

# SMOKING AND ALCOHOL DRINKING DURING PREGNANCY AS THE RISK FACTORS FOR POOR CHILD NEURODEVELOPMENT – A REVIEW OF EPIDEMIOLOGICAL STUDIES

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## Abstract

Maternal active and passive smoking and low or moderate alcohol drinking during pregnancy, taking into account the level of exposure and developmental or behavioral outcomes, are recognized as a significant issue from both a clinical and a public health perspective. The article aims at evaluating the impact of prenatal exposure to tobacco smoke constituents and low or moderate alcohol drinking during pregnancy on children neurodevelopment by reviewing the most recently published literature. Relevant studies were identified by searching the Pubmed, Medline and Ebsco literature databases. This review is restricted to 29 human studies published in English in peer reviewed journals since 2006. The studies published recently continued to show some relationship between tobacco smoke exposure, from active and passive maternal smoking during pregnancy, and children's psychomotor development independent of other variables, but this relationship is not straightforward. The association is mostly consistent for measures of academic achievements and behavioral problems which require further attention. The results of the studies on low or moderate exposure to alcohol are not fully conclusive, but some of them suggest that consumption of alcohol during pregnancy may adversely affect children's intelligence quotient (IQ), mental health, memory and verbal or visual performance. As the reviewed studies indicate, maternal lifestyle during pregnancy like alcohol drinking or smoking may affect children neurodevelopment. All effort should be taken to eliminate such exposure to ensure appropriate children's development.

## Key words:

Children, Behavior, Prenatal smoking, Prenatal alcohol, Neurodevelopment

## INTRODUCTION

Nowadays special attention is focused on maternal active and passive smoking and low or moderate alcohol drinking during pregnancy and their impact on children's neurodevelopment. Child cognitive development and behavior is determined by genetic, environmental,

and social factors interacting in complex ways. None of them is sufficient to explain population neurodevelopmental abnormalities. Except for single-gene disorders, heredity accounts for about 50% of the variance of cognitive, behavioral, and personality traits among individuals [1]. This, of course, implies that the other 50% of

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variability must be due to environmental and/or lifestyle influences.

In general, the fetal development is regarded as the most vulnerable period of exposure to 2 modifiable lifestyle factors, such as tobacco and alcohol. Even a small increase in developmental risk associated with prenatal exposure to the above factors may be sufficient to move significant numbers of children into the developmentally delayed range of functioning, requiring early intervention services. As children grow, deficits in socio-emotional function and intellectual abilities become increasingly salient, particularly with regard to social judgment, interpersonal skills, antisocial behavior and academic achievements.

Previously published literature review [2] indicated that maternal smoking, drinking and cannabis use during pregnancy may be associated with neurobehavioral and cognitive outcomes, although not all research supports this statement. The review mostly pointed the limitations in study design and analysis such as retrospective study design, exposure assessment based on questionnaire data and lack of adequate control over confounding factors.

The aim of the present paper is to provide the review of the literature to assess the potentially harmful impact of fetal exposure to the risk factors such as tobacco and low and moderate alcohol intake on children cognitive development and behavioral problems and to identify directions for future research.

#### **Criteria for inclusion of studies into the review**

Epidemiological studies focused on the prenatal exposure to tobacco and alcohol and children neurodevelopment were identified by a search of the Pubmed, Medline and Ebsco literature databases. The combination of the following key words was used:

- referred to the exposure: pregnancy, prenatal exposure, maternal smoking, environmental tobacco smoke exposure [ETS], alcohol;

- referred to outcome: neurodevelopment, neurobehavior, psychomotor development, behavioral problems, cognitive development, IQ, mental health, school achievements and learning abilities.

Relevant studies were also identified via review of references cited in all published studies. To be eligible for the review, each study must have used a measure of exposure to maternal active/passive smoking or low/moderate alcohol drinking during pregnancy period and at least 1 measure of neurocognitive function in the offspring. For this review, postnatal exposure to tobacco constituents and heavy or binge drinking by pregnant women was not considered for inclusion.

Additionally, studies were excluded if the exposure to different types of toxicants were combined into a single variable, making it impossible to determinate the association between exposures of interests and child neurodevelopment. From each study, the following information was abstracted: year of publication, country in which the study was performed, study design and population, assessment of exposure (including biomarkers), child neurodevelopment (including a neurodevelopmental test used) and confounding factors.

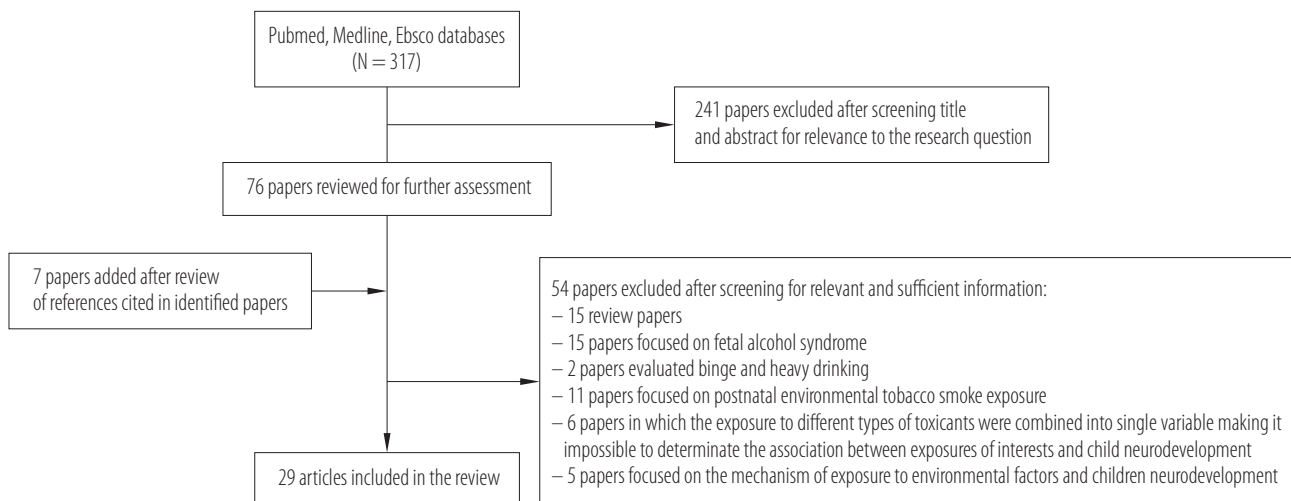
Finally, this review includes human studies published in English in peer reviewed journals since 2006. Fully adjusted analyses are presented where available. Taking into account the great heterogeneity between the studies, mostly in outcome assessment and statistical analyses, a meta-analysis, although considered, was not possible.

