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# Systematic Review: Polysubstance Prevalence Estimates Reported during Pregnancy, US, 2009–2020

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## Abstract

**Introduction—**The objective of this systematic review is to describe polysubstance studies and their prevalence estimates among pregnant people in the US.

**Methods—**This review was not subject to protocol preparation or registration with the International Prospective Register of Systematic Reviews (PROSPERO) because outcome data were not reported. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist was followed. Four scientific literature databases were used to identify articles published from January 1, 2009 to June 3, 2020 reporting prenatal exposure to two or more substances in the US. A standardized process of title and abstract screening followed by a two-phase full-text review was used to assess study eligibility.

**Results—**A total of 119 studies were included: 7 case–control studies, 7 clinical trials, 76 cohort studies, and 29 cross-sectional studies. Studies varied with respect to study design, time period, region, sampling and participant selection, substances assessed, and method of exposure ascertainment. Commonly reported polysubstance prevalence estimates among studies of pregnant people included combinations with alcohol, marijuana, and/or tobacco/nicotine. The range of prevalence estimates was wide (alcohol 1–99%; marijuana 3–95%; tobacco/nicotine 2–95%).

**Discussion—**Polysubstance use during pregnancy is common, especially with alcohol, marijuana, and/or tobacco/nicotine. Future research to assess polysubstance use during pregnancy

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**Author Contributions** ELT, LJE, YP, and CHD led the evidence acquisition. ELT led the synthesis of evidence, data analysis, and writing of the manuscript. LJE, CHD, and SYK provided conceptualization oversight. LJE, YP, CHD, and SYK provided guidance, subject matter input, and manuscript editing.

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**Consent to Participate** Not applicable.

**Consent for Publication** Not applicable.

could help better describe patterns and ultimately help mitigate its effects on maternal and infant health outcomes.

**Keywords**

Pregnancy; Polysubstance; Prevalence; Systematic review

## Introduction

Substance use during pregnancy continues to be a major public health challenge. The National Survey on Drug Use and Health (NSDUH) indicated that in 2019 and 2020 between 18 and 21% of pregnant females reported using alcohol tobacco products, and/or illicit drugs in the past month (Substance Abuse and Mental Health Services Administration, 2020a). Polysubstance use (intentional or unintentional exposure to more than one substance) (Centers for Disease Control & Prevention, 2021) is a growing public health concern. According to the Survey of Key Informants' Patients (SKIP) program, which includes individuals in treatment at a participating opioid use disorder (OUD) treatment center, more than 90% of participants who used opioids reported using at least one other non-opioid drug in the past month (Cicero et al., 2020).

Polysubstance use during pregnancy may complicate clinical assessments during pregnancy or delivery hospitalization. For example, neonatal abstinence syndrome (NAS), or the occurrence of drug withdrawal symptoms in newborns, is a treatable condition that can occur in the first few weeks of life, but more evidence is needed regarding how to tailor management based on which substance exposures occurred during pregnancy (Choo et al., 2004; Jones et al., 2013; Morris et al., 2020; Patrick et al., 2020). Moreover, the risk of overdose in the pregnant individual can increase when substances with central nervous system depressant effects (e.g., alcohol, barbiturates, benzodiazepines, opioids) are used in combination with one another (U.S. Food and Drug Administration, 2017).

For pregnant individuals, national prevalence estimates of polysubstance use in any combination are usually limited to sub-groups from surveys (e.g., NSDUH), administrative data [e.g., the Treatment Episode Data Set (TEDS)], or hospital discharge data [e.g., the National Inpatient Sample (NIS)]. There are several limitations to these approaches as definitions are limited to self-report or what is available in medical records, which often are not comprehensive (England et al., 2020; Jarlenski & Krans, 2021; Jarlenski et al., 2020; Washio et al., 2018). Additionally, survey data such as those from NSDUH need to be weighted appropriately to generate national prevalence estimates (Substance Abuse and Mental Health Services Administration, 2020b). A systematic review describing the estimated prevalence of polysubstance use during pregnancy across multiple types of study designs could inform future prevention research and recommendations for management and treatment. The objective of this systematic review is to describe polysubstance prevalence during pregnancy from studies published in the US from 2009 to 2020.

# Methods

## Protocol and Registration

This systematic review on prevalence estimates of polysubstance use among pregnant people in the US was not based upon a clinical study and was not subject to protocol preparation or registration with the International Prospective Register of Systematic Reviews (PROSPERO) because outcome data were not reported. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Checklist was followed to guide reporting methods and results (Online Appendix Tables A1 and A2).

## Information Sources and Searches

The authors and a librarian from the Centers for Disease Control and Prevention (CDC) developed the search strategy (Table 4). Using a comprehensive approach, the librarian searched for articles published in four scientific databases (i.e., CINAHL, Embase, Medline, and PsycINFO) from the date of inception of each database to June 3, 2020. Search terms, based on substances included in the 2019 NSDUH (Substance Abuse and Mental Health Services Administration, 2020a), included "*pregnancy*" and variations on and combinations of the following terms: *polysubstance, substance use, alcohol, amphetamine, cocaine, hallucinogen, inhalant, cannabis, nicotine, opioid*, and *stimulant*. Additional articles published after 2009 included one article identified through relevant citations, four articles through PubMed email alerts related to opioid, tobacco, other substance use, and pregnancy, and thirteen articles from the full text of articles of the original database results. Database results were imported, deduplicated, and filtered by articles published on or after 2009 in an EndNote Library to capture literature from the most recent past decade. A flowchart of the study selection process is shown in Fig. 1.

## Eligibility Criteria, Data Collection, and Study Selection

Two independent reviewers screened 3377 titles and abstracts for eligibility utilizing a standardized process in Microsoft Excel and Covidence (Covidence systematic review software, 2020). Full-text articles in the English language were eligible for inclusion during title and abstract screening if they reported the use of at least one substance during pregnancy in the US as studies that focused on one substance could have referred to other substance exposures during pregnancy within the full text. During title and abstract screening, articles were excluded for the following reasons: animal-related; basic science/in vitro-related; data only available as an abstract or poster; duplicate of an article already included in search results; not original data (e.g., review article, guidelines, recommendations); non-English language; study location outside of the US; non-pregnant study population; or no mention of at least one substance. Discrepancies between reviewers were resolved among the reviewers or by a third reviewer. Title and abstract screening resulted in 961 articles for full-text review.

A two-phase full-text review was conducted to further assess study eligibility in a standardized process in Microsoft Excel. For phase 1, the full text of articles that passed title and abstract screening were retrieved and independently reviewed for eligibility. For full-text review, polysubstance use was defined as the use of two or more substances from different

drug classes at any time during the index pregnancy. Phase 1 exclusions were based on a more detailed list of criteria and were prioritized in the following order: non-pregnant study population; the article did not report two or more substances from different drug classes or did not clearly define at least one substance for a given polysubstance combination; the study was not written in English; the study location was outside of the US; the data were only available as an abstract, poster, dissertation, or commentary; the article was a review; the study did not include enough data to calculate a prevalence estimate for polysubstance use; the article was a duplicate. Phase 1 full-text screening resulted in 186 articles for phase 2 of full-text review.

Phase 2 of full-text review was conducted by two reviewers using a standard form in Microsoft Excel. Data were abstracted by an individual reviewer and included general study characteristics (i.e., study location, study time period, strengths and limitations), study methods [i.e., study design, sampling and/or survey methods, how pregnancy was determined, substances measured, how exposure was ascertained (e.g., self-report, abstracted from the medical record, maternal or infant biomarkers)], study population (e.g., inclusion and exclusion criteria, race and ethnicity), and polysubstance prevalence estimates. Race and ethnicity categories were based on the Office of Management and Budget minimum categories for data collection standards (Office of the Assistant Secretary for Planning & Evaluation, 2011). Study locations were based on the US Census Bureau regions (U.S. Census Bureau, 2021).

Prevalence estimates were abstracted for any combination of two or more defined substances from different drug classes (e.g., alcohol and tobacco/nicotine) or for at least one defined substance in combination with a group of substances (e.g., alcohol and illicit drugs). The base substance was the primary substance reported defining the study population and served as the denominator for polysubstance prevalence calculations (e.g., people who used alcohol during pregnancy). The secondary substance was the other substance reported and served as the numerator of polysubstance prevalence calculations (e.g., tobacco/nicotine use among people who used alcohol during pregnancy). Although most studies reported polysubstance prevalence estimates from the perspective of a base substance category used during pregnancy, some studies reported overall use patterns without reference to a base substance (referred to as the “no base substance” category). To better describe more specific subpopulations of polysubstance groups, if either methadone or buprenorphine products were specified from the “opioids” base substance category, these prevalence estimates were moved to a separate base substance category for “medications for opioid use disorder (MOUD).” Additionally, prevalence estimates for “amphetamine/methamphetamine” and “cocaine” were separated from the “other” base substance category, and the “barbiturates” and “benzodiazepines” were separated from the “other” secondary substance category.

To finalize the phase 2 full-text review, a secondary reviewer conducted an unblinded review of abstracted data on study characteristics to ensure accuracy and completeness, and a blinded review of abstracted polysubstance prevalence estimates. Discrepancies were resolved between the two reviewers. Articles were excluded during phase 2 for the following reasons: pre-pregnancy or postpartum periods were included in prevalence estimates, or it was not possible to confirm estimates were solely based on pregnancy period; exposure

was reported by a caregiver other than the birthing parent; the study design was a case series or data were from focus groups; article only reported the quantity of substance consumed (e.g., number of cigarettes smoked; days of drinking) but did not report the number of people who used each substance. Articles using the same data source in the same study years were included if they included a unique study population and/or unique polysubstance combination and prevalence estimates. Among cohort studies with overlapping study populations and study years, the studies that reported the least number of unique polysubstance combinations were excluded. Excluded articles were categorized based on the prioritized list mentioned previously, but articles could fall under more than one exclusion criteria category (Fig. 1).

