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RESEARCH ARTICLE

Effects of prenatal alcohol exposure on infant lung function, wheeze, and respiratory infections in Australian children

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Abstract

Background: Prenatal alcohol exposure (PAE) is a known risk factor for a range of adverse outcomes, such as facial dysmorphism, adverse birth outcomes, and neurodevelopmental changes. Preclinical research shows that PAE also inhibits lung development, lowers surfactant protein expression, has detrimental effects on alveolar macrophages, and decreases both T and B cell numbers. However, clinical evidence of respiratory impacts from PAE is limited. This study explored whether lung function, wheeze, and incidence of respiratory infections differ in children with PAE compared with unexposed children.

Methods: Data from the Barwon Infant Study ($n = 1074$) were examined. PAE data were extracted from maternal questionnaires at trimesters 1 and 2 (combined), and trimester 3, and included as "total standard drinks" during each trimester and total pregnancy intake, a binary yes/no for PAE, and binge drinking (>5 standard drinks in one session). Respiratory outcomes were parent-reported wheeze, lung function (measured by multiple breath washout), and parent report and medical record indicators of health service attendances for respiratory conditions. Linear and logistic regressions were performed to quantify relationships between PAE and respiratory outcomes, controlling for socioeconomic status, birthweight, sex, gestational age, and maternal smoking.

Results: Binge drinking was associated with increased health service attendance for respiratory condition(s) in the first 12 months of life (OR = 5.0, 95% CI (1.7, 20.7), $p = 0.008$). We did not find a relationship between binary PAE and binge drinking with lung function at 4 weeks of age or wheeze at 12 months. The number of standard drinks consumed in trimester two was associated with a lower lung clearance index ($\beta = -0.011$ turnovers, 95% CI (−0.0200, −0.0013), $p = 0.03$), and a small increase in functional residual capacity ($\beta = 0.34$ mL, 95% CI (0.02, 0.66), $p = 0.04$).

Conclusions: We found an association between binge drinking and health service utilization for respiratory conditions in infancy, but no evidence that low-level PAE was associated with adverse respiratory outcomes.

KEYWORDS
lung function, pregnancy, prenatal alcohol exposure, respiratory tract infections, wheeze

INTRODUCTION

Prenatal alcohol exposure (PAE) is a known risk factor for facial dysmorphology, adverse birth outcomes (Bailey & Sokol, 2011), and neurodevelopmental changes (Lange et al., 2017; Sarman, 2018). The global prevalence of PAE has been calculated at 9.8% (95% CI 8.9, 11.1), with regional variations from 0% in some Middle Eastern countries such as Oman, to 60.4% in Ireland (Popova et al., 2017). A recent meta-analysis of PAE in Australian cohort studies reported an overall prevalence of 48% (Young et al., 2022). Importantly, 50–60% of women reported alcohol consumption before they become aware of their pregnancy, suggesting PAE is more common in very early pregnancy. There does not appear to be a safe threshold for drinking, with adverse outcomes associated with low levels of PAE during the pregnancy period (Flak et al., 2014) as well as heavy exposure in the very early stages of pregnancy (Alvik et al., 2013) (i.e., before a woman is aware of her pregnancy).

A wide range of outcomes can result from PAE. Emerging evidence suggests that adverse outcomes can extend beyond structural and functional brain development to the other organs and systems of the body. A series of recent systematic reviews found clinical and preclinical evidence that PAE may have negative impacts on cardiovascular and renal function (Reid, Akison, et al., 2019), body composition (Akison, Reid, et al., 2019; Hayes et al., 2021), metabolic markers, such as insulin, glucose, and dyslipidemia (Akison, Reid, et al., 2019), immune function, namely allergic disease and risk of infection (Reid, Moritz, & Akison, 2019), and reproductive and hormonal changes (Akison, Moritz, & Reid, 2019). What is missing from our understanding of PAE is the effect on the developing respiratory system. Fetal lung development may also be sensitive to the effects of PAE; preclinical evidence shows that PAE inhibits lung development and cellular growth (Inselman et al., 1985; Wang et al., 2007) and has been associated with lower levels of surfactant protein expression (Sozo et al., 2011). Surfactant is vital in reducing surface tension in the lung and has important innate immune functions postnatally. Further, detrimental effects on alveolar macrophages (Brown et al., 2009; Gauthier et al., 2010) and decreases in pulmonary T and B cell counts with impaired function have been found after PAE (Gurung et al., 2009; McGill et al., 2009).