In summary 29, out of total 83 articles identified, meet eligibility criteria and were included in the present review (Figure 1).

#### **Description of the state of knowledge**

Exposure to active and passive smoking during pregnancy and children neurodevelopment

Based on the data from epidemiological studies, we can assume that about 20–30% of women actively smoke during



**Fig. 1.** Flowchart showing the process of identification of relevant studies for the review

pregnancy and about half of the non-smoking pregnant women are exposed to passive smoking [3]. It is also important to notice that almost half of the child population is involuntarily exposed to tobacco smoke at home [4].

The effect of maternal active smoking during pregnancy on neurodevelopment in young children (aged 4 or younger) has been inconsistent (Table 1). This can be due to not sufficiently sensitive assessment tools for small children, difficulties in testing very young babies, or the fact that effects of pollutants may become apparent only with maturation of the brain over time. The results from population-based birth cohort (Generation R Study) indicated that children of mothers who continued smoking during pregnancy had higher risk of behavioral problems at 18 months compared to the children of mothers who never smoke with adjustment for age and gender ( $p < 0.05$ ) [5]. That association was strongly confounded by parental characteristics. After additional adjustment for parental education, family income and parental psychiatric symptoms the results were not statistically significant ( $p > 0.1$ ). The data from Quebec Longitudinal Study of Children's Development showed an association between maternal smoking in pregnancy and reduced intelligence and memory scores ( $p \leq 0.003$ ) in unadjusted analysis with no changes after

adjustment for birth weight [6]. No statistically significant association was found after adjustment for additional covariates ( $p > 0.05$ ). The analysis by Julvez et al. (2007) suggests that maternal smoking during pregnancy lowered cognitive development in children at 4 years of age (represented by global cognitive score, verbal score, quantitative score, executive function score and working memory) [7]. Recently published analysis, based on the data from prospective Polish Mother and Child Cohort, with assessment of exposure based on biomarker measurements (3 times in pregnancy and in children at 1 and 2 years of age), indicated that cotinine level in saliva collected during pregnancy was significantly associated with decreased motor abilities at 24 months of age ( $p = 0.02$ ) and not with cognitive and language achievements after controlling for variety of confounders including ETS exposure after birth [8].

The larger amount of studies evaluating the impact of prenatal exposure to active maternal smoking on cognitive development, intelligence, and intellectual impairment focused on older children including preschool children and adolescents [9–15]. Although some of them indicated the association between such exposure and decreased IQ score or cognitive delay, there is the controversy whether possible confounders have been adequately

**Table 1.** Exposure to active and passive smoking during pregnancy and children neurodevelopment

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
United States: 5 578 children between 5–14 years of age	US National Longitudinal Survey of Youth	interview with mothers during pregnancy	Peabody Individual Achievement Test	ethnicity, maternal age, maternal IQ, maternal education, income, birth weight, birth order, child gender, cognitive stimulation, emotional support, alcohol consumption during pregnancy, illicit drug use, breastfeeding, mother residing with spouse or partner	in unadjusted analysis the offspring of mothers who smoked $\geq 1$ pack of cigarettes/day during pregnancy had IQ score 2.9 points lower than children of non-smoking mothers ( $p < 0.001$ ), the light exposure was associated with 1.7 point decrement ( $p < 0.001$ ); after adjustment the results were not statistically significant ( $p = 0.9$ )	Batty et al. (2006) [9]
Sweden: offspring at age 15 years among more than 400 000 male and female students born 1983 through 1987	population-based Swedish Cohort study	information about maternal smoking from Medical Birth Register	school performance from National School Register	maternal age, parity, maternal education, maternal socioeconomic category, home ownership, child gender, Apgar score at 5 min, birth weight, length, head circumference, gestational age	maternal smoking compared with no tobacco use during pregnancy was associated with an increased risk of poor school performance: for 1–9 cigarettes/day OR = 1.6 (95% CI: 1.59–1.63) and for 10 or more cigarettes/day OR = 1.9 (95% CI: 1.86–1.98); the risk remained unchanged with adjustment for birth outcomes; if the mothers had smoked in 1st but not 2nd pregnancy, the younger siblings was also at increased risk of poor school performance	Lambe et al. (2006) [17]

Finland: 6 388 children at 6 months, 5 and 12 years of age	Helsinki Longitudinal project	interview with mothers during pregnancy at each prenatal visit and at follow-up	Infant Temperament Questionnaire, Preschool Temperament Questionnaire, School-Age Temperament Questionnaire, School-Age Behavior Problems Questionnaire, Student Grade Reports	socioeconomic status, maternal age, the symptoms of upper respiratory infection and nausea, maternal psychiatric hospitalization, psychological distress during pregnancy, hospitalization from accidents	maternal smoking during pregnancy was significantly associated with infant temperament (distress to novelty: $f = 3.0$ , $p < 0.05$ ; biological irregularity: $f = 3.7$ , $p < 0.05$ ), preschool temperament (activity level: $f = 5.7$ , $p < 0.01$ ; negative emotionality: $f = 3.1$ , $p < 0.05$ ) and 12 years of age temperament (task orientation: $f = 3.7$ , $p < 0.05$ ; emotional reactivity: $f = 3.8$ , $p < 0.05$ ), behavior problems (distractibility: $f = 4.1$ , $p < 0.05$ ; immaturity: $f = 4.0$ , $p < 0.05$ ; negative emotionality: $f = 3.3$ , $p < 0.05$ ) and academic performance (overall academic average: $f = 4.6$ , $p < 0.01$ )	Martin et al. (2006) [16]
Canada: 1 544 children at 3.5 years of age	Québec Longitudinal Study of Children's Development	interview with mothers after birth	Peabody Picture Vocabulary Test, Wechsler Preschool and Primary Scale of Intelligence, Visually Cued Recall task	birth weight, maternal education, family income, maternal responsiveness, involvement, family dysfunction	exposure associated with reduced intelligence (Wechsler scale: $\beta = -0.08$ , $p = 0.003$ ; Peabody test: $\beta = -0.1$ , $p < 0.001$ ) and memory (Visually Cued Recall: $\beta = -0.1$ , $p < 0.001$ ) scores in unadjusted analyses, with no change after adjustment for birth weight; there is no statistically significant association after adjustment for additional covariates ( $p \leq 0.3$ )	Huijbregts et al. (2006) [6]
Australia: 3 794 children at 14 years of age	Mater-University Study of Pregnancy, population-based birth cohort study	interview with mothers during pregnancy	Raven's Standard Progressive Matrices	child gender, maternal age at birth, ethnicity, gravidity, family income, maternal education, paternal education, foetal distress, duration of labour and mode of delivery, Apgar scores, birth weight-for-gestational-age, breastfeeding, height and BMI z-scores at age 5	exposure associated with a 1.4-point reduction ( $p = 0.01$ ) in intelligence scores controlling for child sex and parental characteristics, 1.2 point reduction ( $p = 0.03$ ) with additional controlling for characteristics of labour, Apgar scores and birth weight; no association after additional adjustment for breastfeeding, height and weight ( $p = 0.4$ )	Lawlor et al. (2006) [10]

