36.6)	648	(44.2)	978	(42.4)	260	(18.8)	
Neighbourhood deprivation (NZDEP)									<0.001
1-2 (Least deprived)	1,091	(16.2)	324	(17.0)	555	(19.1)	212	(11.0)	
3-4	1,225	(18.2)	359	(18.9)	597	(20.6)	269	(14.0)	
5-6	1,159	(17.2)	328	(17.2)	538	(18.6)	293	(15.2)	
7-8	1,410	(21.0)	377	(19.8)	570	(19.7)	463	(24.0)	
9-10 (Most deprived)	1,845	(27.4)	515	(27.1)	640	(22.1)	690	(35.8)	
Mother's Health Pre-pregnancy: General									<0.001
Poor/Fair	684	(10.2)	216	(11.4)	273	(9.42)	195	(10.1)	
Good/Very Good	4671	(69.4)	1267	(66.6)	2011	(69.4)	1393	(72.4)	
Excellent	1,372	(20.4)	420	(22.1)	615	(21.2)	337	(17.5)	

Health Status: Depression									<0.001
Never	5576	(82.9)	1493	(78.5)	2392	(82.6)	1691	(87.8)	
Before not during	820	(12.2)	288	(15.1)	378	(13.1)	154	(8.0)	
During	329	(4.9)	122	(6.41)	127	(4.38)	80	(4.2)	
Health Status: Anxiety									<0.001
Never	6042	(89.8)	1660	(87.2)	2606	(90.0)	1776	(92.2)	
Before not during	468	(7.0)	175	(9.2)	203	(7.0)	90	(4.7)	
During	216	(3.2)	69	(3.6)	87	(3.0)	60	(3.1)	
Perceived Stress									0.005
(<= 13) Low	3283	(53.8)	919	(52.4)	1486	(56.2)	878	(51.5)	
(14-26) Moderate	2,676	(43.9)	783	(44.7)	1,109	(41.9)	784	(46.0)	
(>= 27) High	144	(2.4)	51	(2.9)	49	(1.9)	44	(2.6)	

Notes. All values are N and % unless otherwise stated. Mean (M) and Standard Deviation (SD) reported for age. NZE indicates New Zealand European.

Of those that had consumed any alcohol during pregnancy (N=1.905), most respondents were classified as having had Very Low (46.2%) or Low (30.0%) levels of alcohol exposure. Alcohol exposure was classified as Very High for only 2.8% and High for 21.0% of participants consuming alcohol during pregnancy. Most responses were classified as Early exposure (52.7%), with 20.1% classified as Late exposure and 27.2% as Both (Figure 2).

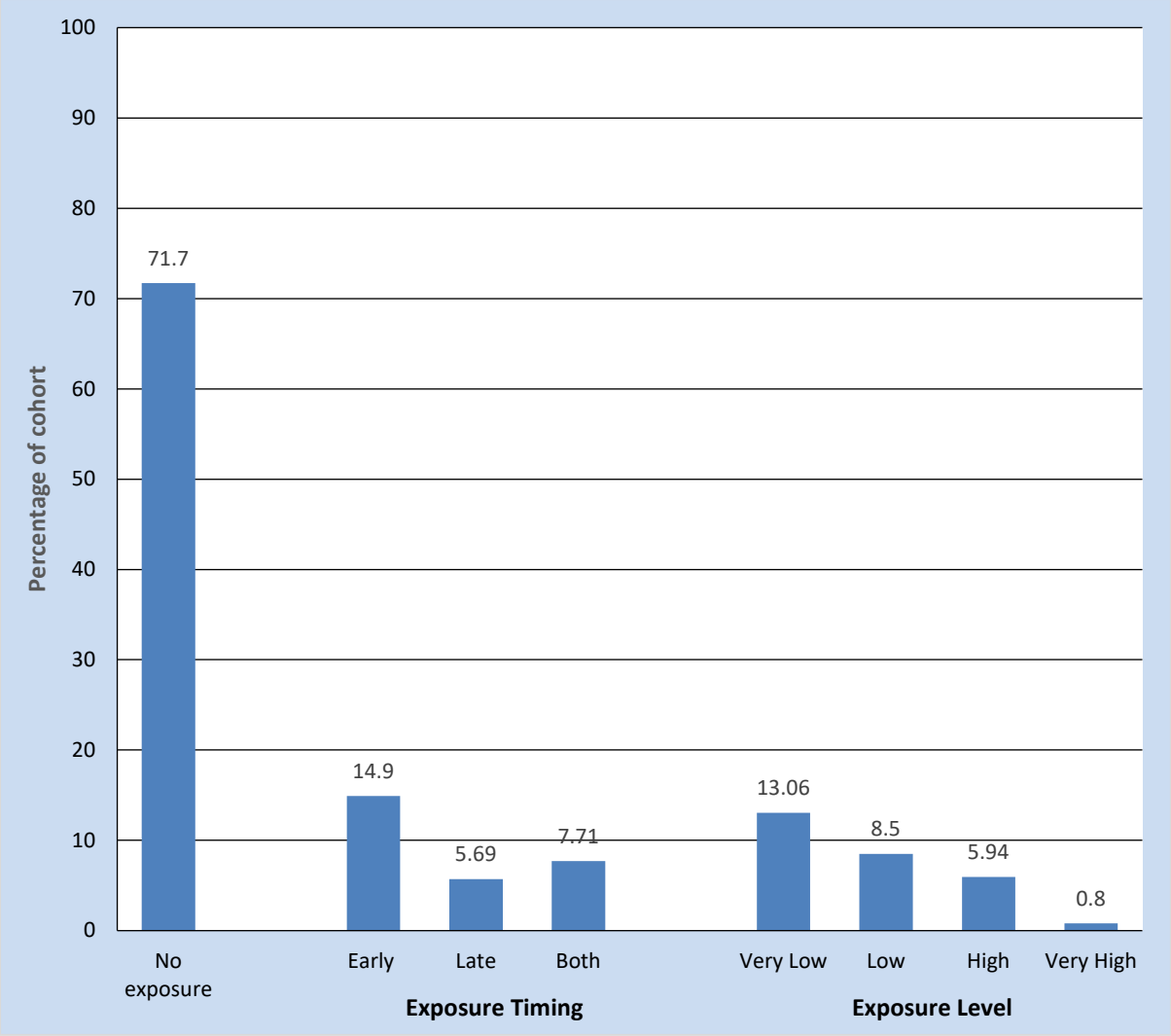

Figure 2: Proportion of births exposed to alcohol by timing and level of exposure

Child Outcomes at Birth

Child outcomes at birth did not differ across the exposure groups (Table 4). Regression analysis found no significant differences for birth outcomes by exposure group (Appendix 5). Overall, 51.5% of the children were male, 91.3% were born to term, and the mean weight at birth was 3.48 kgs (SD=0.58). At nine months, most parents rated their child's health as Excellent (59.8%) or Very Good (27.9%).