Despite the clear evidence from preclinical studies, clinical research on the effect of PAE on the respiratory system is limited. We identified only two studies that explored the relationship between PAE and lung function (Bisgaard et al., 2009; Gray et al., 2017). In a study of infants enrolled in the Drakenstein child health study, PAE was associated with lower respiratory rates, higher tidal volumes, and lower time to reach peak tidal expiratory flow as a proportion of total expiratory time compared with nonexposed infants (Gray et al., 2017). This study was conducted in a low socioeconomic environment. These findings contrast with a study of 4-week-old infants enrolled in the Copenhagen Prospective Study on Asthma in Childhood (COPSAC), which found no relationship between PAE exposure and lung function (Bisgaard et al., 2009.). This cohort recruited from women who had a history of asthma. Lung function was measured using different techniques in these two cohorts, making it difficult to directly compare the findings. The Drakenstein study looked at problem PAE levels, defined as daily or weekly PAE for at least 3 months, while the COPSAC study used a binary y/n for any alcohol exposure, with no distinction between low or high intake. The relationship between respiratory infection outcomes in children exposed to PAE has been reported in two previous studies (Libster et al., 2015; Magnus et al., 2014) with contrasting findings. PAE was not associated with increased hospitalizations for lower respiratory tract infections (Magnus et al., 2014), whereas, PAE intake in the third trimester was associated with life-threatening respiratory infections (Libster et al., 2015). Therefore, the aim of this study was to estimate the effects of PAE on infant lung function, wheeze episodes, and on respiratory tract infections requiring medical treatment. Compared to previous cohorts exploring PAE and lung function, we propose a cohort of children that are largely representative of the general population and with measures of PAE representing total pregnancy exposure, the number of standard drinks consumed in each trimester of pregnancy, and early pregnancy binge drinking.

MATERIALS AND METHODS

Data source

The Barwon Infant Study (BIS) is a longitudinal study of Australian children from the region of Geelong, Victoria. The cohort has been described elsewhere (Vuillermin et al., 2015). Briefly, women were recruited from two major hospitals in the Barwon region and eligible women were invited to participate in the study at a routine antenatal appointment occurring around 15 weeks of gestation. Recruitment occurred between 2010 and 2013 with follow-up continuing. A total of 1064 women who delivered 1074 infants were recruited and eligible for follow-up (from a total of 1158 women recruited). The families were followed up at multiple time points in early life, including 28 weeks gestation, birth and 1, 3, 6, 9, and 12 months of age. Each review took 1–1.5 h to complete, and parents completed comprehensive questionnaires administered by trained researchers, either via the phone or at the research office. These questionnaires used validated instruments where possible, and was designed to allow pooling with both national and international cohorts studies (Vuillermin et al., 2015). Physical

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review was performed at each time point, and lung function was measured at 1 month of age. Data were acquired for this study up to and including the 12-month follow-up.

Outcomes

The outcomes used in this study are parent reported wheeze, number of episodes of wheeze, lung function measured using tidal breathing analyses and SF_6 Multiple Breath Washout, and health care use for respiratory tract infections. Infant lung function allows for an assessment of how the prenatal environment affects lung function, before postnatal factors start to influence lung development. Wheezing and respiratory infections are common in the first year of life (Alvarez-Alvarez et al., 2018; Irwin et al., 2022).

