Systematic review showed that low and moderate prenatal alcohol and nicotine exposure affected early child development

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Abstract
Aim: We systematically reviewed the literature on the influence of low and moderate amounts of prenatal alcohol and nicotine exposure on early child development. This paper also suggests possible directions for future research in order to tackle the controversial findings identified.

Methods: The PubMed and Web of Science electronic databases were searched together with the reference lists of the selected papers. Empirical studies were included if they focused on the effects of low or moderate exposure, reported outcomes on child development within the first 2 years of life and were published in English between January 2009 and December 2019. The eligibility of the included studies was based on three authors reading the full text.

Results: The final sample comprised 17 papers. Of these, 13 focused on the effects of prenatal alcohol exposure and they reported decreased sensory sensibility, smaller body sizes and increased cognitive capacities. The other four looked at prenatal nicotine exposure, and they primarily found impairments in children’s orienting, communication and motor skills.

Conclusion: Any amount of prenatal alcohol and nicotine exposure appeared to risk healthy child development. There were many reasons for consumption and numerous effects on the child, but representative data from interdisciplinary research were missing.

KEYWORDS
alcohol exposure, early child development, nicotine exposure, pregnancy, prenatal

1 | INTRODUCTION

From the time of fertilisation, human offspring are sensitive to environmental factors.1,2 Toxic substances are the most influential factors for the development of the unborn child,3 and alcohol and nicotine are increasingly being consumed during pregnancy.3,4 Both substances pass directly through the placenta into the foetal blood circulation, causing toxic effects, for example on cell development.4 In addition, the biochemically immature organism delays detoxification processes.5 Hence, prenatal exposure to alcohol and nicotine is one of the highest risks for the course of a healthy pregnancy. Different consumption patterns, like high, moderate and low amounts of substances, may have distinct influences on early child development.4 This review focused on the effects of low and moderate amounts of prenatal alcohol and nicotine exposure. The current literature lacks coherent definitions of...
different consumption patterns, particularly for low and moderate consumption. High amounts are mostly defined as four to six alcoholic drinks per occasion 6,7 and between 10 and more than 20 cigarettes per day.8 We referred to low and moderate consumption patterns in the same way that they were reported by the authors of each study, including their classification of low or moderate. Consequently, low and moderate amounts had to be clearly delineated by the authors from high amounts. Previous studies on prenatal alcohol and nicotine consumption tended to investigate mothers that consumed high amounts or that suffered from clinically relevant substance abuse. These studies demonstrated that alcohol and nicotine may have affected the unborn child during all stages of pregnancy, from fertilisation to embryogenesis and the foetal period.4,9,10 Postnatal developmental deficits appeared in the form of a broad spectrum of negative, or even pathological, outcomes.1 concerning behavioural, cognitive and morphological development.3,11,12 Atypical development that is often assessed in the later stages of childhood may already be observable prenatally and in the first years of life.5,9,10 Early detection, adequate prevention and interventions for affected children, and those who are at risk, might change the course of an otherwise atypical development. Studies on prevalence have indicated that low, moderate and high amounts of alcohol and nicotine are consumed by women throughout pregnancy across the world.3,6 However, data are only available for certain countries, so far. In addition, data collection has been very heterogeneous, which complicates global comparisons. For example, the majority of studies have reported data on prevalence, without including the period between conception and the confirmation of pregnancy.13 Consequently, prevalence may be underestimated, particularly for low and moderate consumption. In order to reduce the existing risk of biases, alternative methods, like the implementation of biomarkers of alcohol and nicotine, have been established.14,15 Thus, the validity of data on prevalence, as well as the conclusions on the effects on early child development, should be improved. In comparison with the negative effects based on high amounts of consumption, the influence of low and moderate amounts of alcohol and nicotine exposure is scarcely understood.16,17 The number of studies remains small, with inconsistent results. Previous review papers reported results that focussed on different developmental outcomes. An association between low amounts of nicotine exposure and reduced foetal size and growth has been found in the second trimester.18 Further evidence for growth deficits has been associated with exposure to low amounts of alcohol.19 Negative effects on behaviour, like social engagement, have found based on exposure to moderate amounts of alcohol.7 However, some reviews did not find evidence for effects based on low or moderate amounts.19,20 Nevertheless, the majority of the literature reviews7,18-22 have indicated that there is neither a safe period, nor a safe amount, that can be consumed without risking negative effects among offspring. As previous research has lacked coherent results, it is crucial to describe and summarise the current findings of empirical research consistently. This review provides a comprehensive picture of the current knowledge on the effects of low and moderate prenatal alcohol and nicotine exposure on early child development. In addition, we have used the findings of physiological measures and questionnaires to discuss which kind of studies may reveal consistent results. Our review also debated whether the use of consistent parameters, like the amounts of consumption and further risk factors, increased the comparability of results across studies. Finally, we focused on what parameters had been overlooked, but might provide further valuable insights, such as studies in non-Western countries.

