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LETTER FROM THE FACILITATORS

We are excited to share the fourth issue of the CHILD journal that continues to highlight dedication to scientific inquiry among students in the Child Health Specialization (CHS) of the Honours Health Sciences Program at McMaster University.

Through this co-created initiative, our students ask meaningful questions about child health, critically appraise evidence-based literature, find gaps in knowledge, gather and synthesize evidence, and concisely communicate their findings. Students take initiative to divide themselves into subcommittees to work collaboratively and explore logistics and organizational processes that bring to fruition the publication. In addition to working within their cohort, our students engage with CHS alumni in the peer review process, as they learn what it means to contribute to the world of child health in a rapidly changing world.

We hope this exploration of topics highlights that investigating child health requires multifaceted and diverse perspectives. Whether we are exploring inequities at a systems level or analyzing family and local supports, each part contributes to a more holistic understanding of the well-being of children and their families.

In publishing this issue, we continue to celebrate the power of trusting students to engage with real-world questions as academic scholars. We hope this journal models student-led, collaborative learning. As always, we invite educators and researchers alike to consider how student voices can shape the future of health scholarship.

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SCOPING REVIEW EXAMINING THE EFFECTIVENESS OF PEANUT ORAL IMMUNOTHERAPY IN MANAGING PEANUT ALLERGIES IN PEDIATRIC POPULATIONS

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ABSTRACT

Background: Peanut allergy is a prevalent food allergy amongst pediatric populations and a leading cause for food-related allergic reactions. Peanut oral immunotherapy is a promising, emerging therapeutic that can be used to initiate desensitization, remission, and tolerance.

Objective: To determine the effectiveness of peanut oral immunotherapy in managing peanut allergies in pediatric populations (defined as birth - 18 years).

Methods: PubMed was searched on December 22nd, 2024, for relevant studies on children published in the last five years. Studies were reviewed in duplicate by two independent reviewers.

Results: Five studies highlighted peanut oral immunotherapy's positive impact on the management of peanut allergy in children. Chu et al. (2022) found that P-OIT with or without antihistamines induced similar levels of desensitization. Jones et al.'s (2022) data suggest that following peanut oral immunotherapy, 71% of participants achieved desensitization and 21% of participants achieved remission. As per Loke et al. (2022), 46% of children in the PPOIT and 51% of children in the P-OIT group achieved the primary outcome of remission. Furthermore, Loke et al. (2024), found that when P-OIT induces remission, it also has long-term benefits including higher peanut ingestion rates, fewer and less severe reactions, as well as improved HRQL. Uhl et al. (2024) reported an 84% success rate in children for accomplishing peanut protein tolerance for a limit of over 750 mg.

Conclusion: Literature on P-OIT demonstrates effectiveness in desensitization, remission, and tolerance for pediatric PA management. Given the therapeutic novelty, further research is necessary to create a standardized treatment method and confirm the effectiveness of P-OIT in pediatric populations.

ABBREVIATIONS

DBPCFC - Double-blind placebo-controlled food challenge
HRQL - Health-related quality of life
OFC - Oral food challenge
OIT - Oral immunotherapy
PA - Peanut allergy
P-OIT - Peanut oral immunotherapy
PPOIT - Probiotic peanut oral immunotherapy
ps-IgE - Peanut-specific IgE skin prick test
SPT - Skin prick test

INTRODUCTION

1.1 Peanut Allergies

Peanut allergy (PA) is the leading cause of food-related allergic reactions and the most common cause of food anaphylaxis-related fatality, with 1-3% of children (birth to 18 years of age) in Western countries receiving a diagnosis for a peanut allergy (PA) [1,2]. PA typically manifests in childhood and often persists throughout one's life. In fact, 80% of children with an allergy diagnosis in infancy will have a PA persist into adulthood [2].

Currently, the only supported PA management is strict peanut avoidance and the use of rescue medication (for instance, epinephrine auto-injectors) following accidental

exposure [1]. Due to peanuts being present in many foods and possible contamination within the manufacturing process, accidents are common, and avoidance can be challenging [1]. Strict allergen avoidance and PA self-management can often cause anxiety for patients and caregivers as PAs are typically long term [3]. It may also lead to impairment in health-related quality of life (HRQL) and act as a significant burden on children and their families [1-4]. As reported by a United States cross-sectional study from 2021, with 637 participants, PA patients and caregivers of peanut-allergic children indicated worse HRQL than a sample of chronically ill patients, with adolescents with PA reporting total HRQL scores approximately 5 points lower than those of children with other chronic illnesses [5]. In fact, 24.8% of study participants indicated being somewhat dissatisfied with current approaches of PA reaction prevention [5].

