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REVIEW

The Long-Term Effects of Prenatal Alcohol Exposure on Offspring: Insights from the ALSPAC Cohort

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Abstract
Prenatal alcohol exposure (PAE) is a significant public health concern, associated with adverse developmental outcomes throughout the lifespan. The Avon Longitudinal Study of Parents and Children (ALSPAC), a globally recognized longitudinal birth cohort, provides a robust dataset for examining the effects of PAE on physical, cognitive, and behavioral health outcomes. A structured search was conducted to identify peer-reviewed studies that utilized ALSPAC data to explore the effects of PAE. Studies were included if they satisfied the inclusion criteria (i.e., published between in English language 1999–2024, and examined the associations between PAE and outcomes in children and adolescents. The results reveal mixed findings. While conclusions from some studies suggest significant association exist between moderate levels of PAE and mild cognitive deficits and/or increase behavioral problems, especially in specific domains such as hyperactivity and inattention, other studies showed no relationship between low-to-moderate PAEs and cognitive or behavioral outcomes. Conversely, higher PAE levels were more often significantly associated with adverse outcomes such as reduced Intelligence Quotient (IQ), behavioral and emotional problems, lower birth weight, increased risk of depression, and adolescent drug and alcohol-related problems. ALSPAC-based studies demonstrate that higher levels of PAE are linked to significant risks for cognitive, behavioral, and physical development, even though low-level PAE exposure may not cause significant harm to development. The findings underscore the necessity of cautious public health engagement concerning alcohol consumption during pregnancy and emphasize the significance of critical consideration of multiple confounding factors.

Keywords ALSPAC · Prenatal alcohol exposure (PAE) · Child development · Adolescent development · Developmental risks

Introduction

Health concerns regarding prenatal alcohol exposure (PAE) have been documented for decades. Exposure to alcohol in utero has been linked to craniofacial abnormalities, growth restriction, and cognitive deficits [1]. Fetal Alcohol Spectrum Disorder (FASD) is the broad diagnostic term encompassing a wide range of effects that can result from PAE [2]. Still, in Canada and the United States an estimated 10–15% of pregnant women consume alcohol during pregnancy, with 3%– 5 % of women binge drinking [3, 4]. Due to obvious ethical and logistical considerations, studying the dose-dependent effects of alcohol is challenging. The amount, frequency, and timing of alcohol consumption, in addition to genetics, diet, and overall health, all have a substantial moderating impact on how much PAE affects the outcomes of children [5–7]. While research on animals elucidates a multitude of pathophysiological mechanisms by which alcohol consumption during pregnancy disrupts fetal development, extrapolating the conclusions from these studies to human subjects continues to present difficulties, and there are gaps in our understanding regarding the degree to which conclusive clinical recommendations can be made for humans.

The Avon Longitudinal Study of Parents and Children (ALSPAC), commonly referred to as the"Children of the 90 s"study examined, among a number of prenatal factors, the effects of PAE using a prospective birth cohort study approach. The study was designed and conducted in Avon, UK examined genetic and environmental determinants of

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health and development. The study recruited over 14,000 pregnant women gathering information on their alcohol consumption using a mailed survey at approximately 18–23 weeks' gestation [8]. A wealth of information on a variety of factors, including maternal health, lifestyle choices, and environmental exposures, as well as specific postnatal outcomes like the child's physical, behavioral, cognitive, and emotional development, were included in the massive dataset that came from the ALSPAC study. This information was extremely valuable for researching the long-term effects of PAE.

The Avon Longitudinal Study of Parents and Children (ALSPAC) cohort was selected for this review due to its exceptional strengths in exploring the impacts of prenatal alcohol exposure on offspring outcomes. ALSPAC is remarkable for its rigorous data gathering approach ensuring fidelity and accuracy across its longitudinal tracking of over 14,000 pregnancies since the 1990 s. Its validated and standardized measures minimize bias and the study's governance framework facilitate transparent data sharing to researchers worldwide. This has notably resulted in a vast body of peer-reviewed publications, demonstrating its value as a robust data resource. The cohort's relatively uniform demographic profile—including participants with similar socioeconomic, ethnic, and social class backgrounds—reduces confounding variables, enabling more precise analyses of the impacts of prenatal alcohol exposure. Furthermore, the ALSPAC dataset offers comprehensive longitudinal metadata, showing detailed information on prenatal exposures and a range of cognitive, behavioral, and psychiatric outcomes in offspring. These features, in addition to the international reputation of the cohort study for data integrity and extensive oversight, make ALSPAC particularly suited for investigating nuanced developmental trajectories associated with prenatal alcohol exposure.

ALSPAC data have been used in several research studies to investigate a wide range of aspects of the influence of PAE on fetal development throughout the life course. Several ALSPAC investigations have leveraged genetic approaches—such as Mendelian Randomization (MR) and Polygenic Risk Score (PRS) analyses—as well as negative-control comparisons (e.g., paternal exposures) to help distinguish causal intrauterine effects from shared familial confounding. However, the results and recommendations derived from these investigations vary and are often contradictory. A comprehensive review with an emphasis on research employing data from the ALSPAC cohort is necessary to critically synthesize the information that is already available.

This paper's objective is to provide a critical analysis and summary of research findings from studies that have explicitly looked at the connection between PAE and offspring outcomes utilizing ALSPAC data. The main goal of this study is to clarify the consequences of prenatal alcohol consumption as reported in one of the largest longitudinal studies to date, therefore expanding the field of maternal-fetal health research. It is important to note that, owing to the observational designs of the included ALSPAC-based studies, our aim is to synthesize reported associations between PAE and offspring outcomes rather than to draw causal inferences.

Methods

Search Strategy

This comprehensive review was conducted in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to identify and synthesize peer-reviewed research articles focusing on the relationship between prenatal alcohol exposure and outcomes in offspring using data from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort. A structured literature search across multiple electronic databases was conducted, including EMBASE, PubMed, PsycINFO, and MEDLINE, to identify peer-reviewed research articles published from 1990 up to September 2024. Additionally, the ALSPAC website contains a "Publications" page which lists all publications by year. Each year's tab, from 1990 through 2024, was searched using a combination of the following keywords and terms, while employing Boolean operators (AND, OR) were to ensure a comprehensive search: "alcohol", and "exposure" in all listed article titles:"Avon Longitudinal Study of Parents and Children,""ALSPAC,""Prenatal alcohol exposure,""fetal alcohol spectrum disorders", "FASD","offspring outcomes,""cognitive outcomes,""psychiatric outcomes,"and"behavioral outcomes". Reference lists of relevant studies that met the inclusion criteria were also manually screened to identify additional articles. The search was conducted between August 2023 and September 2024 to ensure recently published articles were included. While several primary ALSPAC articles discuss causal pathways, this review focuses on summarizing the associations reported, without applying formal causal inference criteria.

Inclusion and Exclusion Criteria

Studies were included in the review if they were original articles employing any study design and utilizing data from the ALSPAC cohort to investigate the impact of PAE (defined as any self-reported or biomarker-confirmed alcohol consumption during gestational period), on at least one

outcome, including but not limited to neurodevelopmental, behavioral, or physical health measures. Other criteria for inclusion include publication in English between 1991 (inception of ALSPAC) to September 2024. Articles were excluded if they did not specify the use ALSPAC data or simply mentioned ALSPAC without reporting any direct analysis of its data, did not focus on PAE and/or did not focus on offspring outcomes. Studies using multi-cohort designs without disaggregated ALSPAC-specific results (e.g., [9] were excluded from this review.

