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CRITICAL REVIEW

The international prevalence of prenatal alcohol use obtained via meconium biomarkers: A systematic literature review

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Abstract

Fetal alcohol exposure is a growing public health concern. However, ascertaining its true extent remains challenging as maternal self-reports may lack validity. Increasingly, interest has turned to more objective measures of prenatal alcohol use (PAU) of which one, meconium, is recognized as a valuable tool. This review assesses both the international prevalence of PAU obtained using meconium biomarkers in general maternity populations and, when feasible, the level of agreement between meconium biomarkers and self-reported PAU. A systematic literature search for studies reporting the prevalence of PAU, as determined by meconium biomarker testing, was conducted using multiple electronic databases from 1990 to 2023. Seventeen studies were identified for inclusion and evaluated for methodological quality. Using fatty acid ethyl esters (FAEEs) meconium biomarkers, PAU prevalence varied from 2.4% to 44%. Rates based on EtG (ethyl glucuronide) analysis ranged from 0% to 16.3%, and EtS (ethyl sulfate) analysis from 7.8% to 16.7%. Studies were of moderate quality with high heterogeneity. Prevalence rates based on self-report data ranged from 0% to 46.4%. When reported, none of the reviewed studies identified agreement between meconium-based and self-report-based PAU prevalence rates. Using both self-reports to detect early pregnancy alcohol use, and meconium biomarkers to detect the occurrence of alcohol use later in pregnancy, may provide a more complete picture of PAU prevalence. Furthermore, research is warranted to develop stringent guidance on the ascertainment, storage, analysis, and reporting required in this field.

KEYWORDS
alcohol, biomarkers, meconium, prenatal, prevalence, systematic review

INTRODUCTION

Alcohol consumption is culturally accepted by many societies, despite contributing 5.1% to the global burden of disease (World Health Organization, 2018). Between 1990 and 2017, consumption has increased, particularly in lower- and middle-income countries; although it remains highest in Europe (World Health Organization, 2018) where there exists greater social acceptance and minimization of the associated risks. Of particular concern is prenatal alcohol use ("PAU"), with the current global prevalence rate of PAU estimated at 9.8%, rising to above 40% in several European countries including Ireland, Denmark, and the UK (Popova et al., 2017). Alcohol is a teratogen, with prenatal consumption increasing the risk of structural and functional anomalies, low birthweight, miscarriage, preterm births, and perinatal mortality.

PAU is the direct cause of fetal alcohol spectrum disorder (FASD) (National Institute of Alcohol Abuse and Alcoholism, 2021); an umbrella term for the range of cognitive, behavioral, and neurodevelopmental impairments observed as a consequence of alcohol exposure in utero. While country-level prevalence rates of the condition vary greatly, there is growing agreement that FASD is the most common, known cause of neurodiversity in the Western world (Popova et al., 2017). FASD is a lifelong condition; consequently, it is associated with a wide range of adverse secondary effects including lower life expectancy, poorer psychosocial outcomes, and higher risk of co-occurring mental and physical health conditions (McLachlan et al., 2020; Streissguth et al., 2004; Thanh & Jonsson, 2009). Those who receive a late diagnosis, or who are misdiagnosed, are particularly vulnerable as an early diagnosis of FASD is critical for individuals to receive sufficient care and support to reduce the risk of secondary effects (Streissguth et al., 2004; Temple et al., 2021). However, FASD diagnoses typically rely on maternal self-report of PAU, leading to a "diagnostic dilemma" as there are few objective measures of PAU postbirth (Bakhireva et al., 2018; Brown et al., 2011). Research on PAU epidemiology is further constrained by the different diagnostic methodologies and criteria used (Andrew, 2011). Prevalence and incidence data on PAU, and consequently FASD, are thus not well understood.

Given their low-cost and ease of administration, maternal self-report is the most typically used assessment tool for PAU screening. Likewise, self-assessment of alcohol consumption remains the gold-standard measurement for many healthcare professionals and researchers (Henderson et al., 2023a). However, such self-reports are subject to biases, including socially desirable responding, challenges in recall, and accidental or intentional underreporting. Research has consistently demonstrated that pregnant women commonly underreport alcohol use (Abernethy et al., 2018; Derauf et al., 2003; Ernhart et al., 1988) and, estimates based on alcohol sales data, suggest this gap could be over 40% (Boniface & Shelton, 2013). Lack of understanding of alcohol unit measures, alongside the stigma associated with PAU, is likely contributing toward its underreporting. Such limitations both impact the reliability of estimates of PAU's prevalence and limit opportunities to identify and diagnose those at-risk of FASD.

Objective methods have been explored to ascertain more accurate data on PAU prevalence. Recently, attention has shifted to identifying alcohol metabolites for use as screening and diagnostic tools (Papaseit et al., 2019). Alcohol metabolites can be detected in a range of biological matrices from the mother (e.g., blood), newborn (e.g., meconium), and from the fetal–maternal exchange (e.g., placental tissue) (Concheiro et al., 2017). With the exception of amniotic fluid, these matrices are advantageous as their collection is noninvasive and can detect PAU at different gestational periods (Lozano et al., 2007). Among these, meconium has been considered the "gold-standard" to detect alcohol and drug exposure in utero (Concheiro et al., 2017; Concheiro-Guisan & Concheiro, 2014). Meconium typically begins to form from week 20 of gestation and continues to accumulate until delivery; thus, it can detect PAU during the second and third trimesters of pregnancy (Morini et al., 2013).

Fatty acid ethyl esters (FAEE), a metabolite of alcohol, do not cross the placenta and therefore represent alcohol metabolized within the fetus (Goh et al., 2010). Indeed, high levels of FAEE have been documented in the meconium of babies of women who drank heavily during pregnancy (Bearer & Singer, 1996; Chan et al., 2004). Research has illustrated that meconium FAEE analysis has a fivefold increase in sensitivity over self-report methods (Gareri et al., 2008) and has demonstrated 100% sensitivity and 98% specificity when a cumulative cutoff of 2.0 nmol/g is used (Chan et al., 2004). Other alcohol metabolites, EtG (ethyl glucuronide) and EtS (ethyl sulfate), have also been identified as valid biological markers, although there are fewer published reports on these in comparison with FAEE (Himes et al., 2015). Unlike FAEE, both EtS and EtG can cross the placental barrier and therefore largely represent alcohol metabolites of maternal origin (Hanna et al., 2019; Matlow et al., 2013). Research has shown that concentrations of EtG >30 ng/g have high rates of sensitivity and specificity in identifying regular PAU (82% and 75%, respectively) and has shown moderate correlation to self-reported PAU (Himes et al., 2015). Moreover, while meconium EtS is less established as a marker of PAU compared to EtG, its inclusion during analysis may provide more robust evidence of alcohol consumption when compared to EtG alone (Bager et al., 2017; Hanna et al., 2019). Several reviews have been undertaken on the diagnostic accuracy of biomarkers, which have reported variability in the accuracy of FAEEs, EtG, and EtS (Kable & Jones, 2023); however, methodological issues noted in an earlier review suggested that further large-scale research on population samples is required (McQuire et al., 2016). Nevertheless, meconium is an easily obtainable noninvasive neonatal screening tool for identifying PAU and has the potential to provide more accurate PAU prevalence data than maternal self-reports (Papaseit et al., 2019).

This review sought to identify the prevalence of PAU obtained using meconium biomarkers of alcohol including FAEEs, EtG, and EtS in general maternity settings in order to inform policy. It does so by: (i) reporting the international prevalence of PAU in representative maternity populations as indicated by meconium biomarkers; (ii) determining the prevalence of PAU as indicated by meconium FAEEs, EtG, and EtS biomarkers independently; (iii) assessing the utility of meconium biomarkers as a valid method of assessing PAU to provide estimates of the prevalence of PAU derived from biomarkers; and (iv) when authors have collected self-reported data on prenatal alcohol use, the review will aim to compare the abilities of both meconium biomarkers and self-reports, collected in tandem, in detecting PAU.

METHOD

This systematic review was conducted in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses standards (PRISMA (Moher et al., 2009)) and adhered to the principles recommended by the Centre for Reviews and Dissemination (available at: https://www.york.ac.uk/crd/). Prior to formal screening, a protocol was registered on PROSPERO international prospective register of systematic reviews and is available at https://www.crd.york.ac.uk/prospero/ (record number: CRD42021229732).