Lung function

Testing was performed on a subset of the study participants at 4 weeks of age during natural sleep (Vukcevic et al., 2015) using the SF_6 multiple-breath washout (MBW) technique on the Exhalyzer-D system (EcoMedics AG, Switzerland). Measurements were performed during supine sleep with the use of a pediatric face mask. Once stable tidal breathing was established, the infant was switched in to breathing 4.0% SF_6 and tidal breathing continued until an end concentration of 1/40th the starting concentration was achieved. MBW gives indices of lung size (functional residual capacity, FRC) and ventilation distribution (lung clearance index, LCI) (Robinson et al., 2013). Specifically, FRC refers to the volume of air remaining in the lungs after passive expiration and is influenced by the overall compliance of the lung, as well as the presence of airway obstruction and gas trapping. LCI measures the unevenness of ventilation within the lungs, and thus is used as a sensitive marker of early lung disease development. All children who completed the 1 month review were invited to undergo lung function testing, 570 children attempted MBW testing and 318 had acceptable and reproducible measurements. Three hundred and fifteen children had data on both MBW and PAE and were included in this study. Two records were excluded from the analysis based on implausible lung function values (>6 L for FRC and <1 LCI).

Parent reported wheeze

A researcher-facilitated questionnaire was used to assess health status at multiple time points. BIS is part of an existing international child cohort consortium (Brown et al., 2007), and as such the questionnaire used questions from the Danish National Birth Cohort (Olsen et al., 2001), the Avon Longitudinal Study of Parents and Children (Sherriff & Golding, 2002), and the Western Australian Pregnancy Cohort Study (Oddy et al., 2002) to assess respiratory and infective symptoms. Parents were provided with a definition of wheeze and then asked the following questions: did their child had any episodes of wheeze or whistling from the chest since the previous visit at 1, 3, 6, 9, and 12 months; if yes, how many episodes of wheeze had the child experienced since the last review; and, whether these wheeze episodes caused the child to be short of breath. Infant wheeze in the first 12 months was the main wheeze outcome of interest and was coded as a binary yes/no variable. Two wheeze phenotypes were defined: wheeze with shortness of breath and recurrent wheeze (more than one episode of wheezing within first 12 months). More information on these outcomes is available (Gray et al., 2019).

Primary health care utilization for respiratory conditions

Parents were asked whether their child had presented to a general practitioner or emergency doctor at each visit in the first 12 months of age for a respiratory-based condition (both upper and lower airway), and whether they could recall the diagnosis. This outcome is previously described in this cohort (Gray et al., 2019).

Hospital presentations for respiratory tract infection

Information was gathered from clinical notes, and a binary variable was created that captured presentation to emergency room (ER) with a respiratory tract infection (both upper and lower) during the first 12 months of life or an admission to hospital with a respiratory tract infection during the past 12 months.

Exposure

The exposure was PAE, as reported in a validated and interviewer-administered questionnaire, based on the questions in the Danish National Birth Cohort (Olsen et al., 2001), and answered at each time point (trimesters 1 and 2 combined, and trimester 3). Participants were asked how many standard drinks were consumed during each trimester and were shown a visual guide as to what constituted a standard drink. They were also asked how many times they consumed more than five standard drinks on one occasion (defined as in a space of a few hours). From these questions, we created three PAE variables. "PAE (Y/N)" was used to indicate any PAE and calculated for the whole pregnancy, and for each trimester to assess trimester specific effects. Number of standard drinks consumed was a continuous variable representing the number of standard drinks reported during each trimester and across the entire pregnancy. Lastly, binge drinking was coded into a binary any/none, based on the number of times more than five standard drinks was consumed in one session. This variable was only included for the first trimester due to the small numbers classed as "any" at T2 ($n = 5$) and T3 ($n = 6$).