2 | METHODS

2.1 | Search strategy

The PubMed and Web of Science electronic databases and the reference lists of the papers we identified were searched to identify relevant studies on the effects of low and moderate prenatal alcohol and nicotine exposure on early child development. These two databases were selected because their extensive collection of literature on natural science would maximise the number of potentially relevant studies identified. The search procedure, presented in Figure 1 and Table S1, was carried out in April 2019 and updated in December 2019. It followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.23 In order to detect relevant papers, appropriate keywords and comprehensive combinations of these keywords were used as search terms. This was done in order to generate an adequate amount of papers, avoiding preselection. To detect studies on the effects of low and moderate amounts of prenatal alcohol exposure, the following combinations of keywords were used: pregnancy OR prenatal AND low level alcohol exposure OR moderate level alcohol exposure OR alcohol exposure AND early child development. To detect relevant papers on the effects of low and moderate amounts of prenatal nicotine exposure, the following combinations of keywords were used: pregnancy OR prenatal AND low level nicotine exposure OR moderate level nicotine exposure OR nicotine exposure AND early child development. The reference lists of the relevant literature were screened for additional records.

Key notes
- This review was carried out to clarify whether low and moderate prenatal alcohol and nicotine exposure represented a risk for healthy child development.
- The reviewed studies suggested that there was no safe limit of alcohol and nicotine that could be consumed during pregnancy without potentially harming the offspring.
- There were many reasons for consumption and numerous effects on the child, but representative data from interdisciplinary research are missing.
2.2 | Selection criteria

The inclusion criteria were empirical research papers published between January 2009 and December 2019. This time span was chosen to present a state-of-the-art overview on the effects of low and moderate amounts of alcohol and nicotine consumption. The selection of the eligible studies followed a three-step procedure. First, duplicates and papers not published in peer-reviewed English-language journals were eliminated. Secondly, titles and abstracts were checked to exclude all papers that were obviously irrelevant to the aims of the current study. Finally, the remaining 86 studies assessed for eligibility were thoroughly read to ensure that they met all inclusion criteria.

To focus on early child development, only papers that addressed the effects on children up to, and including, 24 months of age were included. In addition, only studies with non-clinical samples and pregnant women who did not abuse substances were included. Thus, we only considered results of low to moderate levels of prenatal alcohol and nicotine exposures. The degree of exposure needed to be described as low or moderate or clearly delineated from heavy, high and binge exposure. Following detailed screening, 69 papers were excluded. The main exclusion criteria were studies that investigated clinical samples, children older than 24 months and review papers. The entire literature search procedure was conducted independently by two authors (PR, CZ). Two other authors (BM, TR) additionally carried out the final full text assessment. Studies that were rated differently were discussed and included once consensus had been reached.