## Results

All decisions to exclude any article during the screening process were made by group consensus among coauthors. Descriptive analysis of abstracted data from 119 eligible articles (Table 1) was conducted using SAS software (SAS Institute, version 9.4).

### Study Characteristics

Tables 1 and 2 describe study characteristics of 119 included articles: 7 case–control studies, 7 clinical trials, 76 cohort studies, and 29 cross-sectional studies.

Articles published from 2017 to 2020 contributed to 49% of the total articles, though almost half (48%) of these included study time periods that started between 2000 and 2009. Among articles that provided any prevalence estimates by race and ethnicity (n = 100), American Indian/Alaska Native (AI/AN) and Hispanic were the two categories reported by the lowest number of articles. Study locations were most commonly reported in the following regions: South (28%), Northeast (22%), and West (15%). About 11% of total articles included states across two or more regions, and about 17% of total articles represented coverage across 45 or more states. Most articles for the base substances of “alcohol” (20%) and “opioids” (38%) were from studies that represented 45 or more states of the US, while most other base substance categories were based in the South (Table 5). About 27% of total articles used a population-based sampling method. Based on a review of the articles’ titles, about 39% of total articles had a research objective related to the use of multiple substances. Therefore, 61% of articles likely would not have been identified if the search strategy were limited to include only articles with research objectives specific to the use of multiple substances. Moreover, these studies contributed to 19 of 27 studies with more recent study time periods starting in 2010–2017 (data not shown). Of note, about 18% of all articles involved substance use treatment settings (data not shown).

### Polysubstance Prevalence Estimates

Table 3 presents a summary of the number of prevalence estimates reported for each polysubstance combination, with base substance categories in columns and secondary substances in rows.

Figure 2 shows bubble plots of prevalence estimates for each base substance category with secondary substances represented in the X axis.

"Alcohol" and "tobacco/nicotine" were the most commonly reported secondary substances (Table 3). In the "no base substance" category, "alcohol + cannabis" and "cannabis + tobacco" had the greatest number of contributing prevalence estimates (Table 3). Moreover, regardless of the base or secondary substance, prevalence estimates for polysubstance combinations with "alcohol" (range 1–99% for population-based studies; 1–84% for nonpopulation-based studies), "cannabis" (range 3–60% for population-based studies; 7–95% for nonpopulation-based studies), and "tobacco/nicotine" (range 2–82% for population-based studies; 1–95% for nonpopulation-based studies) had the highest prevalence estimates but with wide ranges (Fig. 2a, b, and d). Additionally, one population-based estimate was reported for the three-drug combination with "alcohol + tobacco" in the "cannabis" base substance category (48%) (Fig. 2b). Prevalence estimates for polysubstance combinations with "alcohol," "cannabis," and "tobacco/nicotine" as secondary substances were often population-based, with exception of the base substance categories of "amphetamine/methamphetamine" and "MOUD," which did not include any population-based estimates (Fig. 2).

Prevalence estimates for a given combination of substances can vary depending on the base substance for a particular study (Fig. 2). For example, though "alcohol," "cannabis," and "tobacco/nicotine" had the three highest prevalence estimates for the base substance of non-MOUD "opioids," non-MOUD "opioids" as a secondary substance was not among the highest reported estimates across "alcohol," "cannabis," and "tobacco/nicotine" base substance categories. Also, in the "alcohol" base substance category, "opioids" were not among the highest prevalence estimates and had a relatively narrower range of prevalence estimates (range 2–7%) (Fig. 2a). In contrast, "alcohol" had the highest prevalence estimate as a secondary substance for the "opioid" base substance category, but with a much wider range of prevalence estimates (range 1–99%) (Fig. 2c).

Substance use during pregnancy was ascertained using various approaches across studies and by base substance (Table 6). The base substance categories that most often used self-report as a single method to ascertain exposure were "alcohol" (55%), "tobacco/nicotine" (51%)," cannabis" (43%), "cocaine" (35%), and "methamphetamine" (35%), with other categories more often relying on medical records or biochemical validation. The base substance categories that most often used biochemical validation and self-report for two methods of ascertaining exposure were "methamphetamine" (19%), "amphetamine" (15%), "cocaine" (15%), and "cannabis" (13%). The base substance categories that most commonly used three methods for exposure ascertainment (i.e., biochemical validation, medical record, and self-report) were "methamphetamine" (15.4%), "amphetamine" (10%), "cocaine" (9.3%), and "cannabis" (9.3%).

## Discussion

Prevalence estimates for polysubstance combinations that included alcohol, cannabis, or tobacco/nicotine were the highest among studies of pregnant people. Possible explanations for common reporting of alcohol, cannabis, and tobacco use may include the relative ease of attainment of licit substances (i.e., alcohol and tobacco), and the increase in cannabis legalization across the nation (Encyclopaedia Britannica, 2020). The routine practice of

documenting the use of licit substances, such as alcohol (Centers for Disease Control & Prevention, 2014), through substance use screening during prenatal visits in the US might also contribute to the high number of reports in the literature by self-report and/or medical record compared to other substances included in this review.

These findings are consistent with recent results from NSDUH, which estimated that about 38% of pregnant individuals who reported current drinking also reported current use of at least one other substance, primarily tobacco or cannabis (England et al., 2020). Another recently published study of NIS data found that among pregnant women at delivery who were diagnosed with cocaine, amphetamine, alcohol, or opioid use disorders, the most common secondary substances used were tobacco and cannabis (Jarlenski & Krans, 2021). Overall, this review reflects similar trends of previous studies and included data from studies using various methods of exposure ascertainment, such as diagnoses at in medical records and self-report (Table 6).

Polysubstance use has had an increasing role in estimates of overdose mortality (Ciccarone, 2021). From 2000 to 2020, deaths involving methamphetamine combined with opioids were most commonly among the AI/AN racial group, and death rates in 2020 impacted multiple regions across the US with state-level variation (The National Institute for Health Care Management (NIHCM) Foundation, 2022). The current review demonstrated that there are a limited number of articles reporting estimates for racial groups and regions that may be disproportionately impacted by polysubstance use and overdose. Given that overdose is one of the leading causes of pregnancy-associated death in the US (Campbell et al., 2021), there is a need for more data on how polysubstance use affects morbidity and mortality in the pregnant population.

This review could not be used to assess some patterns in polysubstance use. Studies often assessed “any” exposure during pregnancy without detailed information on timing, dose, or frequency, and drug use was often reported by drug class (e.g., “stimulants” rather than amphetamine or methamphetamine). Moreover, race and ethnicity were not uniformly captured across studies. These constraints limited the authors” ability (1) to assess the trajectory of polysubstance use over the course of pregnancy, (2) to differentiate between the use of more than one substance simultaneously vs concurrently (within the same time period but not simultaneously) during pregnancy, (3) to assess polysubstance use more granularly for use of multiple substance within the same drug class, and (4) to analyze prevalence data on polysubstance use during pregnancy by clearly defined categories for race and ethnicity. To better ascertain patterns of polysubstance use and prevalence estimates for specific polysubstance groups, researchers are encouraged in future studies to clearly define the base substance categories and periods of exposure during pregnancy and to delineate polysubstance use by race/ethnicity when possible.

Of note, most studies included in this systematic review were based on non-probability sampling and cannot be generalized to the broader population of pregnant people (Non-Probability Sampling, 2013). Approximately 73% of studies used non-probability sampling, which resulted in a heterogenous group of studies with prevalence estimates among subgroups that differed widely by base substance and inclusion and exclusion criteria.

Methods to ascertain exposure also varied, with most studies relying on a single measure of exposure, which typically results in underestimating prevalence. For example, measuring substance use by self-report would likely underestimate the true prevalence if pregnant people were reluctant to disclose use due to concern about stigma or legal implications; similarly, biochemical validation as a single method could result in underestimations of prevalence (e.g., urine testing may only detect drug use within four days of specimen collection). Reliance on diagnosis codes in medical records to define exposure may result in the over-representation of individuals with more advanced disease. These study limitations hinder the ability to assess the true prevalence for specific combinations of polysubstance use during pregnancy in the US. Only 1–19% of studies used more than one method to establish exposure (Table 6). Combining methods, such as self-report and serial biochemical testing, can result in greater sensitivity and more accurate estimates of overall disease burden.

A meta-analysis was not performed since the purpose of the review was not to provide a single summary estimate for the US, but rather to summarize polysubstance prevalence estimates across various geographic locations and polysubstance subgroups. Additionally, many differences existed between studies (i.e., study design, location, setting, time period, sampling and participant selection, method for determining pregnancy, and exposure), and not all studies reported confidence intervals or standard errors. Future reviews that aim to provide a single summary estimate for the prevalence of polysubstance use during pregnancy in the US are encouraged to carefully review the current literature as models and approaches to meta-analyses of prevalence are continuing to evolve (Munn et al., 2015).

## Strengths and Limitations

This review on the prevalence of polysubstance use during pregnancy included many studies with research objectives specific to both single-substance and polysubstance use, and multiple prevalence estimates could have been derived from the same article or data source. Although the methods of this review were labor intensive, the comprehensive approach led to a more complete ascertainment of relevant articles and polysubstance prevalence estimates. Another strength of this review's methodology relates to the exclusion criteria for studies with overlapping study populations and study years, which prevented overreporting of duplicative results from different articles using the same datasets. Overall, this review strengthens the existing evidence on national prevalence estimates of polysubstance use during pregnancy by describing a heterogenous compilation of studies with varying study catchment areas and time points, methods of exposure ascertainment, and definitions of exposure and timing of exposure during pregnancy. Additionally, as shown in Fig. 2, this review revealed gaps in the literature by demonstrating the variations in prevalence estimates reported due to differences in sampling methods and sample sizes, which can help to identify where more or better data are needed.