Information sources and search strategy

A systematic search was conducted to identify published and unpublished studies that investigated the prevalence of prenatal alcohol exposure in general maternal populations using meconium biomarkers. Searches were initially conducted between December 11, 2020, and January 17, 2021, and were updated on July 25, 2023, using the following electronic bibliographic databases: APA PsycInfo, Embase Classic+Embase, Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily, ProQuest Dissertations and Thesis Global, Cumulative Index to Nursing and Allied Health Literature (CINAHL Plus), and Scopus. References of included full-text studies were examined for additional relevant literature. While no date limits were set, publications were limited to English language. Searches were limited to English language publications. The search was conducted utilizing numerous combinations of the following key words:

1. Predict*, assess*, detect*, prevalen*, epidemiolog*, frequenc*, occur*, inciden*, probability, rate* OR statistic*; AND,
2. Prenatal, pregnan*, antenat*, postnat*, primigravida, expect* mother*, matern*, maternal-fetal exchange, infant, newborn*, baby; AND,
3. Alcohol*, ethanol, binge drinking, ARBD, ARND, drunk*, FAS, FASD, Intoxicat*, PAE OR pFAS; AND,
4. meconium, FAEE, “alcohol metabolite*”, “fatty acid* ethyl ester*”, EtG, “ethyl glucuronide*”, “ethyl sulfate” OR EtS.

Eligibility criteria

Articles were retained if the following inclusion criteria were met: (i) observational study designs including retrospective and prospective cohort studies and cross-sectional studies; (ii) original and quantitative in nature and published in a peer-reviewed or scholarly report; (iii) report an estimated prevalence of prenatal alcohol exposure or report results, which allow for its calculation; (iv) prevalence must have been measured by meconium biomarkers; (v) population of pregnant/postpartum women and/or neonates in general maternity settings. Articles were excluded if they were: (i) animal studies, individual case studies, and studies, which did not provide data to assess primary outcomes, or which included secondary analysis of data; (ii) review studies or meta-analyses; (iii) studies reporting a pooled estimate of PAU by combining several studies; (iv) specific populations not representative of the general population, such as substance use populations and neonates born in high-risk obstetric/antenatal units; (v) studies published in iteration (i.e., if papers were subsequent publications of results already included).

Study selection

Identified studies underwent deduplication, and titles and abstracts were screened for eligibility by the authors. For those deemed relevant, or where there was insufficient information to determine relevance, full texts were retrieved or requested. Authors assessed relevance of studies as per the inclusion criteria, and any discrepancies were resolved by discussion. Studies that did not meet criteria were excluded. Full-text screening for eligibility was completed for 76 articles. Interrater reliability was calculated at both stages of screening. The level of agreement as indicated by Cohen's Kappa was 0.88 at the title and abstract screening stage, and 0.94 at full-text stage indicating almost perfect agreement between reviewers. Where ratings differed, these were discussed, and an agreement reached.

Data extraction

For included studies, data extraction was initially completed independently by the lead author followed by the verification of table entries by a second reviewer. The following data were extracted, where available: first author; title; year of publication; journal; study design; aims; population characteristics; country/location of recruitment, study setting, the year(s) in which data collection took place; prevalence/incidence of PAU (*n*, %) via self-reported data (*n*, %, and 95% confidence intervals); assessment tool used to obtain self-report PAU and level of agreement; maternal and infant sample demographics; trimester of PAU; biomarker utilized; estimates of prevalence/incidence of PAU via meconium testing (*n*, %, and 95% confidence interval); cumulative FAEE cutoff concentration used, EtG and EtS cutoff; details of collection; analysis used; testing and storage of meconium; inclusion and exclusion criteria; and primary outcome and secondary outcomes.

Evaluation of methodological quality

Methodological quality and risk of bias was assessed using the Joanna Briggs Institute Critical Appraisal Checklist for Studies Reporting Prevalence Data (Joanna Briggs Institute, 2017). The tool was used to evaluate included studies on the following criteria: representative sample frame, appropriate recruitment, adequate sample size, detailed description of study subjects and setting, data analysis, methodology used, validity of methodology, reliability of measurement of the condition of interest, appropriate statistical analysis, and adequate response rate. For all included studies, quality was independently assessed by two reviewers to ensure consistent application of the tool and to improve validity and accuracy. Discrepancies were resolved by clarifying details of the items and a consensus reached via discussion. No studies were excluded based on the quality assessment.

Statistical analysis

The review aimed to establish a pooled estimate of the prevalence of PAU as indicated via meconium biomarkers. Data on prevalence were gathered from all included studies and assessed for heterogeneity prior to analysis.

RESULTS

Search results

Electronic searches and additional sources yielded a total of 1670 citations, with publication dates ranging from 1984 to 2023. Following removal of duplicates ($n=319$), 1351 citations were screened using title and abstracts of which 1275 were excluded for not meeting inclusion criteria. Subsequently, 76 full-text articles were assessed for inclusion, 59 of which were excluded. A total of 17 studies fulfilled the inclusion criteria and were retained for data extraction, as illustrated in Figure 1. Importation of citations and screening and exclusion of records were managed using the Covidence Systematic Review Management Software (https://www.covidence.org/). Duplicated studies identified at the data extraction stage were merged and reported as single studies (Derauf et al., 2003; Henderson et al., 2023a).

Characteristics of included studies

Characteristics of studies

Study characteristics are summarized in Table 1. All studies were published in peer-reviewed journals. One study was published in 2003 (Derauf et al., 2003) and the remaining between 2008 and 2023. Studies were either cohort- or population-based and included data on prevalence across four continents including Europe, North America, South America, and Africa.

Maternal and infant characteristics

Maternal samples were recruited from maternity settings (e.g., general hospitals, neonatology wards, and obstetrics units). Thirteen studies reported age ranges for their participants, with the mean maternal age ranging from 24.9 to 34.0 years (English et al., 2016; La Maida et al., 2023). Socioeconomic status (SES), when reported, varied between the reviewed studies; with one study's sample earning <$19,999 USD per annum (Bakhireva et al., 2019), while the majority of another study's sample had an income of >$80,000 (57.8% (Delano et al., 2019)). Employment rates were consistent ranging from 72% to 75.4%, respectively (Bana et al., 2014; Lamy et al., 2017). Mothers had typically completed secondary education and/or obtained a college/university degree at a rate of 43.2% to 73.7% (Bakhireva et al., 2019; La Maida et al., 2023). In contrast, 55% of women in English et al. (2016) were categorized as having primary/no education, and 95% of Hutson et al. (2010) had completed less than secondary-level education. An overview of the maternal and infant characteristics is shown in Table 2.

Methodological quality review

The agreed ratings for each item on the quality assessment tool are displayed in Table 3. The number of criteria met ranged from three (Sanvisens et al., 2016) to eight (e.g., Lamy et al., 2017), and the average number of criteria fulfilled was six of the nine. Interrater reliability of the quality appraisal was high between reviewers, as demonstrated by a Cohen's Kappa value of 0.87. Discrepancies were resolved via discussion.

All studies benefited from a clear description of their rationale and objectives. Where power calculations were not reported, these were calculated as per the quality assessment tools guidance on epidemiological studies using Naing et al.'s (2006) statistical formula. Using a PAU prevalence rate of 18.9%, as obtained via meconium measures in a systematic review and meta-analysis conducted by Popova et al. (2017), calculations indicated a minimum sample size of 236 was required; a criterion met by 76.5% of studies in this review. All but two studies (Bakdash et al., 2010; Sanvisens et al., 2016) evidenced appropriate recruitment and described their approach comprehensively. Appropriate descriptions of response rates were provided by eleven of the seventeen studies except for Bakdash et al. (2010), Bakhireva et al. (2019), Morini et al. (2010), Morini et al. (2013), Pichini et al. (2012), and Sanvisens et al. (2016).