2.3 | Data extraction

The final sample comprised 17 papers, with 13 papers that focused on prenatal alcohol exposure and four papers on prenatal nicotine exposure. Information from the included papers was extracted by one author (PR) and subsequently checked for accuracy and completeness by two additional authors (PS, CZ). The data extraction was based on adequate methods according to the guidance for
| Authors/Year | Age of affected children | N  | Defined consumption pattern of pregnant women | Measures                                                                 | Main outcomes of affected children                                                                 | Region/Country |
|-------------|-------------------------|----|-----------------------------------------------|--------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|---------------|
| Krishnamoorthy et al, 2010 | During early embryogenesis (as a model of early human development) | Sample of embryonic stem cells | Low-level ethanol exposure (equivalent to moderate level alcohol consumption) | Genome expression analysis | Altered mRNA levels for nicotinic acetylcholine receptor alpha5 subunits. | USA |
| Comasco et al, 2012 | Newborns | 2264 | Moderate level exposures (Score 4-7 in the AUDIT-Test) | Serum- and blood sample analysis | Higher birthweight for female offspring | Sweden |
| Bakhireva et al, 2018 | 6 mo | 93 | Low to moderate level alcohol exposure | Bayley III Scales of Infant and Toddler development | No neurobehavioural deficits. Higher scores in the parenting stress index | New Mexico |
| Williams-Brown et al, 2010 | 9 mo | 1070 | 1-3 drinks per week | Bayley II Scales of Infant and Toddler development | Lowered sensory regulatory responses in comparison with controls | USA |
| McCormack et al, 2018 | 12 mo | 1331 | Low (≤7 drinks per week up to 2 drinks per occasion) to Moderate (>2-≤4 drinks per occasion) level alcohol exposure | Bayley III Scales of Infant and Toddler development | Higher scores on cognition in children of mothers that consumed low levels of alcohol in comparison with controls; evidently affected through sociodemographic factors. No association with moderate amounts | Australia |
| Hutchison et al, 2019 | 12 mo | 1324 | Low-level alcohol exposure | Bayley III Scales of Infant and Toddler development | No association between low-level prenatal alcohol exposure and gross motor development | Australia |
| Muggli et al, 2017 | 12 mo | 415 | Low-level alcohol exposure | Analysis of 3-dimensional craniofacial images. Performed with objective, holistic craniofacial Phenotyping using dense surface models of the face and head | Differences in the forehead between groups with low exposure vs. no exposure in the first trimester | Australia |
| Sundleir et al, 2017 | 18 mo | 291 | Low to moderate level alcohol exposure | CBDQ | Smaller Body sizes; Negative influences on infant’s behaviour and development | Sweden |
| Ouilet et al, 2011 | 19 mo | 130 | Low-level alcohol exposure | Saliva sample analysis | Disrupted pattern of cortisol activity in males | Canada |
| Halliday et al, 2017 | 24 mo | 60 | Low-level alcohol exposure in tm 1; low/moderate alcohol exposure in tm 2 and/or 3 | Bayley III Scales of Infant and Toddler development | No associations between low and moderate-level prenatal alcohol exposure and cognition and language scales | Australia |
undertaking healthcare reviews from the Centre for Reviews and Dissemination, University of York, UK.\textsuperscript{30} Minimal disagreements that occurred during the data extraction were discussed and resolved between the authors. Tables 1 and 2 summarise the consensus of the relevant information regarding alcohol and nicotine exposure, respectively. Both tables code the following aspects for each study: the authors and the year of publication, the age of the affected children, the total number of affected children and the defined consumption pattern of pregnant women. Furthermore, the coded tables applied measures to assess early child development and the main outcomes on the affected children. When possible, the data were differentiated according to the prenatal consumption pattern of pregnant women. Lastly, the sample’s country of origin was listed.