Table 4. Birth outcomes by exposure group

	Alcohol Exposed		Abstainer		Non-Drinker		P-value
Variable	**N**	**%**	**N**	**%**	**N**	**%**	

Total	**1,923**		**2,946**		**1,952**		
Gender							0.23
Boy	999	(52.0)	1,541	(52.3)	974	(49.9)	
Girl	924	(48.1)	1,405	(47.7)	978	(50.1)	
Term of Birth							0.59
Preterm (<37 GW)	113	(5.9)	196	(6.7)	121	(6.2)	
Term (37-41 GW)	1,753	(91.3)	2,678	(91.1)	1,783	(91.4)	
Post Term (>41 GW)	54	(2.8)	66	(2.2)	46	(2.4)	
Days in hospital							0.68
0	156	(8.4)	207	(7.2)	149	(7.8)	
1-3	1,131	(60.7)	1,767	(61.4)	1,178	(61.8)	
4-7	517	(27.7)	796	(27.7)	508	(26.6)	
8-14	39	(2.1)	68	(2.4)	54	(2.8)	
15+	21	(1.1)	41	(1.4)	18	(1.0)	
Weight at Birth (g) Mean (SD)	51.85	(3.4)	51.69	(3.4)	51.72	(3.3)	0.12
Child's Health at 9 months							0.32
Excellent	1,095	(60.5)	1,656	(59.2)	1,106	(60.2)	
Very good	475	(26.2)	812	(29.0)	513	(27.9)	
Good	188	(10.4)	251	(9.0)	158	(8.6)	
Fair	45	(2.5)	62	(2.2)	52	(2.8)	
Poor	8	(0.4)	16	(0.6)	8	(0.4)	

Notes. GW= gestation week. Number of participants (N) and % reported unless specified as Mean and Standard Deviation (SD).

Primary Outcome: Affect Regulation at 8 years

SDQ scores at 8 years were available for 4,550 children. The mean Total Difficulties score was 7.55 (SD 4.55); 93.0% of children had Total Difficulties scores that fell in the normal range, and this was similar across all three exposure groups. There was no significant association between alcohol use in pregnancy and total difficulties scores. The stepwise adjusted mean difference in Total Difficulties score between Drinkers and Abstainers was -0.034 (95% CI -0.44 to 0.371, p=0.87).

Most children scored in the normal range for each of the subscales, with the proportion ranging from 87.6% for Peer Problems to 96.2% for the Pro-social scale with similar scores across exposure groups. There was no significant association between alcohol use in pregnancy and any of the SDQ subscales. There was no significant association between alcohol use in pregnancy and risk of borderline/abnormal scores for Total Difficulties score or any of the subscales (Table 5).

Table 5. Stepwise Adjusted Model for risk of borderline/abnormal SDQ Scores at 8 years

	Alcohol Exposed v Abstainer			Alcohol Exposed v Non-Drinker			Abstainer v Non-Drinker		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Total Difficulties	0.78	0.52-1.17	0.24	0.92	0.58-1.46	0.73	1.18	0.80-1.75	0.41
Subscales									
Emotional Problems	1.06	0.74-1.50	0.76	1.32	0.88-1.98	0.18	1.25	0.87-1.81	0.24
Conduct Problems	0.81	0.56-1.15	0.25	1.00	0.66-1.49	0.98	1.23	0.87-1.76	0.25
Hyperactivity	0.84	0.61-1.16	0.29	1.05	0.73-1.52	0.78	1.25	0.91-1.73	0.16
Peer Problems	0.92	0.68-1.24	0.58	1.09	0.78-1.53	0.60	1.19	0.89-1.61	0.25
Prosocial	0.80	0.49-1.34	0.42	1.20	0.65-2.24	0.56	1.50	0.89-2.60	0.14

Note. Model adjusted for offspring gender, ethnicity, weight at birth, prenatal tobacco exposure, maternal mental health at 8 years, CHAOS at 8 years, and neighbourhood deprivation at 8 years. See Appendix 3 for full stepwise analysis.

Level and Timing of Alcohol Exposure

For the regression analysis comparing SDQ scores across levels of alcohol exposure. There were no significant differences in the Total Difficulties Score by level of alcohol exposure, and no difference in risk of abnormal/borderline scores. Similarly, there were no significant differences in Total Difficulties Score or risk of abnormal/borderline scores by timing of alcohol exposure.

Secondary Outcomes

No significant adverse effects were found for any of the secondary outcomes (Table 6 and 7). The only significant association between PAE and secondary outcomes was an unexpected significant association between alcohol use and scores on PROLL. Compared to the offspring of mothers who abstained during pregnancy, PROLL scores were higher for offspring of mothers who consumed alcohol in pregnancy (MD=0.67, 95% CI 0.016-0.11, p=0.0106) indicating better oral language (Table 6). However, there was no significant change in risk of PROLL scores classified as severe (i.e., two standard deviations below mean).