Several methodological weaknesses were also observed; (i) seven of the studies failed to describe their sample or setting in sufficient detail (Bakdash et al., 2010; Bryanton et al., 2014; Delano et al., 2019; Derauf et al., 2003; Gareri et al., 2008; Morini et al., 2010; Sanvisens et al., 2016); (ii) eight studies did not specify exclusion criteria (Bakdash et al., 2010; Bakhireva et al., 2019; Bryanton et al., 2014; Derauf et al., 2003; Henderson et al., 2023a; La Maida et al., 2023; Morini et al., 2010; Sanvisens et al., 2016); (iii) five studies did not provide an adequate description of the participants' demographic information (Bakdash et al., 2010; Bryanton et al., 2014; Derauf et al., 2003; Gareri et al., 2008; Morini et al., 2010), and (iv) seven of the studies either did not conduct appropriate statistical analysis, as they did not utilize recommended cutoff points for analysis or were

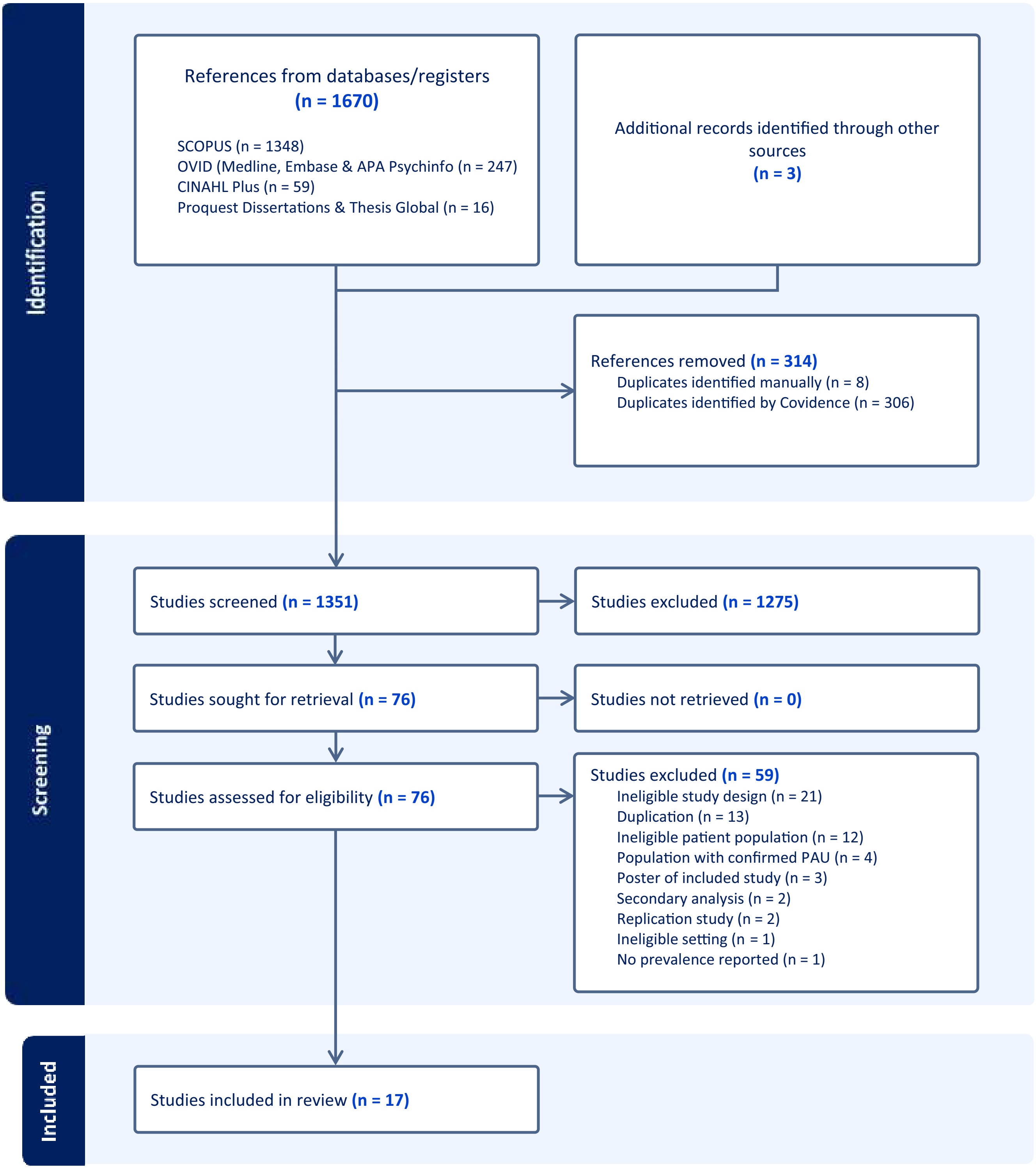

FIGURE 1 Systematic literature search and study selection process illustrated using PRISMA flow diagram (Moher et al., 2009).

unclear in their reporting of the methodology and analytical strategies (Abernethy et al., 2018; Bakdash et al., 2010; Bana et al., 2014; Derauf et al., 2003; English et al., 2016; Pichini et al., 2012; Sanvisens et al., 2016). Only three of the quality criteria were met in Sanvisens et al., 2016; this study did not demonstrate adequate sample size or management of response rate and failed to provide an adequate description of the study participants and setting.

Detailed procedures for meconium collection and storage were not specified by all studies, thus prohibiting an evaluation of the validity and methodological rigor of their findings. Meconium samples require careful collection and preservation to avoid the possibility of contamination, and improper storage can increase the possibility of false-negative results (Gray & Huestis, 2007). More specifically, FAEEs are sensitive to light and temperature, and samples degrade

TABLE 1 Overview of study characteristics.

Study	Country	Design	Aims	Inclusion criteria	Exclusion criteria
Derauf et al. (2003)	USA: Hawaii	Observational, population-based study	To assess agreement between maternal self-reported tobacco use and PAU and detection of metabolites associated with tobacco use (cotinine) and ethanol intake (FAEE)	All newborns delivered in center in Nov–Dec 1999	NS
Gareri et al. (2008)	Canada: Ontario	Cross-sectional, population-based study	To establish an objective PAU prevalence value and compare results with the rate of PAU as obtained in self-reported PAU	All neonates born within a 12-month period at each birthing site in the region of Grey Bruce	Neonates born to women living outside the region and all neonates whose mothers refused to provide a meconium sample
Bakdash et al. (2010)	Erlangen: Germany	Prospective cohort study	To explore the use of meconium FAEEs and EtG in detecting alcohol abuse during a maternal health evaluation study	Mothers who consented to a meconium sample being taken 24 h postbirth	NS
Hutson et al. (2010)	Uruguay: Montevideo	Cross-sectional study	To determine the incidence of PAU in the public health care sector in Montevideo, Uruguay, using FAEE in meconium	The mother had to be in good health, between the ages of 13 and 45 years, and had to provide written consent	Twins or subjects with missing data
Morini et al. (2010)	Italy: Reggio Emilia, Florence and Rome; and Spain: Barcelona	Cross-sectional, population-based study	To evaluate the correlation between amount of meconium-derived FAEEs with EtG and EtS volume in meconium and hair samples	Any consenting mother who delivered within the participating neonatal units	NS
Pichini et al. (2012)	Italy: Reggio Emilia	Cross-sectional, population-based study	Multicenter study to assess PAU by objective measurement of meconium biomarkers	All term neonates born in the center during an established time period (usually about 1 month, with the exception of Reggio Emilia, where collection lasted 3 months)	Those with severe pathologies requiring intensive care (eight newborns were excluded)
Morini et al. (2013)	Italy: Belluno Spain: Barcelona	Cross-sectional, population-based study	To evaluate the correlation between EtG volume in maternal hair and nail samples, with meconium-derived EtG volume	Any consenting mother who delivered within the participating neonatal units between the end of 2011 and the first 2 months of 2012	Neonates with severe pathologies requiring intensive care
Bana et al. (2014)	Spain: A Coruna	Prospective cohort study	To determine the prevalence of the positive biomarkers of alcohol in newborns with PAU and establish the analytic procedures to identify EtG and FAEEs in meconium	Neonates ≥32 weeks of gestation and/or ≥1500 g weight at birth and in health area	Babies affected from major malformations or severe diseases, or consent refusal from the parents
Bryanton et al. (2014)	Canada: Prince Edward Island	Anonymous birth cohort study	To establish the incidence of PAU via analysis of meconium samples	All neonates born to women in PEI over a 1-year period	NS