Statistical analysis

Descriptive analyses were performed, and variables summarized as mean (SD) and frequency as appropriate. The continuous variables of number of standard drinks per trimester and whole pregnancy were heavily skewed and were further summarized as median (min, max) after removing data from women who did not report drinking during pregnancy. Differences between the outcomes by PAE (y/n) were calculated using Student's *t*-test and Fisher's exact test. A directed acyclic graph (DAG) was developed to assist in covariate selection (Figure S1). DAGs are causal diagrams, depicting the exposure–outcome relationship and supported with expert opinion and previous research. DAGs allow for exploration of the potential causal mechanism/s between exposure and outcome and are a useful tool in exploring potential bias the in relationship (Shrier & Platt, 2008; Williams et al., 2018). We used DAGitty to draw our DAG (Textor et al., 2011) and explored the relationship between variables to assess the role of confounding and to look for instrumental variables and mediators. Multiple linear and logistic regressions were performed for continuous and dichotomous outcomes, respectively, and the following were included as covariates in the final model: child birthweight, gestational age, sex, maternal smoking, and socioeconomic status. Maternal smoking and environmental tobacco smoke exposure (ETS) were assessed via researcher-facilitated questionnaire for each trimester of pregnancy with the enrolled child. Women were asked "how many cigarettes and/or tobacco products did you smoke (on average) per day (none, 1–10/day, 11-20/day, 21+/day)", and the responses across each trimester were categorized into any maternal smoking (y/n) during pregnancy. Two questions assessing exposure to ETS were asked at the same time (y/n, and number of hours exposed in 24 h period). We did not have data for babies ETS exposure at the same time point of the lung function measurements, so third trimester ETS exposure was used as a proxy for infant ETS exposure in sensitivity analysis. The neighborhood based socioeconomic status was matched by residential address to the corresponding socio-economic indexes for areas (SEIFA) scores produced by the Australian Bureau of Statistics. SEIFA scores are compiled from numerous indictors or advantage and disadvantage, and we categorized these into tertiles where deciles 1–4 were categorized as disadvantaged, 5–7 as middle and 8–10 as advantaged.

Sensitivity analyses were performed to assess the effect of higher levels of maternal smoking, maternal smoking, and ETS exposure, interactions between maternal smoking and PAE, and interaction between maternal smoking and ETS.

RESULTS

There were 894 children (from 1074 recruited) who completed the 12 month assessment time point. Participant characteristics for children with data on wheeze status are shown in Table 1 ($n=834$), and for those with lung function are shown in Table 2 ($n=312$). Alcohol use during pregnancy was reported by 392/834 (47%) women, with a median total of 7 (IQR 17) standard drinks over the whole pregnancy. Most women consumed alcohol at low levels with 250/834 (30%) reporting less than one standard drink a month and only 39/834 (4.7%) reporting greater than three standard drinks per month, averaged over the whole pregnancy. However, 69/834 (11.4%) of women reported binge drinking in trimester one, defined as >5 standard drinks in one session. At 12 months, 429 children were reported to have experienced wheezing, 608 had visited a primary health care provider with a respiratory condition, and 52 presented to hospital with either an upper or lower respiratory tract infection. Rates of maternal smoking, mean birthweight, and mean gestational age were similar across PAE exposed and nonexposed infants (see Table S1). PAE was slightly more common for those living in more advantaged neighborhoods (top tertile of SEIFA score). Of babies with PAE, 59.7% lived in advantaged neighborhoods compared with 51.6% of non-PAE exposed ($p=0.01$). There were no significant differences between mean lung function variables, or numbers of children with wheeze or hospital presentation for respiratory infections across categories of PAE (Table S1).

Lung function

There was no evidence of a relationship between PAE (y/n) and either LCI ($\beta=0.05$ turnovers, 95% CI (−0.05, 0.14), $p=0.35$), or FRC ($\beta=-0.46$ mL, 95 CI (−3.68, 2.75), $p=0.78$) at 4 weeks of age in fully adjusted models. The number of standard drinks consumed in trimester two was associated with lower LCI results ($\beta=-0.011$ turnovers, 95% CI (−0.0200, −0.0013), $p=0.03$), and a small increase in FRC ($\beta=0.34$ mL, 95% CI (0.02, 0.66), $p=0.04$) (Table 3). Models were free from multicollinearity (as tested with variance inflation factor) and there were no obvious outliers. Inspecting the DAG (see Appendix S1) showed that birthweight and/or gestational age could be acting as either a mediator on the pathway between PAE and lung function. When these variables were removed from the model, both individually and together, the relationship was no longer evident. Lastly, there was no relationship between binge drinking in the first trimester and either LCI ($\beta=0.02$ turnovers, 95% CI (−0.14, 0.17), $p=0.84$), or FRC ($\beta=2.65$ mL, 95% CI (−2.40, 7.69), $p=0.30$).