**Table 1.** Exposure to active and passive smoking during pregnancy and children neurodevelopment – cont.

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
Spain: 420 children at 4 years of age	Asthma Multicenter Infant Cohort Study	interview during 3rd trimester of pregnancy and every ear up to age 4 years of the child	McCarthy Scales of Children's Abilities	home location, maternal alcohol consumption, mother's social class, level of education during pregnancy, parity, marital status, father's education, child gender, birth weight and height, breastfeeding duration, passive smoking, school season, age during test administration and evaluator	maternal smoking during pregnancy was associated with a decrease of children's global cognitive ( $\beta = -0.6$ ; 95% CI: $-1.1 - (-0.09)$ ), verbal ( $\beta = -0.6$ ; 95% CI: $-1.1 - 0.07$ ), quantitative ( $\beta = -0.6$ ; 95% CI: $-1.1 - 0.06$ ), executive function ( $\beta = -0.7$ ; 95% CI: $-1.2 - 0.2$ ) and working memory scores ( $\beta = -0.5$ ; 95% CI: $-0.9 - 0.01$ )	Julvez et al. (2007) [7]
Taiwan: 145 children at 2 years of age	Taiwan Birth Panel Study	interview within 3 days after delivery and 2 years postpartum, cotinine level in cord blood	The Comprehensive Developmental Inventory for Infants and Toddlers	maternal education, nationality, income, child gender, gestational age, home observation for measurement of the environment score, postnatal ETS exposure	maternal ETS exposure during pregnancy was significantly negatively associated with developmental quotients of the whole test ( $\beta = -7.9$ , $p = 0.002$ ), cognitive ( $\beta = -5.4$ , $p = 0.04$ ), language ( $\beta = -7.9$ , $p = 0.002$ ), fine-motor ( $\beta = -7.5$ , $p = 0.004$ ), social ( $\beta = -7.2$ , $p = 0.03$ ) subtests; CYP1A1 Ile462Val and GSTT1 metabolic genes can modify the effect of cord blood cotinine on early child neurodevelopment	Hsieh et al. (2008) [21]
United States: 4 827 children at 4 and 7 years of age	Collaborative Perinatal Project, birth cohort study	interview with mothers during pregnancy	Stanford-Binet Intelligence Scale, Wechsler Intelligence Scale for Children, academic performance with Wide Range Achievement Test	parental education, occupation, income, maternal marital status, maternal employment status, presence of the husband or father of the baby in the household, household crowding, family history of mental illness, number of neurologic and psychiatric conditions present during pregnancy, maternal age, number of prior pregnancies, paternal age	heavy exposure ( $\geq 20$ cigarettes) associated with reduced intelligence at age 4 years ( $\beta = -0.6$ , $p = 0.01$ ) and age 7 years ( $\beta = -1.3$ , $p < 0.001$ ) and academic achievement at age 7 years (reading: $\beta = -1.4$ , $p < 0.001$ ; spelling: $\beta = -1.0$ , $p < 0.001$ ), but not significant in fixed effects model for sibling relationship ( $p > 0.05$ )	Gilman et al. (2008) [11]

<p>The Netherlands: 4 680 children at 18 months of age</p>	<p>The Generation R Study, population- based birth cohort study</p>	<p>interview with mothers at each trimester of pregnancy</p>	<p>Child Behavior Checklist for Toddlers</p>	<p>age, child gender, national origin, parental education, family income, parental psychiatric symptoms</p>	<p>children of mothers who continued smoking during pregnancy had higher risk of behavioral problems compared to the children of mothers who never smoke (OR = 1.6, 95% CI: 1.2–2.1) with adjustment for age and gender; smoking by father when mother did not smoke was related to higher risk of behavioral problems; after adjustment for additional confounders the results were not statistically significant (<math>p &gt; 0.1</math>)</p>	<p>Roza et al. (2009) [5]</p>
<p>United States, Arkansas, Georgia, North Carolina and Utah: 105 572 children at 8 years of age</p>	<p>Active Surveillance Project</p>	<p>mother's smoking determined from birth certificate</p>	<p>intellectual disability (IQ <math>\leq</math> 70)</p>	<p>maternal education, maternal race, maternal age, marital status, child gender, birth year and study site</p>	<p>the risk of intellectual disability was mildly elevated among children whose mothers smoked <math>\geq</math> 20 cigarettes/day during pregnancy (RR = 1.3, 95% CI: 1.0–1.9) after adjustment; the effect of exposure significantly differed for males (RR = 1.8, 95% CI: 1.2–2.6) compared with females (RR = 0.81, 95% CI: 0.4–1.5); supplemental analyses reveal substantial confounding of this relationship by socio-economic indicators</p>	<p>Braun et al. (2009) [12]</p>

**Table 1.** Exposure to active and passive smoking during pregnancy and children neurodevelopment – cont.

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
Canada: 503 children at 12–18 years of age	Saguenay Youth Study	interview with mothers	Wechsler Intelligence Scale for Children; Woodcock-Johnson III, Spelling; Children's Memory Scale; Self Ordered Pointing Task; Ruff2-&-7 Selective Attention Test; Stroop Colour-Word Test; Verbal Fluency Test	household income, parental education, maternal alcohol use during pregnancy, ETS exposure during pregnancy, number of pregnancies, maternal age at delivery, birth weight, breastfeeding, birth order, parental warmth, parent monitoring, parental antisocial behavior	no effect of maternal smoking during pregnancy on cognitive abilities of adolescent offspring after matching by maternal education	Kafouri et al. (2009) [13]
Australia: 4 294 children at 14 years of age	Mater-University Study of Pregnancy, population-based birth cohort study	interview with mothers during pregnancy and at each follow-up (6 months, 5 and 14 years after delivery)	reports of academic performance overall and in English, science and mathematics	exact age at examination, child gender, maternal age, education, income, marital status, maternal alcohol consumption, maternal depression, family communication, birth weight, breastfeeding, behavioral problems at 14 years	maternal smoking during pregnancy was associated with small decrements in offspring academic performance (OR = 1.4, 95% CI: 1.1–1.7) after adjustment for variety of factors	O'Callaghan et al. (2010) [14]
Poland: 468 children at 3 years of age	Birth Cohort Study	questionnaire during pregnancy and after delivery	Bayley Mental Development Index of Bayley Scales of Infant Development (BSID-II)	maternal education, child, prenatal exposure to lead	the mental development index score correlated inversely with the number of cigarettes smoked daily by other household members at home over pregnancy period ( $r = -0.2$ , $p < 0.001$ )	Jedrychowski et al. (2010) [22]