TABLE 1 (Continued)

Study	Country	Design	Aims	Inclusion criteria	Exclusion criteria
English et al. (2016)	Uganda: Mbarara	Cross-sectional, population-based study	To assess the prevalence and predictors of PAU in Southwestern Uganda	All pregnant women presenting to the maternity ward at in active labor between September 23 and November 23, 2013, were eligible for enrollment. All consented neonates born during the 2 months. An equal number of rural and urban mothers were enrolled in the study, therefore after reaching the quota for a certain demographic (rural or urban), only women of the remaining demographic were permitted to be included in the study	If (1) the child died following delivery or was transported to another ward where meconium collection was not possible; (2) the mother–child pair was discharged prior to the passing of the first meconium; or (3) the mother was sufficiently ill to preclude adequate informed consent, as deemed by study personnel
Sanvisens et al. (2016)	Spain: Barcelona	Cross-sectional study	To analyze prevalence of alcohol consumption in mothers and PAU	A series of parturient women who were admitted to the Obstetric Unit between Sept 2011 and March 2012	NS
Lamy et al. (2017)	France: Normandy	Cross-sectional, population-based study	To compare the prevalence of alcohol, tobacco and/or cannabis use during the third trimester of pregnancy (using maternal self-reports) with the results of meconium testing of their metabolites in newborns (cotinine, EtG, and cannabinoid metabolites)	Any pregnant women aged 18 or over and living in catchment area that delivered a child in one of three maternity hospitals, was included	269 deliveries were excluded; 61 mothers refused to participate, 48 did not speak and/or understand French language, six were younger than 18 years, 145 were living outside of our catchment area, 12 left the maternity hospital before inclusion, two had a critical illness at inclusion, stillbirths occurred in six cases, and one mother delivered anonymously
Abernethy et al. (2018)	Scotland: Glasgow	Observational, cross-sectional, population-based study	To investigate the feasibility of determining the pattern and prevalence of alcohol consumption in pregnancy by measuring ethanol biomarkers (FAEE &EtG) in meconium	All mothers delivering singleton infants born after 36 completed weeks' gestation, during every eighth 24-h period over 5 months	Multiple births
Bakhireva et al. (2019)	USA: New Mexico	Birth cohort study	To estimate PAU prevalence among newborns in the Navajo Nation, using ethanol biomarkers measured in meconium	Pregnant women: (a) age: 14–45 years, (b) lived on Navajo Nation for at least 5 years at any time in their life, (c) agreed to receive prenatal care and deliver at one of five participating hospitals and (d) willing to have their child followed up for biological sample collection and developmental assessment through the first year of life	NS
Delano et al. (2019)	Canada	Birth cohort study	To estimate the prevalence of heavy PAU via analysis of meconium FAEEs	Women aged 18 years or older; <14 weeks gestation; ability to communicate in English or French; plan to deliver at a local hospital; and willingness to provide a cord blood sample	Any known fetal chromosomal abnormalities or major malformations in the current pregnancy, and/or a history of medical complications including epilepsy, hepatitis, cancer, hematological disorder, threatened spontaneous abortion, illicit drug use, or disease of major organs (heart, kidney, liver, lung)

(Continues)

TABLE 1 (Continued)

Study	Country	Design	Aims	Inclusion criteria	Exclusion criteria
Henderson (2023a)	Scotland: Glasgow	Observational, cross-sectional, population-based study	To explore if FAEEs and EtGs in meconium are predicted by maternal or newborn demographics; and if meconium biomarkers concentration correlates with self-reported PAU	Mothers delivering a live singleton infant within each fourth consecutive 24-h period	NS
La Maida et al. (2023)	Italy	Cross-sectional, population-based study	To assess fetal exposure to maternal alcohol use via meconium and maternal hair EtG concentration	Any consenting mother who delivered within the participating neonatology units	NS

Abbreviations: EtG, ethyl glucuronide; EtS, ethyl sulfate; FAEE, fatty acid ethyl esters; NS, not specified; PAU, prenatal alcohol use.

by approximately 86% within a 24-h period when stored at room temperature. As such, samples require storage following collection in a −20°C freezer (Moore et al., 2003). Nine studies adhered to this protocol, with a further five studies storing at lower temperatures (e.g., −40°C, Henderson et al., 2023a; −80°C, Bakhireva et al., 2019).

The timing of collection is also paramount as false-positive FAEE results can occur as a result of delayed sample collection (Zelner, Hutson, et al., 2012). Zelner, Hutson, et al. (2012) proposed that results of meconium analysis should be interpreted with caution for samples passed after the first 24 h postbirth, or samples collected after the first meconium sample was passed, due to the possibility of contamination and elevated FAEEs. Only four studies specified collection of samples within 24 h postbirth (Bakdash et al., 2010; Henderson et al., 2023a; Morini et al., 2010, 2013), with a further three authors, indicating that meconium was collected up to 48 h postbirth (Abernethy et al., 2018; Bryanton et al., 2014; Pichini et al., 2012). A lack of information on the timing of collection was observed across nine studies, thus highlighting a concern around methodological rigor.

Lastly, most studies (*n* = 15) required informed consent from the mother for meconium samples to be collected and analyzed. Exceptions were Bryanton et al. (2014) and Gareri et al. (2008), whereby collection of samples was anonymous and so did not require consent; however, once informed of the study, postbirth mothers retained the right to withdraw consent. It is possible therefore that women who did drink during pregnancy chose to withhold their consent, particularly given the lower rates of uptake in some studies (e.g., 52%; Bakhireva et al., 2019).

Of concern was the inconsistency in the reporting of prevalence data and how rates were calculated. Different units of PAU measurement, their cutoff points, and different expressions of prevalence data were complicating factors in the included studies. Even within studies analyzing FAEEs alone, there was no consensus on the number of FAEE's summed to calculate prevalence, with some studies not specifying this in their methodology. Furthermore, the "limit of detection" (LOD), or the lowest quantity of a concentration that can be measured, was inconsistent with the laboratories conducting these analyses using different reference points (see Table 4). For example, Gareri et al. (2008) utilized an LOD of 50 ng/g, which could have resulted in different prevalence rates if the typical LOD of 100 ng/g was used.

Meconium analysis and prevalence of PAU

Differences across biomarkers utilized and their respective cutoff points, inconsistencies in reporting outcomes, and diversity of protocols surrounding meconium collection and storage procedures precluded a statistical synthesis of the included studies. A narrative synthesis of the data is therefore presented. Data on the prevalence of prenatal alcohol exposure as obtained using meconium biomarkers are illustrated in Table 4.

With respect to biomarkers utilized, FAEEs were used to assess prevalence in all but four studies; Bakdash et al. (2010), La

Maida et al. (2023), and Lamy et al. (2017) used EtG; and Sanvisens et al. (2016) used both EtG and EtS. However, the way prevalence rates were calculated differed between studies. A total of seven studies employed the internationally accepted cumulative cutoff point for FAEE analysis of 2 nmol/g (Bryanton et al., 2014; Delano et al., 2019; English et al., 2016; Gareri et al., 2008; Hutson et al., 2010; Morini et al., 2010, 2013). Based on a molecular weight of 280 g/mol, 2 nmol/g equates to approximately 560 ng/g. As such, the cutoff point of >600 ng/g as used by Abernethy et al. (2018) and Henderson et al. (2023a) is comparable with the studies reporting rates in terms of nmol/g. Therefore, results of these studies were found to be comparable with the previous seven studies reporting rates in terms of nmolg/g. However, the cutoff used by Bana et al. (2014) at 1000 ng/g was higher than recommended, reflecting the possibility of an underestimation of prevalence. Inversely, the cutoff of 500 ng/g used by Bakdash et al. (2010) may have overestimated prevalence.