Maternal smoking and ETS are important co-variables with PAE and sensitivity analyses were conducted. Across all sensitivity analyses, the inclusion of different measures of maternal smoking or ETS did not change the association between PAE and lung function, with one exception (see Tables S5–S8). We found a significant interaction in trimester 1, where PAE combined with higher levels of smoking was associated with an increase in FRC at 1 month of age (FRC ml 9.80, 95% CI (0.69, 18.90), $p=0.035$) as well as a main effect of smoking which worked in the opposite direction. The total of the main effect and interaction effect for those with PAE was a small clinically nonsignificant increase in FRC of approximately 3 mL.

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TABLE 1 Characteristics of 834 mothers and children in the Barwon Infant Study with data on wheeze at 12 months of age.

Characteristic		
Any self-reported alcohol use in pregnancy	*n* (%)	392 (47.0)
Number of standard drinks consumed in trimester one	Mean (SD)	5.9 (14.2)
	Median[a] (min, max)	5 (1, 168)
Number of standard drinks consumed in trimester two	Mean (SD)	3.4 (7.9)
	Median[a] (min, max)	4 (1, 98)
Number of standard drinks consumed in trimester three	Mean (SD)	6.8 (9.4)
	Median[a] (min, max)	4 (1, 80)
Total number of standard drinks consumed in pregnancy	Mean (SD)	6.5 (16.0)
	Median[a] (min, max)	7 (1, 176)
Any binge drinking (>5 standard drinks per session) in trimester one[c]	*n* (%)	69 (11.4)
Any maternal smoking	*n* (%)	104 (12.6)
Birthweight in grams	Mean (SD)	3549 (515)
Gestational age in weeks	Mean (SD)	39.2 (1.5)
Socioeconomic status[b]		
Disadvantaged	*n* (%)	191 (22.9)
Neither disadvantaged nor advantaged	*n* (%)	160 (19.2)
Advantaged	*n* (%)	482 (57.9)
Wheeze in the first 12 months	*n* (%)	429 (51.4)
Primary health care for respiratory condition	*n* (%)	608 (82.3)
Hospital presentation for respiratory tract infection	*n* (%)	52 (6.2)

[a]Median has nondrinkers removed due to large numbers of low values skewing the median toward 0.

[b]SEIFA = socio-economic indexes for areas, FRC = functional residual capacity, LCI = lung clearance index.

[c]Binge drinking was only examined in first trimester due to low numbers in trimester two ($n = 5$) and trimester 3 ($n = 6$).

Wheeze

There was no evidence of a relationship between PAE (y/n) and infant wheezing in the first 12 months (OR = 1.29, 95% CI (0.97, 1.70), $p = 0.08$), and this lack of association persisted when exploring number of standard drinks consumed by trimester (see Table S2). There was no association between binge drinking and infant wheezing in the first 12 months (OR = 1.31, 95% CI (0.78, 2.22), $p = 0.31$). Additionally, two wheeze phenotypes were explored, recurrent wheeze and wheeze with shortness of breath, with neither showing an association with PAE (y/n) (see Tables S3 and S4).