Table 6. Linear regression stepwise adjusted model of secondary outcomes

	Alcohol Exposed v Abstainer		Alcohol Exposed v Non-Drinkers		Abstainer V Non-Drinker	
	MD	95% CI	MD	95% CI	MD	95% CI

Affect Regulation						
SDQ (DCW2)	-0.14	-0.52-0.24	-0.32	-0.74-0.09	0.85	-0.67-1.09
CBQ VSF (DCW5) Surgency	0.02	0.04-0.08	-0.03	-0.10-0.03	0.06	-0.12-0.00
CBQ VSF (DCW5) Effortful Control	0.03	-0.02-0.08	0.02	-0.03-0.08	-0.00	-0.05-0.04
CBQ VSF (DCW5) Negative Affect	0.01	-0.05-0.07	0.02	-0.05-0.08	0.01	0.06-0.07
Communication and Adaptive Behaviour						
CDI II (DCW1)	-0.07	-0.33-0.18	-0.10	-0.38-0.18	-0.03	-0.29-0.23
PPVT (DCW5)	0.01	-0.05-0.08	-0.04	-0.11-0.04	-0.05	-0.11-0.02
SIP (DCW8) Aggression-avoidance	-0.05	-0.52-0.43	0.20	-0.33-0.72	0.24	-0.23-0.72
SIP (DCW8) Assertive	-0.23	-0.80-0.34	-0.24	-0.86-0.39	-0.01	-0.57-0.56
Academic						
PROLL (DCW5)	0.07*	0.02-0.12	0.06	0.00-0.11	-0.01	-0.06-0.04
DIBELS (DCW5)	0.29	-0.55-1.13	-0.23	-1.15-0.69	-0.52	-1.36-0.32
Counting (DCW5)	-0.19	-0.64-0.26	-0.02	-0.51-0.48	0.17	-0.28-0.62
Executive Function						
Hand Clap (DCW5)	-0.13	-0.52-0.27	-0.20	-0.63-0.23	-0.08	-0.47-0.32

Table 7. Logistic regression stepwise adjusted model of secondary outcomes

	Alcohol Exposed v Abstainer		**Alcohol Exposed v Non-Drinkers**		**Abstainer V Non-Drinker**	
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Affect Regulation						
SDQ (DCW2)	0.85	0.67-1.09	1.01	0.78-1.29	0.86	0.66- 1.12
Academic					1.06	0.77- 1.46
PROLL (DCW5) Severe	0.91	0.65-1.26	1.00	0.67-1.38	1.09	0.63- 1.95
B4 School (DCW6) Learning Difficulties	0.87	0.48-1.53	0.95	0.50-1.80	1.04	0.64- 1.71
B4 School (DCW6) Behaviour	1.00	0.61-1.61	1.03	0.60-1.78	1.24	0.47- 3.62
B4 School (DCW6) Mobility	0.80	0.27-2.11	0.99	0.31-3.19	1.22	0.83- 1.83
B4 School (DCW6) Speech	0.93	0.63-1.36	1.14	0.73-1.77	0.83	0.57- 1.21
Executive Function					0.94	0.78- 1.12

Stack and Topple (DCW2) Joint Attention	0.93	0.65-1.32	0.77	0.51-1.32	1.01	0.81- 1.25
Stack and Topple (DCW2) Inhibitory Control	1.16	0.96-1.39	1.09	0.89-1.33	0.86	0.66- 1.12
Stack and Topple (DCW2) Sustained Attention	1.17	0.93-1.46	1.18	0.92-1.51	1.06	0.77- 1.46

Māori Subgroup Analysis

At baseline, 931 women identified as Māori, of which 922 were singleton births (Table 8). One-fifth (20.7%) were classified as non-drinkers, 37.7% were classified as abstaining during pregnancy, and 41.6% reported consuming alcohol during pregnancy. Of those that consumed alcohol during pregnancy, the majority reported consuming alcohol only in early pregnancy (63.8%) or in both early and late pregnancy (26.6%). Most women reported consuming very low (30.5%) or low (28.4%) amounts of alcohol, with 34.1% reporting consuming considerable amounts of alcohol and 7.0% reporting consuming very high amounts of alcohol. Unlike in the overall sample, Māori did not differ significantly across exposure groups for most baseline characteristics. There was a significant difference in the age of participants, smoking status, household structure and perceived stress. Compared to the other groups, a larger proportion of women in the Alcohol Exposed group were under 25 years of age, current smokers, and parenting alone, and a smaller proportion reported low levels of perceived stress.

Table 8. Baseline characteristics of Māori mothers by exposure group

Variable	Alcohol Exposed (N=387) N	%	Abstainer (N=351) N	%	Non-Drinker (N=193) N	%	p-value
Age Mean (SD)	26.46	(6.5)	27.23	(6.0)	28.77	(6.5)	<0.001
Education							0.54
None	92	(23.8)	60	(17.1)	35	(18.1)	
Secondary School	105	(27.2)	106	(30.3)	50	(25.9)	
Diploma	137	(35.5)	126	(36.0)	70	(36.3)	
Bachelor's Degree	36	(9.3)	46	(13.1)	26	(13.5)	
Higher Degree	16	(4.2)	12	(3.4)	12	(6.2)	
Labour Status							0.23
Employed	132	(35.5)	144	(43.0)	64	(35.0)	
Unemployed	59	(15.9)	42	(12.5)	20	(10.9)	
Student	39	(10.5)	46	(13.7)	25	(13.7)	

Not in Workforce	142	(38.2)	103	(30.8)	74	(40.4)	
Current Smokers	151	(43.1)	94	(29.8)	35	(20.6)	<0.001
Household Income							0.56
<=$30K	56	(22.7)	46	(18.9)	22	(15.4)	
$30-50K	60	(23.3)	32	(13.2)	30	(21.0)	
$50-70K	41	(15.9)	45	(18.5)	27	(18.9)	
$70-100K	57	(22.1)	56	(23.1)	37	(25.9)	
>$100-150K	44	(15.1)	64	(26.3)	27	(18.9)	
Neighbourhood deprivation (NZDEP)							0.38
1-2 (Least deprived)	18	(4.7)	29	(8.3)	8	(4.2)	
3-4	31	(8.0)	38	(10.8)	20	(10.4)	
5-6	43	(11.1)	46	(13.1)	32	(16.6)	
7-8	95	(24.6)	75	(21.4)	48	(24.9)	
9-10 (Most deprived)	200	(51.7)	163	(46.4)	85	(44.0)	
Mother's Health Pre-pregnancy: General							0.084
Poor	25	(6.5)	21	(6.0)	5	(2.6)	
Fair	68	(17.6)	67	(19.1)	24	(12.5)	
Good	156	(40.3)	118	(33.6)	69	(35.9)	
Very Good	87	(22.5)	106	(30.2)	59	(30.7)	
Excellent	51	(13.2)	39	(11.1)	35	(18.2)	

SDQ scores were available for 524 children in the subsample. There was no significant difference in the Total Difficulties Score at 8 years by alcohol exposure category for offspring of Māori women (Alcohol Exposed v Abstainer aMD=-0.099, 95% CI -1.364-1.165, p=0.6426). However, there was a significant difference in risk of abnormal scores on two the SDQ subscales (see Appendix 6). Children born to Māori women who consumed alcohol during pregnancy were at increased risk of abnormal scores on the Emotional Problems scale compared to non-drinkers (OR=4.336, 95% CI 1.118-21.995, p=0.468), as well as increased risk of Peer Problems compared to non-drinkers (OR=2.319, 95% CI 1.061-5.293, p=0.039). There were no significant differences between Alcohol Exposed and Abstainer categories. Children born to Māori women who abstained in pregnancy were also at increased risk of Peer Problems compared to non-drinkers (OR=2.595, 95% CI 1.277-5.601, p=0.011).