Ten studies reported prevalence based on EtG and/or EtS analysis, although these also differed in the cutoff points used. Only three studies (Abernethy et al., 2018; Henderson et al., 2023a; La Maida et al., 2023) used the recommended cutoff of 30 ng/g (Himes et al., 2015), while the other five used alternative cutoffs ranging from >5 ng/g (Bakhireva et al., 2019) to >274 ng/g (Sanvisens et al., 2016). Additionally, while most studies reported prevalence as per individual biomarker and cutoff point, two studies did not and reported prevalence as indicated by either a positive result of ≥2 biomarkers (Bakdash et al., 2010; Bakhireva et al., 2019), or a summation of biomarkers (Bana et al., 2014; Sanvisens et al., 2016). Overall, the prevalence of PAU as indicated by FAEE biomarkers in meconium ranged from 2.4% (Delano et al., 2019) to 44% (Hutson et al., 2010). Rates based on EtG results ranged from 0% (Morini et al., 2013) to 16.3% (Bakdash et al., 2010), and EtS prevalence rates were between 7.8% (Bakhireva et al., 2019) and 16.7% (Sanvisens et al., 2016).

Self-reported prenatal alcohol use

All studies with the exception of Bryanton et al. (2014), Morini et al. (2010) and La Maida et al. (2023) collected information on self-reported PAU. Prevalence rates based on self-report data ranged from 0% in Erlangen, Germany (Bakdash et al., 2010), to 46.4% in Glasgow, Scotland (Henderson et al., 2023a). Five studies conducted analysis on comparability/level of agreement between self-reported PAU and meconium biomarker data, with all authors finding no significant agreement between self-reports and detection of positive biomarkers in meconium (Derauf et al., 2003; English et al., 2016; Henderson et al., 2023a; Hutson et al., 2010; Lamy et al., 2017). A further two studies reported no relation between self-report and meconium data but did not present any statistical results to support such conclusions (Delano et al., 2019; Pichini et al., 2012).

PAU data collection methods varied across the studies and are summarized in Table 5. In short, the majority collected self-report data once, after delivery, and asked mothers to report on their PAU intensity and/or frequency (e.g., by asking alcohol units consumed per week), either across the whole pregnancy (Abernethy et al., 2018; Bana et al., 2014) or for each trimester (Bakdash et al., 2010; English et al., 2016; Henderson et al., 2023a; Lamy et al., 2017; Pichini et al., 2012). A further three studies did not collect intensity and/or frequency data, instead asking mothers only to report if they had consumed alcohol at any point during pregnancy (Gareri et al., 2008; Hutson et al., 2010; Sanvisens et al., 2016). Four studies collected PAU self-report data while the participants were pregnant at time of study involvement, with one collecting data during pre- and early pregnancy (Bakhireva et al., 2019), one collecting data during every trimester of pregnancy (Delano et al., 2019), one using medical records to determine alcohol use across the entire pregnancy (Morini et al., 2013), and one using medical records to determine alcohol use during the third trimester (Derauf et al., 2003).

Taken together, a total of seven studies collected self-report data either across each trimester or from the second trimester onward; thus, it can be deduced that such data captured PAU during the same period that meconium began and continued to formulate (Bakdash et al., 2010; Delano et al., 2019; Derauf et al., 2003; English et al., 2016; Henderson et al., 2023a; Lamy et al., 2017; Pichini et al., 2012). The remaining studies either captured PAU at a point where meconium formation had not occurred yet (Bakhireva et al., 2019), or it was not possible to delineate alcohol use per trimester based on the authors' data collection methodologies (Abernethy et al., 2018; Bana et al., 2014; Gareri et al., 2008; Hutson et al., 2010; Morini et al., 2013; Sanvisens et al., 2016).

DISCUSSION

This review investigated the prevalence of PAU as determined by the use of meconium biomarkers of alcohol consumption. From the seventeen studies identified in the searches, reported meconium-based prevalence rates demonstrated a large heterogeneity, ranging from 0.74% (La Maida et al., 2023) to 44% (Hutson et al., 2010).

The observed heterogeneity in PAU prevalence rates likely reflects differences in both cultural attitudes toward alcohol use and societal knowledge of PAU's adverse consequences. Indeed, lower prevalence estimates tended to come from countries, such as Canada (e.g., 2.50%, Gareri et al., 2008) and the USA (e.g., 7.8%, Bakhireva et al., 2019), which have implemented longer-standing public health interventions and PAU awareness-raising campaigns (e.g., Casiro et al., 1994), whereas higher estimates tended to come from countries, such as the UK (e.g., 39.2%, Henderson et al., 2023a), that have implemented more recent public awareness campaigns of alcohol-exposed pregnancies (e.g., Reynolds et al., 2021). Such findings are in accordance with previous pooled PAU prevalence estimates, whereby the UK was found to have the fourth highest rate of alcohol-exposed pregnancies globally (41.3%), in contrast to Canada and the USA (10%–15%) (Popova et al., 2017).

TABLE 2 Overview of participant characteristics.

Author	Population	Setting	Sample size	Maternal characteristics	
				Age in years; *M* (SD)	SES/Income/Employment status
Derauf et al. (2003)	Consecutive newborns	Large urban regional perinatal center in Hawaii	546	–	–
Gareri et al. (2008)	Newborns	Five regional birthing hospitals in Ontario	1076	–	–
Bakdash et al. (2010)	Random sample of newborns	Teaching hospital in Nuremberg, Germany	602	–	–
Hutson et al. (2010)	Newborns	Two public hospitals in Uruguay	900	25.35	Low SES, 84% unemployed
Morini et al. (2010)	Mother–child dyads	Neonatology wards in Barcelona, Spain and Reggio Emilia, Italy	99	–	–
Pichini et al. (2012)	All term newborns	Neonatology wards of 7 public hospitals in Italy	607	32.1 (5.4)	–
Morini et al. (2013)	Mother–child dyads	Neonatology wards in Rome, Florence, and Belluno in Italy, and Barcelona in Spain	151	32 ± 6.0	5.8% in managerial role, 17.9% skilled, 30% semiskilled, 31% unskilled
Bana et al. (2014)	Random sample of newborns	Maternity ward of hospital in Spain	110	32.3 (3.9)	72% working, 16% unemployed, 12% housewife
Bryanton et al. (2014)	Consecutive newborns	3 General hospitals in Nova Scotia	1307	–	–
English et al. (2016)	Mother–child dyads	Maternity ward in Uganda	505	24.9 (5.8)	41% rural (village), 47% urban (city), 12% semiurban (trading center)
Sanvisens et al. (2016)	A series of parturient women	Obstetric Unit at Hospital in Spain	51	Mdn = 30 [IQR = 26–34]	–
Lamy et al. (2017)	All women that delivered a child	Maternity hospitals in France	724	Mdn = 29.6 [IQR = 18.7–44.2]	75.4% employed
Abernethy et al. (2018)	Random sample of singleton newborns	Maternity hospital in Scotland	325	29.9 (5.0)	Low SES; DepCat score 6/7
Bakhireva et al. (2019)	Cohort newborns	5 hospitals in Arizona & New Mexico	570	27.4 (6.0)	71.3% < $19,999 per annum, 10% $20,000–39,999, 3.3% > $40,000
Delano et al. (2019)	Volunteering women attending prenatal clinics during first trimester of pregnancy	Prenatal clinics across 10 cities in Canada	2001	32.2 (5.1)	3.9% < $20k, 18.6% $20–60k, 14.9% $60 – 80k, 19.6% $80-100k, 38.2% > $100k
Henderson (2023a)	Singleton mother/infant dyads	Inner-city maternity unit in Glasgow	840	29.8 (5.7)	Scottish Index of Multiple Deprivation Mdn = 3
La Maida et al. (2023)	All term newborns	53 neonatology wards and 47 maternity wards in Italy	1489	34.0 (±5.2)	36.2% were administrative employees, 10.4% were senior managers, 16.2% were unemployed, 10.3% were homemakers

Note: Median and interquartile ranges (Mdn & IQR) recorded in some cases.