Study Selection Process

Three independent reviewers screened all the identified titles and abstracts to determine their relevance to the topic while duplicates were expunged. Full-text articles of potentially eligible studies were subsequently retrieved and assessed against the inclusion and exclusion criteria. The studies were independently examined by all reviewers for possible biases related to participant recruitment, confounding, and exposure and outcome measurement. Discrepancies between the reviewers were resolved via critical discussions and by consulting a third reviewer (MM) to reach a consensus. The study selection process is as documented in the PRISMA flow diagram show in Fig. 1. It provides details of the total number of studies screened, assessed for eligibility, included, or excluded, and reasons for exclusions at each stage.

Data Extraction and Synthesis

Information extracted from each study include demographic characteristics of the participants, study design, sample size, quantity, and trimester-specific details on PAE, outcomes on the offspring including cognitive, physical, psychiatric, behavioral, or developmental, and age at outcome assessment. Other details which helped to provide nuanced interpretation of the overall evidence and the potential sources of variations in study findings include the reported effect modifiers, confounders, confidence intervals and key conclusions. A narrative synthesis was conducted to summarize the findings from the included studies. The review synthesized findings thematically according to the reported outcomes of each study (e.g., effects of PAE on cognitive and neurodevelopmental variables, behavioral, mental health etc.) while

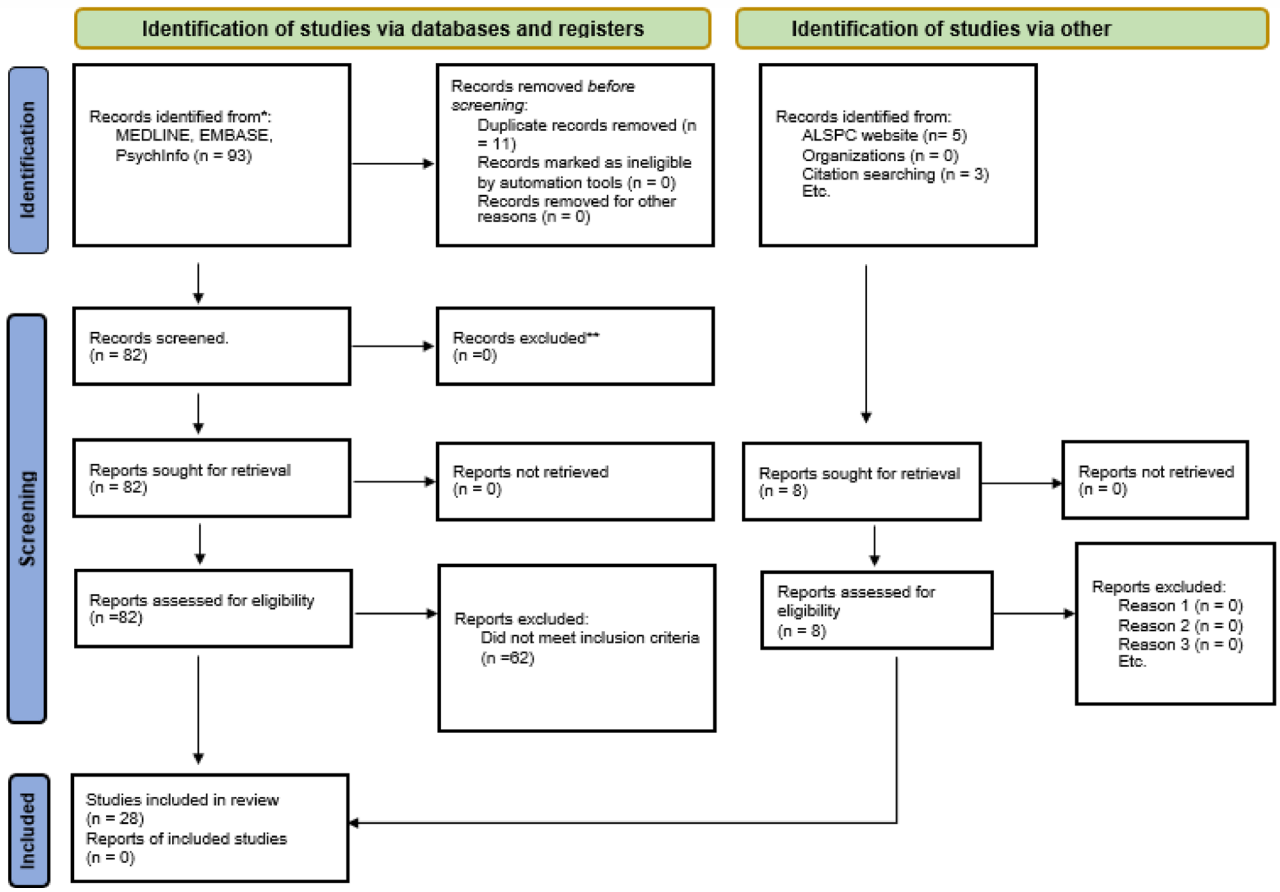

Fig. 1 PRISMA flow chart

recognizing variations in methodological approaches, and exposure/outcome measurements.

Risk of Bias

In this review, we conducted qualitative assessment of potential biases across the studies included by examining whether outcomes of the studies were objectively reported, including unfavorable or non-significant findings. Although no statistical analysis of the risk of publication bias was conducted (e.g., Egger's test) as the study was not concerned with a meta-analysis of results, the authors acknowledge the potential for selective reporting, especially in studies demonstrating significant associations between PAE and child outcomes. Overall, many of the studies showed low to moderate risk of bias, with only a few suggesting high risk, particularly due to insufficient control of confounding factors. These potential biases were considered in interpreting the overall strength and reliability of the evidence and also articulated in the discussion of findings.

Results

The initial database search yielded a total of 93 articles. After eliminating 11 duplicates, 82 articles remained for title and abstract screening. These 82 articles were further deemed potentially eligible and were selected for full-text review. The full-text review led to the removal of 54 articles for not meeting inclusion criteria and advancing the remaining 28 chosen as eligible for this review. The reasons for exclusion at each stage are detailed in the PRISMA flow diagram (Fig. 1). All included studies were conducted with data drawn from the Avon Longitudinal Study of Parents and Children (ALSPAC) study and investigated the relationship between prenatal alcohol exposure (PAE) and various offspring outcomes. Among the 28 ALSPAC-based articles, 18 used standard observational analyses, 3 employed negative-control comparisons, 6 applied genetic instruments (i.e. MR = 5 or PRS = 6), and 1 was a narrative review (please see Table 1).

Exposure/Outcome Assessment

The included studies analyzed data on PAE at different trimester. There were variations in the definitions of PAE, with most studies classifying exposure levels based on the frequency of alcohol consumption (e.g., drinks per day, drinks per week, or units per week) as well as quantity (e.g., units of alcohol per week). Some studies evaluated timing effects by further stratifying exposure based on gestational period. Nevertheless, there were variations in the cut-offs and measurement instruments used to categorize low, moderate, and high alcohol consumption levels.

The reviewed studies examined a wide range of offspring outcomes associated with PAE such as Cognitive and Neurodevelopmental outcomes (namely; Intelligence Quotient [IQ], and educational outcome [Academic achievement], using the Weschler Intelligence Scale, and the KS2 exam scores); Mental Health outcomes (Behavioral and emotional outcomes which assessed inattention, hyperactivity, conduct problems, antisocial behavior, and adolescent drug and alcohol problems), using parent/teacher reported scales; Physical Health and Growth outcomes (e.g. Birth weight, and growth trajectories); and Psychiatric outcomes (namely: Psychosis Like Symptoms [PLIKS], Borderline Personality Disorder [BPD], Tourette Syndrome, and Chronic Tic Disorder).

