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Review Paper

Effect of Exposure to Toxic Compounds on Developmental Language Disorder: A Brief Review

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ABSTRACT

Background: Exposure to toxic compounds is a significant risk factor for developmental language disorder (DLD) in children. This review article aimed to evaluate and discuss the adverse effects of four groups of major toxic compounds, such as phthalates, cigarette and/or substance smoking, alcohol consumption, and exposure to heavy metals on DLD.

Methods: In this review, we analyzed research data from studies conducted between 1990 and 2024. We searched relevant MeSH terms in international databases, resulting in the identification of 312 articles. After applying inclusion and exclusion criteria, 42 articles were selected for analysis.

Results: The evaluated toxic compounds were found to affect children and lead to DLD in them. Two main routes of exposure of fetuses and babies to toxic compounds were identified: ***a)*** indirect exposure through mothers during pregnancy and ***b)*** direct exposure after birth. It was observed that essential metals for the body's metabolism, such as zinc and selenium, had inverse relationships with DLD, unlike toxic metals.

Conclusion: To minimize the risk of DLD, it is essential to reduce fetus and newborn exposure to toxic compounds. We recommend measuring levels of toxic compounds in pregnant mothers' blood during the last trimester and again at six months after the babies' birth. Cases with high levels of toxic compounds should be followed by clinical and laboratory examinations and appropriate treatment to minimize or prevent language development disorders later in children.

Keywords: Developmental language disorder, Neurodevelopmental, Specific language impairment, Toxic compounds

Introduction

Traumatic brain injury and autism spectrum disorder are two medical conditions that can cause language disorders in children [1-3]. However, some children experience profound language difficulties for no apparent reason, known as developmental language disorder (DLD), which constitutes 5-7% of the child population [4]. Moreover, DLD has been referred to as specific language impairment (SLI) in the literature [5]. Children with DLD face challenges in communicating with others and participating in social activities [6, 7] despite the availability of effective linguistic treatments and speech therapy methods [8, 9]. Diagnosing DLD in children is challenging due to the considerable differences in typical language development and the diverse characteristics within the DLD community [10]. In addition to language deficits, children with DLD may have difficulty with auditory comprehension, motor skills, working and long-term memory, statistical learning, and sustained attention [11-18].

The exact causes and mechanisms of DLD remain unclear. However, this condition is believed to be a complex disorder of neurological development. Multiple risks, including hereditary and environmental factors, impact brain activities and influence the child's neural growth and development. The risk factors include gender differences, family history, nutrition,

breastfeeding, maternal health problems, infections, timing, and exposure to toxic compounds through various routes [19-23]. This review article is a novel attempt to evaluate the impact of exposure to toxic compounds, as identified earlier, by searching relevant articles in reputable journals and discussing the various relationships with DLD in children.

Materials and Methods

This systematic review article presents the results of studies conducted between 1990 and 2024, as shown in Figure 1. Our main task began with determining the most significant and frequently used medical terminologies associated with the subject. Therefore, the MeSH terms were explored in reputable databases, such as Google Scholar, Scopus, PubMed, and Web of Science. Initially, 312 articles were identified, and 42 of them were selected for the final analysis based on inclusion and exclusion criteria. We used "AND" and "OR" to conduct an effective search. Additionally, we reviewed the references in the selected articles to ensure their relevance to the subject under study. The inclusion and exclusion criteria were as follows:

- Only studies about DLD or SLI were selected, and studies related to other speech and language disorders were excluded.
- Only studies that investigated the effect of toxic compounds on DLD or SLI were included.
- Investigations with a small sample size were excluded.
- Articles published in non-authoritative sources were also excluded.
- Articles and reports published on public and non-scientific websites were not considered.