Sweden: 654 707 children at 15 years of age	data collected from population-based registers	Medical Birth Register, completed before 15th week of gestation	school performance based on a summary grade point score of 16 different subjects from the National School Register, Grade 9 – mathematics score	maternal age, paternal age, birth order, gestational age, not cohabiting, maternal and paternal education and occupation	exposure associated with 0.5 SD decline in summary grade point in unrelated offspring ( $\beta = -0.6$ , $p \leq 0.05$ ), reduced to 0.03 SD increase in full siblings ( $\beta = 0.00$ , $p > 0.05$ ); exposure associated with 0.4 SD decline in mathematics score in unrelated offspring ( $\beta = -0.5$ , $p \leq 0.05$ ), reduced to 0.02 SD increase in full siblings ( $\beta = 0.00$ , $p > 0.05$ )	D'Onofrio et al. (2010) [18]
Republic of Korea: 414 infants at 6 months of age	multicenter prospective cohort study	questionnaire during pregnancy and at 6 months postpartum	Bayley Scales of Infant Development (BSID-II)	residential area, maternal age, pregnancy BMI, education, income, child gender, parity, birth weight, type of feeding	ETS exposure during pregnancy was associated with decrease in mental developmental index score ( $-2.8$ ; 95% CI: $-5.2$ to $-0.4$ ), and increased the risk of developmental delay (OR = 2.4, 95% CI: 1.2–4.6), psychomotor developmental index score was not associated with ETS exposure	Lee et al. (2011) [23]
United States Pittsburgh: 330 children at 10 years of age	Maternal Health Practices and Child Development Project, prospective study	interview with mother during 2nd trimester and after delivery	continuous performance test; Stroop Colour Word Test; Wide Range Assessment of Memory and Learning; Test of Variables of Attention	maternal substance use during childhood, age, ethnicity, child gender, child custody, single motherhood, SES, maternal stressful life events, maternal social support, quality and quantity of support available to the child for cognitive, social, and emotional development	exposed offspring had more delinquent, aggressive, and externalizing behaviors than offspring who were not exposed to tobacco prenatally; they were more active and impulsive, had more problems with peers, and had more difficulty on tasks requiring selective attention and response inhibition; the significant effects of exposure on neurobehavioral outcomes were found for $\geq 10$ cigarettes/day and mostly for 1st trimester exposure	Cornelius et al. (2011) [19]

**Table 1.** Exposure to active and passive smoking during pregnancy and children neurodevelopment – cont.

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
United States, Chicago: 234 at 5.9 years of age at 1st assessment and 2nd assessment 1 year later	Project on Human Development in Chicago Neighbourhoods, neighbourhood clusters	interview with mothers	attention network test	socioeconomic status, prenatal alcohol exposure, baseline performance, gestational age, birth weight, head circumference	exposure throughout pregnancy associated with 40 ms slower reaction times compared to no exposure or exposure through some of pregnancy ( $p = 0.002$ ), exposure not associated with accuracy ( $p = 0.7$ )	Mezzacappa et al. (2011) [20]
Denmark: 1 782 children at 5 years of age	Danish National Birth Cohort	interview with mothers at 17 gestational weeks	Wechsler Primary and Preschool Scales of Intelligence	parental education, maternal IQ, maternal alcohol consumption in pregnancy, the gender and age of the child, tester, prenatal paternal smoking, maternal age and BMI, parity, family/home environment, postnatal parental smoking, breast feeding, the child's health status, and indicators for hearing and vision impairments	unadjusted analyses showed a statistically significant decrement of 4 points on full-scale IQ associated with smoking $\geq 10$ cigarettes/day compared to non-smoking; after adjustment for potential confounders, no significant effects of prenatal exposure to tobacco smoking were found	Falgreen Eriksen et al. (2012) [15]
Poland: 406 children at age of 1 year and 198 at age 2 years	Polish Mother and Child Cohort	cotinine level in saliva collected once in each trimester of pregnancy	Bayley Scales of Infant and Toddler Development	examiner, child gender, age at assessment for combined analysis (1 or 2 years of age), parental age, parental education, marital status, child nursery attendance, cotinine level within 1st years of life	cotinine level in saliva collected during pregnancy was significantly associated with decreased motor abilities at age of 24 months ( $\beta = -2.6, p = 0.02$ ); there were no statistically significant effects of prenatal exposure tobacco constituents on cognitive and language abilities after controlling for variety of confounders	Polanska et al. (2013) [8]

ETS – environmental tobacco smoke; BMI – body mass index; IQ – intelligence quotient; SES – socioeconomic status; SD – standard deviation; HOME – quality of home environment.

controlled for [9–11,15]. Most of the studies pointed that child cognitive development is strongly influenced by parental IQ, socioeconomic status, home environment and sibling relationship.