Characteristics of the included studies

The 26 included studies were published between 1996 and 2023. Study sample sizes ranged from 186 to 13,617 participants, with the majority - 8 studies (30.76%) examining the impact of PAE on mental health outcomes and cognition, 6 studies (23.07%) investigating the impact of PAE on child's educational performance, 5(19.23%) on behavioral and emotional outcomes, and 3(11.53%) on the impact of PAE on birth weight. The characteristics of the included studies are summarized in Table 1.

Alcohol consumption was measured at multiple points during pregnancy, including reports for each trimester. Alcohol intake was self-reported by mothers through structured questionnaires administered during pregnancy. In some studies [10–15], retrospective recall was utilized in later assessments to account for alcohol use in early pregnancy. Alcohol use was also frequently classified as low (1 to 2 units of alcohol per week), moderate (up to 3 to 6 units of alcohol per week) or heavy (binge drinking - defined across the studies as consumption of more than 6 or 7 units of alcohol in a short period). In line with UK national health guidelines, a unit of alcohol is defined as 8 grams (10 milliliters) of pure ethanol, to standardize the classification across studies. For many of the studies, participants who reported complete abstinence during pregnancy were classified as non-drinkers. Heavy drinking was associated with increased risk of adverse fetal outcomes (please see Table 1). Those with incomplete or inconsistent data on alcohol use were excluded from the analyses. In all the studies, specific attention appears to have been given to the frequency, timing, and intensity of alcohol consumption during pregnancy to better understand its impact on child development across various life stages. In most of the studies, outcome variables (IQ/cognitive abilities, behavioral, physical,

Table 1 Summary of the studies included in the review

	Authors	Year	Objective	Study design	Study population	Outcome measure	Findings
1.	Alati et al.,	2008	To test the hypothesis that moderate PAE in pregnancy is associated with IQ scores through intrauterine mechanisms	Negative-control comparison: – Uses parental (maternal vs. paternal) exposure comparison to isolate potential intrauterine effects from shared familial confounding	4332 participants at age 8 with complete data on maternal and paternal use of alcohol and tobacco at 18 wk. gestation	Cognitive function measured with the Weschler Intelligence Scale for Children (WISC-III^{UK})	There is no intrauterine explanation between moderate PAE and childhood IQ
2.	Alati et al.,	2013	Investigate the effects of low-to-moderate maternal alcohol use in pregnancy on school test scores at age 11	Negative-control comparison – Contrasts maternal vs. paternal exposure associations to help isolate intrauterine effects from familial confounding	7062 participants with complete data on: maternal and paternal patterns of alcohol use in the 3–18 weeks' gestation at age 11	Cognitive function Using National Curriculum Key Stage 2 (KS2) test scores	Consumption of 4 units of alcohol during pregnancy adversely affect childhood academic outcomes via intrauterine mechanisms (Mean change in KS2 score: 20.68 (21.03, 20.33) for maternal alcohol categories compared to 0.27 (0.07, 0.46) for paternal alcohol categories. While low-mod PAE does not affect test scores, maternal binge drinking may have an influence
3.	Bandoli et al.,	2023	Summarize inconsistencies in research about PAE and neurodevelopmental outcomes	Narrative review	Children between the ages of 9 months and 18 years	Cognitive function, behavioral and emotional outcomes; measured using the Bayley Scales of Infant Development, Strength, and Difficulties Questionnaire (SDQ), and Child behavior checklist	No consistent patterns between low to moderate PAE and offspring neurodevelopmental outcomes
4.	Dodge et al.,	2014	To determine whether the presence of the ADH1B 3 (alcohol dehydrogenase 1 Allele B) allele in the mother/offspring continues to be protective in alcohol-exposed adolescence	Genetic instrument approach – Candidate-gene analysis using the ADH1B*3 variant to assess how genetic differences in alcohol metabolism modify PAE effects	186 adolescent offspring	Behavior function; measured with the Achenbach TRF (Teacher Report Form)	Maternal ADH1B*3 allele protects against alcohol problems in adolescent PAE is related to attention/behavior problems in adolescents

Table 1 (continued)

	Authors	Year	Objective	Study design	Study population	Outcome measure	Findings
5.	Easey et al.,	2020	To investigate the association between PAE and offspring depression at 18	Negative-control comparison – Contrasts maternal vs. partner (paternal) alcohol consumption to help distinguish intrauterine effects from shared familial confounding	For mothers who provided information on alcohol frequency or pattern of drinking, 4,191 and 4,169 offspring, respectively, provided information for CIS-R diagnosis of depression at age 18	Psychiatric function measured using the computerized version of the Clinical Interview Schedule- Revised (CIS-R)	Offspring with maternal PAE at 18 weeks gestation were at increased odds of having a diagnosis of depression at age 18 (unadjusted OR = 1.18, 95% CI 1.03 to 1.34). After adjustment for socioeconomic and maternal behaviors, these associations were attenuated only slightly (OR = 1.13, 95% CI 0.99 to 1.29)
6.	Fraser et al.,	2013	To investigate whether AMH levels are influenced by parental characteristic and the intrauterine environment	Standard observational cohort – Describes the design, recruitment, and data collection methods of the ALSPAC birth cohort; not an analytical study of PAE effects	1,399 female children (mean age of 15.4)	Reproductive function measured with Anti-Mullerian hormone	PAE is not associated with offspring AMH levels
7.	Haan et el.,	2021	To investigate the association between ADHD symptoms and PAE by using alcohol metabolizing genes as proxies. alcohol dehydrogenase (ADH) and aldehyde dehydrogenase (ALDH)	Genetic instrument methods (Polygenic Risk Scores) – Uses maternal and offspring polygenic risk scores for alcohol exposure as instrumental variables to probe potential causal effects on ADHD risk	8,237 offspring (with genome-wide data) around the age of 7–8 years	Psychiatric function measured using maternal report of the Development and Well-Being Assessment (DAWBA) questionnaire	PAE is not associated with ADHD symptoms
8.	Hines et al.,	2002	Investigate the role of PAE to childhood gender role behavior	Standard observational cohort – Prospective population-based cohort study examining associations between PAE and later gender-role behavior	14,138 offspring at 42 months of age	Sexual function/behavior assessed by using the Pre-School Activities Inventory	PAE does not influence gender behavior in boys, there is a possibility that there is little influence on girls
9.	Howe et al.,	2019	To determine the effects of low-moderate PAE on facial morphology	Standard observational cohort – Examined associations between self-reported maternal alcohol intake and offspring facial shape using 3D imaging in the ALSPAC cohort	4747 children at the age of 15, with usable facial scans	Physical characteristics analyzed using a high-resolution facial image	No strong evidence that low-mod PAE influences facial morphology variation
10.	Humphriss et al.,	2013	To investigate the association between PAE and balance in 10-year-old children	Standard observational cohort examining associations between maternal self-reported alcohol intake and offspring balance measures in the ALSPAC cohort	6915 children who had a balance assessment at age 10	Physical function assessed by looking at dynamic balance (DB), static balance eyes open (SBEO), and static balance eyes closed (SBEC)	Moderate PAE was not found to have adverse effects on offspring balance at age 10

Table 1 (continued)