This review was subject to at least five limitations. First, this review was only based on substances included in the 2019 NSDUH and therefore did not include other emerging substances (Musial et al., 2022; Substance Abuse and Mental Health Services Administration, 2020a). However, based on recent studies (England et al., 2020; Qato et

al., 2020), substances included in the search criteria likely captured the most common substances used in the past decade. Second, the authors did not include articles published beyond June 2020 due to the low likelihood of the addition of one year of data leading to a major change in conclusions (Bashir et al., 2018). Third, almost a fifth of articles in the current review involved substance use treatment settings, which may reflect higher substance use prevalence estimates than the general pregnant population, though results were not able to be reported by study setting type. Fourth, an interrater reliability (IRR) test was not conducted for this review. However, details including the number of reviewers at each phase and methods to resolve disagreements were fully described. To facilitate reliability and consistency in coding decisions, future systematic reviews should consider conducting IRR testing at appropriate points of the review process (Belur et al., 2021). Fifth, this review was unable to determine the intention of use for prescribed medications. However, describing the prevalence of specific polysubstance combinations used during pregnancy is still essential to inform guidance on the most common polysubstance groups of concern.

## Conclusions

Polysubstance use during pregnancy is common, especially in combinations including alcohol, cannabis, and/or tobacco/nicotine. Current expert opinions and recommendations for the management of polysubstance use during pregnancy include screening for use of multiple substances, provision of patient education and behavioral counseling using person-centered language and current medical terminology, and treatment of each substance use disorder simultaneously, when indicated (Smid & Terplan, 2022). Given the steady or increased rates of overdose mortality involving CNS depressants as well as psychostimulants (e.g., methamphetamine and cocaine) (Bruzelius & Martins, 2022; The National Institute for Health Care Management (NIHCM) Foundation, 2022), it is important to understand the most common substance combinations and patterns in timing of exposure that may occur during pregnancy to inform future work on prevention and treatment. Future research could help researchers and clinicians better describe (1) factors that influence polysubstance use patterns during pregnancy; (2) associations between specific combinations of polysubstance use and adverse maternal, infant, and child outcomes; and (3) what timepoints during pregnancy represent periods of vulnerability for maternal and infant health outcomes and should be prioritized in areas of clinical management and research.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgements

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# Appendix

See Tables 4, 5 and 6.

**Table 4**

Search strategy for prenatal polysubstance use among databases from conception to June 3, 2020

| Database | Strategy | Total number of citations |
|---|---|---|
| All databases | | 8736 |
| MEDLINE (Ovid) 1946- | (Exp substance-related disorders/ep OR (Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR co-abuse OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant)) OR (smoking ADJ2 drinking) OR (tobacco ADJ5 alcohol) OR (marijuana ADJ5 alcohol) OR (tobacco ADJ5 marijuana) OR (cannabis ADJ5 alcohol) OR (tobacco ADJ5 cannabis) OR (cigarette* ADJ5 alcohol) OR (cigarette* ADJ5 marijuana) OR (cigarette* ADJ5 cannabis) OR (alcohol ADJ5 substance*) OR (alcohol ADJ5 drug*) OR (drinking ADJ5 substance*) OR (drinking ADJ5 drug*) OR (opioid* ADJ5 smoking) OR (opioid* ADJ5 drinking) OR (opioid* ADJ5 alcoholyt) OR (opioid* ADJ5 tobacco) OR (opioid* ADJ5 cigarettes) OR (opioid* ADJ5 marijuana) OR (opioid* ADJ5 cannabis)).ti,ab<br>OR<br>(<br>((Polysubstance OR polysubstance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR co-abuse OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant))) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic*<br>OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish)) OR ((drinking OR smoking OR alcohol OR tobacco OR cigarette*) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic* OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish))<br>)<br>AND<br>(pregnancy/AND (risk behavior OR risk taking OR health behavior)) OR Pregnant OR during pregnancy OR in pregnancy<br>Limit English; (202006* OR 202007* OR 202008* OR 202009* OR 202010* OR 202011* OR 202012* OR 2021*).dt | 3149 |
| Embase (Ovid) 1988- | Exp drug dependence/ep OR (Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant OR co-abuse)) OR (smoking ADJ2 drinking) OR (tobacco ADJ5 alcohol) OR (marijuana ADJ5 alcohol) OR (tobacco ADJ5 marijuana) OR (cannabis ADJ5 alcohol) OR (tobacco ADJ5 cannabis) OR (cigarette* ADJ5 alcohol) OR (cigarette* ADJ5 marijuana) OR (cigarette* ADJ5 cannabis) OR (alcohol ADJ5 substance*) OR (alcohol ADJ5 drug*) OR (drinking ADJ5 substance*) OR (drinking ADJ5 drug*) OR (opioid* ADJ5 smoking) OR (opioid* ADJ5 drinking) OR (opioid* ADJ5 alcohol) OR (opioid* ADJ5 tobacco) OR (opioid* ADJ5 cigarettes) OR (opioid* ADJ5 marijuana) OR (opioid* ADJ5 cannabis)).ti,ab<br>OR<br>(<br>((Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR co-abuse OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant))) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR | 2905 |

| Database | Strategy | Total number of citations |
|---|---|---|
| | psychedelic* OR psychotomimetic*<br>OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish)) OR ((drinking OR smoking OR alcohol OR tobacco OR cigarette*) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic* OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish))<br>)<br>AND<br>(pregnancy/AND (risk behavior OR risk taking OR health behavior)) OR Pregnant OR during pregnancy OR in pregnancy<br>Limit English; not pubmed/medline; (202006* OR 202007* OR 202008* OR 202009* OR 202010* OR 202011* OR 202012* OR 2021*).dc | |
| PsycINFO (Ovid) 1987- | Exp drug abuse/OR (Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR polyconsumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant)) OR (smoking ADJ2 drinking) OR (tobacco ADJ5 alcohol) OR (marijuana ADJ5 alcohol) OR (tobacco ADJ5 marijuana) OR (cannabis ADJ5 alcohol) OR (tobacco ADJ5 cannabis) OR (cigarette* ADJ5 alcohol) OR (cigarette* ADJ5 marijuana) OR (cigarette* ADJ5 cannabis) OR (alcohol ADJ5 substance*) OR (alcohol ADJ5 drug*) OR (drinking ADJ5 substance*) OR (drinking ADJ5 drug*) OR (opioid* ADJ5 smoking) OR (opioid* ADJ5 drinking) OR (opioid* ADJ5 alcohol) OR (opioid* ADJ5 tobacco) OR (opioid* ADJ5 cigarettes) OR (opioid* ADJ5 marijuana) OR (opioid* ADJ5 cannabis)).ti,ab<br>OR<br>(<br>((Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple ADJ2 drug*) OR (multiple ADJ2 substance*) OR co-abuse OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) ADJ3 (multiple OR co-use OR concomitant))) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic*<br>OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish)) OR ((drinking OR smoking OR alcohol OR tobacco OR cigarette*) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic* OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish))<br>)<br>AND<br>(pregnancy/AND (risk behavior OR risk taking OR health behavior)) OR Pregnant OR during pregnancy OR in pregnancy<br>Limit English; (202006* OR 202007* OR 202008* OR 202009* OR 202010* OR 202011* OR 202012* OR 2021*).up | 2150 |
| CINAHL (EBSCO) | (MH “substance-related disorders + ”/EP) OR (Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR poly-consumption OR (multiple N2 drug*) OR (multiple N2 substance*) OR ((“substance abuse*” OR “substance use*” OR “drug abuse*” OR “drug use*”)<br>N3 (multiple OR co-use OR concomitant)) OR (smoking N2 drinking) OR (tobacco N5 alcohol)<br>OR (marijuana N5 alcohol) OR (tobacco N5 marijuana) OR (cannabis N5 alcohol) OR (tobacco N5 cannabis) OR (cigarette* N5 alcohol) OR (cigarette* N5 marijuana) OR (cigarette* N5 cannabis)<br>OR (alcohol N5 substance*) OR (alcohol N5 drug*) OR (drinking N5 substance*) OR (drinking N5 drug*) OR (opioid* N5 smoking) OR (opioid* N5 drinking) OR (opioid* N5 alcohol) OR (opioid* N5 tobacco) OR (opioid* N5 cigarettes) OR (opioid* N5 marijuana) OR (opioid* N5 cannabis))<br>OR<br>(<br>((Polysubstance OR poly-substance OR polydrug OR poly-drug OR polyconsumption OR polyconsumption OR (multiple N2 drug*) OR (multiple N2 substance*) OR co-abuse OR ((substance abuse* OR substance use* OR drug abuse* OR drug use*) N3 (multiple OR co-use OR concomitant))) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic*<br>OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish)) OR ((drinking OR smoking OR alcohol OR tobacco OR cigarette*) AND (stimulants OR Ritalin OR Adderall OR crystal meth OR methamphetamine OR amphetamine* OR cocaine OR crack OR hallucinogen* OR psychedelic* OR psychotomimetic* OR LSD OR ketamine OR inhalant* OR sniff* OR hash OR hashish))<br>) | 532 |

| Database | Strategy | Total number of citations |
|---|---|---|
| | AND<br>((MH pregnancy) AND (“risk behavior” OR “risk taking” OR “health behavior”)) OR<br>Pregnant OR “during pregnancy” OR “in pregnancy”<br>Limit English; exclude Medline records | |