Moreover, when reported, participant demographics varied widely across the samples recruited, with the lowest PAU prevalence rates coming from mothers, where high rates of marriage (95%) and high SES (e.g., gross annual income >$80,000) (Delano et al., 2019) were observed. Conversely, the highest prevalence of PAU (44%) was observed in a cross-sectional study conducted in Uruguay, in

				Infant characteristics	
Level of education	Marital status	Tobacco use	Parity/Gravidity	Average gestational age in weeks (SD)	Average birth weight (kg; SD)
–	–	13.3% during pregnancy	–	–	–
–	–	–	–	–	–
–	–	–	–	–	–
95% < secondary-level education, 11% < primary level education, 0.9% university	18% married	42%	–	–	
–	–	–	–	–	–
5.7% manager, 7.6% partly skilled, 26.9% skilled, 30.9% unskilled	–	–	9.9% primigravida 64.2% multigravida	–	3.25 (0.51)
11.1% primary school, 12.5% median school, 42.2% high school, 16.9% degree	–	–	11.2% primigravida, 37.7% multigravida	–	3.18 (0.55)
27% primary education, 55% secondary education, 17% university education	–	–	–	–	–
–	–	–	–	–	–
55% primary/no education, 30% secondary education, 15% postsecondary education	94% married/cohabiting, 6% single	0.2% current smoker	Mean of 2 previous pregnancies (SD = 1.3)	–	–
–	–	12%	43.1% nulliparous 45.1% primiparous	Mdn = 40 [IQR 38.9–41]	Mdn = 3.24 (IQR = 3.05–3.67)
54.5% university degree	7 (1%) living alone	17.1% during third trimester	–	39.5 (1.5)	3.35 (0.50)
–	–	19% smoker	43% primiparous	39.7 (1.3)	3.46 (0.5)
22.4% high school grad, 32.9% high school grad/GED, 40.8% college/vocation or higher	83.5% married/cohabiting, 7.6% separated/divorced, 8.9% single	1.8% regular use, ceremonial purposes only 35.9%	29.7% nulliparous, 25.6% primigravida	38.7 (1.8)	3.36 (0.5)
–	95.3% married/common law, 0.4% divorced/separated, 4.2% single	5.9% current smoker, 6.1% quit during pregnancy, 61.7% never smoked, 26.3% former smoker	44% nulliparous, 40.4% primigravida	39.2 (1.9)	3.40 (0.6)
–	–	17.8%	56.3% primiparous	38.9 (1.7)	3.37 (0.53)
39.2% had secondary education, 43.2% had tertiary education	–	–	–	39.3 (1.4)	3.31 (0.93)

which 18% of participants were married and 95% had completed less than secondary-level education (Hutson et al., 2010). Similarly, high PAU prevalence rates of 39.4% and 42% were observed in studies recruiting from an inner-city maternity unit in Glasgow, Scotland (Abernethy et al., 2018; Henderson et al., 2023a). These results align with previous research where higher PAU has been observed among

TABLE 3 Study quality criteria ratings.

Study	Representative sample	Appropriate recruitment	Adequate sample size	Subjects & setting described	Sufficient data analysis	Appropriate methodology	Reliable measurement	Appropriate statistical analysis	Response rate described	Temperature samples stored at (°C)	Time sample collected (h)
Derauf et al. (2003)	UN	✓	✓	✗	NA	✗	✓	UN	✓	−20	>48
Gareri et al. (2008)	UN	✓	✓	✗	NA	✓	✓	✓	✓	−20	UN
Bakdash et al. (2010)	✓	UN	✓	✗	NA	✓	✓	✗	✗	−80	24
Hutson et al. (2010)	✓	✓	✓	✓	NA	✓	✓	✗	✓	−80	UN
Morini et al. (2010)	✓	✓	✓	✗	NA	✓	✓	✓	UN	−20	24
Pichini et al. (2012)	✓	✓	✓	✓	NA	✓	✓	✗	UN	−20	<48
Morini et al. (2013)	✓	✓	✓	✓	NA	✓	✓	✓	UN	−20	24
Bana et al. (2014)	✓	✓	✗	✓	NA	✓	UN	UN	✓	UN	UN
Bryanton et al. (2014)	UN	✓	✓	✗	NA	✓	✓	✓	✓	−20	<48
English et al. (2016)	✓	✓	✓	✓	NA	✓	UN	UN	✓	UN	UN
Sanvisens et al. (2016)	✓	UN	✗	✗	NA	✓	✓	UN	✗	UN	UN
Lamy et al. (2017)	✓	✓	✓	✓	NA	✓	✓	✓	✓	−20	UN
Abernethy et al. (2018)	✓	✓	✓	✓	NA	✓	✓	✗	✓	−20	<48
Bakhireva et al. (2019)	✓	✓	✓	✓	NA	✓	✓	✓	✗	−80	UN
Delano et al. (2019)	✓	✓	✓	✗	NA	✓	✓	✓	✓	−80	UN
Henderson (2023a)	✓	✓	✓	✓	NA	✓	✓	✓	✓	−40	24
La Maida et al. (2023)	✓	✓	✓	✓	NA	✓	✓	✓	✓	−20	UN

Abbreviations: ✓, Yes (item adequately addressed); ✗, no (item not adequately addressed); NA, not applicable; UN, unclear (item not stated).

unmarried women and, in the third trimester specifically, among lower-income groups (e.g., Shmulewitz & Hasin, 2019).

However, such findings should not confirm a negative linear relationship between PAU risk and SES level, as evidence suggests other predictive factors are relevant. While Abernethy et al. (2018) demonstrated a high prevalence of PAU in their predominantly low-SES sample, subgroup analysis revealed that positive meconium results were more common in women living in more affluent areas. Furthermore, past investigations have demonstrated that women of higher SES report more frequent prenatal alcohol use than those of lower SES, while rates of FASD are higher in lower SES cohorts, possibly due to heavier consumption or binge drinking (May & Gossage, 2011; Shmulewitz & Hasin, 2019). Increased rates of inadequate prenatal care and social disadvantage are more prevalent in lower SES groups, limiting possible protective factors, which may also underpin both higher PAU and FASD prevalence (Singal et al., 2019). Regarding marital status, possible explanations for higher rates of PAU in unmarried women include lower levels of social support, which has been found to be a protective factor for reducing alcohol use in women (Leonardson et al., 2007), and higher rates of unplanned pregnancies, which can contribute toward higher PAU risk (McQuire et al., 2020).

A previous review found that prevalence estimates based on meconium biomarkers were on average four times higher than those obtained using self-reports (Lange et al., 2014). Here, 14 studies provided information on self-reported PAU and the level of meconium biomarkers within the same samples; seven of which indicating higher prevalence rates from meconium testing. Within these studies, positive meconium results ranged from 1.2 to 16 times higher than self-reported rates of PAU. With regard to the other seven studies, PAU prevalence rates, based on self-reported data, ranged from 1.2 to 3.7 times higher than meconium biomarker-based prevalence rates.

As described before, meconium begins to form from gestational week 20 and is thus unable to detect early fetal alcohol exposure. As such, self-report data that reflect PAU from the second trimester onward would allow for more accurate comparisons between self-report-based and meconium biomarker-based prevalence estimates to be made. However, only half of the studies reviewed collected self-report data from this time period, with one study capturing solely alcohol use during early pregnancy (Bakhireva et al., 2019) and a further six studies either asking mothers about their alcohol use without considering the frequency/intensity of alcohol intake (e.g., Sanvisens et al., 2016) or not specifying the pregnancy trimester(s), in which instances of alcohol use occurred (e.g., Bana et al., 2014). Consequently, the data collection methodologies used across these studies precluded the opportunity to accurately compare the self-report- and meconium-based prevalence rates across all studies. Based on the studies that collected self-reported data which aligned with meconium formulation however, three studies reported meconium-based prevalence rates higher than self-reported-based prevalence rates (e.g., Bakdash et al., 2010) and two studies reported higher self-reported-based prevalence rates when compared to meconium-based prevalence rates (e.g., Lamy et al., 2017). Therefore, across the reviewed studies, the most sensitive method in detecting alcohol use in pregnant populations was not clearly identified.