	Authors	Year	Objective	Study design	Study population	Outcome measure	Findings
11.	Kendler et al.,	2013	Identify a potential link between PAE and complex traits	Standard observational cohort – Prospective cohort analysis examining associations between parental alcohol use/ problems and offspring outcomes	3454 children ranging from 38 months to 18 years	Cognitive and behavioral function measured using a self-reported questionnaire	Maternal alcohol consumption predicted childhood temperament, externalizing traits, and age of alcohol initiation in childhood and adolescence
12.	Lewis et al.,	2012	Examine the effects of moderate prenatal alcohol consumption on offspring cognition	Standard observational cohort – Population-based analysis of ALSPAC data examining associations between self-reported PAE and child IQ including gene–environment interaction analyses	4167 children aged ≤ 8 years at age 8	Cognitive function measured by using a shortened version of the Wechsler Intelligence Scale for Children (WISC-III)	Four genetic variants in alcohol metabolizing genes were strongly related to lower IQ at age 8. Especially amongst the offspring of mothers who were moderate drinkers (1–6 units alcohol per week during pregnancy
13.	Macleod et al.,	2008	To estimate the prevalence of alcohol and tobacco use among children at age 10 years and to investigate possible influences on behavioral and cognitive outcomes	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between parental drug use and children's substance use	6895 children at age 10	Social function, and behavioral/cognitive outcomes. These are measured using self-answered questionnaires	Post-natal alcohol use, rather than PAE predicted alcohol use in offspring
14.	Mathews et al.,	2014	Examine the association between pre- and peri-natal alcohol exposures and Tourette syndrome/chronic tic disorder	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between reported pre- and perinatal exposures and Tourette/chronic tic outcomes	6090 children at ages 13–14	Physical/psychiatric health measured by analyzing maternal questionnaires, and pediatric medical records	PAE was associated with Tourette syndrome, Tourette syndrome/chronic tic disorder (OR 1,72 (1.13–2.62) p=0.01 and OR= 1.27 (0.95–1.69) p-0.11 respectively
15.	Murray et al.,	2016	To study the possible effects of moderate PAE on children's conduct problems	Genetic instrument methods (Mendelian randomization) – Uses maternal genetic variants as instruments for PAE to infer causal effects on child conduct problems	3,544 children between 4–13	Behavioral function; measured using Strengths and Difficulties Questionnaire	Moderate PAE contributes to an increase in risk for early-onset persistent conduct problems
16.	North and Golding	2000	To investigate the role of the maternal diet with the prevalence of hypospadias	Standard observational cohort – Prospective cohort analysis examining associations between maternal diet and hypospadias risk;	7928 male children	Physical function	There was no significant increase in hypospadias cases among mothers who consumed alcohol while pregnant
17.	O'Keeffe et al.,	2015	To examine the association between PAE and trajectories of offspring weight and height from 0 to 10 years	Standard observational cohort – Prospective analysis of ALSPAC data examining maternal alcohol consumption and offspring growth trajectories	7597 children range from ages 0–10	Physical function; measured by birthweight (kg) and height (cm)	Offspring exposed to heavy PAE were born 0.78 cm shorter (95% CI −1.34, −0.22) and 0.22 kg lighter (95% CI −0.34, −0.09) than infants with no PAE However, by age 10, infants exposed to heavy PAE were of similar height (mean difference 0.59 cm, 95% CI −0.93, 2.11) and weight (mean difference 0.41 kg, 95% CI −0.70, 1.52) to no PAE group

Table 1 (continued)

	Authors	Year	Objective	Study design	Study population	Outcome measure	Findings
18.	Passaro et al.,	1996	To investigate the association between maternal drinking with infant birth weight	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between maternal alcohol consumption and infant birthweight	10,539 singleton live born infants	Physical function measured with birthweight (grams)	Infants born to women who reported drinking 1–2 drinks/day with at least one binge, or ≥ 3 drinks/day with or without binges, had an adjusted mean birthweight ~150 gm less than that of infants whose mothers reported abstaining during pregnancy
19.	Sayal et al.,	2007	Investigate whether very low levels of alcohol consumption are associated with childhood mental health problems and if these effects are moderated by gender	Standard observational cohort – Prospective population-based cohort analysis of maternal PAE and offspring mental health outcomes	9086 and 8046 children at 47 and 81 months 5648 children at 93 and 108 months	Psychiatric outcomes measured using parental and teacher reports	There is a possible effect of low alcohol consumption on offspring mental health outcomes. No clear dose-relationship or gender differences
20.	Sayal et al.,	2009	Investigate whether patterns of alcohol consumption are independently associated with child mental health, cognitive outcomes, and whether there are gender differences in risk	Standard observational cohort – Prospective cohort analysis examining associations between self-reported maternal binge drinking patterns and child mental health outcomes	13617 children from singleton births (to minimize clustering effects) ranging from 47–81 months of age	Cognitive and psychiatric outcomes measured with the SDQ, Intelligence Quotient (IQ) data from the Wechsler Pre-school and Primary Scale of Intelligence (WPPSI)	The consumption of ≥4 drinks/day on an occasional basis during pregnancy may increase risk for child hyperactivity and inattention problems in the absence of moderate daily levels of drinking
21.	Sayal et al.,	2013	Investigate whether light drinking in pregnancy is associated with adverse child mental health and academic outcomes	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between self-reported PAE and mid-childhood mental health and academic outcomes	11-year-old children from ALSPAC with parent (n=6587) and teacher (n=6393) completed SDQs and data from Key Stage 2 examination results (n=10,558)	Cognitive and psychiatric outcomes measured with the Key Stage 2 (KS2) questionnaire and Strengths and Difficulties Questionnaire (SDQ) respectively	Light drinking during pregnancy is not associated with adverse mental health/ academic outcomes
22.	Sayal et al.,	2014	To investigate whether episodic binge drinking during pregnancy is independently associated with child mental health and academic outcomes	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between self-reported PAE and childhood mental health and academic outcomes	7,965 11-year-old children	Cognitive and psychiatric outcomes measured using the SDQ and KS2	Binge-pattern drinking was associated higher levels of inattention/hyperactivity in girls It may increase risk for child mental health problems and lower academic attainment even if daily average levels of alcohol consumption are low
23.	Shaheen et al.,	2014	To study the relationship between PAE and atopy	Genetic instrument methods (Mendelian randomization) – Uses genetic variants associated with alcohol metabolism as instruments to infer causal effects of PAE on atopic disease	(n= 5301) 7.5-year-old children	Physical attributes measured by parent-answered questionnaires and medical records	No indication that PAE increases the risk of asthma or atopy in childhood.

Table 1 (continued)