*CINAHL* Cumulative Index of Nursing and Allied Health

**Table 5**

Number of prenatal polysubstance use-related articles reporting information on region[a], by base substance category, 2009–2020

| Region | Total | Alcohol (n = 15) | Cannabis (n = 17) | Medications used for opioid use disorder (n = 23) | Opioid (n = 16) | Tobacco/ nicotine (n = 26) | Amphetamine/ methamphetamine (n = 8) | Cocaine (n = 10) | Other (n = 24) | No base substance[b] (n = 20) |
|---|---|---|---|---|---|---|---|---|---|---|
| Coverage across 45 or more states | 20 | 4 (26.7%) | 3 (17.7%) | | 8 (50%) | 4 (15.4%) | | 1 (10%) | 5 (20.1%) | 4 (20%) |
| Includes states across two or more regions[c] | 13 | 3 (20%) | 3 (17.7%) | 1 (4.4%) | | 3 (11.5%) | 3 (37.5%) | 2 (20%) | 2 (8.3%) | 3 (15%) |
| Midwest | 13 | 2 (13.3%) | 2 (11.8%) | 1 (4.4%) | 1 (6.3%) | 3 (11.5%) | | 1 (10%) | 1 (4.2%) | 6 (30%) |
| Northeast | 24 | 2 (13.3%) | 2 (11.8%) | 6 (26.1%) | 2 (12.5%) | 8 (30.8%) | | 4 (40%) | 5 (20.1%) | 2 (10%) |
| South | 30 | 3 (20%) | 5 (29.4%) | 11 (47.8%) | 5 (31.3%) | 4 (15.4%) | 1 (12.5%) | 2 (20%) | 6 (25%) | 3 (15%) |
| West[d] | 5 | | 1 (5.9%) | 3 (13%) | | | 1 (12.5%) | | | |
| Pacific West | 13 | 1 (6.7%) | 1 (5.9%) | 1 (4.4%) | | 3 (11.5%) | 3 (37.5%) | | 5 (20.1%) | 2 (10%) |
| Not reported | 1 | | | | | 1 (3.9%) | | | | |

[a] Study locations were grouped into regions based on the U.S. Census Bureau: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

[b] The “no base substance” category included estimates from studies that reported polysubstance use among pregnant people without respect to a base substance

[c] This category includes the following combinations of regions: Midwest, Northeast, Pacific West, South (n = 1); Midwest, Northeast, Pacific West, South, West (n = 1); Midwest, Northeast, South (n=3); Midwest, Pacific West, South (n = 3); Midwest, South, West (n=1); Northeast, Pacific West (n = 1); Northeast, South, West (n = 1); Midwest, West (n = 2)

[d] West does not include states categorized as Pacific West

## Table 6

Number of prenatal polysubstance use-related articles describing the exposure ascertainment method, by base substance category[a] 2009–2020

| Exposure ascertainment method | Base substance | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Alcohol (n = 80) | | Cannabis (n = 75) | | MOUD (n = 24) | | Opioids (n = 53) | | Tobacco/ nicotine (n = 96) | | Amphetamine (n = 20) | | Methamphetamine[b] (n = 26) | | Cocaine (n = 54) | | Other[c] (n = 57) | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| Single method | | | | | | | | | | | | | | | | | | |
| Biochemical validation[d] | 4 | 5 | 16 | 21.3 | 4 | 16.7 | 14 | 26.4 | 4 | 4.2 | 9 | 45 | 3 | 11.5 | 14 | 25.9 | 15 | 26.3 |
| Birth certificate | 1 | 1.3 | | | | | | | 2 | 2.1 | | | | | | | | |
| Medical record[e] | 11 | 13.8 | 3 | 4 | 7 | 29.2 | 10 | 18.9 | 14 | 14.6 | 1 | 5 | 3 | 11.5 | 4 | 7.4 | 7 | 12.3 |
| Part of study criteria/ protocol | | | | | 6 | 25 | | | | | | | | | | | | |
| Self-report | 44 | 55 | 32 | 42.7 | 1 | 4.2 | 14 | 26.4 | 49 | 51 | 2 | 10 | 9 | 34.6 | 19 | 35.2 | 24 | 42.1 |
| Two methods | | | | | | | | | | | | | | | | | | |
| Biochemical validation + medical record | 2 | 2.5 | 4 | 5.3 | 3 | 12.5 | 4 | 7.6 | 1 | 1 | 3 | 15 | 2 | 7.7 | 4 | 7.4 | 4 | 7 |
| Birth certificate + medical record | | | | | | | | | 2 | 2.1 | | | | | | | | |
| Biochemical validation + part of study criteria/ protocol | | | | | 1 | 4.2 | 1 | 1.9 | | | | | | | | | | |
| Biochemical validation + self-report | 5 | 6.3 | 10 | 13.3 | 2 | 8.3 | 6 | 11.3 | 11 | 11.5 | 3 | 15 | 5 | 19.2 | 8 | 14.8 | 2 | 3.5 |
| Medical record + self-report | 5 | 6.3 | 1 | 1.3 | | | | | 4 | 4.2 | | | | | | | | |
| Self-report + other (physical features of FASD) | 1 | 1.3 | | | | | | | | | | | | | | | | |
| Three methods | | | | | | | | | | | | | | | | | | |
| Biochemical validation + medical record + self-report | 3 | 3.8 | 7 | 9.3 | | | 4 | 7.6 | 4 | 4.2 | 2 | 10 | 4 | 15.4 | 5 | 9.3 | 4 | 7 |
| Not reported | 4 | 5 | 2 | 2.7 | | | | | 5 | 5.2 | | | | | | | 1 | 1.8 |

*FASD* Fetal alcohol spectrum disorders, *MOUD* Medications for opioid use disorder

[a] The base substance was the primary substance reported that defined the study population and served as the denominator for polysubstance prevalence calculations

[b] For the purposes of this table, methamphetamine and amphetamine were assessed separately

[c] The "other" base substance category represents studies assessing polysubstance use with unspecified substances or substances other than the existing base substance categories. This category included the use of any unspecified substance (e.g., "other illicit drug use"; "any drug use"); hallucinogens (unspecified); stimulants (unspecified); tranquilizers or

sedatives (unspecified); gabapentin; phencyclidine; smokeless tobacco or e-cigarettes; and any diagnosis of "other" substance use disorder

[d] Biochemical validation may include any toxicology screening or testing of mother or newborn

[e] Medical record may include the review of the medical record for relevant diagnoses (e.g., substance use disorders, infant or childhood outcomes), prescriptions, or documented substance use

## Data Availability

Not applicable.

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## Significance

**What is already known on this subject?**

Polysubstance use has potential to increase the risk or severity of adverse maternal and infant outcomes compared with single-substance use. Current approaches to estimate prevalence for pregnant individuals are limited to definitions using self-report or what is available in medical records, which often are not comprehensive.

**What this study adds?**

Polysubstance combinations with alcohol, marijuana, and/or tobacco/nicotine were common during pregnancy. Among included articles, there was variation in study design, time period, region, sampling and participant selection, substances assessed, and method of exposure ascertainment. Future research to assess polysubstance use during pregnancy could help better describe patterns and ultimately help mitigate its effects on maternal and infant outcomes.

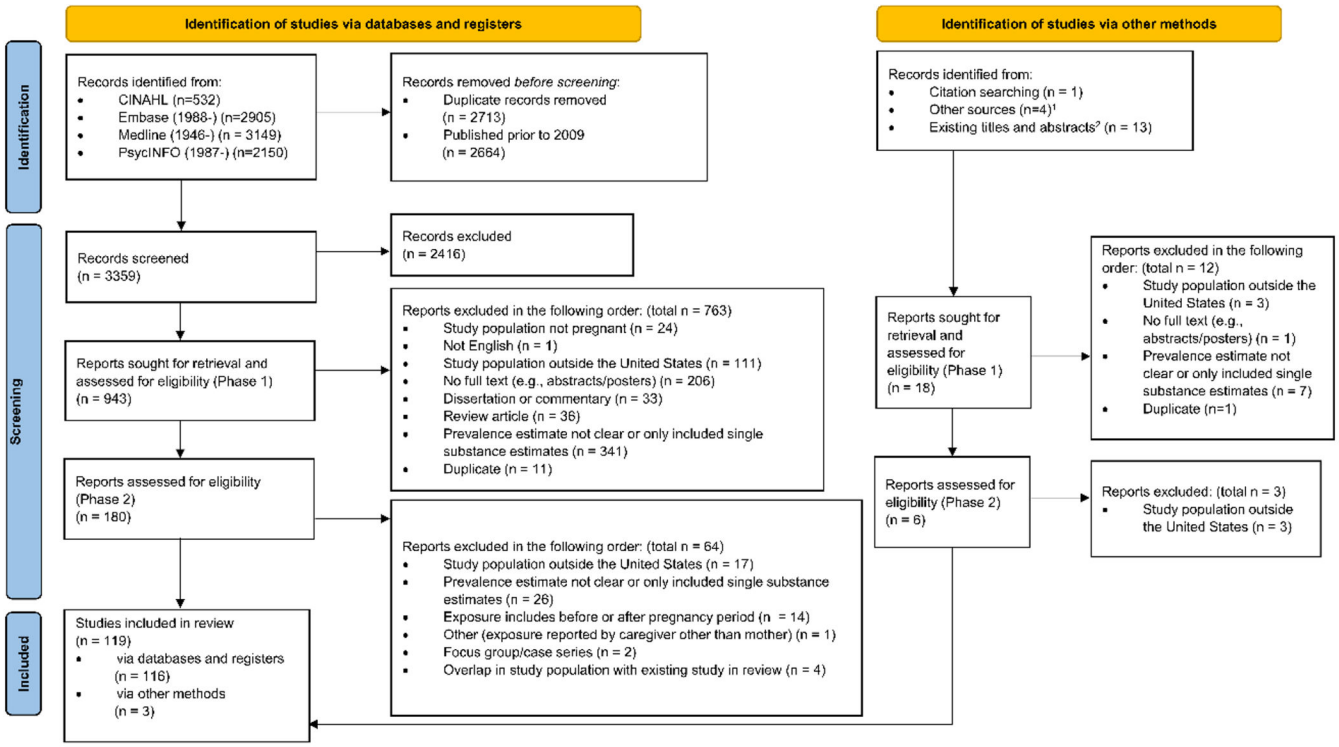


**Fig. 1.**

Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of studies included in a systematic review describing polysubstance prevalence estimates reported during pregnancy, U.S., 2009–2020