1.2 Peanut Allergy and Oral Immunotherapy

Recently, peanut oral immunotherapy (P-OIT) has emerged as a novel, promising therapeutic for managing PA and was approved by the US Food and Drug Administration and European Medicines Agency in 2020 [6-8]. Oral immunotherapy (OIT) consists of daily low-dose ingestion of the allergen, starting at a dose below what would cause a reaction [9,10]. Gradually, the doses increase until a maintenance dose is reached [9,10]. This process can yield OIT effectiveness on PA [9].

For the purposes of this review, effectiveness is defined in relation to desensitization, remission, and ideally, tolerance [9]. Desensitization is defined as temporary tolerance to the allergen when eaten regularly. In contrast, remission is the absence of clinical reactivity that persists after treatment has been discontinued for a period of time. Finally, tolerance is the complete ability to consume the allergen without an adverse reaction [9].

The objective of this scoping review is to determine the effectiveness of peanut oral immunotherapy in managing peanut allergies in pediatric populations (defined as birth - 18 years).

METHODS

2.1 Search Strategy and Eligibility Criteria

A scoping review was performed by searching PubMed on December 22nd, 2024, to gain a broad understanding of the effectiveness of P-OIT. Medical subject headings strung together by Boolean operators were used to produce the following search strategy: (treatment* OR therap*) AND (efficacy OR effectiveness) AND ("oral immunotherapy" OR OIT) AND (allerg* OR "allergic disease") AND (pediatric OR child* OR youth OR adolescen*). Filters were applied to include only individuals with peanut allergies and exclude papers published outside of the last five years, non-RCTs, non-English studies, preprints, and study populations that were not pediatric (defined as birth-18 years).

2.2 Data Collection

Four reviewers (MB, TC, LM, and PM) independently screened articles for titles, abstracts, and full texts in duplicate using Covidence. Conflicts were resolved by a third reviewer. The search produced 454 results. Seven duplicates were identified and automatically removed by Covidence. The included studies were then reduced to 5 through the exclusion of the papers that were not RCTs and those that did not include P-OIT as an intervention for PA during title and abstract screening and full-text review. Extracted data included study characteristics, methodology, intervention characteristics, outcomes, study strengths and limitations, and areas for future research.

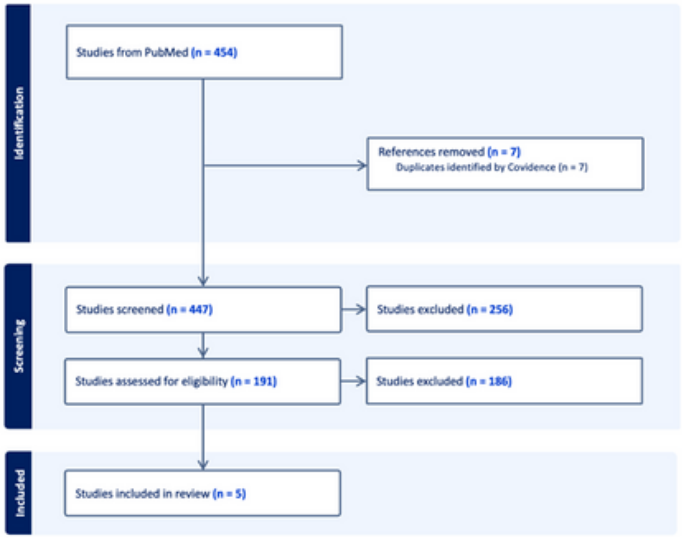

Figure 1. PRISMA Flow Diagram

RESULTS: EFFECTIVENESS OF P-OIT FOR PEDIATRIC PA

Research has demonstrated the effectiveness of P-OIT mainly by evaluating its success in inducing desensitization, remission, and tolerance. Below are five randomized controlled trials that are synthesized to highlight important findings on the effectiveness of P-OIT. The following articles were particularly chosen for their focus on P-OIT's effectiveness and their unique contribution to the ongoing discourse on P-OIT effectiveness in the scientific literature.

3.1 Peanut Oral Immunotherapy With or Without Antihistamine Premedication for Peanut Allergy

In 2022, Chu et al. conducted a placebo-controlled RCT at Hamilton Health Sciences' McMaster Children's Hospital in Canada to compare the effectiveness of P-OIT with or without concomitant use of desloratadine

and ranitidine, which are second-generation H1 antihistamines and H2 histamine blockers, respectively. Effectiveness was measured by the ability to induce desensitization. The primary outcome was the risk and incidence of adverse reactions.