Nevertheless, the current review highlights the strengths and limitations of both PAU detection methods. On one hand, PAU may reduce or cease completely upon pregnancy confirmation, as evidenced in one reviewed study, which noted a 32.8% reduction in self-reported alcohol use after week 20 of gestation (Henderson et al., 2023a). Consequently, self-reports may be more reliable at detecting alcohol use early in pregnancy; a time when fetal development is especially sensitive to alcohol's teratogenic effects (O'Leary et al., 2010). On the other, while it is unlikely that mothers will falsely report alcohol use when it has not occurred, it is possible that the frequency and intensity of their alcohol consumption will be underreported, especially if questions about their alcohol use across the entire pregnancy are asked during the postpartum period. In contrast, while at-risk of false negatives (Gifford & Bearer, 2015) and low sensitivity and specificity in detecting low levels of PAU (Henderson et al., 2023a), meconium biomarkers may be more fruitful in identifying alcohol-exposed pregnancies in mothers who continue to use alcohol after pregnancy recognition and/or into the second and third trimesters of pregnancy.

The World Health Organization proposes that parameters for screening programs must be developed on best evidence, cost-efficacy, and feasibility (World Health Organization, 2020). On one hand, self-reports of PAU are more cost-effective, are less invasive, and require less specialized staff training when compared to biospecimen collection. On the other, meconium biomarkers may be more objective in their measurement of PAU during the latter stages of pregnancy and less sensitive to recall biases. However, implementation of routine, "opt-out" meconium screening may be precluded by growing ethical concerns. Specifically, given that meconium testing can reveal sensitive information about the mother's lifestyle choices, a breach of medical confidentiality and privacy rights can occur if maternal consent is not explicitly provided (Arkell & Lee, 2023). Moreover, despite it being classified as a waste product, some have argued that meconium belongs to the mother, not the neonate, and routine testing may therefore disregard maternal bodily autonomy (Arkell & Lee, 2023; Dickens, 2011). In addition, biomarker detection would require significantly higher staffing and training costs when compared to self-reported questionnaires, with past estimates indicating an $50,400 to $93,600 (CAD) annual cost to each healthcare practice with the implementation of routine meconium screening (Zelner, Shor, et al., 2012). Thus, there remains inconclusive evidence of a cost–benefit ratio supportive of routine meconium screening (Marcellus, 2007).

Taken together, the current review suggested that self-report measures, administered across each trimester of pregnancy to limit the recall period, are potentially more effective at detecting lower PAU than meconium biomarkers despite likely underreporting, in accordance with the speculations of Muggli et al. (2015) and McQuire et al. (2016). Despite this, results of the current review also suggest

TABLE 4 Overview of study results across meconium biomarker analysis and self-reported PAU.

Study	Bio-Marker	Cumulative cut-points	Analysis	Specimens analyzed (*n*)
Abernethy	FAEEs, EtG	FAEE >600 ng/g EtG >30 ng/g	LC–MS/MS	235
Derauf et al. (2003)	FAEEs	FAEE ≥50 ng/g	GC/MS	422
Gareri et al. (2008)	FAEEs	FAEE ≥2 nmol/g	GC/MS	682
Bakdash et al. (2010)	FAEEs, EtG	FAEE >500 ng/g EtG > 10 ng/g	GC–MS	602 (FAEES) 596 (EtG)
Hutson et al. (2010)	FAEEs	FAEE ≥2 nmol/g	GC/MS	824
Morini et al. (2010)	FAEEs, EtG, EtS	FAEEs ≥2 nmol/g EtG ≥1.5 nmol/g EtS ≥0.012 nmol/g	LC–MS/MS	98
Pichini et al. (2012)	FAEEs, EtG, EtS	FAEE & EtG ≥2 nmol/g	LC–MS/MS	607
Morini et al. (2013)	FAEEs, EtG	FAEEs & EtG ≥2 nmol/g	LC–MS/MS	151
Bana et al. (2014)	FAEEs, EtG	FAEE >1000 ng/g EtG >50 ng/g	GC/MS & LC–MS/MS	101
Bryanton et al. (2014)	FAEEs	FAEE ≥2 nmol/g	GC/MS	1271
English et al. (2016)	FAEEs	FAEE ≥2 nmol/g	GC/MS	503
Bakhireva et al. (2019)	FAEEs, EtG, EtS	Ethyl laurate[b] (>LOQ: 50 ng/g), ethyl myristate (> LOQ: 250 ng/g), ethyl palmitate (> LOQ: 50 ng/g), ethyl palmitoleate (> LOQ: 15 ng/g), ethyl stearate (> LOQ: 50 ng/g), ethyl oleate (> LOQ: 15 ng/g), ethyl linoleate (> LOQ: 15 ng/g), ethyl linolenate (> LOQ: 25 ng/g), and ethyl arachidonate (> LOQ: 15 ng/g). EtG > LOQ: 5 ng/g, EtS > LOQ: 3 ng/g	LC–MS/MS	333
Delano et al. (2019)	FAEEs	FAEE ≥2 nmol/g	SPME GC–MS	1315
Henderson (2023a)	FAEEs, EtG	FAEE >600 ng/g EtG >30 ng/g	LC–MS/MS	840
La Maida et al. (2023)	EtG	EtG ≥30 ng/mg	GC/MS	1489

Abbreviations: EtG, Ethyl glucuronide; EtS, Ethyl sulfate; FAEE, fatty acid ethyl esters; GC, gas chromatography; LC, light chromatography; LOD, Limit of detection; LOQ, Limit of quantification; MS, mass spectrometry; MS/MS, tandem mass spectrometry; PAU, prenatal alcohol use.

[a] No statistical evidence provided by authors.

[b] Authors deemed prevalence of PAU as % of population that was positive for ≥ biomarkers.

[c] Authors defined "social-drinking" as less than two standard drinks per week.

Prevalence estimates (%)	Prevalence of self-report PAU	Measure of self-report PAU	Agreement level
42% (FAEEs), 15% (EtG)	3% at any point during pregnancy	Informal postpartum questionnaire	–
17.10%	5.30% at any point during pregnancy	Informal questionnaire administered during third trimester	No agreement ($K = -0.02$, 95% CI: −0.04, 0.00)
2.50%	0.50% at any point during pregnancy	Informal postpartum questionnaire	–
7.1% (FAEEs) 16.3% (EtG)	0% reported drinking more than 1 unit of alcohol per day, at any point during pregnancy	Informal postpartum questionnaire	–
44%	37% questionnaire; 14% CAGE questionnaire (at any point during pregnancy)	Informal postpartum questionnaire and CAGE questionnaire	No agreement ($K = 0.06$; 95% CI: −0.02 to 0.14)
FAEEs: 34% in Barcelona, 10.4% in Reggio Emilia EtG: 6.1% in Barcelona, 6.1% in Reggio Emilia EtS: 8.2% in Barcelona sample, 10.2% in Reggio Emilia	–	–	–
7.9%	28.9% at any point during pregnancy	AUDIT questionnaire administered postpartum	No agreement[a]
11.9% (FAEEs), 0% (EtG)	42.1% in mothers with neonatal meconium negative for biomarkers, 22.2% in mothers with neonatal meconium positive for biomarkers	Medical records of alcohol use during pregnancy	–
34.65%; 17% positive for both	4.50% reported alcohol use at any point during pregnancy	Informal postpartum questionnaire	–
3.1% (for samples collected within 24 h) (range 3.1–4.4%)	–	–	–
11.2%	16% any use during pregnancy, 3.2% consistent use, 6.3% heavy consumption during any trimester, 5.3% during second and third trimesters. Of $n = 81$ who reported PAU, 53% scored ≥2 points in TWEAK	Informal postpartum questionnaire & TWEAK	No agreement ($p = 0.118$)
7.8% (EtS), 5.1% (EtG); 5.4% positive for ≥2 biomarkers	12.5% for “risky” alcohol use in the 12 months before enrollment	AUDIT-C questionnaire, administered 12 months before enrollment, to capture pre- and early pregnancy alcohol use	–
2.4%; 1.16% for samples collected within 24 h	32%[c] “social level” drinking during pregnancy in gestational weeks 32 to 35	Informal questionnaire administered during third trimester	No agreement[a]
39.6% (FAEEs), 14.5% (EtG)	46.4% before 20 weeks' gestation, 13.6% after 20 weeks' gestation	Informal questionnaire administered at gestation week 20	No agreement; 9.8% positive predictive value of combined FAEE and EtG for self-reported alcohol use
0.74% (EtG)	–	–	–

TABLE 5 Summary of self-reported PAU data collection methods.