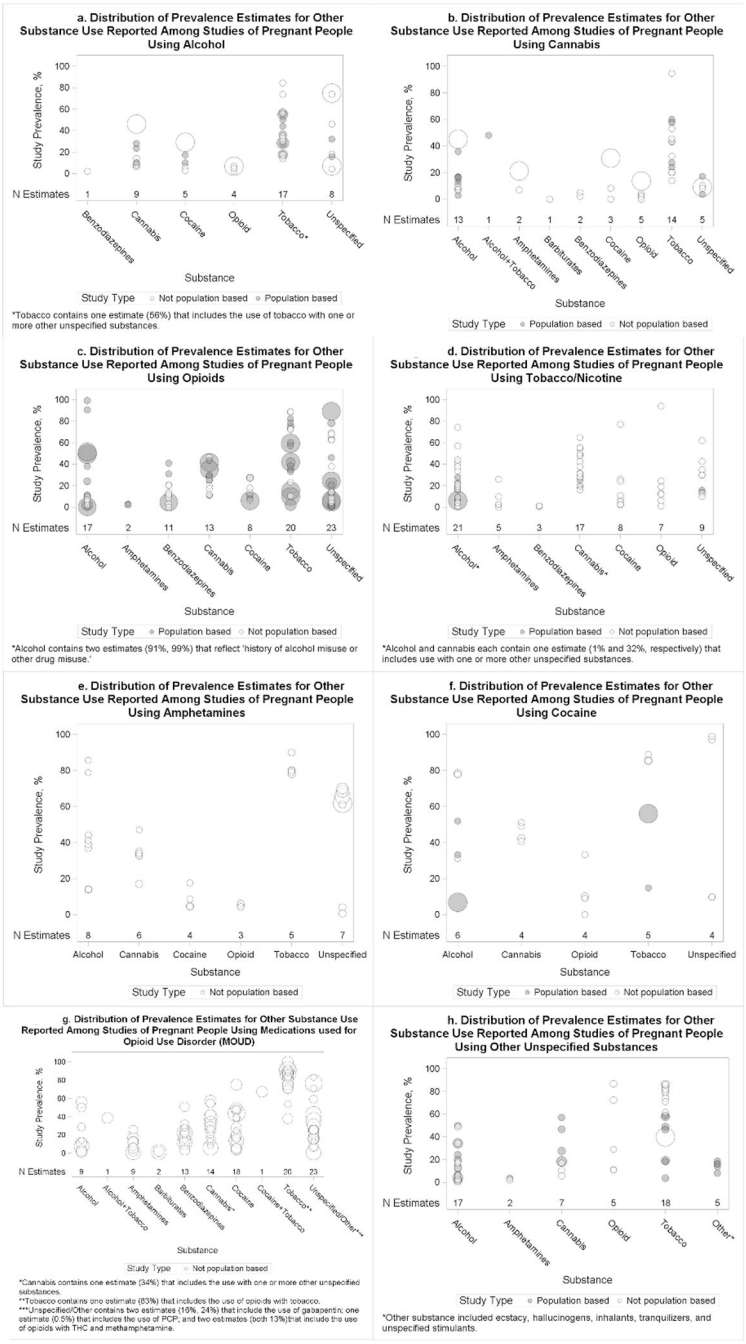


**Fig. 2.**

Bubble plots[1] representing the distribution of polysubstance estimates reported among studies of pregnant people, by base substance[2,3] U.S. 2009–2020 (N = 119)

**Table 1**

Characteristics of studies that reported polysubstance prevalence estimates among pregnant people, US, 2009–2020 (N = 119)