	Authors	Year	Objective	Study design	Study population	Outcome measure	Findings
24.	Von Hinke Kessler Scholder et al.,	2014	To examine the effect of PAE on child academic achievement (AA)	Genetic instrument methods (Mendelian randomization) – Uses a maternal ADH1B genetic variant as an instrument for PAE, while controlling for the child's genotype, to estimate causal effects on academic achievement	Between 1,922 and 4,088 mother–child matches ranging from ages 4–16	Cognitive outcomes; using the Key Stage 1 (KS1), Key Stage 2 (KS2), Key Stage 3 (KS3) and Key Stage 4 (KS4, or GCSE) examinations	Mothers of higher SES were more likely to consume alcohol during pregnancy but less likely to binge drink There is no clear correlation between PAE and AA
25.	Winsper et al.,	2014	To observe if there is an association between PAE and borderline personality disorder (BPD)	Standard observational cohort – Prospective cohort analysis linking maternal-reported PAE to offspring borderline personality symptoms	6050 children ages 11–12	Psychiatric function measured using a face-to-face semi-structured interview: the UK Childhood Interview for DSM-IV Borderline Personality Disorder (UK-CI-BPD)	The association between PAE and BPD were relatively weak and became nonsignificant once **postnatal** alcohol consumption was controlled for
26.	Zammit et al.,	2009	To examine whether maternal use of alcohol during pregnancy increases risk of offspring psychotic symptoms	Standard observational cohort – Prospective cohort analysis of ALSPAC data examining associations between self-reported prenatal substance use and adolescent psychotic symptoms	6356 children at age 12	Psychiatric function measured using the psychosis-like symptoms semi structured interview (PLIKSi)	There was an association between PAE and any suspected or definite PLIKS in the crude analysis (OR per 10-unit increase in alcohol 1.24, 95% CI 1.03–1.50), and this was not significantly changed after adjustment (adjusted OR per 10 units 1.19, 95% CI 0.97–1.45)
27.	Zaso et al.,	2021	Examine whether adolescents exposed to heavy PAE began drinking earlier than their non-exposed peers	Standard observational cohort – Prospective, population-based analysis using ALSPAC data; applied survival and generalized negative binomial models to test associations of heavy PAE and adolescent re-exposure with alcohol outcomes	2640 adolescents (17 years old)	Physical/social function; using a computerized interview	Heavy PAE has no significant effect on age of alcohol initiation. However, heavy PAE diminishes the normal protective effects of delayed alcohol exposure in adolescence
28.	Zuccolo et al.,	2013	Investigate the effect of moderate PAE on cognitive/educational performance in school	Genetic instrument methods (Mendelian randomization) – Leverages genetic variants (e.g., ADH1B) as instruments for prenatal alcohol exposure to infer causal effects on child cognition and academic performance	8530 children ≤ 8 years for KS2 analysis 5711 children at 11 years for IQ analysis	Cognitive outcomes: measured using the Wechsler Intelligence Scale for Children and age standardized (KS2) scores	Women with moderate drinking before and during early pregnancy were from higher SES compared to women with lighter drinking habits, and their offspring had higher KS2 and IQ scores. Children whose mothers' genotype predisposes to lower consumption/abstinence during early pregnancy had higher KS2 scores (mean difference +1.7, 95% confidence interval +0.4, +3.0) than offspring of mothers whose genotype predisposed to heavier drinking

social, and psychiatric) were measured using various scales as shown in Table 1.

Cognition, Intelligence Quotient and Academic Achievements

Alati et al. [16] reported that maternal use of alcohol in the first trimester was not associated with offspring IQ at age 8 to any greater degree than was paternal alcohol use during the same period of pregnancy. Over 19% of the variance in child IQ at age 8 was explained by parental education, whereas alcohol and tobacco consumption during pregnancy only accounted for 0.04% of the variance. Similarly, Zuccolo et al. [17] did not find any negative effect of first trimester light to moderate maternal alcohol consumption on offspring IQ at age 8. Findings, however, showed moderate use (up to 6 units of alcohol per week) was associated with better cognitive outcomes. The use of 7 or more units of alcohol per week during the first trimester of pregnancy was related to lower child IQ scores [17].

Other studies reported a negative effect of moderate PAE on childhood cognition, particularly in a specific subset of individuals. Lewis et al. [18] demonstrated a negative effect of moderate (1–6 glasses of alcohol/week) PAE on childhood IQ at age 8 amongst children with any of four specific variants of alcohol metabolizing enzymes. Bandoli et al. [10] showed that low to moderate PAE is not associated with adverse neurocognitive or behavioral outcomes on offspring. Sayal et al. [19] examined binge pattern alcohol consumption (defined as 4 or more drinks per occasion) in the second and third trimester of pregnancy, and offspring IQ at 49 months (measured by the Wechsler Preschool and Primary Scale of Intelligence). Their findings demonstrated that binge drinking was associated with lower IQ scores in univariate analyses, but after confounding variables were controlled for, the relationship was not significant [19]. It should be noted that only a small subset of the ALSPAC cohort population (n=924) was analyzed in this study due to limited IQ data availability [19].

A number of studies utilizing the ALSPAC database examined the impact of PAE on academic achievement (AA) [10, 17, 20–23]. Findings on the effects of PAE on offspring AA have produced mixed findings, with some studies demonstrating clear associations between PAE and lower academic performance, while others have found little to no significant effects. In one study by Sayal et al. [21], light drinking in first trimester of pregnancy (defined as <1 drink per week) had no effect on childhood academic outcomes at age 11 as measured on the Key Stage 2 (KS2) exams. Zuccolo et al. [17] found that children of mothers reporting moderate drinking (1–6 units of alcohol/week) had better KS2 scores than did children of mothers reporting light levels of drinking (<1 unit of alcohol/week) during pregnancy. In another study maternal binge pattern alcohol consumption was related to lower offspring KS2 scores at age 11, independent of maternal regular daily drinking [22].

Episodic binge drinking during pregnancy may therefore decrease offspring academic achievement, even in the absence of maternal daily drinking patterns [22]. In contrast, moderate drinking patterns (at least 1 drink/day) were not associated with AA in the absence of binge drinking [22]. In a more recent narrative review [10] reported that light-to-moderate drinking had no association with AA. Within the ALSPAC cohort, mothers of higher SES were more likely to consume alcohol during pregnancy but less likely to binge drink [17, 23]. Alati et al. [20] compared the effects of maternal and paternal alcohol exposure during the period of pregnancy on KS2 scores at age 11. Their analysis ruled out the potential confounding effects of Socioeconomic status (SES) on childhood and found that maternal consumption of up to one unit of alcohol (10 grams) was not associated with AA. Frequent consumption of 4 or more units of alcohol on any one occasion was related to poorer offspring academic achievement at age 11 (mean change in KS2 score of −0.68). The difference in the relationship between maternal and paternal drinking pattern with child AA suggests an intra-uterine mechanism of binge alcohol consumption that may reduce offspring AA.

Mental Health

A variety of mental health related factors have been studied in relation to PAE amongst the ALSPAC cohort. Three main themes were apparent in the literature: behavioral and emotional problems, psychiatric outcomes, and adolescent drug and alcohol problems.

Behavioral & Emotional Problems

Several ALSPAC studies utilized the Strengths and Difficulties Questionnaire (SDQ) to assess childhood behavioral and emotional mental health outcomes [19, 24–26]. The SDQ was designed to be completed by parents or teachers and contains four sub-scales: hyperactivity/inattention, conduct problems, emotional symptoms, and peer relationships, which are summed to generate a total general difficulties score [27]. The SDQ also contains a prosocial scale.

Sayal et al. [26] studied the relationship between alcohol use during the first trimester and mental health outcomes measured by parent rated SDQs at 47 and at 81 months and by teacher completed SDQs at 93–108 months. Some negative effect was noted for boys on parent rated SDQs, but only when higher SDQ score cutoffs for severity were used and with higher levels of maternal drinking. Similarly, Sayal

et al. [21] looked at the effects of low prenatal alcohol consumption (<1 unit/week) during the first trimester on child mental health outcomes at age 11. No association was found between low levels of PAE, and teacher rated SDQ scores. Although an insignificant negative effect for low-level alcohol consumption on parent-rated SDQ scores was found for girls, there was no evidence of any dose-dependent response in any of the SDQ subscales or overall [21]. A weak association was, however, found for teacher rated SDQ scores demonstrating lower total problem scores for offspring of mothers who consumed ≥1 unit of alcohol per week compared to abstainers.