2.4 | Quality and risk of bias assessment

The quality and risk of bias assessment for all 17 eligible studies according to the Newcastle-Ottawa Scale\textsuperscript{40} is summarised in Tables S2 and S3. The Newcastle-Ottawa Scale was used to evaluate three aspects: the selection of the study groups, the comparability of the groups and the ascertainment of either the exposure or outcome of interest for case-control or cohort studies, respectively. These three aspects comprise different items. For each quality item, stars are given. The number of stars serves as a quality assessment. A maximum of nine stars were awarded for each study in total, and a higher score represented higher quality. The rating was conducted by one author (PR) and subsequently checked for accuracy and completeness by two additional authors (PS, CZ).

3 | RESULTS

The final sample of 17 studies comprised 11 cohort studies and six case-control and cross-sectional studies. The total number of studies in the final sample remained small, especially those for nicotine, which comprised only four studies. Research on both substances contained analyses on outcomes at different developmental stages. These stages included gestation, the newborn infant phase, 3-12 months after birth and the second year of life. An overview is presented in Tables 1 and 2.

3.1 | Quality and risk of bias

The included studies scored between six and nine stars on the Newcastle-Ottawa Scale. As a study can be awarded a maximum of nine stars, all the included studies presented adequate quality and a low risk of bias.

Alcohol intoxication in pregnancy results in prenatal alcohol exposure (PAE), and smoking smoking results in nicotine exposure. The neural and psychological effects of PAE and nicotine exposure have been assessed using different outcomes at different developmental stages.

| Authors/Year | Age of affected children | Defined consumption pattern of pregnant women | Measures | Main outcomes of affected children |
|--------------|--------------------------|---------------------------------------------|----------|-----------------------------------|
| Robinson et al, 2010 | 24 mo | Low to moderate level alcohol exposure | CBCL | No effects between low to moderate levels of prenatal alcohol exposure and behaviour problems |
| O’Leary et al, 2010 | 24 mo | Low-level alcohol exposure | CBCL | No association with infant behaviour problems; Anxiety and depression problems |
| O’Leary et al, 2009 | 24 mo | Moderate level alcohol exposure | CBCL | No association with infant language delay |

Abbreviations: ASQ-3: Ages and Stages Questionnaire; AUDIT Test: Alcohol Use Disorders Identification Test; CBCL: Child Behavior Checklist; CBQ: Child behavior and development questionnaire; CHADD: Children with Attention Deficit Hyperactivity Disorder; DQ: Developmental Questionnaire; HAD: Hospital Anxiety and Depression Scale; PAE: Prenatal alcohol exposure; TM: Trimester; WHO: World Health Organization.
Effects of low to moderate levels of prenatal nicotine exposure on early child development

Table 2: Effects of low to moderate levels of prenatal nicotine exposure on early child development

| Authors/Year          | Age of affected children | N   | Defined consumption pattern of pregnant women | Measures                     | Main outcomes of affected children                        | Region/Country |
|-----------------------|--------------------------|-----|-----------------------------------------------|------------------------------|-----------------------------------------------------------|----------------|
| Taal et al, 2011     | 30 wk gestation          | 1031| <5 cigarettes per day                         | Ultrasound                   | Larger foetal kidney volume. Smaller foetal kidney volume | Netherlands    |
| Chahal, et al, 2017   | Newborns (2-3 d)         | 3459| <20 cigarettes per day                        | Blood sample analysis        | Increased levels of the inflammatory biomarker IL-8 cytokines, No increased levels of IL-8 | New York       |
| King et al, 2018      | 3-5 mo                   | 48  | ≤20 cigarettes per day                        | EEG; auditory paired-click paradigm | Smaller amplitude of the N550 component and reduced delta-band power within elicited K-complexes; Less orientation with a head turn to a novel auditory stimulus, in comparison with controls | USA            |
| Mohamed et al, 2018   | 24 mo                    | 107 | Second-hand smoke                             | ASQ-3                        | Lower neurodevelopment especially for communication and fine motor skills | Malaysia       |

Abbreviations: ASQ-3, Ages and Stages Questionnaire; EEG, Electroencephalography.

at least one other factor. In addition, they used adequate ascertainment of exposure and the same methods to analyse cases and controls.