Eligible participants were between 5 to 10 years old and determined to be allergic to peanuts based on a positive ps-IgE, presenting clinical symptoms following ingestion of peanut, and a positive serum-specific IgE result. From 2012 to 2015, 43 participants underwent randomization with 10 randomized to placebo-OIT + placebo premedication, 16 to P-OIT with placebo H1 and H2 premedication, and 17 to P-OIT with H1 and H2 premedication.

Participants underwent a baseline OFC. Patients assigned H1 and H2 premedication were orally given desloratadine 2.5 mg in 5 mL once daily along with ranitidine 75 mg in 5 mL twice daily. A dosage of 500 mg of peanut protein was reached and maintained for 12 months. Chu et al. found that P-OIT with or without antihistamines induced similar levels of desensitization, with the highest dose prior to reaction being 3643 ± 1053 mg peanut protein in the P-OIT and placebo antihistamines group and 3683 ± 724 in the P-OIT with antihistamines group. This suggests that antihistamine premedication did not increase desensitization beyond the ability of P-OIT. However, patients randomized to P-OIT with antihistamines had fewer adverse events than those without.

A strength of this study is its randomized, double-blind, placebo-controlled design, which reduces bias and enhances its reliability. However, a major limitation to the generalizability of the findings is its small sample size. The study did not assess long-term tolerance which means no conclusions can be made about lasting benefits of P-OIT [11].

This study confirms the effectiveness of P-OIT in inducing desensitization and suggests that antihistamine premedication may enhance safety without altering overall effectiveness.

3.2 Efficacy and Safety of OIT in Children Aged 1-3 Years with PA

In a double-blind randomized placebo-controlled study conducted by Jones et al. in 2022, P-OIT effectiveness was assessed through desensitization and remission. Eligible participants were children aged 0-12 who were reactive to 500 mg or less of peanut protein during a double-blind placebo-controlled food challenge (DBPCFC). Participants were collected across five academic medical centers in the United States. They were randomly assigned to receive P-OIT or placebo for 134 weeks with 2000 mg peanut protein per day followed by a 26-week avoidance period. The final sample size contained 146 children with the primary outcome being desensitization at the end of week 134, and the secondary outcome being remission after avoidance at week 160.

At week 134, 71% of participants who received P-OIT compared with 2% of participants who received placebo met the primary outcome of desensitization. After avoidance, 21% of participants receiving P-OIT compared to 2% of participants who received placebo met the secondary outcome of remission. While this study demonstrates several strengths such as double-blinding, randomized assignment to treatment, and the presence of a control group, there are notable limitations. Specifically, although the study included children aged 0-12, only 12% of participants were younger than 4, limiting the generalizability to younger children. Additionally, there was a high dropout rate during the 26-week avoidance period. Further, 27% of participants who received P-OIT and 20% of those who received placebo did not reach the maximal maintenance dose of 2000 mg [12].

The findings of this study support the effectiveness of early-life P-OIT in achieving desensitization and remission, though adherence challenges and age distribution limit the generalizability of its effectiveness.

3.3 Probiotic Peanut Oral Immunotherapy Versus Oral Immunotherapy and Placebo in Children With Peanut Allergy

In 2022, Loke et al. conducted a randomized controlled trial to assess the outcome of sustained unresponsiveness, otherwise known as “remission,” to probiotic peanut oral immunotherapy (PPOIT). Eligible participants were children aged 1-10 years old, weighing more than 7 kg, with a PA confirmed by a DBPCFC and either a positive peanut skin prick test (≥3 mm) or the presence of peanut-specific IgE (≥0.35 kU/L). Participants were recruited from three tertiary hospitals in Australia. Random assignment was done in a 2:2:1 ratio and participants were randomly assigned to PPOIT, placebo probiotic and P-OIT, or placebo probiotic and placebo P-OIT.

Treatment involved dose escalation of peanut protein until a 2000 mg daily maintenance dose was reached, for a duration of 18 months, followed by an 8-week peanut avoidance period. The primary outcome was remission, defined as no allergic reaction to a cumulative 4950 mg dose of peanut protein during a DBPCFC at the end of the 18-month treatment period (T1), and after the 8-week avoidance period (T2).