Pacific Subgroup Analysis

At baseline 983 women identified as Pacific, among whom 972 had singleton births (Table 9). Almost half of Pacific women were classified as Non-drinker (47.5%), with 33.1% Abstainer and 19.4% reported consuming alcohol in pregnancy. Of those that consumed alcohol during pregnancy, 78.5% reported exposure in early pregnancy only, 3.1% late pregnancy only, and 18.3% both; 39.8% reported High or Very High alcohol use and 24.6% reported Very Low use. There were significant differences in across exposure groups for the following baseline characteristics: maternal age, education, smoking status, household structure, and household income. Compared to Non-drinker and Abstainer groups, a larger proportion of the Alcohol Exposed group were under 25, reported no formal qualification, and parented alone; and compared to Abstainer, a greater proportion of Alcohol Exposed and Non-drinker had a household income of $30,000 or below.

Table 9. Baseline characteristics of Pacific mothers by exposure group

Variable	Alcohol Exposed (N=191)		Abstainer (N=325)		Non-Drinker (N=467)		p-value
	N	%	N	%	N	%	
Age Mean (SD)	26.39	(6.4)	27.14	(6.2)	29.36	(6.2)	<0.001
Education							<0.001
None	42	(22.2)	35	(10.8)	45	(9.7)	
Secondary School	62	(32.8)	128	(39.5)	233	(50.0)	
Diploma	62	(32.8)	121	(37.4)	159	(34.1)	
Bachelor's Degree	14	(7.4)	27	(8.3)	24	(5.2)	
Higher Degree	9	(4.8)	13	(4.0)	5	(1.1)	
Labour Status							0.11
Employed	80	(44.2)	138	(45.4)	148	(34.3)	
Unemployed	35	(19.3)	45	(14.8)	74	(17.1)	
Student	7	(3.9)	18	(5.9)	25	(5.8)	
Not in Workforce	59	(32.6)	103	(33.9)	185	(42.8)	
Current Smokers	52	(29.9)	60	(21.1)	18	(4.5)	<0.001
Household Income							0.0016
<=$30K	25	(21.2)	35	(16.3)	74	(25.4)	
$30-50K	29	(24.6)	45	(20.9)	90	(30.9)	
$50-70K	20	(17.0)	45	(20.9)	61	(21.0)	
$70-100K	15	(12.7)	44	(20.5)	44	(15.1)	
>$100-150K	29	(24.6)	46	(21.4)	22	(7.5)	
Neighbourhood deprivation (NZDEP)							0.059
1-2 (Least deprived)	1	(0.5)	10	(3.1)	7	(1.5)	
3-4	16	(8.4)	15	(4.6)	13	(2.8)	
5-6	10	(5.2)	27	(8.3)	22	(4.7)	
7-8	36	(18.9)	68	(20.9)	97	(20.8)	

9-10 (Most deprived)	128	(67.0)	205	(63.1)	328	(70.2)	
Mother's Health Pre-pregnancy: General							0.29
Poor	13	(6.8)	17	(5.2)	16	(3.4)	
Fair	32	(16.8)	39	(12.0)	59	(12.7)	
Good	95	(49.7)	155	(47.7)	209	(44.9)	
Very Good	34	(17.8)	68	(20.9)	102	(21.9)	
Excellent	17	(8.9)	46	(14.2)	80	(17.2)	

SDQ scores at 8 years were available for 390 children in the subsample. There was no significant different in the Total Difficulties Score at 8 years by alcohol exposure category for offspring of Pacific women (Alcohol Exposed v Abstainer aMD=-0.417, 95% CI -2.018-1.184, p=0.442) or a significant increased risk in abnormal scores (OR:0.715, 95% CI 0.205-2.198, p=0.13). There were no significant differences for any of the SDQ subscales.

Discussion

Main findings

We found no significant differences in affect regulation at 8 years between exposure categories after controlling for tobacco exposure, neighbourhood deprivation, maternal mental health, and household chaos.

We did not detect a significant difference in affect regulation at 8 years when we compared various levels and timing of exposure.

The findings may have been affected by attrition at 8 years, as SDQ scores were only available for less than 70% of children, with particularly high attrition in Pacific and Māori subgroups.

We found no significant difference for the secondary variables, except for performance on the PROLL, for which PAE was associated with significantly higher parent-rated oral language.

Among Māori mothers we found an association of PAE with a significantly increased risk of abnormal scores on two of the SDQ subscales (i.e., emotional and peer problems). However, we did not detect any differences in the Total Difficulties score. We did not detect any significant differences among Pacific mothers. It is possible the findings are due to measurement error or chance, rather than a real association.

One of the key differences in our analysis from previous studies (62) was the categorisation of three exposure groups: Alcohol Exposed, Non-Drinker, and Abstainer in pregnancy. Typically, analyses have compared only exposed and unexposed offspring, combining Non-drinker and Abstainer categories.

The three exposure groups differed significantly at baseline along maternal demographic, socioeconomic and health status variables.

Also of note is our finding of significant differences in neighbourhood deprivation and smoking status. A previous study found concomitant use of alcohol and tobacco during pregnancy was associated with increased risk of delays in fine motor skills (33). Use of alcohol and tobacco are both associated with being resident in more deprived neighbourhoods, which in turn significantly impacts neurocognitive outcomes. Significant baseline differences between alcohol exposed and unexposed groups have been noted in studies of other cohorts (24, 43, 61, 62).

Unlike previous studies we did not find any effect of alcohol exposure on SDQ (20, 24, 28). However, the effects of alcohol use may have been masked by the large proportion in the exposure group that reported very low levels of alcohol consumption in pregnancy, that is, less than one drink per week. We did not detect an effect of alcohol when comparing different levels of exposure, but this null

finding may be due to the small number of mothers reporting high or very high levels of exposure.