All of the 11 cohort studies that were included presented cohorts that were representative of the community they studied. The selection of the non-exposed cohort was drawn from the same community as the exposed cohort. They reported outcomes of interest that were not present at the start of study and controlled for at least one other factor.

Ratings of certain items by the Newcastle-Ottawa Scale presented evidence for reductions in quality and a higher risk of bias for all 17 individual studies. For example, all the studies were controlled for one other factor, like maternal age, but only 15 studies controlled for any further factors, such as maternal socio-economic status. In addition, six studies lacked any follow-up analysis with regard to child outcomes, and in four studies, the outcomes were not based on blinded assessment. The assessment of alcohol or nicotine exposure was not obtained through biomarkers but based on questionnaires in 11 studies.

When the data quality and the risk of bias was considered across studies, disparities were possible because of the differences in the way the studies were designed or conducted. Furthermore, the studies presented methodological heterogeneity to assess prenatal alcohol and nicotine exposure, as well as the outcomes of the affected children. The exclusion of non-English papers may also have led to excluding critical studies. Yet, there is little evidence that the exclusion of non-English-language papers leads to a high risk of bias in systematic reviews. Publication bias may exist, as results with positive developmental outcomes or no association between prenatal substance exposure and development may not be submitted or published.

3.2 | Effects of low and moderate alcohol exposure on early child development

Results on the effects of low to moderate prenatal alcohol exposure revealed different developmental outcomes in the children who were affected. Of the 17 included studies, six reported negative effects, five reported no effects and two found positive outcomes like higher scores in developmental tests in comparison with controls. The effects on gestation, for example on fertilisation, embryogenesis and the foetal period, were reported with a sample of embryonic stem cells as a model of early human development. The low-level ethanol exposed group was reported to be equivalent to moderate level alcohol consumption. For this group, altered levels of messenger ribonucleic acid were found in nicotinic acetylcholine receptor alpha5 subunits during embryogenesis. This may lead to an alteration of gamma-aminobutyric acids and N-Methyl-D-aspartate receptor expression and, consequently, to abnormal development of the frontal cortex. These outcomes suggest that low to moderate alcohol exposure can alter early neurological development. This may raise the risk of addiction and other developmental abnormalities for the foetus and its further development. One study related to the effects of moderate prenatal alcohol exposure higher birthweights for female offspring. However, the authors reported that the validity of results was limited by the low response rates. The effects on infants aged 3-12 months revealed different results. No association between low prenatal alcohol exposure and neurobehavioural deficits was found in a study of 6-month-old infants. Lowered sensory regulatory responses were found in 9-month-old infants in comparison with non-exposed controls. Infants aged 12 months, whose
mothers consumed low amounts of alcohol during the second trimester, scored higher on cognition scales than controls. However, the authors pointed out that child cognitive development was evidently affected through sociodemographic factors like the social environment or socio-economic status of their mothers. In addition, there was evidence for anatomical differences in the forehead between groups with low exposure versus no exposure during the first trimester. Despite this, gross motor development 12 months after birth did not appear to be affected by prenatal low-level alcohol exposure. One study looked at the effects on toddlers aged 13-24 months and showed that 18-month-old toddlers who were exposed to low and moderate amounts were less cautious when approching strangers. In addition, they had smaller body sizes than the controls. Another study showed disrupted patterns of cortisol activity in 19-month-old boys that were exposed to low amounts of alcohol during pregnancy. The same study found different patterns for 24-month-old toddlers. Moderate alcohol exposure was associated with higher scores on anxiety and depression scales in one study. Furthermore, an initial analysis of another study suggested a positive association between cognitive development and low-level alcohol consumption. However, the evidence was reduced by the influence of many other covariates, like maternal age or education. Hence, no associations between low-level prenatal alcohol exposure and cognition and language scales could be concluded. No association with low-level prenatal alcohol exposure in 24-month-old toddlers was found for either language delays or behavioural problems.