Some studies indicated that prenatal tobacco smoke exposure can be related to children's academic performance. The studies performed in Finland [16], Sweden [17,18] and Australia [14] have shown a significant association between prenatal exposure and academic performance. Data from Collaborative Prenatal Project indicated significant impact of maternal smoking during pregnancy on academic achievement at 7 years of age including reading, spelling, arithmetic abilities, but the results were confounded by sibling relationship [11]. Studies focused on the impact of prenatal tobacco smoke exposure on memory, attention and executive function provided mixed findings. For example, Kafouri et al. (2009) did not find significant impact of maternal smoking in pregnancy on verbal, visual or visuospatial memory performance and Stroop Test interference score whereas Cornelius et al. (2011) indicated that performance on Stroop Test at 10 years of age was reduced with such exposure but no differences were seen on other task such as the Continuous Performance Test and Test of Variables of Attention [13,19]. Mezzcappa et al. (2011) described that the children exposed to tobacco smoke throughout the pregnancy demonstrated average reaction times 40 ms slower on the Attention Networks Tests compared to these who were not exposed or whose mothers stopped smoking at the beginning of pregnancy [20]. The relationship between maternal environmental tobacco smoke (ETS) exposure during pregnancy and children neurodevelopment was evaluated in 3 studies [21–23]. A Taiwanese cohort study reported a negative association between cotinine levels and 2-year child neurodevelopment assessed by developmental quotients of the whole test and cognitive, language, fine motor and social subtests of the Comprehensive

Developmental Inventory for Infants and Toddlers [21]. Similarly, a birth cohort study in Kraków showed an inverse association between mental development scores at 3 years of age and the number of cigarettes smoked daily by household members at home over the pregnancy period ( $p = 0.001$ ) [22]. Another study also suggests that the children of non-smoking women exposed to secondhand smoke during pregnancy are at risk of developmental delay [23].

In summary, although many studies are focused on the association between active and passive maternal smoking during pregnancy and children's cognitive, intellectual abilities, memory and attention, their results are not fully consistent. However, taking into account that there is some evidence of a risk of such exposure to children's psychomotor development that may last into adulthood, the problem requires further attention. There is a need to perform better designed studies with adequately assessed exposure level and controlled for potential confounding factors that may contribute to such outcomes, particularly genetic and environmental influences. Additionally, since differences have been reported depending on the timing and dose of exposure future studies addressing those issues may provide important information.

#### Exposure to low and moderate alcohol levels during pregnancy and children neurodevelopment

Maternal alcohol use during pregnancy contributes to a range of effects in exposed children, including hyperactivity and attention problems, learning and memory deficits and problems with social and emotional development. The most serious consequence of maternal drinking during pregnancy is fetal alcohol syndrome (FAS) [24,25]. Although it seems clear that heavy alcohol consumption during pregnancy can result in FAS, the effects of drinking at low-to-moderate levels on children neurodevelopment are much less clear.

Depending on the reviewed studies, the definition of low or moderate alcohol consumption was different. In most of the studies, the low alcohol drinking was defined as not more than 1–2 units of alcohol per week or less than 4 drinks per week and moderate drinking as not more than 3–6 units per week or 5 to 8 drinks per week.

In the prospective study performed among children from Avon Longitudinal Study of Parents and Children in England, the consumption of less than 1 drink per week during the 1st trimester was independently associated with mental health problems in girls at 47 months [26] (Table 2). In the study performed in United States (Pittsburgh, Pennsylvania) moderate alcohol exposure during the 1st and 2nd trimesters was related to the poorer composite score for African American children at age of 10. Significant relations were also found for the verbal, abstract/visual, and quantitative subscales [27].

Whereas Underbjerg et al. (2012) based on the Danish National Birth Cohort found no significant effects on test performance in children of mothers drinking up to 8 drinks per week [28]. Also O'Callaghan et al. (2007) did not find association between consumption of less than 1 glass/day in early or late pregnancy and attention, learning or cognitive outcomes among 14 years old children [29]. The strongest estimates of effect were noticed among those consuming 1 or more glasses/day, but the results were not statistically significant. Also, in the prospective cohort study (UK Millennium Cohort Study), children born to mothers who drank up to 1–2 drinks per week during pregnancy were not at increased risk of clinically relevant behavioral difficulties or cognitive deficits at 5 years of age [30].

One study assesses the low and moderate alcohol consumption and executive functioning in children [31]. Executive functions are defined as higher-order psychological abilities involved in goal-oriented behavior under conscious control [32]. Executive functions comprise several cognitive processes, including planning, organisation,

and measures of self-control [33]. Skogerbøet al. (2012) did not observe significant effects of low and moderate alcohol consumption during pregnancy on executive functioning at 5 years of age among children from the Danish National Birth Cohort [31]. The next group of the studies is associated with the children IQ measures. In the study performed in United States (Atlanta, Georgia) significantly lower IQ was found for African-American children at 15 years of age prenatally exposed to alcohol [33]. Alati et al. (2008) assessed the IQ at 8 years of age among children from Avon Longitudinal Study of Parents and Children in England [34]. Prenatal alcohol exposure was associated with lower IQ scores only in univariate analyses. In fully adjusted models, there was no strong statistical evidence that maternal alcohol and tobacco consumption during pregnancy were associated with childhood IQ. Falgreen Eriksen and co-workers (2012) observed that maternal consumption of low to moderate quantities of alcohol during pregnancy was not associated with the mean IQ score of preschool children, compared with children of mothers who abstained [35].

The Danish researchers performed also a combined analysis of the estimated effects of maternal average weekly alcohol consumption in early and mid-pregnancy on general intelligence, attention and executive function. Multivariate analysis showed no statistically significant effects of average weekly alcohol consumption, either individually or in combination on child's intelligence, attention and executive function [36]. These results replicate findings from separate analyses of alcohol consumption on child's intelligence, attention and executive function [31,35].

In summary, more compelling and stronger evidence is needed to evaluate the effect of low-to-moderate levels drinking during pregnancy. The evidence needs to be strengthened and the quality of information about drinking pattern should be improved. As the acceptable, safe levels of alcohol use during pregnancy have not yet been

**Table 2.** Exposure to low and moderate alcohol levels during pregnancy and children neurodevelopment

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
United States, Pittsburgh Pennsylvania: 636 mother-child pairs examined at birth, at 8 and 18 months; and 3, 6, and 10 years	Maternal Health Practices and Child Development Project – prospective study	quantity and frequency of beer, wine, liquor, beer cooler and wine cooler use during each trimester of pregnancy; prenatal alcohol use was expressed as the ADV or the average number of drinks/day	Stanford-Binet Intelligence Scale	maternal IQ, age, income, marital status, height, weight gain during pregnancy, race, parity, gestational age, depression, social support	relation between alcohol exposure during the 1st ( $\beta = -2.75$ , $p < 0.05$ ) and 2nd trimesters ( $\beta = -7.15$ , $p < 0.01$ ) and the composite score for African American children at age 10; significant relations were also found for the verbal (2nd trimester $\beta = -5.69$ , $p < 0.05$ ), abstract/visual (1st trimester $\beta = -3.33$ , $p = 0.05$ ; 2nd trimester $\beta = -6.32$ , $p < 0.05$ ), and quantitative reasoning subscales (2nd trimester $\beta = -5.78$ , $p < 0.05$ )	Willford et al. (2006) [27]
United States, Atlanta, Georgia: 265 low SES adolescents (mean age = 15.1 years), 128 prenatally exposed to alcohol, 53 controls, and 84 special education students born to mothers first recruited between 1980 and 1985 from a prenatal clinic in serving a predominantly African-American population	longitudinal cohort	women were recruited if they reported drinking at least 2 drinks/week during pregnancy	Wechsler Intelligence Scale for Children, Wechsler Individual Achievement Test, Vineland Adaptive Behavior Scales	age, education, monthly income, smoking, gender of the child	adolescent prenatally exposed to alcohol had significantly lower IQ (full scale IQ $p < 0.007$ ; verbal IQ $p < 0.01$ ; performance IQ $p < 0.01$ )	Howell et al. (2006) [33]