Primary health care utilization for respiratory conditions

Primary health care for a respiratory condition was previously reported for this cohort, and data were accessed in 82.2% of children (Gray et al., 2019). Parents were able to recall a diagnosis for the respiratory condition in 98.8% of cases (1289/1305 total events). The most common diagnoses were a cold/common cold (21.1%), viral infection (19.5%), or bronchiolitis (9.7%) (Gray et al., 2019). In the current study, there was no association between presentation to primary health care for respiratory conditions within the first 12 months and either PAE (y/n) (OR = 0.98, 95% CI (0.67, 1.44), $p = 0.92$) or number of standard drinks consumed during pregnancy (OR = 1.00, 95% CI (0.99, 1.01), $p = 0.56$). There was no evidence of a trimester-specific effect (data not shown). There was an association between binge drinking in the first trimester and presentation to primary health care; in those participants with reported binge drinking, there was a nearly 5-fold increase in the odds of seeking primary health care in the first 12 months for a respiratory condition, however, the confidence interval was broad (OR = 5.0, 95% CI (1.7, 20.7), $p = 0.008$).

Hospital presentations for respiratory infections

There was no association between PAE (y/n) and the odds of a child presenting for care at a hospital for a respiratory tract infection (OR = 0.66, 95% CI (0.36–1.17), $p = 0.16$). Further, there was no association between number of standards drinks consumed and hospital presentation for respiratory infections (OR = 1.01, 95% CI (0.99, 1.02), $p = 0.34$). There was no evidence of trimester-specific effects (data not shown). Lastly, there was no relationship with binge drinking and increased odds of hospital presentation (OR = 0.79, 95% CI (0.18, 2.33), $p = 0.71$, see Appendix S1).

TABLE 2 Characteristics of 312 mothers and children in the Barwon Infant Study with data on lung function at 4 weeks of age.

Characteristic		
Any self-reported alcohol use in pregnancy	*n* (%)	148 (47.4)
Number of standard drinks consumed in trimester one	Mean (SD)	7.29 (16.13)
Number of standard drinks consumed in trimester two	Mean (SD)	3.01 (6.56)
Number of standard drinks consumed in trimester three	Mean (SD)	5.88 (7.96)
Total number of standard drinks consumed in pregnancy	Mean (SD)	7.04 (17.38)
Any binge drinking (>5 standard drinks per session) in trimester one	*n* (%)	33 (14.7)
Any maternal smoking	*n* (%)	48 (15.7)
Birthweight in grams	Mean (SD)	3519.07 (489.77)
Gestational age in weeks	Mean (SD)	39.12 (1.47)
Socioeconomic status[a]		
Disadvantaged	*n* (%)	77 (24.7)
Neither disadvantaged nor advantaged	*n* (%)	73 (23.4)
Advantaged	*n* (%)	162 (51.9)
Wheeze in the first 12 months	*n* (%)	148 (54.0)
Primary health care for respiratory condition	*n* (%)	219 (84.6)
Hospital presentation for respiratory tract infection	*n* (%)	13 (4.2)
FRC (mL)	Mean (SD)	87.83 (14.90)
FRC (mL/kg)	Mean (SD)	18.52 (3.54)
LCI (turnovers)	Mean (SD)	6.79 (0.42)

[a]SEIFA = socio-economic indexes for areas, FRC = functional residual capacity, LCI = lung clearance index.

TABLE 3 Lung function estimates at 4 weeks of age for number of standard drinks consumed (1-unit increment) from adjusted models in the Barwon Infant Study, Australia.

	LCI			FRC		
Predictors	**Estimates**	**CI**	***p***	**Estimates**	**CI**	***p***
Number of drinks during whole pregnancy (*n* = 306)	−0.0010	−0.0038 to 0.0018	0.48	0.06	−0.03 to 0.15	0.22
Number of drinks in trimester one (*n* = 171)	0.0001	−0.0037 to 0.0039	0.95	0.08	−0.06 to 0.21	0.26
Number of drinks in trimester two (*n* = 170)	−0.0106	−0.0198 to −0.0013	**0.03**	0.34	0.02–0.66	**0.04**
Number of drinks in trimester three (*n* = 69)	0.0001	−0.0004 to 0.0006	0.59	0.19	−0.31 to 0.69	0.45

Note: Models adjusted for child birthweight, gestational age, sex, maternal smoking, and socioeconomic status.
Bold values are statistically significant *p* values.