3.3 | Effects of low and moderate nicotine exposure on early child development

In comparison with research on the effects of prenatal alcohol exposure, only four studies focused on nicotine effects. However, the research shows mainly negative effects of low to moderate amounts of prenatal nicotine exposure on early child development.

Findings for effects on gestation in 30 weeks old foetuses revealed a dose-dependent modification of the foetal kidney volume. A larger foetal kidney volume was found based on less than five cigarettes per day. A smaller kidney volume was found based on a consumption pattern of more than 10 cigarettes per day. In addition to the liver, the kidneys are among the detoxifying organs of the human body. It remains unclear whether these differences in foetal kidney volume have postnatal consequences. For kidney function and blood pressure, it is known that smaller kidney volumes result in fewer nephrons. Nephrons are basic units of the kidney, which might predispose a child to the development of hypertension and kidney disease in later developmental stages.

Concerning effects on newborn infants, increased levels of the inflammatory cytokine interleukin-8 were found based on a consumption pattern of less than 20 cigarettes per day. No increased levels of interleukin-8 were found in newborns infants whose mothers were exposed to second-hand smoke during pregnancy. Interleukin-8 is an inflammatory mediator. Increased levels result in permanent changes in neonatal inflammation. This may lead to respiratory disorders, like bronchitis or asthma.

Electroencephalography experiments indicated impairments in auditory sensory gating on infants aged 3-12 months. The results were based on consumption of up to 20 cigarettes per day. These impairments caused reduced auditory discrimination, learning, attention, re-orienting and arousal during wakefulness in infants aged 35 months. In addition, it led to disrupted sleep behaviour. Affected infants showed less orientation with a head turn to a novel auditory stimulus during wakefulness, in comparison with controls. In addition, they showed a smaller amplitude of the N550 component and reduced delta-band power within elicited K-complexes during sleep. In typical development, the averaged so-called K-complex wave form shows a large amplitude and a late negative deflection, peaking between 500 and 650 ms. Hence, this peak is often labelled as N550 and appears during stage two of sleep maintaining into slow wave sleep. Smaller amplitudes of the N550 component could provide evidence for impaired sleep behaviour. Nevertheless, the study did not control for any confounders like maternal social surroundings and any support that may have had an impact on the neurodevelopment of children.

The effects on 24-month-old toddlers revealed that second-hand smoke exposure during pregnancy was associated with lower neurodevelopment. Affected children showed poorer fine motor skills, for example hand and finger movements, and impaired communication skills in vocalising, listening and understanding. However, the authors stated that the participants only lived within a small geographical area that was not representative of the whole country. In addition, the extent of second-hand smoke exposure was obtained from nicotine levels in the hair of pregnant women living in smoker households. Here, it was not considered that children of non-smoker households representing the control group could be exposed to second-hand smoke through other sources as well. For example, in other households or in restaurants, this may distort the results. Furthermore, neurodevelopment was only assessed by using a questionnaire that may lack adequate psychometric properties. This may have reduced the evidence of the presented results.

4 | DISCUSSION

There were only 17 studies that investigated the effects of low to moderate amounts of prenatal alcohol and nicotine exposure during pregnancy. The results on the consequences for those children that were affected appear to be controversial. While six studies reported detrimental effects of alcohol exposure on early child development, five studies found no effect, and two studies even found positive effects. The four studies on prenatal nicotine exposure revealed negative effects, but further research to confirm these outcomes is vital. The small amount of research could be explained by previous research being primarily focused on the effects of high-level consumption. This may have been in order...
to consolidate knowledge about pathological outcomes. As the pathogenesis based on high-level consumption has been extensively researched, current analyses have started to focus on the effects of consuming smaller quantities. Another effect of the small number of studies may be the focus on early child development. If the focus was extended to children who were older than 24 months of age, there would certainly be more literature. However, the amount of research that has analysed the effects of low to moderate consumption amounts remains small compared to the literature that focused on the effects of high amounts. Hence, the lack of representative research on this important public health topic is notable.