The final sample size included 201 participants, and the researchers applied an intention-to-treat analysis to ensure results were unbiased and the randomization process was preserved. The results showed that 46% of children in the PPOIT and 51% of children in the placebo probiotic and P-OIT group achieved remission compared to only 5% of children in the placebo probiotic and placebo P-OIT group.

Strengths of this study include the use of randomization, the presence of multiple control groups, and the application of an intention-to-treat analysis applied—offering pragmatic results. However, some limitations include the lack of available data on participant demographics, differences in group sizes, and the absence of a clear rationale for choice of probiotic [4].

While probiotics did not enhance outcomes, this study reinforces the effectiveness of P-OIT alone in achieving remission in children with PA.

3.4 Two-Year Post-Treatment Outcomes Following P-OIT

In 2024, Loke et al. conducted a long-term follow up study to the previous 2022 randomized controlled trial, to assess the long-term outcomes of PPOIT and P-OIT.

Methods of the 2022 study have been thoroughly reported above. Based on the results of the previous study, participants were classified into the following groups: remission (passed both T1 and T2), DWR (desensitized at T1 but no remission at T2), or allergic (failed T1). Following these classifications, participants with remission were instructed to consume peanuts without restriction, DWR participants to ingest one to two peanuts daily, and allergic participants to continue strict avoidance.

Peanut ingestion, reactions, and HRQL measures were monitored prospectively over two years post-treatment. At two years, peanut ingestion rates were both substantially higher for PPOIT (86.7%) and P-OIT (78.7%), than for placebo (10.3%). Reactions decreased across all groups over time. At two years, remission and allergic groups had comparable reaction rates, but DWR participants experienced significantly more reactions than remission and allergic groups. Adrenaline injector use was 0% for remission participants compared to 5.3% for DWR and 2.3% for allergic participants. Remission participants also showed significantly greater HRQL improvements than DWR and allergic participants.

Strengths of this study include a high retention rate of participants continuing in the long-term follow up study, blinding, and treatment adherence. Despite these strengths, there are some limitations such as potential bias from clinical outcome awareness, a potent concentration of highly motivated participants due to their desire to follow-up, conservative classification of allergic participants, heterogeneity within groups, and the reliance on caregiver-reported quality of life measures [13].

This follow-up study demonstrates the long-term effectiveness of P-OIT and PPOIT in maintaining peanut ingestion rates and improving quality of life in children with prior remission.

3.5 High Degree of Desensitization After 1 Year of Early-Life P-OIT

In 2024, Uhl et al. conducted an interim analysis on the Small Children Oral Immunotherapy (SmaChO) study, an open-label randomized controlled trial at Sachs' Children and Youth Hospital in Sweden, to assess the effectiveness and safety of P-OIT. The primary outcome of this interim analysis was tolerance to a minimum of 750 mg of peanut protein following 1 year of P-OIT or avoidance.

Eligible participants were children aged 1 to 3 years living in Stockholm with IgE-antibodies to peanut protein. To be included, participants had to react to a baseline OFC of 250 mg peanut protein. 75 randomly selected participants underwent block randomization 2:1 to P-OIT or avoidance, forming groups of 50 and 25, respectively. In the P-OIT group, up-dosing of peanut protein occurred every 4 to 6 weeks until the maintenance dose of 285 mg was reached. P-OIT continued with a daily maintenance dose and clinical visits every 3 months for 1 year with 63 participants.

43 participants in the P-OIT group and 20 in avoidance received the 1-year OFC. 7 participants in the P-OIT group withdrew. At the 1-year OFC, 36 of 43 participants in the P-OIT group (84%) and 1 of 20 participants in the avoidance group (5%) tolerated a minimum cumulative dose of 750 mg of peanut protein. The P-OIT group had a median cumulative tolerated dose of 3,500 mg of peanut protein, compared with 2.8 mg in the avoidance group.

The study has a well-powered study size and relatively low dropout rates. However, it is limited by its open study design. These findings indicate that P-OIT with slow up-dosing and a low maintenance dose may be a safe and effective method of developing tolerance to peanuts in children aged 1 to 3 years [9].

The results of this study support the effectiveness of low-dose, early life P-OIT in safely achieving substantial desensitization among young children with PA.