Study	Time when data was collected?	Was PAU self-reported data collected iteratively?	Frequency and/or intensity of PAU investigated?	Self-report data aligned with meconium formation?	Trimester(s) of pregnancy captured in self-reported-based prevalence rates?			Higher estimated prevalence rate from self-report or meconium data?
					First	Second	Third	
Derauf et al. (2003)	During pregnancy[a]	Unclear	Yes; across each trimester	Yes	✗	✗	✓	Meconium-based
Gareri et al. (2008)	Postpartum	No; single measurement	No	Unclear	?	?	?	Meconium-based
Bakdash et al. (2010)	Postpartum	No; single measurement	Yes; in third trimester	Yes	✗	✗	✓	Meconium-based
Hutson et al. (2010)	Postpartum	No; single measurement	No	Unclear	?	?	?	Meconium-based
Pichini et al. (2012)	Postpartum	No; single measurement	Yes; across each trimester	Yes	✓	✓	✓	Self-report-based
Morini et al. (2013)	During pregnancy[a]	Unclear	Unclear	Unclear	?	?	?	Self-report-based
Bana et al. (2014)	Postpartum	No; single measurement	Yes, across whole pregnancy	Unclear	?	?	?	Meconium-based
English et al. (2016)	During pregnancy	No; single measurement	Yes; across each trimester	Yes	✓	✓	✓	Self-report-based
Sanvisens et al. (2016)	Postpartum	No; single measurement	No	Unclear	?	?	?	Self-report-based
Lamy et al. (2017)	Postpartum	No; single measurement	Yes; in third trimester	Yes	✗	✗	✓	Self-report-based
Abernethy et al. (2018)	Postpartum	No; single measurement	Yes; across whole pregnancy	Unclear	?	?	?	Meconium-based
Bakhireva et al. (2019)	Postpartum	No; single measurement	Yes; in pre- and early pregnancy	No	✓	✗	✗	Self-report-based
Delano et al. (2019)	During pregnancy	Yes; measured every trimester	Yes; across each trimester	Yes	✗	✓	✓	Meconium-based
Henderson (2023a)	Postpartum	No; single measurement	Yes; across each trimester	Yes	✓	✓	✓	Self-report-based

Abbreviation: PAU, prenatal alcohol use.

[a] Studies that used medical records to determine self-reported alcohol use during pregnancy.

that meconium may still be a useful follow-up PAU measure after disclosure of alcohol use during early pregnancy, aligned with the views of Popova and Dozet (2023). However, given the dearth of methodologically sound prevalence studies using meconium biomarkers and self-report PAU measures, both the development of clinical recommendations and the validation of biomarker concentration cutoff points are currently limited and further research is required to establish these. Indeed, reaching consensus on the best methods to collect reliable PAU data would have far-reaching benefits, across both clinical and stakeholder levels. A more rigorous method to collect PAU information would ameliorate some of the challenges faced by individuals seeking a FASD diagnosis, which often relies solely on maternal self-report. Consequently, PAU may be underestimated, or not reported at all, limiting the ability to reach diagnostic conclusions. Furthermore, failure to identify infants at-risk of FASD means appropriate screening and interventions cannot be implemented, significantly increasing the risk of secondary effects of the condition.

Lastly, the results of this review also highlight the need to consider the links between social determinants of health and FASD. PAU can be determined by numerous social, economic, and cultural factors, including poverty, genetics, traumatic experiences, and level of social support (Jonsson et al., 2014); all of which need to be considered in future research. Here, higher rates of PAU, as indicated by meconium, were observed in lower SES groups, but more evidence is required to examine the determinants of this relationship and its veracity. These factors, in addition to the inconsistent methodologies employed in research to assess prevalence of FASD, suggest that a high degree of caution is required in interpreting prevalence studies. The literature on the best practices for screening of PAU is limited and further highlights the ethical challenges associated with use of meconium biomarkers for screening PAU. Results indicate the need to consider these ethical implications and, more broadly, the need to approach this field with sensitivity and caution.

This review is not without its limitations. First, as observed by Lamy et al. (2017), biomarker analyses are susceptible to false-negative results, emphasizing previous calls for researchers to exercise caution when using biomarkers to identify PAU (Henderson et al., 2023a; McQuire et al., 2016). Second, biomarker-based PAU prevalence estimates produced in this review were determined via meconium-derived FAEEs, EtG, and EtS concentrations. As these biomarkers can be detected in other tissues (e.g., umbilical cord, urine, and nail samples; Bager et al., 2017), it is possible that using alternative biospecimen(s) may produce differing PAU prevalence estimates. However, to date, comparisons between the biospecimens in their abilities to detect PAU have yet to be conducted. Moreover, PAU was solely determined by FAEEs, EtG, and EtS. More recent evaluations have investigated the feasibility of using phosphatidylethanol (PEth) to detect PAU, obtained via neonatal or maternal blood, to reflect alcohol use in the final month of pregnancy. However, like FAEE, EtG, and EtS, initial findings indicate the unreliability of PEth when compared to self-reports (Henderson et al., 2023b). Third, consensus on the standardized criteria for the identification of PAU using alcohol metabolites, including proposed cutoff levels of concentration, has not been reached. For example, across the studies reviewed, FAEE cutoff points ranged from 500 to 1000 ng/g, and EtG from 5 to 50 ng/g. Consequently, sensitivity and specificity rates of these cutoffs vary considerably, between 43.1% to 100% and 11.6% to 98.4%, respectively (Chan et al., 2004; Henderson et al., 2023a). As a result, pooling estimates of prevalence rates is challenging, even across studies that appear homogenous in terms of recruitment and design. Fourth, our eligibility criteria identified 17 studies for inclusion in this review; a small number given that research investigating the prevalence of PAU via meconium biomarkers began in the 1990s (Bearer & Singer, 1996; Mac et al., 1994; Niemelä et al., 1991). Nonetheless, piloting of the search strategy and independent screening and assessment of quality by two reviewers permits confidence that the conclusions drawn from this systematic review are based on the synthesis of all available evidence. Fifth, our choice to review the prevalence of PAU only in general populations may have consequently limited the relevance of the findings to high-risk neonatal populations. Similarly, random sampling was utilized in only a small number of reviewed studies (i.e., Abernethy et al., 2018; Bakdash et al., 2010; Bana et al., 2014), with the majority of studies using opportunistic-sampling methods within nonrandomly selected hospitals. The generalizability of the review's findings may therefore be limited, even to the general population; this is especially true in regions that may observe cohort effects in hospital populations due to self-funded healthcare (e.g., the USA). Moreover, a proportion of the reviewed studies ($n=7$) did not collect the demographic information necessary to evaluate the tested populations' representativeness (e.g., maternal SES, education level, and income), potentially further restricting the generalizability of the review's findings. The estimated PAU prevalence rates generated within the current review thus require validation within randomly selected mother–child dyads recruited from randomly selected hospitals or clinics in catchment areas with population characteristic of the national census. Similarly, future investigations within this field are recommended to collect sufficient demographic data, facilitating confirmation of sample representativeness. Lastly, it is possible that the social desirability biases, observed using self-reports of PAU, may also be seen in biomarker-based methodologies. For example, those with elevated rates of prenatal alcohol use may have chosen not to participate in the reviewed studies and/or refused consent; potentially leading to conservative prevalence rates and reduced generalizability of the results. Despite this, findings may be utilized in their locality and may be helpful in determining the risks of PAU within certain populations and regions so that universal screening strategies can be implemented.

CONCLUSION

Prevalence of PAU varied widely, ranging from 0.74% to 44% using data from meconium biomarkers, and 0% to 46.4% using self-reported data. Significant variation in study methodologies precluded the utility of establishing a pooled prevalence of PAU. Nonetheless, the review highlighted the diversity of prevalence rates across maternal populations in different countries and provides support for the need for public health initiatives to direct attention toward prenatal alcohol use. While capturing PAU prevalence rates remain a significant challenge, gaining accurate estimates is critical for the assessment of potential risk, obtaining early FASD diagnosis, and access to adequate postdiagnostic services. Meconium biomarkers of PAU potentially hold promise as an objective and valuable method that can be used in-tandem with self-reports of alcohol use. However, further research is required on its validity and acceptability to population-based samples to best inform screening strategies for use in routine clinical practice.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interests to declare.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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