An alternative explanation could be that there were limitations in the alcohol use data collected during pregnancy. Where a negative association has been detected between alcohol use in pregnancy and affect regulation, the type of exposure has been heavy episodic ('binge') drinking (i.e., consumption of 6 or more standard drinks in a single episode) rather than regular alcohol consumption (i.e., daily consumption of fewer than two drinks per night). Unfortunately, the maternal baseline survey in the GUiNZ study did not ask about binge patterns of alcohol use and participants reported their average consumption over a three-month period. Thus, it is not possible to distinguish between exposure to binge drinking and daily or regular alcohol exposure. This is an unfortunate oversight, because heavy episodic drinking poses the greatest risk to child development because of sustained high levels of blood alcohol during binge drinking episodes.

Our analysis detected a small, but significant increase in parent-rated oral language, but there was no difference in the risk of clinically significant scores (i.e., severe difficulties). Communication deficits are quite common in individuals with FASD, but these deficits can be hard to detect in parent or teacher ratings of oral language, whereas when assessed by trained professionals using objective measures such as the Clinical Evaluation of Language Fundamentals and Comprehensive Test of Phonological Processing (63, 64), or formal assessment by a Speech Language Therapist they may be evident. The finding highlights the importance of complete testing of neurocognitive domains in identifying the effects of PAE.

Although the effects of heavy alcohol consumption in pregnancy are well established, our systematic review highlights that the effects of moderate or episodic alcohol consumption are less clear. The inconsistent findings suggest that effect of alcohol on an individual pregnancy is determined by a variety of prenatal and postnatal factors that are presently unmeasured and unknown. Our statistical model suggested that several variables influence affect regulation outcomes, both before and after birth neighbourhood deprivation and socioeconomic position, (identified in our Systematic review) maternal mental health and the household environment after birth. Ethnicity also was a significant moderator, although it should be noted that ethnicity is likely to be a proxy for unmeasured confounding variables including socioeconomic determinants of health, intergenerational trauma, and discrimination.

As part of our analysis, we intended to use a range of psychosocial measures to identify children at risk of FASD, based on the multiple domains associated with FASD. However, as external data users we were not permitted access to the data on these additional measures. The Ministry of Health project being undertaken by a research team from within GUiNZ, led by Dr Raimond Jacquemard, has access to the NIH Toolbox and Vinelands Adaptive Behaviour Scales and to non-aggregated data, and is better placed to estimate the prevalence of children within

the GUiNZ cohort at risk of FASD and in need of further assessment for possible FASD or other neurodevelopmental impairments.

Limitations and future directions

Strengths and Limitations

Our study has a number of strengths: it is the first study to analyse the impact of PAE on neurocognitive outcomes at 8 years using the GUiNZ cohort. This is important, as 8 years is often the age at which FASD is first able to be detected due to the complexity and demands of the neurocognitive assessments required to diagnose FASD. The study revealed gaps in knowledge and understanding on the impact of PAE on neurocognitive outcomes.

The study was complemented by a systematic review of previous literature which was used to inform the moderators included in our analysis of the impact of PAE.

The GUiNZ cohort is a large ethnically diverse cohort which allows for subsample analyses of Māori and Pacific subgroups. Data collection began during pregnancy, which makes it possible to analyse the relationship between maternal factors and childhood outcomes.

However, there were a number of limitations. The most important limitation is that relating to the sole PAE variable: self-reported average alcohol use over a prolonged period. Self-reported consumption is likely to underestimate actual consumption because of social desirability response bias, particularly in the case of the stigma associated with maternal consumption of alcohol (65).

The data may also be subject to recall bias as data was collected in late pregnancy or in some cases postnatally rather than contemporaneous with each period (i.e., early pregnancy and late pregnancy). More regular assessment periods or use of different methodology may increase the quality of data produced and allow for more extensive analysis of pattern, frequency, and quantity of consumption across the pregnancy. Previous studies have used timeline to follow-back method, which allows researchers to capture more detail about how women are drinking over a specific period.

The wording of the questions used to elicit the information potentially conflates women who consumed alcohol pre-pregnancy with those that consumed alcohol before pregnancy awareness. This may unintentionally underreport the number of women who consumed alcohol during pregnancy.

A related issue is that there were limitations in how the GUiNZ data had been processed for external use; we did not have access to the raw data on the number of drinks consumed per week but were provided categorical data that (arbitrarily) collapsed the data on more than 4 drinks per week to 4-19 and 20 or more, which is not in line with definitions of hazardous drinking according to drinking guidelines (66).

As noted, the baseline data collection did not include a measure of heavy episodic drinking, which in previous studies has been shown to be associated with increased risk of poor affect regulation.

A second limitation relates to the outcome measure, the SDQ. The SDQ does not have New Zealand norms and concerns have been raised that the SDQ may not be a good fit for all cultural contexts, including for Māori (67). In this study, we used the Australian norms to classify scores as normal, abnormal, or borderline scores. Confirmatory factor analysis of SDQ at Wave 2 found that internal consistency was relatively low for the Peer Problems subscale (68), and subsequent analyses found poor agreement in scores over time (69). Children were identified as having abnormal scores for Conduct problems at Wave 2 but not in subsequent waves. The SDQ is based on parent report rather than an objective measure and may be subject to reporting biases (70, 71).

A third limitation was the extent to which we were able to identify moderators of the effect of alcohol, limited by the confounders measured in data collection. For example, continued exposure to alcohol use in the household (especially heavy episodic drink) was not collected after 9 months and there were limited measures relating to maternal or parental mental wellbeing in subsequent waves.

Fourth, the extent to which we were able to evaluate the effects of PAE on FASD affected domains was limited by the data available in the GUiNZ study and availability of some measurement tools. For example, language and communication measures were included in the previous waves up to starting school but were not included in Wave 8. Changes in the measures used also made it difficult to compare across different time points, and a data collection error in Wave 5 meant we were only able to evaluate the SDQ at two time points.

Finally, we did not have Māori and Pacific researchers on the research team. The research used a Western research paradigm that may not have adequately considered the voice of Māori and Pacific in the analysis and interpretation of findings.