4.1 | Developmental consequences

The consequences for early child development resulting from prenatal exposure to low and moderate amounts of alcohol and nicotine remain controversial. Although the quality and risk of bias assessment yielded adequate results for all the included studies, some aspects make it difficult to draw reliable conclusions. For example, determining the exposure to alcohol and nicotine and developmental outcomes differed across studies. In addition, further factors, like maternal age or education that may have influenced the reported outcomes, were not assessed in all studies. The majority of the studies also lacked follow-up analyses. Considering the contradictory results, no amount of nicotine or alcohol can be considered without risks for healthy child development. Comparisons with the effects of high-level consumption remain challenging, as research for low to moderate amounts is rare. Effects based on high-level consumption appear in the form of a broad spectrum of disorders, which are clinically defined as foetal alcohol spectrum disorders for alcohol and foetal tobacco syndrome for nicotine. These include neurocognitive and motor deficits or morphological changes. Results for low to moderate exposure to alcohol or nicotine during pregnancy also elicit a variety of developmental deficits. Deficits include lowered sensory regulatory responses or lower communication and fine motor skills. Thus, there is evidence that low and moderate consumption during pregnancy may also impair early child development in a complex way. Consumption of low to moderate amounts during pregnancy is more commonly practiced and more accepted than high-level intake in different societies and regions across the world. In addition, it may be related to current gaps of knowledge about the risks and negative effects of toxic substances on early child development. Specific outcomes and further child development also depend on other moderating factors. Risk factors that affect the prenatal and postnatal health of the mother and child have been extensively discussed. These risk factors include mental health problems, a higher age and low socio-economic status of the mother, Caesarean birth and low birthweight of the child. Such moderating factors have to be considered by investigating further child development.

4.2 | Methodological challenges and relevant confounders

The current literature lacks a coherent definition of different consumption patterns. Definitions vary in amounts and frequencies of consumption like per week or per occasion. They vary in time frames of consumption, like within 1 hour or 1 day and in indications for one drink or one cigarette. Hence, there are variations concerning the exact content of alcohol or nicotine.

In addition to definitions, the validity of the means of data collection has to be considered. Evaluation based on retrospectively collected data or data based on interviews seems critical. Answers may conform to social desirability. Drinking and smoking patterns during pregnancy may be inaccurately recalled.

The controversial effects of prenatal alcohol and nicotine exposure may be explained by methodological challenges in assessing outcomes based on lower doses. It is possible that the measures that are usually used to detect deficits based on high amounts are less useful when it comes to low and moderate amounts. Measures for detecting deficits based on high exposure are more focused on global developmental deficits. These are frequent in children exposed to high amounts or diagnosed with related disorders. Instruments to measure developmental outcomes should be designed in such a way that small abnormalities and precursors of deficits can be captured. Although most studies control for additional factors, consumption during pregnancy has been considered in isolation in some research. Further confounding environmental and social risk factors may influence the consumption behaviour of pregnant women and consequently the outcomes of affected children. Correlations are documented for alcohol and nicotine consumption and sociodemographic factors, for example origin or migration status. Previous findings indicate that women living in Europe, with a cultural background like North Africa, consume less than women without such a background. In regions like North Africa, only low amounts or no alcohol or nicotine are consumed. Consequently, infants born to women with such migration backgrounds are less at risk for atypical perinatal development. In addition, socio-economic status appears to correlate with the drinking and smoking patterns of pregnant women. Prenatal alcohol consumption, particularly low to moderate amounts, appears to be associated with higher socio-economic status. In contrast, nicotine consumption seems to correlate with lower socio-economic status. Furthermore, social environments have been associated with prenatal alcohol and nicotine consumption.