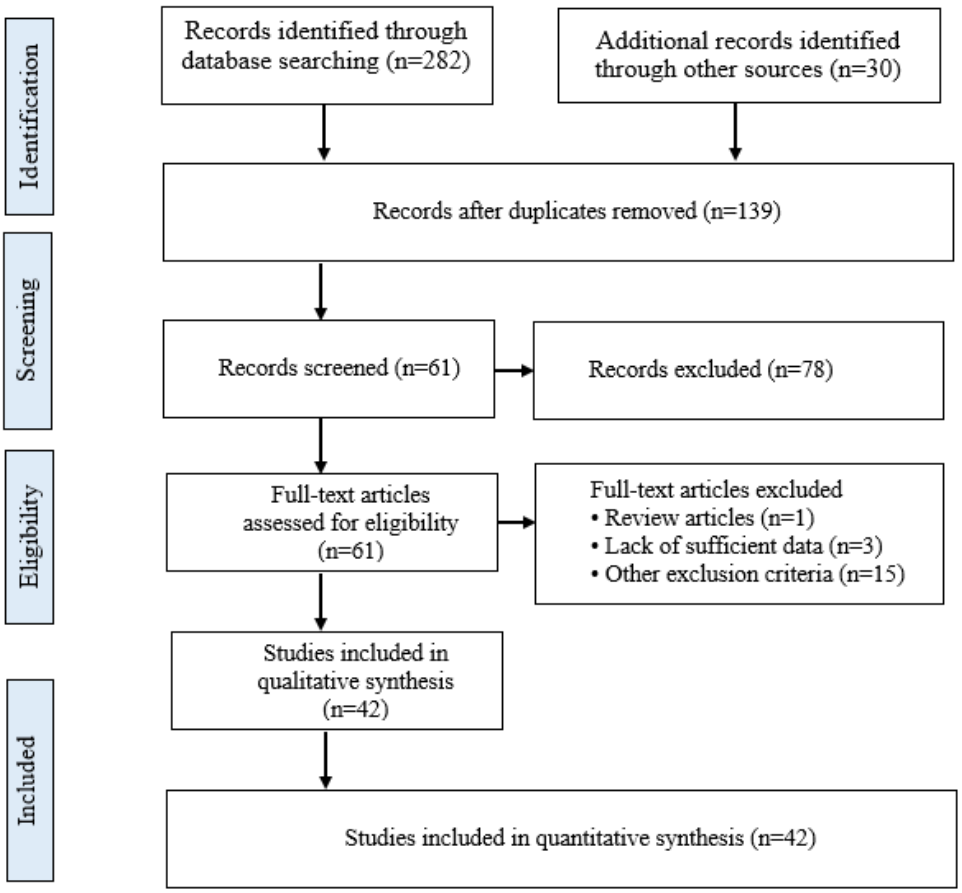

Figure 1. The review flowchart. Step-by-step process of the application of inclusion and exclusion criteria to select the eligible articles for the review

Results & Discussion

Children are likely to be exposed to toxic and harmful compounds at two stages of their lives. The first stage, which is indirect, occurs before birth, during the fetal period. This event may happen when pregnant mothers become exposed to toxic compounds in their environment [24]. The second stage, which is direct, occurs after birth when growing children are often exposed to toxic compounds in their living environment [25]. This brief review article presents the roles of the following four toxic compounds as the main factors responsible for DLD in children before and after birth:

- Phthalates,
- Cigarette and Substance Smoke,
- Alcohol,
- Heavy Metals.

Phthalates: These compounds are chemical

derivatives commonly found in polyvinyl chloride materials, which are often used for enhancing strength and flexibility. Phthalates are also utilized as solvents or stabilizers in certain pharmaceutical formulations [26]. These materials are semi-volatile compounds and are found in household dust and ambient air, which enter children's bodies through foods [27]. Therefore, they can exist in food via plastic bags and are also found in pesticides and household products, such as vinyl flooring materials [28]. Although phthalates are not often considered risk factors, this review explores their influence on the endocrine system during fetal neurodevelopment. Phthalates can affect fetuses and newborn babies through different pathways, and they contribute to neurobehavioral and developmental disorders in children. Routes of exposure include ingestion by pregnant mothers, placental circulation before birth [29], and exposure through breast milk and other foods consumed after birth [30]. Phthalates are semi-volatile compounds, and that is why they exist in household dust and ambient air and can enter children's bodies through food [26, 27].

Reports from several studies have indicated that exposure to phthalates may lead to neurobehavioral developmental disorders, such as growing aggression in children. This compound can also lead to attention deficits, depressive symptoms, prevalence of behavioral and psychomotor delays, and cognitive deficits in children. Other potential problems may be low intelligence quotient (IQ), slow memory and processing speed, and low scores in perceptual reasoning, working memory, and verbal comprehension [31-34]. However, a number of studies [35-39] have suggested no relationship between exposure to phthalates and cognitive deficits. Based on reports from studies, a strong correlation has been found between exposure to phthalates during the third trimester of pregnancy and language development deficits in children [37-39].