In summary, we were unable to identify children at risk of FASD from an analysis of the GUiNZ dataset. The diagnosis of FASD requires assessment along multiple neurocognitive domains by a multidisciplinary team. Some domains, such as memory, have never been assessed as part of the GUiNZ data collection, while others have been assessed in previous waves but not in the Wave 8 data. Due to limitations in the data set, it is not possible to give an indication of the incidence of FASD from the GUiNZ cohort.

Policy implications and recommendations

Although the analysis did not find an association between PAE and affect regulation this finding more likely reflects imprecision in the measures of exposure and outcome available to us, rather than absence of an association. The weight of evidence in the literature suggests there is no safe level of alcohol use (72-74). It

is therefore crucial to continue to promote health messages about the risks associated with alcohol use in pregnancy.

More than one in five women in the GUiNZ cohort reported consuming alcohol after being aware they were pregnant. New Zealand participants in the SCOPE multi-centre population-based study (N=2006) reported even higher rates of alcohol consumption during pregnancy, with 56% reporting consuming any alcohol during pregnancy and 9% reporting binge drinking (75). Alcohol abstinence during pregnancy or planning a pregnancy is advocated by Alcohol Health Watch, The Ministry of Health, The Health Promotion Agency, and health professional groups (see for example https://www.alcohol.org.nz/alcohol-its-effects/alcohol-and-pregnancy/what-you-need-to-know). However, women often receive conflicting and inconsistent advice regarding alcohol consumption in pregnancy. In a national study conducted in 2009, 32% of women received no advice to abstain from alcohol during pregnancy (76). Consistent, clear, and unambiguous messages are urgently needed. Continued surveillance of alcohol use in pregnancy is also needed to evaluate the effectiveness of messaging and resources for pregnant women and determine whether pregnant women are receiving appropriate advice and support when pregnant to prevent FASD and alcohol exposed pregnancies.

Research is needed to address the stigma associated with consuming alcohol during pregnancy and professional ambivalence towards prenatal alcohol exposure. Removing the stigma towards this behaviour may help to bring the issue into the open where women can be better supported towards having alcohol free pregnancies.

Future research using the GUiNZ study to explore FASD should be cognisant of the limitations of the data. While the GUiNZ cohort study provides a potentially rich dataset for analysing the effects of alcohol on neurocognitive outcomes, as we found, the data are not sufficient to detect the extent to which individuals may be affected by PAE or to identify those at risk of FASD. As this was not the question that the GUiNZ was designed to answer, the exposure measures used in baseline about alcohol and other substance use are not sufficient to analyse the effects of alcohol exposure over the course of pregnancy or at various levels of exposure.

Furthermore, the GUiNZ study is restricted in the measures that can be included for specific conditions given that it is designed to cover all of child wellbeing. A cohort study specifically designed to evaluate the impact of prenatal exposure is needed to better differentiate the effects of prenatal alcohol exposure and identify children adversely affected by alcohol. This study would need to include robust measures of alcohol use during pregnancy, including timing of exposure.

The data are limited by the number of neurocognitive domains evaluated and the tools used to evaluate those domains (such as the NIH Toolbox). International cohorts have included a number of measures to address these domains that could be included in future waves, such as standardised tests of educational

achievement (e.g., Wide Range Achievement Test (77)and Key Stage II) (38, 78), IQ tests to evaluate cognition and memory (e.g., Wechsler Intelligence Scale of Children(71)) (43, 79), and measures of executive function and attention (e.g., Behaviour Rating Inventory of Executive Function (80) and Test of Everyday Attention for Children(81)) (40). Including these measures in future data collection waves would allow for analysis to compare the findings of the GUiNZ cohort with other large cohort studies overseas.

If the objective is to estimate the prevalence of FASD in New Zealand, a separate study would be required, ideally one based on the WHO protocol, such as has been conducted in Canada involving a cross-sectional, observational design using active case ascertainment, and retrospective collection of prenatal alcohol exposure information.(70) The Canadian study recruited 2555 elementary school students aged 7 to 9 years and found a prevalence of 2-3%. The estimated cost of such a prevalence study in NZ would be substantial but would provide a baseline on which to assess progress and identify high-risk groups. Without a New Zealand prevalence study, the number of people living with FASD is unknown and the true cost of alcohol on society likely to be significantly underestimated. This information is essential for health, justice, and education systems to plan for and respond to the needs of individuals living with FASD.

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Appendix 1: Systematic Review Search Strategy

Search strategy

We conducted electronic searches of the following databases: EMBASE, Medline, CINAHL, and Psychinfo. Search terms included alcohol (and consum* or expos* or drink*) and (matern* or pregnan* or f?etal or prenatal), combined with keywords for the outcomes (e.g., executive function, motor movement, language) and design (e.g., prospective, birth cohort). Searches were limited to peer reviewed English language studies of human participants published after January 2001. An example of the search strategy is found below. All searchers were conducted on 25th of May 2021 and exported to Endnote. Additional articles were identified from searching the bibliographies of relevant systematic reviews.

Inclusion and exclusion criteria

The inclusion and exclusion criteria are shown in Table 1. Studies were included if they were prospective cohort studies assessing neurodevelopmental outcomes in children exposed to alcohol in utero compared to unexposed children. Relevant outcomes included neurodevelopmental or neurocognitive outcomes associated with FASD including the ten domains identified in the Canadian Guidelines (10) for diagnosing FASD: neurophysiology, motor skills, cognition, language, academic achievement, memory, attention, executive function, affect regulation, and adaptive behaviour, social skills, or communication.(82) Under the most recent Australia guidelines for diagnosis of FASD,(82) hyperactivity and inattention fall under separate domains ('executive function' and 'attention' respectively); however, we classified scales that combine hyperactivity and inattention as 'attention' only. Retrospective and case control studies were excluded due to a high risk of recall bias. Due to the relatively low prevalence of alcohol use during pregnancy, a minimum of 1000 participants were required in each study to have sufficient data for analysis. Studies were required to include a quantitative measure of alcohol consumption (e.g., standard drinks, grams of alcohol).