Studies on both substances show that if pregnant women lack social support from their environment, the probability of drinking and smoking and damaging affected infants’ development increases. Experiencing violence, for example in a partnership, or critical life events, such as deaths, are also among the predictors of alcohol and nicotine consumption. Lack of access to supportive measures, like sessions with midwives or antenatal classes, also increase the likelihood of prenatal substance use. In addition, polydrug use and pre-pregnancy substance
consumption have been associated with alcohol and nicotine consumption during pregnancy. These factors are relevant confounders for analysing the effects of alcohol or nicotine exposure on early child development. The consumption of substances during pregnancy does not constitute the only risk factor for healthy child development.

4.3 Implications for further research and clinical practice

Current estimates of the prevalence of alcohol and nicotine use during pregnancy demonstrate a global problem. Society lacks awareness towards the harmful effects of different kinds of consumption patterns on early child development. In order to identify women at risk, and to facilitate preventive measures, knowledge about the effects of different consumption amounts is needed. Consequently, it is crucial to collect prevalence data with respect to coherent definitions of low, moderate and high consumption levels. To overcome the methodological challenges discussed in this paper, research needs to be interdisciplinary and incorporate disciplines and research areas like psychology, biology, pharmacology or epigenetics. Current research on the detection of consumption behaviour has used biomarkers for alcohol and nicotine. For analyses, direct metabolic products of the substances have been used. These methods for analysing the amounts of metabolites are considered reasonable alternatives, or additional methods, for assessing the coherent prevalence of consumption and the consequent child outcomes.

A considerable advantage is the possible early detection of developmental impairments. This may be missing if diagnostic measures are focused on outcomes that appear later in development. Furthermore, adequate prevention strategies could be applied as early as the first years of life. In this way, at-risk children may be identified before they exhibit atypical development. Other research fields like epigenetics are currently being established in order to detect the influence of substances on gene activity. This activity is altered by environmental conditions and influences endocrine, immunological and molecular processes. When women are exposed chemical substances during pregnancy, this can cause epigenetic effects in the offspring, starting in the womb.

It is useful to include analyses on epigenetic effects in further research, as they provide results on the effects in the earliest developmental stages. In addition, they inform about whether epigenetic processes influence the pathogenesis of psychological disorders, as well as whether these processes are bound to certain developmental stages. Furthermore, future research should interpret the consumption of toxic substances in combination with other environmental factors that influence consumption behaviours and the developmental courses of affected children. Social and healthcare experts, like gynaecologists, paediatricians, midwives or clinical child psychologists, could use this knowledge to identify at-risk families early on. For example, strategies might involve pregnancy screening, early detection by paediatricians or psychological care. Postnatal care and support by midwives and child-family services, as well as counselling for substance addiction, could adequately counteract some of the prenatal consumption effects.

5 CONCLUSION

This review showed that the number of studies on the effects of low to moderate prenatal alcohol and nicotine exposure on early child development was small. The results on perinatal outcomes appear to be controversial and complex. Our findings illustrate the need to clarify current controversies and elucidate the apparent global problem of low and moderate levels of alcohol and nicotine consumption during pregnancy. The results were heterogeneous. Consequently, guidelines should clearly state that there is no safe period and no safe amount of alcohol and nicotine that can be consumed during pregnancy without any harm to the unborn child. First, a continuous assessment of the prevalence of high, low and moderate levels of consumption during pregnancy is essential. This could prevent the consequential damage to affected children. Secondly, social and environmental factors that influence consumption and child development should be included in further analyses. Finally, interdisciplinary research is essential to be able to benefit from the methodical possibilities of certain research areas to establish consistent methods and reduce existing biases.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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**SUPPORTING INFORMATION**

Additional supporting information may be found online in the Supporting Information section.

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