DISCUSSION

In an Australian birth cohort, we found no evidence that PAE effects lung function in 4-week-old infants, with the exception of PAE in trimester two being associated with a small increase in FRC and lower LCI in infants. We also found no association between PAE and parent-reported wheeze up to the age of 12 months or hospital presentation for respiratory tract infections up to 12 months of age; however the odds of presenting to a primary health care practitioner for respiratory conditions with binge drinking in the first trimester was substantially elevated.

Our findings can be compared to previous work conducted by Bisgaard et al. (2009), which found no relationship between PAE and lung function (performed using the raised volume rapid thoraco-abdominal compression technique) in a study of 404 sedated infants aged 6 weeks. Additionally, Gray et al. (2017) found lower respiratory rates, higher tidal volumes and lower time to reach peak tidal expiratory flow as a proportion of total expiratory time in 6 week old infants exposed to PAE, which is in the expected direction. One potential explanation for the differences in findings compared with our study is the way PAE was classified. In the study by Gray et al., PAE was defined as daily and/or weekly use of alcohol for at least 3 months of the pregnancy, making this a higher threshold for risky alcohol use than we used. We identified two studies of PAE and respiratory tract infections. Magnus et al. (2014) found no association between PAE and multiple hospitalizations for lower respiratory tract infection (3+ episodes). However, Libster et al. (2015), reported a significant positive association between

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PAE intake in the third trimester and life-threatening respiratory infections in male children (but not female) at 2 years. PAE was low in both of those cohorts, with "high use" being defined as one standard drink or more per week in Libster et al and only 7.7% of women consuming 11 standard drinks or more during their pregnancy in Magnus et al. Previous work has found that maternal binge drinking (five drinks or more in one sitting) in the second or third trimester was associated with an increased odds of serious infection in neonates (Gauthier et al., 2005). Further, maternal binge drinking has been associated with sleep and temperament issues (Alvik et al., 2011) a reduction in child cognition scores (Flak et al., 2014), and behavioral issues (Chu et al., 2022). To our knowledge, there are no other studies investigating the association with binge drinking and respiratory infections. The findings of the current study need further investigation, especially exploring the role of maternal anxiety in health system use. Maternal anxiety and depression has been shown to be associated with binge drinking during pregnancy (Leis et al., 2012), and we cannot rule out that the increased health care use seen in our study may reflect women's anxiety over their infant's health. Further, the lack of association seen for lung function impairment, but the increased risk for respiratory illness may reflect immune function impairment driven by PAE which is supported in the preclinical literature (Reid, Moritz, & Akison, 2019).

While these findings of the current study do not support our hypothesis, this may reflect the exposure level and outcome measures within this study, and not a true absence of association. Our findings may be reflective of the lower levels of PAE experienced in this cohort (average of six standard drinks across the whole pregnancy compared to daily exposure in some rat studies) or that any potential changes were not yet at a "clinically significant" level using current testing methods. Compared to other studies, our lung function measurements were performed at only one time point. MBW is an attractive technique in pediatric populations as it is particularly sensitive to early changes in the peripheral airways and is often abnormal before the onset of physical symptoms. Despite this, only 89 infants (28.3%) had an LCI value above the upper limit of normal and none at a level that would indicate severe lung function impairment (maximum LCI = 8.24). Of these, 44 experienced PAE and 13 were exposed to binge drinking. It is well acknowledged that early insults to the lungs (such as tobacco smoke exposure and repetitive respiratory infections) have significant impacts on lung development and growth trajectories, however, the influence of PAE is not understood. While outside the scope of the original study, serial measurements of lung function may be more meaningful in patients with PAE to appropriately monitor changes.