DISCUSSION

4.1 Challenges and Risks

Despite the many benefits, P-OIT faces various challenges, specifically when implementing conclusions from controlled trials into real-world situations. Safety is still paramount according to studies led by the University Children's Hospital of Zurich and Basel, specifically during up-dosing, which carries an enhanced risk of anaphylaxis, especially in doses above 300 mg of peanut protein [14]. This indicates that adverse reactions are typically mild to moderate, with gastrointestinal symptoms being the most common in clinical studies evaluating the safety of P-OIT [15]. The time taken to achieve the maintenance phase was longer in patients

with other allergies or asthma, though comorbid conditions did not significantly impact the reaction's severity [14]. Another concern is the variability in patient response, with factors including non-adherence and avoidance of peanut doses commonly reported [11]. The presence of cofactors, such as exercise, have been associated with increasing the risk of allergic reactions and, therefore, may complicate the application of P-OIT in real-life situations [15].

Furthermore, real-world data illustrates that the amount of peanut protein in food products varies and thus might affect treatment effectiveness outside clinical trials [16]. These findings suggest that, while P-OIT is generally well-tolerated with mild to moderate adverse events, including rare cases of eosinophilic esophagitis (EoE), more research is needed to refine treatment protocols and accurately predict patient responses [11,15]. Despite the limitations of trial eligibility criteria and the strict guidelines often present in P-OIT clinical studies, real-world applications may involve a broader patient population, further emphasizing the need for individualized management [15]. Significant knowledge gaps create challenges when applying P-OIT in the real world.

4.2 Research Gaps

Many vital gaps remain in P-OIT research, especially regarding the long-term effects and sustainability of the treatment. A key issue concerns the duration of desensitization post-therapy—after treatment has stopped, it is unclear if protection may or may not be retained [11,15,16]. Moreover, there is a lack of reliable biomarkers that can predict the patient response to P-OIT, which makes the personalization of treatments complex and limits the understanding of how factors such as IgE levels influence the outcomes [14]. The absence of standardized dosing protocols further complicates treatment since different doses may lead to inconsistent results across studies and clinical practices [14,15]. More studies have also been conducted in controlled environments, thus lacking real-life analysis concerning variables such as changing peanut content and poor adherence on the part of patients. Finally, research regarding the psychosocial and immune mechanisms associated with the P-OIT reaction might help develop methods for improving tolerance during treatment or foreseeing specific responses in certain individuals [11]. Addressing these research gaps is crucial for optimizing P-OIT treatment.

4.3 Future Directions

The future of P-OIT is poised for significant advancements through continued research and innovation. One key area of focus is the long-term effects of P-OIT, particularly after the maintenance phase, to understand its sustained impact on patients' lives [16]. Research should be directed to patient goals and challenges so as to improve treatment adherence and success, particularly in diverse real-world settings. More extensive studies are needed to confirm safety data, evaluate the feasibility of higher doses, such as 1000 mg, and test various treatment protocols for optimal protection and the ability to safely introduce peanuts into the diet [14,16]. Moreover, specific IgE levels impact treatment outcomes, highlighting the need for standardized dosing and maintenance protocols in P-OIT to improve both safety and effectiveness [14]. Newer forms of delivering current P-OIT, such as powders, may decrease the burden of therapy. On the other hand, biologics such as anti-IgE therapy-omalizumab hold promise in minimizing adverse reactions while optimizing treatments [11,15]. As well, shared decision-making between allergists and families will be critical in determining the timing for early introduction and P-OIT treatment [17]. With these advancements, the future of P-OIT management looks more promising, focusing on personalized care, patient safety, and improved treatment outcomes.

4.4 Strengths and Limitations

A strength of our scoping review is our reliable data collection methods. Using Covidence and our data extraction table, we were able to identify which articles could be included and analyze their individual information. This plays into our second strength: the replicability of our study. With a clearly defined methodology, search strategy, and inclusion/exclusion criteria, other researchers can replicate our study to test its findings.

Limitations include the solo use of PubMed, which narrows the range of results. Furthermore, the absence of standard P-OIT dosages employed in studies makes comparisons difficult. Standardized protocols would enhance the consistency and applicability of research. Few studies are Canadian-specific, making it challenging to determine the effectiveness of P-OIT in the context of the local health care system. While the studies included within our review are geographically diverse, spanning Canada, the U.S., Europe, and Australia, this broad scope limits the applicability of our findings to the Canadian context, as regional differences in healthcare access and regulations are not standardized. Additionally, since the trials are conducted in varied healthcare systems, drawing accurate cross-context comparisons presents a challenge. Moreover, P-OIT is a novel treatment with unknown long-term consequences. Limited follow-up in studies also influences the data on long-term desensitization and remission. A more precise review could be carried out by research professionals in the field of OIT. The exclusion of grey literature and unpublished research could lead to publication bias, and a majority of the studies involved were conducted in controlled environments, which might not represent real-world situations. These flaws call for additional research efforts to standardize treatment, optimize P-OIT protocols, and determine its long-term effectiveness in pediatric populations.