Supplementary Table S1a: Inclusion/exclusion criteria

Study characteristics	Inclusion	Exclusion
Population	Pregnant women sampled from the population and their offspring (under the age of 18 years)	Postnatal women Adult off-spring
Exposure	Any level of prenatal alcohol consumption.	Alcohol must be the main exposure, or if multiple exposures, it must be an

	Must include a quantitative measure of alcohol consumption	independently evaluated variable
Comparator	Women that did not consume alcohol in pregnancy.	Studies without a comparator
Outcome	Neurodevelopmental outcomes related to FASD: e.g., Developmental delay; Motor skills/function; Neurophysiology; Cognition; Cognitive development; Language; Academic achievement; IQ; Memory; Attention; Executive function; Affect regulation; Behaviour complications; Adaptive behaviour; Social skills; Communication	Studies of unrelated outcomes
Study Design	Prospective cohort studies N>=1000	Retrospective and case-control studies. N<1000

Study selection and data extraction

Titles and abstracts were screened by the reviewer (AW) to identify relevant studies. The full text of potentially relevant articles was obtained to determine their inclusion. A second reviewer (JM) independently screened a random selection (10%) of full text articles, and any discrepancies were discussed, and disagreements were resolved by consensus. Data were extracted using a previously designed extraction form and included the following variables: design, location, population, exposure (timing, amount), measurement method, moderators included in the model, effect of moderators, outcomes and method of measurement, and results. Data were extracted by the first reviewer and checked for accuracy by the second reviewer.

Quality

A quality assessment of included studies was conducted by both reviewers of the included studies using an adapted version of the Newcastle-Ottawa Scale (NOS) (42). This scale has been used in similar previous research (83). It contains 8 questions and scores from 0 (high risk of bias) to 9 (low risk of bias). Questions address representativeness of the cohort, measurement of exposure, statistical analyses (control for confounds), assessment of outcomes, and characteristics of the follow-up.

Supplementary Table S1b: Exemplar of search strategy from CINAHL

#	Search Terms	Results
S1	TI (((alcohol use) OR alcohol) AND (consum* OR expos* OR drink*)) OR AB (((alcohol use) OR alcohol) AND (consum* OR expos* OR drink*)) OR MW (((alcohol use) OR alcohol) AND (consum* OR expos* OR drink*))	52,344
S2	TI (matern* or pregnan* or f?etal or prenatal) OR AB (matern* or pregnan* or f?etal or prenatal) OR MW (matern* or pregnan* or f?etal or prenatal)	315,248
S3	TI (motor skills or neurophysiology or cognition or language or academic achievement or memory or attention or executive function or affect regulation or adaptive behavio?r or social skills or communication or fine motor or gross motor or IQ or intelligence or ((education* or school) and achievement) or inattention or emotional development or emotional regulation or behavio?r problems or developmental delay or neurodevelopment*) OR AB (motor skills or neurophysiology or cognition or language or academic achievement or memory or attention or executive function or affect regulation or adaptive behavio?r or social skills or communication or fine motor or gross motor or IQ or intelligence or ((education* or school) and achievement) or inattention or emotional development or emotional regulation or behavio?r problems or developmental delay or neurodevelopment*) OR MW (motor skills or neurophysiology or cognition or language or academic achievement or memory or attention or executive function or affect	565,786

	regulation or adaptive behavio?r or social skills or communication or fine motor or gross motor or IQ or intelligence or ((education* or school) and achievement) or inattention or emotional development or emotional regulation or behavio?r problems or developmental delay or neurodevelopment*)	
S4	TI (prospective or longitudinal or follow-up or cohort) OR AB (prospective or longitudinal or follow-up or cohort) OR MW (prospective or longitudinal or follow-up or cohort)	818,896
S5	S1 AND S2	4,085
S6	S3 AND S4 AND S5	173

Appendix 2: Quality of Included Studies

Supplementary Table S2. Risk of bias assessment scores based on NOS scale of cohort, longitudinal and cross-sectional studies

Study (First author, year)	Exposed cohort	Non-exposed cohort	Exposure	Outcome Timing	Comparability	Assessment	Length of follow-up	Adequacy of follow-up cohorts	Total
Alati, 2013	1	1	1	1	2	1	1	0	8
Alati, 2008	1	1	1	1	2	1	1	0	8
Alvik, 2013	1	1	1	1	2	1	1	0	8
Alvik, 2011	1	1	1	1	2	0	0	0	6
D'Souza, 2019	1	1	1	1	1	0	1	0	6
Donald, 2019	1	1	1	1	2	1	1	0	8
Faebo Larsen, 2013	1	1	1	1	2	0	1	0	7
Falgreen Eriksen, 2012	0	1	1	1	2	1	1	1	8
Halliday, 2017	1	1	1	1	2	1	1	0	8
Hutchinson, 2019	0	1	1	1	2	1	0	0	6
Kesmodel, 2012	0	1	1	1	2	1	1	1	8
Kesmodel, 2012	0	1	1	1	2	1	1	1	8
McCormack, 2018	0	1	1	1	2	1	0	0	6
Negrao,2020	0	1	0	1	2	1	0	0	5
Niclasen, 2014	1	1	1	1	2	0	1	1	8
Niclasen, 2014	1	1	1	1	2	0	1	0	7
O'Callaghan, 2007	0	1	1	1	2	1	1	0	7
Rodriguez, 2009	1	1	1	1	2	1	1	0	8
Sayal, 2013	1	1	1	1	2	1	1	0	8

Sayal, 2014	1	1	1	1	2		1	1	0	8
Sayal, 2009	1	1	1	1	2		1	1	0	8
Sayal, 2007	1	1	1	1	2		1	1	0	8
Schoeps, 2018	1	1	1	1		2	0	1	1	8
Skogerbo, 2013	0	1	1	1		2	1	1	1	8
Skogerbo, 2012	0	1	1	1		2	1	1	1	8
Streissguth, 2007	1	1	1	1		2	1	1	2	9
Underbjerg, 0212	0	1	1	1		2	1	1	1	8
Weile, 2020	1	1	1	1		2	1	1	1	9
Zuccolo, 2013	1	1	1	1		2	1	1	1	9
Kilburn et al. (2015)	0	1	1	1		2	1	1	1	8
Robinson et al. (2010)	0	1	1	1		2	0	1	0	6

Appendix 3: Confounder Analysis

Supplementary Table S3. Confounders identified in studies included in systematic review