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 1 | Alhusen et al. (2013) | Cohort | 2009 | South | Three urban clinics providing obstetrical care | Total sample size = 166; total subsample of women who used marijuana = 64/166 | Medical record |
| 2 | Aliyu et al. (2009) | Cohort | 1989 | Midwest | Statewide | Total = 655,758; total who reported drinking alcohol = 14,444 | Vital records |
| 3 | Allen et al. (2014) | Cohort | 1993 | Northeast | Hospital-based prenatal clinics in a low socioeconomic status area. Mercer Medical Center in Trenton, NJ and Medical College of Pennsylvania | Total sample = 114; total with prenatal cocaine exposure = 48 | Identified at prenatal care |
| 4 | Almario et al. (2009) | Cohort | 2000 | Northeast | Outpatient methadone treatment center | Total women = 258 | Medical record |
| 5 | Ashford et al. (2019) | Cohort | Not reported | South | Academic and private prenatal clinics | Total sample of pregnant women in first trimester who used tobacco within 30 days = 138; total who only used tobacco (vs tobacco + cannabis) = 100; total who used both tobacco and cannabis = 38 | Medical record |
| 6 | Bada et al. (2012) | Cohort | 1993 | Includes states across ≥ 2 regions | Brown University, University of Miami, University of Tennessee, Memphis, and Wayne State University | Total who used cocaine = 350; total with high prenatal cocaine exposure (PCE) = 115/350; total with some PCE = 235/350 | Identified mothers of living children |
| 7 | Baer et al. (2017) | Cohort | 2005 | Pacific West | N/A | 4588 | Medical record |
| 8 | Baewert et al. (2012) | Clinical Trial | 2005 | Includes states across ≥ 2 regions | Rural (VT, TN) and urban (MD, PA, MI, RI) universities in the US: Johns Hopkins University School of Medicine (lead site), Thomas Jefferson University, Vanderbilt University School of Medicine, Wayne State University, University of Vermont, Alpert School of Medicine at Brown University | Total pregnant who used opioids = 94 | Part of study criteria |
| 9 | Bailey et al. (2012) | Cohort | Not reported | South | 6 rural medical practices providing prenatal care | 265 | Identified at prenatal care |
| 10 | Bakhireva et al. (2019) | Cohort | 2013 | West | Metropolitan clinics | 42 | Medical record |
| 11 | Barlow et al. (2010) | Clinical Trial | 2006 | South | | 322 | Not reported |
| 12 | Beatty et al. (2012) | Cohort | Not reported | Midwest | Urban hospital | 60 | Delivered at hospital site |
| 13 | Bolin et al. (2019) | Cohort | Not reported | South | UAMS Women's Mental Health Program, a tertiary referral center with primary focus on psychiatric disorders | 8 | Part of study criteria |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 14 | Brogly et al. (2018) | Cohort | 2015 | Northeast | Obstetric and addiction recovery clinic at an urban, safety-net hospital | 113 | Medical record |
| 15 | Chabarria et al. (2016) | Cohort | 2011 | South | Tertiary referral hospitals associated with Baylor College of Medicine | Total pregnant women = 12,069; total pregnant women reporting marijuana use = 106 | Delivered at hospital site |
| 16 | Chambers et al. (2019) | Cross-sectional | 2012 | Pacific West | Large urban city in Pacific Southwest | 93 | Identified mothers of children with FASD |
| 17 | Chisolm et al. (2009) | Cross-sectional | 2000 | South | Johns Hopkins Center for Addiction and Pregnancy, a comprehensive program for substance-dependent pregnant women | 122 | Medical record |
| 18 | Chung et al. (2010) | Cohort | 2000 | Northeast | FQHCs and FQHC Look-Alikes | Total women = 1476 | Medical record |
| 19 | Coleman-Cowger et al., (2018a, 2018b) | Cohort | 2017 | South | Two obstetric clinics | Total general pregnant women = 500; total co-use of marijuana and tobacco = 45 | Pregnant at time of study |
| 20 | Coleman-Cowger et al., (2018a, 2018b) | Cross-sectional | 2006 | Coverage across ≥ 45 states | Household survey | Total pregnant women = 8,695 | Self-report |
| 21 | Conner et al. (2015) | Cohort | 2004 | Midwest | Washington University, St. Louis Medical Center, tertiary care facility | Total general pregnant women = 8,138; Total who used marijuana = 680 | Delivered at hospital site |
| 22 | Crume et al. (2018) | Cross-sectional | 2014 | West | N/A | Total general pregnant women = 3,207 | Delivered at hospital site |
| 23 | De Genna et al. (2014) | Cohort | Not reported | Northeast | Magee-Women's Hospital prenatal clinic | 92 | Identified at prenatal care |
| 24 | Desai et al. (2015) | Cohort | 2000 | Coverage across ≥ 45 states | Population-based | Alcohol base substance: pregnant women with a history of alcohol or non-opioid drug misuse or dependence, but no history of opioid misuse or dependence: short-term = 23,580; long-term = 4,973.Opioid base substance: pregnant women with a history of opioid misuse or dependence: short-term = 2,677; long-term = 2,139 | Other (specify): Administrative data |
| 25 | Dukes et al. (2017) | Cohort | 2007 | Midwest | Comprehensive clinical sites | Total pregnancies from people who were reported as American Indian race = 2,021; total pregnancies from people who were reported as White race = 2,672 | Medical record |
| 26 | Eggleston et al. (2009) | Case–Control | 1999 | South | Comprehensive perinatal drug treatment program | 105 | Not reported |
| 27 | Eiden et al. (2020) | Cohort | Not reported | Not reported | Large urban prenatal clinic | Total dyads = 238; total with tobacco exposure = 150/238 | Identified at prenatal care |
| 28 | Forray et al. (2014) | Clinical Trial | 2006 | Northeast | Two inner city hospital-based reproductive health clinics | Total = 176; total who smoked in pregnancy = 122 | Not reported |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 29 | Gaalema et al. (2013) | Clinical Trial | Not reported | Northeast | Obstetric practices in Burlington, Vermont | Total participants = 115 | Not reported |
| 30 | Gallagher et al. (2017) | Cohort | 2006 | Northeast | Records of households receiving PCE (tetrachloroethylene) exposed water | All alcohol exposed. Total prenatally exposed to tetrachloroethylene = 302; total not prenatally exposed to tetrachloroethylene = 201 | Vital records |
| 31 | Garrison-Desany et al. (2020) | Cohort | 1998 | Northeast | Boston Medical Center (urban hospital) | Total mother-newborn pairs = 8,261; total who used stimulant drugs (cocaine, amphetamines) = 131; total who used depressant drugs (heroin, methadone, barbiturates) = 192 | Delivered at hospital site |
| 32 | Gauthier et al. (2010) | Cohort | Not reported | South | Two urban large hospitals | Total women = 321; total who used alcohol = 83/321 | Medical record |
| 33 | Godleski et al. (2018) | Cohort | Not reported | Northeast | Local hospital (appears to be in Buffalo, NY) | Total exposed to tobacco = 178 | Not reported |
| 34 | Goldschmidt et al. (2012) | Cohort | 1982 | Northeast | Urban hospital-based prenatal clinic | Total women = 579; total who smoked = 306/579 | Part of study criteria |
| 35 | Good et al. (2010) | Cohort | 2000 | West | St Joseph's Hospital and Medical Center (697 bed, tertiary care, urban, academic, not-for-profit medical center) | Patients who used methamphetamine = 276 | Medical record |
| 36 | Grant et al. (2009) | Cohort | 1989 | Pacific West | Hospitals | Study 1 = 7178; study 2 = 2230; study 3 = 3118 | Delivered at hospital site |
| 37 | Gray et al., (2010a, 2010b) | Cohort | Not reported | South | Urban, multi-disciplinary care treatment for drug-dependent women | 49 | Not reported |
| 38 | Gray et al., (2010a, 2010b) | Cohort | Not reported | Northeast | Not reported | Total pregnant women = 86; total who used cannabis = 38/86 | Not reported |
| 39 | Guille et al. (2020) | Clinical Trial | 2017 | South | 4 outpatient obstetric practices—Women's Reproductive Behavioral Health Program at Medical University of South Carolina | Total women = 98; total who received in-person treatment = 54/98; total who received telemedicine = 44/98 | Medical record |
| 40 | Hand et al. (2017) | Cross-sectional | 2013 | Coverage across ≥ 45 states | TEDS data from private and public substance use disorder treatment facilities that receive public funding | 8656 | Self-report |
| 41 | Harrison and Sidebottom (2009) | Cohort | 2005 | Midwest | Four urban Federally Qualified Healthcare Centers | Total women = 1492; Total who used alcohol and another drug while pregnant = 40/1,492 | Not reported |
| 42 | Hensley et al. (2018) | Cohort | 2009 | Midwest | 2 large referral and tertiary care centers | 74 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 43 | Holtrop et al. (2010) | Cross-sectional | 2005 | Midwest | Medicaid eligible women in Michigan's enhanced prenatal services program | Total pregnant women = 2203; total who smoked = 566/2203 | Not reported |
| 44 | Huybrechts et al. (2017) | Cohort | 2000 | Coverage across ≥ 45 states | Medicaid records | Total pregnancies with exposure to prescription opioids 45 days before delivery: from article text = 201,275; from article tables = 200,705 | Medical record |
| 45 | Jansson et al. (2017) | Cohort | Not reported | South | Not stated but treatment center is in Baltimore | 49 | Medical record |
| 46 | Jarlenski et al. (2017) | Cross-sectional | 2005 | Coverage across ≥ 45 states | Nationally representative survey | Weighted = 205,979; unweighted = 101 | Self-report |
| 47 | Kiblawi et al. (2014) | Cohort | 2002 | Includes states across ≥ 2 regions | Urban clinical sites | 185 | Delivered at hospital site |
| 48 | Kim et al. (2009) | Cross-sectional | 1996 | Pacific West | State-based | 11,837 (unweighted) | Vital records |
| 49 | Ko et al. (2015) | Cross-sectional | 2007 | Coverage across ≥ 45 states | National | Total pregnant women = 4971; total who used marijuana = 265 (results stratified by past 1 month and past 12 month use) | Self-report |
| 50 | Ko et al. (2018) | Cross-sectional | 2009 | Includes states across ≥ 2 regions | State-based | Total = 9013; total with marijuana use = 463/9013 | Vital records |
| 51 | Kozhimannil et al. (2019) | Cross-sectional | 2007 | Coverage across ≥ 45 states | Rural | Total = 942,798; total with OUD = 4606 | Delivered at hospital site |
| 52 | Kozhimannil et al. (2017) | Cross-sectional | 2005 | Coverage across ≥ 45 states | National | Total pregnant women ages 12–44 = 8721; total weighted = 23,855,041. Total (weighted) with past-month opioid use = 217,106 | Self-report |
| 53 | Kreitinger et al. (2016) | Cohort | | West | Patients at University of New Mexico's prenatal substance use program | 70 | Identified at prenatal care |
| 54 | Kreshak et al. (2016) | Cohort | 2014 | Pacific West | Tertiary care university health system's urban and suburban ambulatory obstetric offices | 295 | Medical record |
| 55 | LaGasse et al. (2011) | Cohort | Not reported | Includes states across ≥ 2 regions | 4 urban hospitals | 183 | Delivered at hospital site |
| 56 | Lappen et al. (2020) | Cohort | 2000 | Midwest | Comprehensive perinatal opioid dependency program (MetroHealth Medical Center) | Total women on MAT = 480; total on methadone = 345; total on buprenorphine = 137 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 57 | Lee et al. (2020) | Cohort | 2016 | Pacific West | Referral clinic serving patient population with public insurance | Total women = 466; total who tested positive for marijuana = 45 | Medical record |
| 58 | Leszko et al. (2020) | Cohort | 2013 | Includes states across ≥ 2 regions | Racially diverse regions | 603 | Identified at prenatal care |
| 59 | Lopez et al. (2011) | Cohort | 2005 | Midwest | Eight maternity clinics; public and private sector prenatal clinics | Total who continued smoking = 197 | Medical record |
| 60 | Lu et al. (2009) | Cohort | Not reported | Pacific West | Unspecified clinical setting | Methamphetamine group = 14 | Identified mothers of living children |
| 61 | MacAfee et al. (2019) | Cross-sectional | 2009 | South | Statewide | Total = 3,042; Total who used illicit substances = 168 | Vital records |
| 62 | Maeda et al. (2014) | Cross-sectional | 2007 | Coverage across ≥ 45 states | Nationally represented | 60,994 | Medical record |
| 63 | Mark et al. (2016) | Cohort | 2009 | South | Single, urban, university-based prenatal care clinic | 116 | Medical record |
| 64 | Mark et al. (2017) | Cross-sectional | 2015 | South | Outpatient Obstetrics and Gynecology Clinic at the University of Maryland Medical Center | Total = 306 | Medical record |
| 65 | Massey et al. (2018) | Cohort | 2003 | Includes states across ≥ 2 regions | GUH: urban hospital-based obstetric clinic in the Northeastern United States; BAM BAM: obstetric clinics, health centers, and community postings in the Northeastern United States; EGDS: Mid-Atlantic, Southwestern, Midwestern, and Pacific Northwestern regions of the U.S | Total smokers in pooled sample = 608; Total = pregnant women in ECDS = 625 | Medical record |
| 66 | May et al., (2020a, 2020b, 2020c) | Case–Control | 2010 | Midwest | 24 public schools, 8 private schools | Total children with ARND = 10; total children with FASD = 31; total control children = 305 | Identified mothers of children with FASD |
| 67 | May et al., (2020a, 2020b, 2020c) | Case–Control | 2007 | Includes states across ≥ 2 regions | City with population of about 60,000 | Total with FASD = 35; total controls = 197 | Identified mothers of children with FASD |
| 68 | May et al., (2020a, 2020b, 2020c) | Case–Control | 2013 | South | 24 elementary schools | Total children with FASD = 47; total control children = 251 | Identified mothers of children with FASD |
| 69 | May et al. (2015) | Case–Control | 2007 | Includes states across ≥ 2 regions | City of 59,000; 17 elementary schools | Total with PFAS/FAS = 26; total who had maternal interview data on exposure = 17 | Identified mothers of living children |
| 70 | Mbah et al. (2012) | Cohort | 1998 | South | Population-based, state-level data | Total births = 1,698,223; total births with cocaine exposure = 5,026/1,698,223 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 71 | Metz et al. (2017) | Cohort | 2006 | Includes states across ≥ 2 regions | Geographically and racially diverse population | Total marijuana use = 48 | Medical record |
| 72 | Metz et al. (2018) | Cross-sectional | 2005 | Coverage across ≥ 45 states | US representative, population-based sample | Total = 818; total with opioids only = 281/818; total with opioid poly-drug use = 241/818; total with other illegal drugs = 296/818 | Self-report |
| 73 | Minnes et al. (2012) | Cohort | 1994 | Midwest | Midwestern urban hospital | Total = 321; total who used cocaine = 158 | Delivered at hospital site |
| 74 | Nellhaus et al. (2019) | Cohort | 2016 | South | MAT programs, Cabell Huntington Hospital, Marshall Health and Valley Health System | Total pregnant women on MAT = 109 (with total of 110 neonates) | Delivered at hospital site |
| 75 | O'Connor et al. (2021) | Cohort | 2013 | Northeast | Rural medical facility | 137 | Medical record |
| 76 | O'Connor et al. (2017) | Cohort | 2007 | Northeast | Rural clinic in family medicine residency program | 191 | Medical record |
| 77 | Obisesan et al. (2020) | Cross-sectional | 2016 | Coverage across ≥ 45 states | N/A (BRFSS) | Total pregnant women = 7,434; total who used E-cigarettes = 2.2% | Self-report |
| 78 | Oga et al. (2018) | Cross-sectional | 2017 | South | Two obstetric practices in urban setting | 494 | Identified at prenatal care |
| 79 | Oh et al. (2017) | Cross-sectional | 2005 | Coverage across ≥ 45 states | N/A (NSDUH) | Total pregnant women = 8240; total adolescents aged 12–17 = 529/8240; total adults aged 18–44 = 7,711/8,240 | Self-report |
| 80 | Oncken et al. (2020) | Clinical Trial | 2012 | Northeast | Unspecified | Total smokers = 129 | Medical record |
| 81 | Patrick et al. (2015) | Cohort | 2009 | South | State-based (Medicare) | Total dyads = 112,029; total prescribed opioids = 31,354/112,029 | Identified mothers of living children |
| 82 | Patterson et al. (2012) | Cohort | 1999 | Northeast | Urban, emergency room at the Hospital of the University of Pennsylvania | Total pregnant women = 1521; total who smoked = 338/1521 | Other (specify): Self-reported and verified using medical record |
| 83 | Qato et al. (2020) | Cross-sectional | 2006 | Coverage across ≥ 45 states | N/A (NSDUH) | 5.1% (4.5, 5.7) of 20,744,268 | Self-report |
| 84 | Ram et al. (2016) | Cohort | 2005 | South | CAP, a comprehensive drug and alcohol treatment program for pregnant women located at the Johns Hopkins Bayview Medical Center | 118 | Part of study criteria |
| 85 | Richardson et al. (2019) | Cohort | 1988 | Northeast | Magee-Women's Hospital prenatal clinic | Total who used cocaine during 1st trimester = 92 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 86 | Roberts and Nuru-Jeter (2012) | Cohort | 2001 | Pacific West | N/A | Total pregnant women = 8,449; total who used alcohol and/or drugs = 508 | Medical record |
| 87 | Rollins et al. (2020) | Cross-sectional | 2015 | Northeast | Single, low-income, urban clinic and local obstetric offices and community centers | Total pregnant women = 1,365; total who used e-cigarettes = 54; total who used conventional cigarettes = 372 | Pregnant at time of study |
| 88 | Roth et al. (2020) | Cohort | 2017 | South | Marshall University | Total women = 176; total neonates = 177 (one mother gave birth to twins) | Medical record |
| 89 | Roussotte et al. (2011) | Cohort | Not reported | Pacific West | Clinical setting | Total participants prenatally exposed to methamphetamine = 19 | Identified mothers of living children |
| 90 | Salas-Wright et al. (2016) | Cross-sectional | 2002 | Coverage across ≥ 45 states | Representative sample of the US civilian | 810 | Self-report |
| 91 | Salzwedel et al. (2015) | Cohort | | South | Local residential and outpatient treatment programs; one OB clinic was noted as low-income | 88 | Identified mothers of living children |
| 92 | Sanlorenzo et al. (2019) | Cohort | 2009 | South | Facilities accepting Medicaid | Total mother-infant dyads = 822; total non-pharmacologically treated for NAS = 224/822; total pharmacologically treated for NAS = 598/822 | Medical record |
| 93 | Schauberger et al. (2014) | Cohort | 2013 | Midwest | Single obstetrical urban-based clinic in a rural area | 200 | Medical record |
| 94 | Serino Ma et al. (2018) | Cohort | 2004 | Northeast | Prenatal clinics in New York City | Total = 146; total people who used cocaine = 35; total people who used marijuana = 38; total people who used methadone = 24 | Identified at prenatal care |
| 95 | Shannon et al. (2010) | Cohort | 2005 | South | Medical center | Rural = 85; urban = 29 | Medical record |
| 96 | Shaw et al. (2014) | Cohort | 1998 | Pacific West | Four urban and five rural counties | Rural = 96; urban = 677 | Part of study criteria |
| 97 | Shen et al. (2020) | Cross-sectional | 2009 | Northeast | Hospitals | Total = 1,463,302; total with OUD = 8324 | Other (specify): Algorithm based on diagnoses, procedures, and DRG codes |
| 98 | Shmulewitz and Hasin (2019) | Cross-sectional | 2002 | Coverage across ≥ 45 states | National | 13,488 | Self-report |
| 99 | Shrestha et al. (2018) | Cohort | 2013 | West | UNM-affiliated clinics in Albuquerque metro area, including general obstetrics and midwifery clinics and a specialized prenatal care clinic for women with SUD, during one of their first prenatal care visits | Total who used medication for opioid use disorder = 26; total who used alcohol = 22; total who used both = 27 | Medical record |
| 100 | Smith et al. (2015) | Cohort | 2005 | Northeast | 137 obstetric practices and hospital-based clinics | Total = 2748; total subsample that used opioids = 165 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 101 | Stewart et al. (2013) | Cohort | 2006 | South | Inpatient hospital | Total women = 95; total with illicit drug use at delivery = 42; total on medication for opioid use disorder (methadone, buprenorphine) = 17 | Medical record |
| 102 | Stitely et al. (2010) | Cross-sectional | 2009 | South | 8 hospitals | Total = 759; total who used drugs = 146/759 | Other (specify): Collected umbilical cord |
| 103 | Stroud et al. (2020) | Cohort | Not reported | Northeast | Sample was low-income from obstetrical offices, health centers, and community postings | Total pregnant women = 111; total who used tobacco = 45; total who used tobacco + marijuana = 24 | Medical record |
| 104 | Tai et al. (2017) | Cohort | 2001 | Northeast | Outpatient substance abuse and mental health treatment center | Total 88; total alcohol use cohort = 57/88 | Medical record |
| 105 | Terplan et al. (2009) | Cross-sectional | 1994 | Coverage across ≥ 45 states | Substance treatment faciltiies that receive federal funding | Year 1994: Total pregnant = 18,034; total who used methamphetamine = 1457. Year 2006: Total pregnant = 22,382; total who used methamphetamine = 5312 | Medical record |
| 106 | Tith et al. (2018) | Cohort | 2012 | Pacific West | University of Washington Medical Center L&D unit | 8 | Medical record |
| 107 | Towers et al. (2019) | Cohort | 2014 | South | Clinic at University of Tennessee Medical Center | 429 | Delivered at hospital site |
| 108 | Towers et al. (2020) | Cohort | 2017 | South | University hospital; obstetrics OUD clinic at University of Tennessee Medical Center | Total who used buprenorphine/methadone = 109; total who used naltrexone = 121 | Part of study criteria |
| 109 | Wachman et al. (2011) | Cohort | 2003 | Northeast | Boston Medical Center—hospital | Total mother-infant dyads = 273; total exposed to methadone = 251/273; total exposed to buprenorphine = 22/273 | Medical record |
| 110 | Washio et al. (2017) | Cross-sectional | 1992 | Coverage across ≥ 45 states | Substance use disorder treatment facilities | 71,960 | Medical record |
| 111 | Washio et al. (2018) | Cross-sectional | 1992 | Coverage across ≥ 45 states | Substance use treatment facilities | Total who used substances = 489,796; total who used cannabis = 198,886/489,796 | Medical record |
| 112 | Winhusen and Lewis (2017) | Clinical Trial | 2007 | Includes states across ≥ 2 regions | Four outpatient substance use disorder treatment facilities for pregnant women | Total smokers = 145 | Medical record |
| 113 | Witt et al. (2015) | Cohort | 2001 | Coverage across ≥ 45 states | Family homes | Total who used cigarettes in the last 3 months of pregnancy: unweighted = 1050; weighted = 413,816 | Identified mothers of living children |
| 114 | Wood et al. (2014) | Cohort | 2008 | Midwest | University of Iowa Hospitals and Clinics | 2,497 | Medical record |