Based on other studies, exposure to phthalates can lead to increased oxidative stress, with its severity being dependent on the extent of exposure [40, 41]. Additionally, cell culture experiments have demonstrated that phthalate exposure can hinder the growth of neurons and cause changes in neurological development [42]. Administering antioxidant therapy with vitamin E and/or melatonin has been found to reduce oxidative stress and alleviate the negative effects [23]. Some other studies have indicated that specific types of phthalate, along with the gender of exposed children, are important factors in determining the adverse effects of phthalate. For instance, studies conducted by Kim *et al.* (2011), Weiss (2012), and Yolton *et al.* (2011) have reported stronger effects in male infants [34, 43, 44]. Alternatively, T'ellez-Rojo *et al.* (2013) and Whyatt *et al.* (2012) have reported these effects being more prominent in female infants [33, 45, 46]. Although the direct relationship between phthalates and language development is not quite clear, disruptions in the hormonal control of brain growth could potentially be responsible for the individual's susceptibility to language deficits [23].

Cigarette and Substance Smoke: Former studies have reported that prenatal exposure to tobacco and substance smoke can have significantly harmful impacts on the language and cognitive function of healthy infants [46, 47]. A review conducted by Peixinho *et al.* (2022) indicated that 57% of the 14 studies assessed provided direct evidence, while 35% offered indirect evidence that smoking impacts children's language development [47]. Additionally, studies by Eicher, *et al.* (2013) and Makin, *et al.* (1991) have indicated that the type and amount of maternal smoking can greatly affect their children's DLD. Specifically, high levels of maternal smoking are likely to be associated with severe clinical outcomes in children with DLD [48, 49]. However, another report has shown that the relationship between cigarette smoking throughout gestation and the occurrence of DLD in children is not necessarily consistent [23]. Studies by Diepeveen, *et al.* (2017) and Tomblin, *et al.* (1998) have found no relationship between mothers' smoking and the severity of their children's DLD [50, 51]. On the other hand, studies by Calder, *et al.* (2022), Law, *et al.* (2009), Rudolph (2017), and Tomblin, *et al.* (1997) have demonstrated that women's smoking during pregnancy increases the risk of DLD in their children [52-54,19].

Cigarette smoke contains toxic compounds, including nicotine. Studies [23,19,43-54] have shown that nicotine exposure can have harmful effects on human neurodevelopment, such as increased neuronal death, apoptosis, and suppression of synaptogenesis. These effects can lead to long-term changes in the hippocampus, somatosensory centers, and prefrontal cortex [55, 56]. Magnetic resonance imaging studies on human infants, adolescents, and rodents have revealed that prenatal nicotine exposure is associated with reduced brain volume, particularly in the frontal lobe, lateral ventricles, and cerebellar canals [57,58]. Further, thinning of the frontal, parietal, and temporal cortices can disrupt their microstructure and reduce the processing efficiency in the thalamus and white matter of the primary cortex [57, 58].

The brain's frontal and temporal lobes play a significant role in processing language skills. These areas are essential for comprehending spoken and written words, analyzing sentence structures, and processing phonological information in a bottom-up manner [59, 60]. Given the above review, it is highly likely that exposure to cigarette smoke, especially its nicotine, can affect brain development, particularly in the cortical regions, which are associated with speech [23]. Multiple studies have shown that prenatal

exposure to other substances, such as cocaine, heroin, and marijuana, is associated with severe impairments in various brain functions. These include cognition, auditory perception, receptive language, semantic abilities, phonological processing, syntactic development, and relevant motor skills [61-65].

Alcohol Consumption: Alcohol consumption during pregnancy by mothers can cause anatomical, cognitive, and language development disorders in the fetuses they carry [66]. The resultant disorders in infants may encompass a wide range of deficits in receptive and expressive language abilities, which can negatively impact the baby's vocabulary, grammar, and narrative skills [67-71]. Studies that examined the adverse effect of moderate alcohol consumption on infant language development have yielded inconsistent findings. This is likely due to significant variations in the factors associated with varying levels of alcohol exposure. Former studies conducted by Coggins, *et al.* (2007), Mattson and Riley (1998), Terband, *et al.* (2018), and Weinberg (1997) have reported that children whose mothers consumed alcohol during pregnancy were more likely to have speech and language disorders [71-73]. Coggins, *et al.* (2007) have reported that alcohol consumption by pregnant mothers may result in "negligence" in their children born during the same period of pregnancy [71].