CONCLUSION

Through our scoping review, we were able to identify the literature surrounding P-OIT and its effectiveness for achieving desensitization, remission, and allergen tolerance in pediatric populations in the last five years, following its approval in 2020. In this study we found a lack of standardization between P-OIT treatment in doses and timelines. Implementing a standardized P-OIT treatment may improve P-OIT utilization and improve patient outcomes. Based on our findings, P-OIT is a promising therapeutic as assessed through effectiveness. However, given the novelty of the treatment, future studies are necessary to standardize P-OIT methods and confirm its effectiveness in pediatric populations.

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APPENDIX

Study ID	Location	Study Design	Study Objective	Sample Size	Age of Participants	Outcomes
Chu et al., 2022	Canada	Randomized controlled trial	To determine whether premedication with desloratadine and ranitidine results in fewer side effects during peanut OIT/desensitization.	43	Median = 7.6 years	Risk and incidence rate of adverse reactions over time, HRQL
Jones et al., 2022	United States	Randomized controlled trial	To assess whether peanut oral immunotherapy can induce desensitisation or remission in children aged 1-3 years.	146	1-4 years (median = 3.3 years)	Adverse events, desensitization
Loke et al., 2022	Australia	Randomized controlled trial	To investigate whether addition of a probiotic adjuvant improved the efficacy or safety of peanut oral immunotherapy.	201	1-5 years = 104 (52%), 6-10 years = 97 (48%)	SU, ps-IgE and SPT results
Loke et al., 2024	Australia	Randomized controlled trial	To follow-up on outcomes at 1-year and 2-years post-treatment in participants completing the probiotic and peanut oral immunotherapy (PPOIT) -003 randomized trial	151	Mean age = 5.9 years	HRQL, number and severity of reactions, desensitization
Uhl et al., 2024	Sweden	Randomized controlled trial	To determine the safety and effectiveness of peanut OIT with a slow up-dosing strategy and low maintenance dose in children aged 1 to 3 years who were allergic to peanuts, through a 1-year interim analysis.	75	1-3 years (median = 30.5 moths)	Tolerance, adverse events

Table 1. Extracted Information from Included Studies

SOCIOEMOTIONAL DEVELOPMENT OF CHILDREN WITH CLEFT LIP WITH OR WITHOUT CLEFT PALATE (CL/P) ACROSS SOCIOECONOMIC BACKGROUNDS AND POTENTIAL IMPACTS ON FAMILIES: NARRATIVE REVIEW

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ABSTRACT

Cleft lip with or without cleft palate (CL/P) is a congenital developmental defect of the hard palate and is one of the most common congenital craniofacial abnormalities, resulting in common symptoms like feeding difficulties, hearing problems, and dental issues. In addition to these common physical implications, children with CL/P may also face challenges within the socioemotional domain. These challenges may also be worsened depending on individuals' social determinants of health: in particular, their socioeconomic status (SES). Database searches were conducted to understand the literature on the experiences of children with CL/P and their caregivers, and how these experiences intersect with SES. Barriers associated with SES include challenges regarding psychological impacts on caregivers, perception and stigma, socialization opportunities surrounding language, and access to medical interventions. These concerns emphasize the significance of considering the effect of socioeconomic implications on children with CL/P, highlighting the push for further research and resources to support their socioemotional development into adulthood.

KEY WORDS

cleft lip with or without cleft palate; socioeconomic status; child development; socioemotional development; psychological impact; stigma; socialization; medical interventions

INTRODUCTION

According to the Global Oral Health Status Report conducted by the World Health Organization in 2022, oral diseases affect 3.5 billion people worldwide, with orofacial clefts having a prevalence of 1 in every 1000-1500 births [1]. Amongst these is cleft lip with or without cleft palate (CL/P), which is the fourth most common congenital, hereditary craniofacial abnormality, often visualized as an opening in the upper lip and/or palate [2]. Typical oral development begins at week four of human embryogenesis and is complete by week ten: cleft lip develops due to the incomplete fusion of nasal processes with the maxillary process around week four, while a cleft palate forms due to the failed fusion of the palatal shelves around week eight [3]. The incomplete and/or failed fusion results in feeding problems from difficulties latching, hearing troubles from eustachian tube dysfunction, and articulation errors from hypernasality [4]. However, the clinical implications of CL/P extend beyond physical problems, affecting children's psychosocial development and social skills as well [4].