Article Number	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	Total
Confounder																															
Offspring gender	x	x	x	x	x	-	x	x	x	-	x	x	-	-	-	-	-	-	-	-	-	-	x	x	x	x	-	-	x	-	15
Offspring age		-	-	-	x	-	-	x	-	-	x	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	-	-	x	x	9
Offspring comorbid externalising disorders	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	-	1
Parity and/or number of siblings	x	x	-	-	x	-	-	x	x	x	x	x	x	-	-	-	-	-	x	x	x	x	-	x	x	x	x	x	x	-	19
Maternal ethnicity	x	x	-	-	x	-	-	-	-	x	-	-	x	-	-	-	-	-	-	-	x	x	x	-	-	-	-	-	-	-	8
Maternal age at offspring birth	x	-	x	x	x	-	x	x	x	x	x	x	x	x	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	27
Parental socio-economic characteristics (social class, education, income, marital status)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	30
Parenting behaviour and/or home environment	-	-	-	-	-	-	-	x	x	-	x	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	-	-	x	-	8
Other parental psychopathology (including externalising disorders) and substance use disorders	-	-	x	-	-	-	-	-	x	-	-	-	-	-	x	x	-	-	-	-	-	x	-	-	-	x	-	x	-	-	7
Maternal mental health during pregnancy	-	-	x	x	-	x	-	-	x	x	-	-	x	x	-	x	-	-	x	x	x	x	x	-	-	-	-	-	-	x	14
Maternal other substance use during pregnancy	-	-	-	-	-	-	-	-	-	x	-	-	x	-	-	-	-	-	x	x	x	x	-	-	-	-	-	-	-	-	6
Maternal smoking during pregnancy	x	x	-	x	-	-	x	x	x	x	x	x	x	-	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	26
Partner's or household member substance use during pregnancy	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	0
Paternal drinking during pregnancy	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	2
Parental postnatal drinking	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	x	-	-	-	2
Paternal smoking during pregnancy	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	3
Parental postnatal smoking	-	-	-	-	-	-	-	x	-	-	x	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	-	-	x	-	7
Planned/unplanned pregnancy	-	-	-	x	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	3

Maternal physical health in pregnancy (e.g., anaemia, BMI, diet, folate supplements)	-	-	-	-	-	x	-	x	x	x	x	x	x	-	-	x	x	-	-	-	-	-	-	x	x	x	x	x	x	-	15
Breastfeeding	-	-	-	-	-	-	-	-	-	x	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1
Perinatal factors (birth weight, gestational age, birth complications)	-	-	x	x	x	x	x	-	-	x	-	-	x	-	-	-	-	x	x	x	x	x	x	x	-	-	-	-	-	-	-	14
Offspring health status	-	-	-	-	-	-	-	x	-	-	x	x	-	-	-	-	-	-	-	-	-	-	-	x	x	x	-	-	x	-		7

Appendix 4: Confounding Variables by Data Collection Wave

Supplementary Table S4: Confounding variables by data collection wave (DCW)

Data collection wave	Outcomes	Confounding Variables
DCW8	SDQ: Total Difficulties, Emotional Problems, Conduct Problems, Hyperactivity, Peer Problems, Prosocial; Social Information Processing: Aggression-Avoidance, Assertive	Gender; Ethnicity (child); Weight at birth; Maternal prenatal smoking status; Maternal depression at 8 years; Household environment at 8 years; Neighbourhood deprivation at 8 years
DCW1	Weight: Birth, 6 weeks, 9 months; Preterm; MacArthur-Bates CDI II	Maternal age; maternal ethnicity; maternal education; maternal labour status; maternal prenatal smoking status; household structure; household income; neighbourhood deprivation; general health during pregnancy; anxiety during pregnancy; depression during pregnancy; postnatal depression risk; interparental relationship; maternal drug use at 9 months; paternal smoking status; Gender; Term; Weight at birth
DCW2	Stack and Topple task; SDQ: Total Difficulties	Gender; Weight at birth; Ethnicity; maternal prenatal smoking status; neighbourhood deprivation at 2 years
DCW5	PPVT (derived); Luria test; DIBELS; PROLL; Child Behaviour Questionnaire: Surgency, Negative Affect, Effortful Control	Gender; Weight at birth; Ethnicity; maternal prenatal smoking status; maternal depression at 5 years; neighbourhood deprivation at 5 years
DCW6	B4School Check: Learning difficulties, behaviour, mobility, speech, no concerns	Gender; Weight at birth; Ethnicity; maternal prenatal smoking status; maternal depression at 5 years; neighbourhood deprivation at 6 years

Appendix 5: Birth Outcomes

Supplementary Table S5a: Regression analysis birth outcomes

	Alcohol Exposed v Abstainer		Alcohol Exposed v Non-Drinkers		Abstainer V Non-Drinker	
Birth outcomes	**Estimate**	**95% CI**	**Estimate**	**95% CI**	**Estimate**	**95% CI**
Weight at birth (kg)	-0.01	-0.05-0.2	0.02	-0.02-0.06	0.03	0.00-0.07
Weight at 6 weeks (kg)	0.01	-0.03-0.05	-0.01	-0.05-0.04	-0.02	-0.06-0.02
Weight at 9 months (kg)	-0.07	-0.16-0.03	-0.07	-0.17-0.04	0	-0.10-0.10
	OR	**95% CI**	**OR**	**95% CI**	**OR**	**95% CI**
Preterm	1.08	0.81-1.47	0.89	0.63-1.25	0.82	0.603-1.12

Appendix 6: Māori Subgroup Analysis

Supplementary Table S6a: Logistic regression stepwise adjusted model of SDQ in Māori mother's subgroup

	Abstainer V Non-Drinker			Alcohol Exposed v Non-Drinkers			Alcohol Exposed v Abstainer		
	OR	95% CI	p	OR	95% CI	p	OR	95% CI	p
Total Difficulties	2.08	0.84-5.58	0.13	2.27	0.81-6.73	0.12	1.09	0.46-2.54	0.84
Subscales									
Emotional Problems	3.38	0.98-15.95	0.08	4.34	1.12-22.00	0.05*	1.28	0.46-3.50	0.63
Conduct Problems	0.95	0.45-2.05	0.90	0.99	0.43-2.31	1.00	1.04	0.47-2.28	0.92
Hyperactivity	1.00	0.45-2.27	0.99	0.87	0.34-2.19	0.77	0.87	0.36-2.01	0.74
Peer Problems	2.60	1.28-5.60	0.01*	2.32	1.06-5.29	0.04*	0.89	0.47-1.67	0.73
Prosocial	7.90	1.37-150.86	0.06	2.04	0.08-55.73	0.63	0.26	0.01-1.60	0.22