A study by Sayal et al. [22] reported that binge drinking was associated with high levels mental health problems in offspring [19, 22]. Gender interactions were significant for behavior and total problems at 47 months, with the relationship being stronger for girls than for boys At 81 months, after adjusting for confounders, maternal binge drinking was associated with higher SDQ scores among both boys and girls, with no gender interactions noted at this age [19]. The main risks were for hyperactivity and inattention problems. At age 11, maternal binge drinking was related to higher teacher-rated SDQ scores for inattention/hyperactivity in both genders and to higher parent-ratings of inattention/hyperactivity and total problems in girls [22]. Parent-rated conduct problems were also higher in girls than boys at age 11, but this trend was not observed in teacher ratings [22]. In both of the aforementioned studies, the mental health risks of maternal binge pattern drinking remained even after daily drinking was accounted for [19, 22]. Another study by Kendler et al. [25] also looked at the impact of PAE on child and adolescent behavior utilizing the Revised Rutter Parent Scale for Preschool Children questionnaire to examine conduct difficulties and hyperactivity at 42 months., PAE was identified as a significant predictor of conduct difficulties and hyperactivity. While antisocial behaviors were predicted by maternal alcohol intake in univariate analyses, the relationship was not sustained in the multivariate analyses.

Psychiatric Outcomes

Several studies from the ALSPAC database have explored the impact of PAE on psychiatric outcomes among adolescents. A study by Zammit et al. (28) examined the association between PAE and psychosis-like symptoms (PLIKS) at age 12 (n=4253). The findings suggested a significant, but non-linear effect between maternal alcohol intake during pregnancy and suspected or definite PLIKS both before (OR per 10-unit increase in alcohol 1.24, 95% CI 1.03–1.50) and after (adjusted OR per 10 units 1.19, 95% CI 0.97–1.45) adjustment for confounders [28]. When trimester of exposure was analyzed, only first trimester alcohol exposure was related to an increased risk of PLIKS (adjusted OR per 10 units 1.41, 95% CI 0.95–2.09). However, once mothers consuming over 21 units of alcohol per week were omitted, there was no evidence of an association between prenatal alcohol use and risk of PLIKS.

Winsper et al. 29] examined the association between PAE at 18 and 32 weeks, and borderline personality disorder (BPD) at age 11–12. A total of 6050 children were interviewed using the UK Childhood Interview for DSM-IV BPD Interview (UK-CI-BPD). The alcohol consumption level cut-off used in statistical analyses was set at 1 or more drinks per day. In the unadjusted analyses, PAE at 18- and 32-weeks' gestation was significantly associated with BPD, but when sex and birth weight were controlled for, only alcohol consumption at 32 weeks remained significant. Once postnatal factors were controlled for (maternal smoking, family adversity, postnatal maternal alcohol consumption, etc.), neither relationship remained significant.

In a more recent study, Easey et al. [30] studied the association between PAE at 18 weeks' gestation and offspring depression at age 18. Depression was measured using a version of the Clinical Interview Schedule-Revised (CIS-R). Results showed that individuals with any PAE by 18 weeks had an increased risk of depression at age 18 (OR= 1.18 95% CI). Additionally, there was a linear trend between the amount of alcohol consumed and the risk of depression in the offspring.

PAE has also been studied in relation to Tourette syndrome and chronic tic disorder [13]. Tourette syndrome is a neuropsychiatric disorder beginning in early childhood that is characterized by multiple vocal and motor tics, while chronic tic disorder is similar but includes only motor or vocal tics but not both. Mathews et al. [13] found that consumption of greater than 2 alcoholic beverages per week during the final 2 months of pregnancy was associated with increased risk of Tourette syndrome at age 13–14 (p=0.03, CI 95% [1.05–2.33]) and that any use of alcohol, tobacco, or caffeine during the third trimester was related with an increased risk of either Tourette syndrome or chronic tic disorder (p=0.05 and p=0.01 respectively). Both of these associations remained significant after adjustment for SES [13].

Haan et al. [31] explored the relationship between PAE and attention-deficit hyperactivity disorder (ADHD) in the offspring. They were unable to find a significant association between the two. The authors attributed the lack of a significant association between prenatal alcohol exposure (PAE) and ADHD in offspring to potential methodological limitations. These included factors such as small sample sizes, variability in the measurement of PAE, and the influence of unmeasured confounding variables like genetic predispositions or postnatal environmental influences. Additionally, they suggested that the effects of PAE on ADHD might be

subtle or mediated by other neurodevelopmental pathways, making them harder to detect in their study.

Adolescent Alcohol Use

In a study by Macleod et al. [24], the strongest predictor of offspring alcohol use at age 10 was maternal alcohol use during early childhood, however PAE was not related to risk of offspring drinking at age 10. Furthermore, the relationship between paternal and maternal alcohol use during pregnancy and offspring outcomes were of similar direction and magnitude, further arguing against an intrauterine influence of PAE on risk of subsequent offspring alcohol use Macleod et al. [24]. Additionally, smoking at age 10 did not appear to be related to PAE either [24]. In another study by Kendler et al. [25], offspring alcohol consumption and alcohol problems at age 15 and 18 were associated with maternal alcohol intake during pregnancy in univariate analyses, but the association was no longer significant in multivariate analyses. In a more recent study Zaso et. al (2021) found that heavy PAE did not have a significant effect on when adolescences first started drinking (compared to their non-exposed peers). However, the study showed that heavy prenatal alcohol exposure diminishes the protective effects of delayed alcohol exposure in adolescence.

Birth weight, gestational age, growth trajectories

Using data from hospital delivery records, Passaro et al. [8] compared birth weight and gestational age at time of delivery between infants born to mothers who consumed alcohol during pregnancy with those who did not. Alcohol consumption during early pregnancy (18–23 weeks' gestation) was not found to affect the risk of preterm delivery overall 8]. Regarding birth weight, Passaro et al. [8] found support for the "J-curve" phenomenon, whereby light drinkers (less than one drink daily), not abstainers, had infants with the highest birth weights. Women who consumed alcohol daily during pregnancy had the highest proportion of low-birth weight infants (< 2500 gm). Compared to infants of light drinkers, those born to mothers consuming one to two units of alcohol daily during pregnancy weighed an average of 100 gm less and infants born to mothers who consumed three or more units of alcohol daily weighed an average of 200 gm less at birth [8]. Of the potential confounding variables accounted for, only maternal smoking seemed to alter the alcohol-birth weight association, with infants of mothers who smoked and drank daily weighing less than infants of mothers who drank daily but did not smoke [8].

A handful of other unrelated studies have examined various other potential health effects of PAE. An investigation of hypospadias found no difference in the prevalence among male offspring of women who consumed alcohol during pregnancy [32]. Alcohol intake during pregnancy was also not associated with female offspring Anti-Müllerian hormone (AMH) levels, a marker of ovarian reserve, during adolescence (mean age 15.4) [11, 12]. Shaheen et al. [33] investigated whether PAE may be related to the risk of atopic outcomes at age 7, no associations were found.

Childhood balance was also studied. Dynamic balance, static balance with eyes open and static balance with eyes closed were not associated with low to moderate levels of maternal drinking at 18 weeks' gestation [34]. High levels of alcohol consumption, defined at 7 or more drinks per week, were, in fact, positively correlated with children's balance abilities, yet the authors suggest this finding was likely due to residual confounding as higher alcohol use was associated with social advantage [34]. The authors also examined the relationship between childhood balance and PAE using a Mendelian randomization approach, and again, no associations were found [34].

Gender

Several studies put forward that effects of low levels of PAE may have a stronger impact on female mental health [19, 20, 22, 26]. In regards to light drinking, two studies found a stronger relationship to mental health outcomes in girls, yet the associations were small and there was a lack of dose-dependent relationship when comparing light drinkers to mothers who drank one or more units of alcohol per week [21, 26].