Conversely, numerous studies conducted between 1990 and 2014 [51, 74-77] have reported no link between maternal alcohol consumption during pregnancy and children's speech and language disorders. While drinking alcohol at any point during pregnancy can potentially hinder the development of neurobehavioral skills, the latter half of pregnancy is particularly critical for the development of language deficits in newborn babies [70]. Further, other studies have indicated that the connection between low to moderate prenatal alcohol exposure and the neuropsychological outcomes of children born during that period is not fully established [78, 79].

Two studies conducted in 2004 and 2017 have revealed that only children who are exposed to alcohol during the first trimester may exhibit an increase in their sensation-seeking behavior [80, 81]. However, these babies do not usually suffer cognitive or language deficits. Since alcohol lacks specific receptors in the brain, it is unlikely that it selectively impacts any particular brain region [23]. DNA methylation plays a role in regulating the expression of many genes involved in various neurological functions. Such functions include neuronal differentiation, axonal guidance, neuronal excitability, neuro-inflammation and degeneration, and cell adhesion. All of these processes may be affected by alcohol-induced regulatory disruption [82]. Additionally, alcohol can alter numerous neurotransmitter systems [23]. For example, it can disrupt the neurotransmitters involved in inhibiting NMDA, which is essential for synaptic plasticity. Moreover, alcohol can have adverse effects on the density of specific GABAergic neurons, causing damage to outer hair cells in the ears and impacting various sensory developments [83-86].

Exposure to Heavy Metals: Heavy metals are chemical elements at high molecular densities and may be toxic even at low concentrations. Specifically, heavy metal ions, such as mercury (Hg), cadmium (Cd), arsenic (As), chromium (Cr), thallium (Ti), and lead (Pb), are known to be toxic to humans and animals. These elements are the natural components of the Earth's crust and cannot be degraded or destroyed. They may enter the human body through foods, drinking water, and breathing air [87]. As trace elements, some other heavy metals, such as copper (Cu), selenium (Se), and zinc (Zn), are necessary for the metabolism in the human body but may only cause toxic effects at high concentrations [87, 88].

Exposure to heavy metals can lead to language and learning disorders. In this context, Pb, Hg, As, and aluminum (Al) can have the greatest adverse effects on children's language development [89]. Lead can cause disorders in language recognition, auditory attention, intellectual function, and hearing function. It may also lead to disorders of reading, behavior, and memory in humans [90]. Manganese may also be implicated in the development of language delay. For instance, a study conducted by Wright, *et al.* (2006) has found that children's general intelligence scores, especially their verbal IQ scores, are significantly but inversely correlated with the level of manganese in their hair [91]. Additionally, reduced Se levels can result in stuttering, as reported by two former studies [92, 93]. Elevated blood levels of heavy metals in children [89] may affect language development and other bodily functions [89]. Another study conducted recently reported that the Zn level in the children's hair with DLD was significantly less than that of healthy children. However, there were no significant differences in terms of other metals, such as magnesium, iron, barium, Pb, and Al, between the two study groups [94]. Finally, the level of Zn in the scalp hair of children with SLI has been significantly lower than that of healthy children [95].

Conclusions

The findings of this brief review indicated that exposure to toxic compounds through alcohol consumption, smoking, substance abuse, and consuming food containing phthalates and toxic metals may result in DLD in children. The two main routes of contact with these toxic compounds are maternal exposure during pregnancy and infant exposure after birth. Mothers need to be fully informed about these factors to minimize their infants and young children's exposure to toxic substances, thereby decreasing the likelihood of developing DLD. It is highly

recommended that the levels of toxic compounds in mothers' blood be measured, especially during the last trimester of pregnancy and when their babies are six months old. Cases with high levels of toxic compounds should then be followed up with relevant clinical and laboratory examinations and follow-up. If these measures are observed, the chance of DLD in children can be prevented or at least minimized.

Conflict of Interests

The authors had no conflict of interest with any entities to disclose while they conducted this study.

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Compliance with Ethical Guidelines

Not applicable.

Authors' Contributions

AS, BM, AK, and KS: Designing the study; TM and AK: searching for past studies; AS and HS: extracting and recording the raw results; AS, BM, AK, AK, KS, and KT: writing the initial draft and revising the final version of the article.

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