**Table 2.** Exposure to low and moderate alcohol levels during pregnancy and children neurodevelopment – cont.

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
Australia: 7223 singletons whose mothers were enrolled at the 1st antenatal visit assessed at 14 years	The Mater-University of Queensland Study of Pregnancy – prospective birth cohort	the alcohol consumption categories were as follows (oz/day): 0, 0.01–0.249, 0.25–0.499, and 0.5 or more, being equivalent to nil, < 1/2 glass, 1/2 to < 1 glass, and ≥ 1 glass/day	Wide Range Achievement Test-Revised, Raven's Standard Progressive Matrices Test, Child Behavior Checklist, Youth Self Report	maternal BMI, cigarette smoking, maternal education, maternal age, single parent status, low income in pregnancy	for consumption of < 1 glass/day in early or late pregnancy was no associated with any attention (OR = 1.0, 95% CI: 0.8–1.3), learning (OR = 1.0, 95% CI: 0.9–1.2) or cognitive outcomes (OR = 0.8, 95% CI: 0.7–1.01); exposure in late pregnancy was associated with increased prevalence of overall learning difficulty (OR = 0.8, 95% CI: 0.7–0.9) in the unadjusted, although not in the adjusted analysis (OR = 1.2, 95% CI: 0.1–2.3)	O'Callaghan et al. (2007) [29]
England: 9 086 children assessed at 47, 8 046 children assessed at 81, and 5 648 children assessed at 93–108 months	Avon Longitudinal Study of Parents and Children – prospective, population-based study	the mother was asked about her frequency of drinking alcoholic drinks; response categories were: never, < 1 glass/week, ≥ 1 glass/week, 1 to 2 glasses/day, 3 to 9 glasses/day, or > 10 glasses/day	Strengths and Difficulties Questionnaire	maternal age, parity, maternal smoking and use of cannabis and other illicit drugs in the 1st trimester, maternal education, housing, marital status	the consumption of < 1 drink/week during the 1st trimester was independently associated with mental health problems in girls at 47 months (OR = 1.10, 95% CI: 0.58–0.61)	Sayal et al. (2007) [26]

England: 4 332 children assessed at 8 years of age	Avon Longitudinal Study of Parents and Children – cohort study	the information about alcohol consumption was based on question: how often they had drunk alcoholic drinks during the first 3 months of pregnancy; Additionally participants and their partners were asked how many days in the previous month they had drunk the equivalent of 2 pints of beer, 4 glasses of wine or 4 pub measures of spirit or more	Weschler Intelligence Scale for Children	socio-economic status, marital status, level of education, head of household, occupational social class, an index indicating the crowding condition of the household, ethnicity, gender of the child, parity	prenatal alcohol exposure was not associated with lower IQ scores in multivariate analysis (OR = 0.98, 95% CI: 0.84–1.11)	Alati et al. (2008) [34]
England: 11 513 children assessed at 5 years of age	UK Millennium Cohort Study	participants were grouped according to mothers' reported alcohol consumption during pregnancy: never drinker, not in pregnancy, light (not more than 1–2 units/week or per occasion), moderate (not more than 3–6 units/week or 3–5 units/occasion	Strengths and Difficulties Questionnaire (SDQ), British Ability Scales (BAS)	no information-based on abstract	at age 5 years cohort members born to mothers who drank up to 1–2 drinks/week during pregnancy were not at increased risk of clinically relevant behavioral difficulties (for boys OR = 0.67, 95% CI: 0.53–0.86; for girls OR = 0.69, 95% CI: 0.50–0.96) or hyperactivity (for boys OR = 0.73, 95% CI: 0.58–0.91; for girls OR = 0.71, 95% CI: 0.53–0.94) compared with children of mothers in the not-in-pregnancy group	Kelly et al. (2010) [30]
Denmark: 1 628 women and their children at 5 years of age	Danish National Birth Cohort – cohort study	information on alcohol intake during pregnancy was derived from the 1st prenatal interview; all mothers were sampled in strata defined by their average alcohol intake (0, 1–4, 5–8, ≥ 9 drinks/week)	The Behavior Rating Inventory of Executive Function (BRIEF)	parental education, maternal IQ, prenatal maternal smoking, age at testing, and gender of child	not significant effects of low to moderate alcohol consumption during pregnancy on executive functioning at the age of 5 years (mean differences 1.20, 95% CI: –0.54–2.95)	Skogerbø et al. (2012) [31]

**Table 2.** Exposure to low and moderate alcohol levels during pregnancy and children neurodevelopment – cont.

Study population	Type of study	Exposure information	Test used for cognitive measurement	Confounding factors	Results	Reference
Denmark: 1 628 women and their children at 5 years of age	Danish National Birth Cohort – cohort study	information on alcohol intake during pregnancy was derived from the 1st prenatal interview; all mothers were sampled in strata defined by their average alcohol intake (0, 1–4, 5–8, ≥ 9 drinks/week)	Test of Everyday Attention for Children at Five (TEACh-5)	parental education, maternal IQ, maternal smoking in pregnancy, the child's age at testing, gender, tester, BMI, parity, home environment, postnatal smoking in the home, child's health status, and indicators for hearing and vision impairments	no significant effects on test performance in children of mothers drinking up to 8 drinks/week (OR = 3.50, 95% CI: 1.15–10.68)	Underbjerg et al. (2012) [28]
Denmark: 1 628 women and their children at 5 years of age	Danish National Birth Cohort – cohort study	information on alcohol intake during pregnancy was derived from the 1st prenatal interview; all mothers were sampled in strata defined by their average alcohol intake (0, 1–4, 5–8, ≥ 9 drinks/week)	Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R)	parental education, maternal IQ, maternal smoking in pregnancy, the child's age at testing, gender, tester, maternal binge drinking, age, BMI, parity, home environment, postnatal smoking in the home, health status, and indicators for hearing and vision impairments	maternal consumption of low to moderate quantities of alcohol during pregnancy was not associated with the mean IQ score of preschool children (full-scale IQ OR = 1.1, 95% CI: 0.5–2.4; verbal IQ OR = 1.3, 95% CI: 0.6–2.8; performance IQ OR = 1.2, 95% CI: 0.6–2.6)	Falgreen Eriksen et al. (2012) [35]