The variability of this condition also differs across gender, race, and geographic location. There is debate regarding the cause of gender disparities and CL/P, but studies generally present how biological male babies are twice as likely to have the disorder than biological females [1,2,5]. Overall, the highest burden of CL/P is reported to be in countries with low social development, where the most significant burden lies in Sub-Saharan Africa, Middle East/North Africa, and South Asia [6]. According to recent studies, there is contradictory evidence illustrating the connection between a higher

incidence of orofacial clefts and lower socioeconomic status (SES), which refers to one's social and economic position in relation to others [2,7]; however, there is not much evidence on how SES influences early child development to adulthood. The scope of this paper is through a global lens, as the differing levels of social development across regions result in global disparities related to CL/P. The socioemotional developmental domain, which focuses on emotional regulation and relationship building [8], was chosen since CL/P can be linked to an increased risk for social problems [9]. Consequently, the socioemotional effects should be targeted in tandem with existing physical interventions when it comes to managing CL/P. While this developmental defect can be divided into cleft lip only, cleft palate only, or cleft lip with cleft palate, the term "CL/P" was most frequently used in the literature to refer to the disorder and will be employed to best encompass the condition. This article aims to explore how CL/P affects children's socioemotional development and their respective implications on caregivers, within the context of different socioeconomic backgrounds.

METHODS

Database searches were conducted while grey literature was consulted. Searches in PubMed, OVID Medline, and the Web of Science detailed the socioemotional challenges experienced by children with CL/P. Specific keywords like ["cleft lip" OR "cleft palate"], ["socioemotional development"], and [child*] were used to explore the connection between SES and implications of CL/P development. We included articles that targeted the socioemotional outcomes of CL/P on children and the psychosocial impacts on their caregivers. The population chosen is the central focus of this article, as examining affected individuals allows the discussion to remain grounded in lived experiences. As CL/P is a multifaceted condition that overlaps many domains, the scope of this paper is rather broad to act as a more comprehensive overview. In addition to peer-reviewed journal articles, grey literature was consulted as well to reflect current care models and policy frameworks. Furthermore, all included articles are in English, allowing authors to critically appraise and interpret the material without translation bias. Databases were searched for results up to February 2025 to best reflect contemporary trends in healthcare delivery and epidemiological patterns. All information from literature reviews and grey literature was ultimately synthesized in the creation of this article.

IMPLICATIONS OF SES

Across race and ethnicity, the prevalence of CL/P is highest among Asian (0.82-4.04 per 1000 live births) and American populations (0.9-2.69 per 1000 live births), and lowest among African-American populations (0.18-1.67 per 1000 live births) [1,5,10]. Based on the Global Burden of Disease Study from 2019, the global prevalence rate per geographic location is highest in South Asia, followed by Africa, East Asia, Europe, Latin America, and North America [6]. Examining the statistics further, the burden rate per 100,000 can be calculated using disability-adjusted life years (DALYs). DALYs measure the overall disease burden expressed in the number of years lost due to mortality or morbidity, where a greater number may be indicative of greater health loss, worse quality of life, or increased deaths [11]. The global burden of CL/P was estimated to be 6.85 and is distributed as follows: Sub-Saharan Africa (13.11), South Asia (10.84), Middle East/North Africa (6.81), East Asia/Pacific (4.37), Latin American/Caribbean (3.26), Europe/Central Asia (2.37), and North America (0.96) [6]. These statistics prompted the article's investigation, as a greater burden rate could be traced back to systemic socioeconomic barriers. In turn, SES could play a role in a child with CL/P's typical socioemotional development, which will be examined through the following four challenges: psychological impacts on caregivers, perception and stigma, socialization opportunities, and access to medical interventions.

Psychological Impacts on Caregivers

The emotional toll on caregivers following the birth of a child with CL/P can be overwhelming. The evidence suggests that mothers often grapple with an intense combination of shock, self-blame, and sadness, interspersed with moments of acceptance and gratitude for their child's life [12]. Hlongwa and Rispel's article highlights a pervasive sense of guilt among caregivers, particularly those who associate the condition with their behaviours during pregnancy, such as smoking or alcohol consumption [12].