| Article ID | Author(s), year | Study design | First year of study time period | Region | Setting | Total sample size[a] | How pregnancy was determined |
|---|---|---|---|---|---|---|---|
| 115 | Wouldes et al. (2013) | Case–Control | 2002 | Includes states across ≥ 2 regions | 7 hospitals | Total = 320; total who reported using methamphetamines = 127 | Medical record |
| 116 | Wright et al. (2011) | Cohort | Not reported | Pacific West | Not stated | Total = 103; total who smoked = 37; total who used street drugs = 28 | Medical record |
| 117 | Wright et al. (2015) | Cohort | 2007 | Pacific West | Path Clinic—prenatal care and social services for women with addictions | Total methamphetamine use during pregnancy = 144 | Identified at prenatal care |
| 118 | de Wit et al. (2013) | Cross-sectional | 2002 | Coverage across ≥ 45 states | National | Total with alcohol use disorder diagnosis = 12,081 | Medical record |
| 119 | van Gelder et al. (2010) | Case–Control | 1997 | Includes states across ≥ 2 regions | Population-based survey | Total women = 5871; total who used illicit drugs during pregnancy = 210/5,871 | Medical record |

[a]Sample size categories defined by each respective study

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## Table 2

Summary characteristics of studies that reported polysubstance prevalence estimates among pregnant people, US, 2009-2020[a] (N = 119)

| Characteristic | No. of articles | % |
|---|---|---|
| Study design | | |
| Case–control | 7 | 5.9 |
| Clinical trial | 7 | 5.9 |
| Cohort | 76 | 63.9 |
| Cohort, prospective | 43 | 36 |
| Cohort, retrospective | 32 | 26.9 |
| Cohort, prospective and retrospective | 1 | 0.8 |
| Cross-sectional | 29 | 24.4 |
| Administrative dataset | 8 | 6.7 |
| Survey | 13 | 10.9 |
| Year of publication | | |
| 2009–2012 | 33 | 27.7 |
| 2013–2016 | 28 | 23.5 |
| 2017–2020 | 58 | 48.7 |
| First year of study time period | | |
| 1980–1989 | 4 | 3.4 |
| 1990–1999 | 13 | 10.9 |
| 2000–2009 | 57 | 47.9 |
| 2010–2017 | 27 | 22.7 |
| Not reported | 18 | 15.1 |
| Race/ethnicity (n = 100)[b] | | |
| American Indian or Alaska Native | 19 | 19 |
| Black or African American | 81 | 81 |
| Hispanic, LatinX, or Spanish origin | 60 | 60 |
| White | 86 | 86 |
| Other race[c] | 67 | 67 |
| Asian or Pacific Islander | 19 | 28.4 |
| Region[d] | | |
| Coverage across 45 or more states | 20 | 16.8 |
| Includes states across two or more regions[e] | 13 | 10.9 |
| Midwest | 13 | 10.9 |
| Northeast | 24 | 20.2 |
| Pacific West | 13 | 10.9 |
| South | 30 | 25.2 |
| West[f] | 5 | 4.2 |
| Not reported | 1 | 0.8 |
| Sampling method | | |

| Characteristic | No. of articles | % |
|---|---|---|
| Not population-based (Non-probability sampling) | 87 | 73.1 |
| Population-based | 32 | 26.9 |
| Study Objective[g] | | |
| Polysubstance use | 46 | 38.7 |
| Single substance use | 73 | 61.3 |