Denmark: 1 628 women and their children at 5 years of age	Danish National Birth Cohort – cohort study	information on alcohol intake during pregnancy was derived from the 1st prenatal interview; all mothers were sampled in strata defined by their average alcohol intake (0, 1–4, 5–8, ≥ 9 drinks/week)	Wechsler Preschool and Primary Scale of Intelligence – Revised (WPPSI-R), Test of Everyday Attention for Children at Five (TEACH-5), Behavior Rating Inventory of Executive Functions (BRIEF)	parental education, maternal IQ, prenatal/maternal smoking, the child's gender, age at testing, tester, parity, maternal marital status, age, BMI, prenatal maternal average number of drinks/week, home environment, postnatal parental smoking, health status, hearing and vision abilities	the analyses showed no statistically significant effects arising from average weekly alcohol consumption, either individually or in combination on child's intelligence (mean difference 0.45, 95% CI: 1.44–2.33), attention (mean difference 0.01, 95% CI: –0.14–0.17 and executive function (mean difference 0.81, 95% CI: –0.63–2.24)	Kesmodel et al. (2012) [36]
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ADV – average daily volume (ADV).  
Other abbreviations as in Table 1.

**Table 3.** Summary of the impact of prenatal exposure to tobacco smoke and alcohol on child neurodevelopment

Outcome	Prenatal exposure			
	low or moderate alcohol drinking	active smoking	passive smoking	
Behavioral difficulties, poorer attention functions, and executive functioning, mental problems	-	+	-	+
Decreased child intelligence, cognitive, language and motor deficits	-	+	-	+
Poorer performance at verbal, abstract/visual, and quantitative scales, memory	-	+	-	-
Lower school achievements, decreased learning abilities	-	-	-	-

“+” – statistically significant association between the exposure to maternal smoking or drinking during pregnancy and child neurodevelopment; “-” – no statistically significant association between the exposure to maternal smoking or drinking during pregnancy and child neurodevelopment.

established, avoiding alcohol use during pregnancy continues to be the advice for women.

### SUMMARY OF THE STUDY RESULTS

The reviewed studies indicate that maternal lifestyle during pregnancy, like active and passive smoking and alcohol drinking may contribute to neurodevelopmental problems in the offspring.

The results of the studies analyzing the association between prenatal exposure to tobacco constituents and children's neurodevelopment are not consistent. Some of them indicated that such exposure is harmful to the developing nervous system and established a link between the analyzed exposure and the neurobehavioral abnormalities (or some of them) in both infants and children [7,8,14,16,19,20–23], whereas other studies did not indicate the association after adjustment for covariates [5,6,9–13,15,17,18]. The association was most consistent for poorer academic achievements and increased risk of behavioral problems in children [7,14,16,19,20].

The results of the studies on low or moderate exposure to alcohol are inconsistent. In some of the studies maternal alcohol intake during pregnancy was associated with mental health problems [26], and poorer composite score and verbal, abstract/visual and quantitative subscales [27]. On the other hand, no effect on attention, learning, cognitive problems [29] also no increased risk of clinically relevant behavioral difficulties or cognitive deficits [30] and executive functioning was found [31]. Additionally the results of the studies on the impact of low to moderate alcohol consumption on IQ are inconclusive. Lower IQ scores were observed in some [33], but not all studies [34,35].

When reviewing the epidemiological studies on the influence of exposure to environmental factors and neurodevelopment in children, it is important to take into account the current limitations of these studies resulting from inadequacies in exposure and outcome assessment, study design and analysis.

### The mechanism of exposure to tobacco and alcohol and children neurodevelopment

The biological mechanism of exposure to active and passive smoking and alcohol consumption during pregnancy on brain development is well-described.

In order to understand mechanisms by which maternal smoking during pregnancy may influence neurodevelopmental performance, it is necessary to consider the effects of exposure not only to nicotine but to large amounts of other toxic substances including carbon monoxide and components of tar that can directly affect development of the fetal brain and nervous system. Increased level of carboxyhemoglobin in the bloodstream and reduced uterine blood flow by nicotine results in the fetus being deprived of oxygen and nutrients. Nicotine acts as a stimulant to cholinergic neurons, affecting neuro- and synaptogenesis and apoptosis [37]. Prenatal tobacco smoke exposure has also been linked to changes in amino-acid transportation, protein synthesis and enzyme activity, which can have a lasting impact on the developing brain. Cigarettes also contain many other toxic chemicals, including lead that can affect a developing fetus.

The teratogenicity of alcohol has been established [38–41]. This literature shows the importance for outcome of the dose, timing and conditions of exposure, as well as individual sensitivity of both mother and offspring [40]. Ethanol enhances migration of nerve cells, which is hypothesized to be involved in behavioral difficulties in childhood. It also interferes with the production of neuroendocrine hormones, which may perturb brain growth [41].

### Exposure assessment

The studies evaluating the impact of prenatal tobacco smoke exposure on child neurodevelopment assessed the exposure based on questionnaire data which may not be reliable. Some of the studies collect the data prospectively (the birth cohort studies) where exposure level during pregnancy was assessed in each trimester or at least once

during pregnancy, but there are also studies which use retrospective report of smoking status which, especially when it is done many years after child birth, may have led to misclassification. It is also important to remember that smoking habits can change over time with the reduction or quitting smoking during pregnancy, so the single measurement at some point in pregnancy may not indicate a true exposure level [37]. Additionally, women who do not smoke may be exposed to passive smoking which is also linked to a child psychomotor development and should be accounted for.

Although the studies on alcohol drinking during pregnancy and children neurodevelopment are well-designed (prospective cohort), the assessment of exposure is based on the information from mothers which can be the limitation of those studies. Alcohol consumption was calculated as the number of glasses of alcoholic drinks consumed weekly. Also, prenatal alcohol use was expressed as the average daily volume (ADV).

This review highlights the need for monitoring of active and passive tobacco smoking as well as alcohol consumption using biomarkers assessment.