One ALSPAC study suggested a possible impact of PAE on offspring gender roles. Gender role behaviors were analyzed at 42 months of age, with the Pre-School Activities Inventory (PSAI), a standardized assessment completed by the child's primary caregiver that includes 24 items reflecting children's participation in sex-typical activities and games. The authors found that girls born to mothers who used alcohol during pregnancy significantly showed more masculine-typical behaviors ($t = 3.226$ $p < 0.01$) Increased masculine-type behavior in boys was also associated with maternal first trimester alcohol consumption [35].

Discussion

The impact of prenatal alcohol exposure (PAE) on various developmental outcomes shows considerable variability in the existing research. Current studies indicate that low levels of PAE, in general, do not have a significant effect on offspring academic achievement (AA) [10, 21]. Similarly, moderate alcohol consumption by pregnant women has not been shown to affect child AA [22]. However, the

overwhelming majority of evidence from the body of literature within the ALSPAC studies suggest that episodic binge drinking during pregnancy negatively affect offspring academic performance, irrespective of the mother's daily alcohol consumption patterns.

One possible explanation for these findings is that binge drinking results in a high concentration of alcohol exposure to the fetus in a short period of time. This intense exposure can cause acute and severe harm to the developing fetus, potentially leading to more pronounced negative outcomes in offspring. In contrast, daily alcohol consumption generally results in lower levels of acute exposure compared to binge drinking, which may mitigate the extent of damage to the fetus in utero. However, the cumulative exposure over time may still pose significant risks. This is a concerning trend, especially given that binge drinking among pregnant women has increased by approximately 8.9% annually from 2012 to 2019 (Howard et al., 2022). Such rising rates underscore the need for increased awareness and preventive measures to address the potential risks associated with high levels of alcohol consumption during pregnancy.

The impact of maternal and paternal alcohol use during the first trimester on child IQ at age 8 was also a central focus of some of the studies reviewed. The findings from the studies appear mixed for many reasons. Maternal alcohol consumption in pregnancy did not have a greater impact on the child's IQ compared to paternal alcohol use. These results suggest that the differences in IQ observed may be more influenced by environmental factors than solely by the direct effects of prenatal alcohol exposure (PAE), although PAE may still contribute as a risk factor for IQ challenges. Expanding on this, Zuccolo et al. [17] found that light to moderate alcohol consumption (up to 6 units per week) in the first trimester did not adversely affect child IQ by age 8; in fact, it was associated with better cognitive outcomes. Conversely, consuming 7 or more units per week was linked to lower IQ scores in children. This suggests a dose-dependent relationship, where higher levels of alcohol consumption may have harmful effects on cognitive development.

Additionally, Lewis et al. [18] reported that moderate PAE had a negative impact on childhood IQ at age 8, but this effect was moderated by specific genetic variants related to alcohol metabolism. First, limitations in methodological approaches, such as variations in research design and differences in how maternal and paternal alcohol use were reported and measured, are major contributors to these inconsistencies. While maternal alcohol use directly impacts the development of the fetus via teratogenic effects, genetic and epigenetic changes in sperm that may influence offspring IQ and neurological development can also result from paternal alcohol use [36, 37]. In addition, postnatal environmental factors, including SES and parenting behaviors, often shaped by both parents, play a significant role in child cognitive outcomes. It is also possible for reporting biases and social norms to conceal the true effects of maternal drinking. The relationship between parental alcohol use and child IQ is therefore complex, requiring more critical study to properly comprehend these dynamics, which involve both direct biological effects and indirect environmental influences. Altered gene expression resulting from epigenetic changes in sperm may impact the child's neurodevelopment and cognitive function [38]. Significant epigenetic alterations caused by paternal alcohol use could impact on the child's IQ that is on par with or even greater than the direct teratogenic effects of maternal alcohol use. The lack of consideration given to paternal genetic and epigenetic contributions in studies investigating the effects of maternal alcohol consumption may account for the observed less significant effect of maternal alcohol consumption in these studies.

This highlights the potential role of individual genetic differences in the way pregnant women metabolise alcohol and the way fetuses respond to PAE. Moreover, other studies, including those by Alati et al. [16, 17, 19], showed minimal impact of maternal binge drinking on childhood IQ by 49 months of age. Overall, these findings emphasize the complexity of how PAE interacts with various factors, including parental education, alcohol consumption levels, genetic factors, and binge drinking patterns, to influence child IQ outcomes.

In the systematic review by Kippin et al [39] which assessed 7 studies examining oral and written communications skills of adolescents with PAE by looking at verbal learning, memory, semantic processing/knowledge, reading and spelling, findings indicated that these skills were weaker in the moderate PAE group compared to the group with no/little PAE. However, the studies differed in their methodologies, and many findings were inconsistent between studies. Arguably, the adolescents with moderate PAE had poorer communication skills due to a combination of neurodevelopmental damage, cognitive deficits, and unfavorable environmental influences.

Notably, none of these studies investigated academic achievement or IQ beyond adolescence. Academic performance can undergo significant changes after the teenage years, particularly as individuals advance through higher education and transition into their professional careers. This shift may be attributed to the increasing complexity of academic material and the demands for enhanced cognitive capacity and advanced abstract reasoning—skills often impaired in individuals with Prenatal Alcohol Exposure (PAE). To gain a comprehensive understanding of PAE effects on academic success, future research should include longitudinal studies that track academic and professional

outcomes well into adulthood. Coles et al. [40] examined individuals who were exposed to alcohol during pregnancy and middle adulthood. Anxiety, depression, and bipolar affective disorder were among the mental health conditions that were more common in those with PAE.

Many studies examining the effects of PAE on cognitive outcomes such as IQ and AA face a significant limitation due to persistent confounding factors, particularly SES. For instance, research within the ALSPAC cohort reveals that higher SES mothers are more likely to consume alcohol during pregnancy but are less likely to engage in binge drinking Von Hinke Kessler Scholder et al. [17, 23]. This discrepancy skew findings on the impact of maternal alcohol consumption on offspring outcomes, as the influence of parental socioeconomic advantages may eclipse the effects of alcohol alone. In contrast, Alati et al. (2014) found that binge alcohol consumption is less influenced by social and lifestyle factors and is more directly associated with intrauterine mechanisms. This suggests that while SES might significantly alter general patterns of alcohol consumption, the adverse effects of binge drinking on fetal outcomes could be more intrinsically related to intrauterine effects. Regardless, this highlights the importance of differentiating the effects of SES from PAE to better understand the true relationship between maternal drinking patterns and child cognitive outcomes. This differentiation is crucial for accurately assessing the direct consequences of PAE and for developing targeted interventions to address it.

The link between PAE and mental health is less vague. While PAE does not have any association with ADHD or BPD it still contributes to issues such as hyperactivity and depression [31]. Using the Revised Rutter Parent Scale for Preschool Children questionnaire Kendler et al., [25] found a strong association between PAE and hyperactivity. Easey et al. [41], discovered that depression has a dose dependent relationship with the amount of maternal alcohol consumption at 18 weeks. Despite minimal effect of cofounders, it is possible that the small number of women in the high-consuming group might differ significantly in other factors, such as mental health or personality traits which may have an influence on offspring. Mathews et al. [13] found that consuming >2 alcoholic beverages per week in the last 2 months of pregnancy was linked to a significant increase in the risk of Tourette syndrome at ages 13–14, after adjusted for SES [13]. In a more current study Clark et. al (2024) shows that 82% of people with PAE have a co-occurring diagnosis - the most common being ADHD, learning disorders and intellectual disability [42].