[a] Search strategy was conducted up to June 3, 2020

[b] Race/ethnicity categories are not mutually exclusive. The following article IDs did not provide any prevalence estimates by race and ethnicity: 46, 59, 71, 82, 84, 88, 89, 96, 98, 100, 108, 109, 112, 115, 120, 124, 139, 141, 142

[c] Data for Asian or Pacific Islander were identified from the data reported in the Other race category. Other race also included categories reported for multiracial, racial minority, Middle Eastern, non-white or Hispanic, non-Hispanic, not African American, and unspecified (which could have included the other listed race categories but were reported as Other or unspecified race/ethnicity by those studies)

[d] Study locations were grouped into regions based on the U.S. Census Bureau: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf

[e] This category includes the following combinations of regions: Midwest, Northeast, Pacific West, South (n = 1); Midwest, Northeast, Pacific West, South, West (n = 1); Midwest, Northeast, South (n = 3); Midwest, Pacific West, South (n = 3); Midwest, South, West (n = 1); Northeast, Pacific West (n = 1); Northeast, South, West (n = 1); Midwest, West (n = 2)

[f] West does not include states categorized as Pacific West

[g] Study objective was determined based on a review of each article title

## Table 3

Number of prevalence estimates[a] and article IDs[b] for polysubstance combinations[c] reported among studies[d] of pregnant people, 2009–2020 (N = 119)

| Secondary substance[e] | Base substance[f] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Alcohol** | **Amphetamine/ methamphetamine** | **Cannabis** | **Cocaine** | **Medications used for opioid use disorder** | **Opioid** | **Tobacco/ nicotine** | **Other[g]** | **No base substance[h]** |
| Total articles | 15 | 9 | 16 | 10 | 22 | 16 | 26 | 22 | 43 |
| Unspecified polysubstance use | 2 Article IDs: [104; 110] | | 1 [94] | | 4 [4; 8; 45; 94] | 8 [40; 42; 46; 72] | 2 [29; 78] | 8 [6; 90; 94; 101; 116] | 2 [54; 93] |
| Alcohol | | **8 [11; 35; 47; 55; 60; 89; 115; 117]** | 13 [21; 22; 49; 50; 57; 63; 98; 102; 111; 119] | **6 [6; 70; 73; 91; 98; 119]** | 9 [4; 10; 17; 39; 53; 95; 108; 102] | 17 [24; 40; 44; 46; 51; 52; 62; 72; 97; 100; 102; 107] | **20 [9; 17; 28; 34; 36; 43; 48; 58; 59; 78; 79; 87; 98; 103; 112; 113]** | 17 [9; 26; 31; 44; 48; 61; 72; 77; 87; 90; 98; 102; 103; 119] | |
| Amphetamines/ methamphetamines | | | 2 [57; 111] | | 9 [4; 10; 39; 53; 74; 108] | | 5 [5; 78; 112; 116] | 3 [19; 26; 90] | |
| Barbiturates | | | 1 [57] | | 2 [4; 74] | | | | |
| Benzodiazepines | 1 [102] | | 2 [57; 102] | | 13 [4; 14; 39; 45; 53; 74; 75; 95; 102; 108; 109] | 11 [40; 42; 44; 92; 102; 107] | 3 [29; 78; 112] | | |
| Cannabis | 9 [16; 30; 66; 67; 68; 69; 102; 110] | 6 [11; 35; 47; 55; 115; 117] | | 4 [6; 73; 91; 94] | 13 [4; 10; 39; 45; 53; 74; 75; 76; 94; 95; 102; 108] | 13 [40; 46; 52; 72; 92; 97; 102; 107] | 16 [5; 9; 12; 27; 28; 29; 33; 34; 48; 65; 78; 82; 112; 116] | 7 [26; 48; 72; 77; 90; 102] | |
| Cocaine | 5 [16; 66; 67; 68; 110] | 4 [11; 35; 115; 117] | 3 [57; 94; 111] | | 18 [4; 14; 17; 37; 39; 45; 53; 56; 74; 94; 95; 108] | 8 [40; 46; 92; 97] | 8 [5; 17; 28; 29; 78; 82; 112; 116] | | |
| Opioid | 4 [16; 102; 110] | 3 [35; 117] | 5 [57; 94; 102; 111] | 4 [6; 91; 94] | | | 7 [5; 17; 29; 78; 80; 112] | 5 [19; 26; 102] | |
| Tobacco/nicotine | **16 [2; 16; 24; 30; 32; 58; 66; 67; 68; 79; 104; 118]** | 5 [35; 47; 55; 115; 117] | **14 [1; 12; 15; 21; 22; 38; 49; 50; 57; 63; 64; 71; 119]** | 5 [6; 71; 73; 91; 119] | **20 [4; 10; 13; 14; 17; 37; 39; 45; 53; 56; 74; 75; 84; 95; 99; 108; 109]** | **19 [24; 42; 44; 46; 51; 52; 62; 72; 81; 88; 92; 97; 100; 107]** | | **18 [7; 9; 31; 44; 61; 72; 77; 86; 87; 93; 96; 101; 116; 119]** | |
| Other | 6 [16; 68; 104; 110] | 3 [35] | 4 [21; 49; 71; 111] | 4 [3; 6; 23; 85] | 18 [4; 8; 10; 14; 39; 53; 56; 74; 75; 76; 84; 101; 108; 109] | 17 [46; 51; 62; 92; 97; 100; 107] | 7 [5; 9; 28; 59; 77; 112] | 6 [26; 90] | |
| Alcohol + tobacco | | | 1 [119] | | 1 [17] | | | | 4 [25; 58; 83; 119] |

| Secondary substance[e] | Base substance[f] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **Alcohol** | **Amphetamine/ methamphetamine** | **Cannabis** | **Cocaine** | **Medications used for opioid use disorder** | **Opioid** | **Tobacco/ nicotine** | **Other[g]** | **No base substance[h]** |
| Alcohol + cannabis | | | | | | | | | **6 [66; 68; 83; 90]** |
| Alcohol + other | | | | | | | 1 [5] | | 2 [41; 86] |
| Amphetamine + cannabis | | | | | | | | | 1 [114] |
| Cocaine + cannabis | | | | | | | | | 1 [114] |
| Cocaine + tobacco | | | | | 1 [17] | | | | 1 [83] |
| Cannabis + opioid | | | | | | | | | 2 [54; 114] |
| Cannabis + tobacco | | | | | | | | | **6 [12; 15; 19; 20; 65; 83]** |
| Cannabis + other | | | | | 1 [76] | | 1 [5] | | 2 [18; 114] |
| Opioid + tobacco | | | | | 1 [17] | | | | 1 [83] |
| Opioid + other | | | | | 2 [106] | | | | 4 [83; 114] |
| Tobacco + other | 1 [104] | | | | | | | | 3 [77; 104; 114] |
| Other combination | | | | | | | | | 5 [83; 114] |

Bolded values denote combinations with the highest number of estimates reported for a given column (i.e., base substance category)

Other entries denote combinations that do not contain the highest number of estimates reported for a given column (i.e., base substance category) or, if blank, data not reported

[a] Multiple estimates may have been reported by a single article. For articles reporting multiple estimates with different subgroups, overall estimates were included in total count of estimates if available. If overall estimates were not reported, reported estimates could have been provided for any of the following subgroups: 'Other' substance or polysubstance subgroups (n = 12); specific drug type (opioid n = 7; medications for opioid use disorder (MOUD) n = 2; amphetamine n = 2; cocaine n = 1); substance use pattern (n = 5); exposure definition (e.g., substance use disorder (SUD) diagnosis, toxicology results or specimen type, unrelated environmental exposure, mental health condition diagnosis) (n = 5); study-specific subgroups (n = 2); rural vs urban area (n = 2); region (n = 1); age (n = 1); race (n = 1); trimester (n = 1); neonatal abstinence syndrome (NAS) treatment subgroups (n = 1)

[b] Article IDs correspond to the list of articles described in Table 1

[c] The following rows for select polysubstance combinations were omitted from the table for brevity since there were no prevalence estimates reported by any study included in the review: Alcohol + Opioid; Alcohol + Cocaine; Alcohol + Benzodiazepines; Alcohol + Barbiturates; Tobacco + Benzodiazepines; Cannabis + Benzodiazepines; Cannabis + Barbiturates; Opioid + Cocaine; Opioid + Benzodiazepines; Opioid + Barbiturates; Cocaine + Benzodiazepines; Cocaine + Barbiturates; Cocaine + Other

[d] Superscripts refer to the Article IDs listed in Table 5

[e] The secondary substance was the other substance reported by the study population and served as the numerator of polysubstance prevalence calculations

[f] The base substance was the primary substance reported that defined the study population and served as the denominator for polysubstance prevalence calculations

[g] The "Other" base substance category represents studies assessing polysubstance use with unspecified substances or substances other than the existing base substance categories. This category included the use of any unspecified substance (e.g., "other illicit drug use", "any drug use"); hallucinogens (unspecified); stimulants (unspecified); tranquilizers or sedatives (unspecified); gabapentin; phencyclidine; smokeless tobacco or e-cigarettes; and any diagnosis of "other" substance use disorder

[h] Data from the "No base substance" base substance category included estimates from studies that reported polysubstance use among pregnant people without respect to a base substance