We noted an increase in FRC and lower LCI results in participants exposed to higher PAE in trimester two. While these results appear to be in the opposite direction to expected, this may be the result of a disruption of the normal alveolarization process. Pregnancies at high risk of premature delivery are commonly treated with glucocorticoids to accelerate fetal lung maturation, with improvements in lung mechanics reported as rapidly as 15 h post administration (Kauffman, 1977). However, this improvement results from a thinning of the alveolar wall caused by an inhibition of cell division, ultimately resulting in an increase in lung gas volumes (Kauffman, 1977; Pinkerton et al., 1997). Previous work in lambs (125d gestation) administered with betamethasone, reported these same paradoxical lung function outcomes seen in our study with increased lung volumes and improved ventilation efficiency index (Jobe et al., 2000). Morphometry revealed that treated lambs had a significant reduction in the number of alveoli units compared to control animals, but that remaining alveoli were enlarged, with thinner walls. It is possible that a similar mechanism of alveolar disruption may be present in our cohort for those exposed to higher PAE levels, however, additional exploration of this in animal models would be needed.

In our study, we found that PAE was more frequently seen in high socioeconomic areas (59.7% of PAE exposed children lived in the highest socioeconomic areas, compared with whole cohort proportion of 55.4%). These findings are similar to an Australian study by McCormack et al. (2017) who found that mothers who consumed alcohol prior to pregnancy awareness and during pregnancy, were more likely to be of higher SES background. This suggests a potential interplay between other risk factors and PAE that help to minimize the risk of adverse lung development, such as maternal body size, higher educational attainment, access to good quality nutrition, and lower maternal stress (May & Gossage, 2011). Detailed data collection regarding maternal risk factors, such as nutrition, body mass, gravidity, wealth index, education and employment status, and other substance use, may help to better understand the development of FASD.

This study has several strengths. This is a large, longitudinal cohort study representative of the population from which they were sourced. The MBW was performed by trained operators using validated methods. The infection variables were extracted from clinical records and not subjected to reporting bias. However, limitations remain due to methodological constraints and data availability. Maternal alcohol use is self-reported and has the potential for under-reporting, meaning some women who drank may be added to the nondrinking group. Additionally, there were no questions included that assessed alcohol use before pregnancy recognition, which means there may have been women who consumed alcohol during trimester 1 before awareness of their pregnancy. Previous Australian research found that most women (60.6%) consumed alcohol between conception and pregnancy recognition, and binge and heavy drinking were more prevalent during this time-period (McCormack et al., 2017). Similar issues around self-reporting applies to maternal smoking, and the lack of data on ETS exposure at the same time point as the lung function testing remains a limitation of our ETS assessment. There were small numbers in some of the outcome categories, affecting our ability to detect small differences. Further, the wheeze outcomes relied on self-report and some recall errors may have occurred, although it is not clear in which direction

they may have been. It is important to note that while our study has not shown deleterious effects of low-level PAE on most respiratory outcomes measured in this cohort, these results may not give reassurance to women who consume more alcohol during pregnancy than seen in our cohort.

It remains unclear whether PAE has adverse effects on the developing respiratory system of the child. Development of the classical signs of FASD, such as neurodevelopmental impairments and dysmorphic features, are well known to be linked to the level and timing of exposure with developmental windows (May & Gossage, 2011). Unfortunately, few studies have explored this with respect to the respiratory developmental windows and future lung health outcomes. Future studies examining the impact of PAE on respiratory outcomes should consider detailed data collection on maternal protective/risk factors (especially maternal smoking and ETS exposure) other clinical measures of disease activity and serial measures of lung function with techniques that are sensitive to early changes and easy to perform on very young children/infants. It would also be beneficial to examine respiratory effects in cohort studies with higher levels of PAE or clinical cohorts of children with FASD who have high levels of PAE and documented adverse outcomes to a severe enough extent to have received a diagnosis.

CONCLUSION

The current study found no evidence to suggest that low levels of PAE were associated with adverse lung function outcomes or parent-reported wheeze, although there was limited evidence of associations between binge drinking and healthcare utilization for respiratory conditions. There are limited available comparable studies, especially in populations with higher levels of alcohol consumption. Further research is needed to examine potential PAE impacts on lung health outcomes across different populations and with various levels of PAE.

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CONFLICT OF INTEREST STATEMENT

The authors have no conflicts of interest to declare.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the Barwon Infant Study. Restrictions apply to the availability of these data, which were used under license for this study.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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