The evidence in the APSPAC studies resonate with past and contemporary studies showing a more profound combined effect of SES and PAE on a child's mental health outcomes than PAE alone due to the interplay of social, environmental, and biological factors associated with low SES. The studies are consistent with previous findings indicating that children exposed to both PAE, and low SES conditions often experience compounded risks, such as limited access to quality education and healthcare, increased exposure to chronic stress, poor nutrition, and unstable living conditions, all of which impact negatively on well-being and affect brain development and mental health. Furthermore, the availability of protective factors—such as early access to intervention support, social support, as well as access to quality educational resources—that may lessen the negative effects of PAE are influenced by SES. Therefore, the synergistic risk environment created by the combined effects of SES and PAE suggests that understanding mental health outcomes of children requires taking into account larger context of socioeconomic conditions rather than focusing solely on PAE.

Other outcomes such as temperament did not have a strong link to PAE when accounting for other confounding variables such as SES. This further suggests that SES and other factors may play a more significant role in mental health outcomes than PAE alone. An updated study should explore how SES contributes to the risk of PAE-related outcomes. By integrating SES into the analysis, we can gain deeper insights into how economic/social conditions exacerbate or mitigate the effects of PAE. This could potentially lead to more targeted and effective interventions by taking a multidimensional perspective in research and policymaking. Studies by Macleod et al. [15, 24] found that PAE does not influence the age at which adolescents start drinking alcohol. Maternal alcohol intake during childhood seemed to have more of an effect on initiation [24, 25]. Zaso et al. [15] showed that children exposed in utero did not experience the normal protective effects that usually come with delayed alcohol exposure.

This suggests that children prenatally exposed to alcohol are at higher risk for alcohol problems even when alcohol initiation is deliberately delayed. Prenatally exposed adolescents should be encouraged to delay starting alcohol use to prevent this problem. These evidences also suggest that a child's social and environmental upbringing—which includes parental modeling of drinking behavior, family attitudes toward alcohol, and the availability of alcohol in the home—have a greater impact on a child's early alcohol use. Early alcohol experimentation is more likely when a child observes their mother drinking, as it may normalize alcohol use for them as they grow older or serve as a coping mechanism in stressful or unstable situations. Thus, these studies challenge the idea that PAE alone is the primary cause of adolescent drinking behavior from an academic perspective, emphasizing the need to consider the more complex, ongoing family dynamics and environmental

exposures throughout childhood. These findings underscore the importance of addressing adolescent drinking behavior through a comprehensive and individualized approach. Individual-level strategies can be designed to integrate family counseling, targeted education, and support systems to help address the unique constellation of risk factors faced by each adolescent. This nuanced approach acknowledges the interplay between biological vulnerabilities and psychosocial influences, fostering more effective prevention and intervention efforts.

Value of Genetic and Triangulation Approaches

The ALSPAC literature spans a spectrum of analytic designs—each with unique bias profiles—that, when combined, impacts inference for prenatal alcohol exposure (PAE). Negative-control comparisons (e.g., Alati et al. {16, 20, 41]) contrast maternal vs. paternal or partner alcohol use to help rule out shared familial and environmental confounders. Genetic instrument methods leverage inherited variants as proxies for exposure: several Mendelian randomization (MR) studies [17, 23, 33, 43, 44] use ADH1B or other metabolism-related alleles to infer causality, while polygenic risk score (PRS) analyses [31] integrate numerous loci to model maternal predisposition to drinking. By triangulating evidence; drawing on negative-control, MR, and PRS results as recommended by Treur et al. [45], complementary strengths and distinct limitations of each approach can be exploited, thereby increasing confidence that observed associations reflect true intrauterine effects rather than residual confounding. Future syntheses should continue to stratify and compare findings by design type to more robustly interrogate PAE's causal impacts.

Recommendations

There are few strategies that can be helpful for healthcare providers, public health experts, and policy makers in preventing prenatal alcohol exposures:

1. Education and Awareness: Provide information about the risks associated with alcohol use, especially for those with a history of prenatal exposure. If adolescents understand the potential impact, it may motivate them to make healthier choices.
2. Supportive Environment: A supportive environment that encourages healthy coping strategies is vital. This can include counseling, mentorship programs, and peer support groups.
3. Early Intervention: Monitoring adolescence so any signs of problematic behavior can be caught early. Providing interventions and support at the first sign of trouble can prevent more serious issues from developing.

In future studies, it would also be beneficial to explore the potential connection between PAE and other substances such as cocaine, marijuana, and cigarettes. It is possible that the co-use of certain substances with alcohol lead to synergistic effects, causing more severe/different developmental issues. Based on various ALSPAC studies, there is no strong correlation between PAE and physical changes such as child balance [34], atopy [33], hypospadias [32], or teenage ovarian reserve (Fraser McNally et al., 2013). There is also no correlation between light-moderate PAE and facial defects such as a smooth philtrum, thin upper lip, and short palpebral fissures, which are usually associated with Fetal Alcohol Spectrum Disorder [46]. However, a few of the ALSPAC studies suggested that girls may be more vulnerable to behavioral and emotional consequences of PAE at the ages of 47–103 months [19, 26] and at age 11 [21, 22]. This increase in vulnerability in early childhood and at age 11 show that there is some consistency in PAE outcomes across different developmental stages. Further studies may benefit from examining whether this trend extends into adulthood as the female offspring of the ALSPAC cohort age.

Limitations

A significant limitation of current research is its focus on adolescents and children, with insufficient attention to adult outcomes. Longitudinal studies that track individuals exposed to alcohol in utero throughout their entire lifespan could help resolve some of the discrepancies in understanding the relationship between PAE and various outcomes. Despite all the studies included in this review utilizing the same data source (ALSPAC), definitions and cut-offs for PAE varied between studies. Timing exposure analyzed also varied between studies. This made direct comparisons between studies difficult. A universal definition of what constitutes light, moderate, and heavy drinking during pregnancy would significantly aid in cross-comparisons of research on PAE. Another limiting factor was the breadth of confounding variables that may have affected results. These include lifestyle factors such as exercise, sleeping pattern, social support etc. For example, women in the ALSPAC sample who drank moderately (1–6 drinks/wk.) during pregnancy were older, from a higher social class, had a higher level of education, and had better diets [17].

Additionally, there are several inherent limitations in obtaining data from a cohort study such as ALSPAC. First there is selective attrition bias, whereby participants who discontinued the study vary from those who remained in the study. For instance, the families who dropped out were more

likely to have experienced PAE than those who did not [29]. Second, self-report data is subject to social desirability bias, whereby participants may have inaccurately reported alcohol consumption to appear more favorable to the researcher.

Finally, the age group of the ALSPAC cohorts limits the examination of any health effects that may arise later in life as the sample ages. Academic or behavioral problems may be less apparent at a younger age, with detriments becoming more pronounced as children transition into independent living. Some effects associated with PAE, such as hearing loss, visual impairments, and nervous system disorders [47] may not become clinically relevant until the later decades of life. As the ALSPAC cohort population continues to age, additional health conditions and concerns should be studied in relationship to PAE.

Conclusion

This review provides an overview of the outcomes of PAE according to the ALSPAC database. Given the overall consequences of PAE, physical and medical outcomes were surprisingly few among the studies reviewed. This further highlights the urgent need for further expansive research to fully understand PAE's impact on the offspring. Given the potential risks underscored in this article that are associated with even light-moderate alcohol consumption during pregnancy, it is important to prioritize prevention through comprehensive education and supportive policies. By promoting total abstinence and increasing awareness, we can help protect the health and well-being of future generations.

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