#### **Tests for measuring specific neurodevelopmental effects**

To find a suitable test to measure different endpoints is a very challenging task. The investigator has to choose from a large number of potential endpoints that can be assessed in a prospective study on any given compound or a mixture of compounds to which the fetus or the child may be exposed. The choice of neurobehavioral domains and the tests used to index them should be determined by what is known about the impact of a particular environmental agent on the development of specific cognitive, neuromotor, and behavioral features. The diversity of test, or subtests used for child neurocognitive development assessment is one of the main obstacles to perform the meta-analysis of existing results.

Most of the studies included in the current review used Wechsler Intelligence Scale for Children, Wechsler

Preschool and Primary Scale of Intelligence, Wechsler or Wide Range Achievement Test or subscales of these tests [6,11,13,15,19,33–36]. For the evaluation of child behavior the authors used The Child Behavior Checklist [5,29] or Test of Everyday Attention for Children [28,36].

#### **Confounding factors**

The discussion to control the variables should be evidence-based on the findings reported in context of these relationships. The results of the most of presented studies were adjusted for well-known confounders. Those confounders are as follows: maternal and child demographic factors, such as maternal age, race, education, marital status, annual household income and child's gender.

Additionally, highly-stimulating home environment may help to counteract negative effects of prenatal tobacco smoke or alcohol exposure, but this was considered only in some of the reviewed studies. In evaluating the impact of active maternal smoking on child neurodevelopment the maternal ETS exposure and the child postnatal ETS exposure is recommended to be included as confounding factors. Other factors that can have an impact on child neurodevelopment are: gestational age, child birth weight and child head circumference.

Nearly all studies included in current review accounted for some of the variables stated above, but the concern is generally not that such factors are unmeasured, but that they are not measured well, which is the crucial point for stress, home environment and social class.

#### **Windows of exposure**

The effects produced by a neurotoxic agent depend on a number of factors: the timing and duration of exposure, the distribution of the toxicant in various parts of the nervous system, the amount or concentration of the agent in nervous tissue, and the ability of a toxicant to interfere with specific developmental processes. Therefore, the neurodevelopmental consequences

of exposure to different neurotoxic agents would be expected to vary, depending on the agent, the developmental stages of exposure, and the pattern and duration of exposure during those stages. An environmental neurotoxic agent may produce impairment in different functional domains, depending on the time of exposure. For example, the same exposure at different points of development could result in an adverse effect on motor systems versus memory or executive functions. Similarly, exposures at different concentrations or for different lengths of time could potentially produce differential effects. Therefore, the constellation of observed effects should not be expected to be the same in different children exposed to the same neurotoxic agent.

The study done by Cornelius et al. (2011) indicated that only exposure to maternal smoking in the 1st trimester of pregnancy was associated with some neurodevelopmental consequences, but it does not appear to be strong evidence of a particular period of pregnancy in which foetus is most vulnerable to tobacco smoke exposure [19]. Mezzacappa et al. (2011) also examined whether the association between prenatal tobacco smoke exposure and cognitive functioning was lessened in children of mothers who reported quitting smoking at early stages of pregnancy compared to children whose mothers smoked throughout it [20]. Although the authors noticed that quitting smoking at the beginning of pregnancy can be beneficial for child neurodevelopment, the further analysis indicated that early quitters tend to be these who smoked fewer cigarettes per day compared to those who continued to smoke. It is thus unclear whether these findings indicate an association with smoking specially during the later stages of pregnancy or with the amount of exposure in early stages. In the case of prenatal alcohol exposure 1 study indicates that developing brain may be especially vulnerable to such exposure in the 1st trimester of pregnancy [26].

### **Differences in the results between the studies**

There are possibly numerous factors contributing to the divergent results between the studies. The various developmental endpoints used may be a possible explanation for the different study results. The choice of covariates for statistical models may also impact the results. Further issue is a possibility of concomitant exposure to other neurotoxicants. Other potential explanations for the differences among studies include the type and timing of exposure, dose, measurement of the exposure or an outcome [42]. Studying neurodevelopmental vulnerabilities in children is very difficult. Varying definitions of endpoints, nonspecific end points caused by multiple factors, confounders and effect modifiers, and long latency periods between exposures and outcomes complicate attempts to reach definitive conclusions through epidemiologic studies.

### **Challenges for future studies**

Long-term studies that follow participants into adolescence and early adulthood are essential to assess the full range of neurodevelopmental consequences of exposure to environmental chemicals.

Some consensus regarding outcome measures should be reached to allow direct comparisons to be made between studies that measure the same neurobehavioral function. The choice of a given test should be determined by what is known about the impact of a particular compound exposure on the development of specific cognitive, neuromotor or behavioral functions.

Reliable exposure assessment, using a biomarker, and repeated measurement of exposure is crucial especially in the case of tobacco smoking or alcohol consumption, for which detrimental health impacts are well established, and for which the self-reported exposure levels may be underestimated. When the influence of confounding factors is possible, these should be taken into account during the stage of study design and data collection and finally in the statistical analysis. The potential effects of

confounding factors from exposure to other chemicals in most presented studies are unclear. Also the risk from a mixture, whether acting by similar mechanisms or not, need to be accurately assessed. Additionally, the impact of stress, nutrition and home environment need to be measured and controlled.

The studies indicated in this review were mostly carried out in the USA and Europe and further research is needed to determine whether these findings would translate to other parts of the world.

## CONCLUSIONS

The results of the reviewed studies suggest that exposure to active and passive smoking and low/moderate alcohol consumption during pregnancy may affect children's neurodevelopment. Exposure to these lifestyle factors can result in a spectrum of adverse outcomes from mental retardation and disability, to more subtle changes in function depending on the agent, timing and target tissue dose.

The reviewed studies have continued to show some relationship between tobacco smoke exposure, from active or passive maternal smoking during pregnancy, and children's psychomotor development, but this relationship is not straightforward. The association is most consistent for measures of academic achievements and behavioral problems but the wide variety of measurements used across different studies make it difficult to reconcile differences in findings for neuropsychological abilities.

Although the results of the studies on low or moderate exposure to alcohol are not fully consistent, some of them suggest that consumption of alcohol during pregnancy may adversely affect children IQ, mental health, memory, performance at verbal, abstract/visual, and quantitative scales. Furthermore, as no safe level of drinking during pregnancy has been established, the most conservative advice for women is not to drink alcohol during pregnancy.

The findings from this review should be included in guidelines for gynaecologists/obstetricians as well as healthcare and public health professionals. All efforts should be taken to eliminate tobacco smoke exposure and alcohol consumption during pregnancy to ensure appropriate children's development.

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