The practical demands of raising a child with CL/P are equally daunting. Feeding challenges necessitate constant attention and frequent hospital visits for specialized treatments, disrupting daily routines [12]. These demands are particularly burdensome for caregivers of rural or low-income backgrounds, where access to healthcare facilities often requires long, costly journeys. Hlongwa and Rispel's article further notes how caregivers, especially those who are unemployed, may struggle to afford public transportation, and how their repeated absences from work further jeopardize their financial stability [12]. The intersection of practical and financial stress underscores the disproportionate inequities affecting populations made vulnerable by systemic or structural factors.

Caregivers of lower SES are frequently challenged with chronic stress from financial struggles, unstable housing, and systemic injustices [13]. The blend of pressures can lead to elevated levels of depression and anxiety, making it even more challenging for them to respond sensitively to their children's needs [13]. The result is a cycle where caregiving stress feeds into the family dynamic, creating further strain [13]. On the contrary, for those of higher

SES, caregiving may often come with a unique kind of stress known as achievement-related stress, which arises from the increased demands of juggling both career and caregiving responsibilities, fueled by societal pressures to excel in both areas [14]. While this stress is real and impactful, caregivers of higher SES are typically better equipped to manage it due to accessible resources such as therapy, paid absences, and stress management programs that could help ease their burdens [14].

The gap in resource availability between caregivers of different SES levels significantly affects their emotional experiences. Although these gaps are non-specific to CL/P, they are highly generalizable to the situation faced by caregivers of children with orofacial clefts [15]. High SES caregivers generally enjoy better access to quality childcare, healthcare, and educational resources, which can relieve some of the caregiving stress; however, it also comes with increased demands for their child to succeed [16]. Meanwhile, low SES caregivers often find themselves without basic necessities, such as healthy food and access to education; this limitation consequently makes it hard for them to focus on long-term goals for their children [17].

Finally, guilt manifests differently for these two groups as well. High SES caregivers may worry that their job commitments take away from their caregiving, especially in a culture that celebrates "competitive parenting" and high achievement [16]. In contrast, low SES caregivers frequently feel guilty about not being able to provide the same material or developmental opportunities for their children, propelled further by societal stigma related to poverty, which can deepen their feelings of inadequacy [18].

Perception and Stigma

Stigma poses a social barrier for individuals suffering from CL/P across numerous communities. Prejudices concerning the disorder often originate from a misrepresentation and misunderstanding of the causes of CL/P [19]. For example, a systematic review conducted by Chung et al., found that many individuals in low-resource areas attribute CL/P to divine punishment, evil spirits, or eclipses [19,20]. This stigmatization often bleeds into societal beliefs by negatively affecting one's experience with marriage, education, and employment [20]. Those with CL/P struggle to find significant others and face bullying in schools and the workplace [20]. Additionally, children with CL/P may experience reduced self-esteem [21]. The lower self-esteem may then hinder their ability to be educated in community spaces, as they often experience alienation from peers or are refused admission due to fear of frightening other students [21]. The emergence of negative experiences ultimately hinders their social function.

Public perceptions further exacerbate psychological strains on caregivers, reeling from stress and burden imposed on their child. A study conducted by Zhang et al. highlights that many caregivers suffered from negative emotions such as social anxiety and depression within the first three months after birthing a child with any orofacial cleft [22]. Negative emotions stem from fear of rejection from peer groups, and caregivers experienced high levels of discrimination [22]. Along with these harmful experiences, many experienced a worsened well-being and life satisfaction [22]. Citing the fact that visible impairments affect their children's social lives, many caregivers sought for their children to receive corrective surgery to reduce social stigma. Additionally, an investigative study found that caregivers with only a junior high school education had a greater stigma perception than participants who had received a minimum college education [22]. While family and close friends often provide much-needed support, societal reactions—ranging from gossip to intrusive questions—can create additional distress [12]. Mothers, in particular, report feeling judged during postnatal clinic visits or public outings [12]. Additionally, fathers' responses varied with some providing support or emotional and financial assistance, whereas others denied paternity, distancing themselves and leaving the mothers with sole responsibility. [12]. The societal scrutiny often delays their willingness to bring their child into public spaces until corrective surgeries are done, reflecting the pervasive stigma caregivers must navigate [12].

Furthermore, a child's social and educational environment can play a major role in perception and stigma. In schools, many children felt unsupported by their teachers when teasing occurred [23]. Additionally, children diagnosed with CL/P experienced decreasing satisfaction with their appearance as they aged [19]. During middle school years, children with CL/P were affected by bullying, discrimination, and teasing [24]. These individuals felt a lesser sense of self as "normal" compared to their peers [24]. Through facilitation of positive school transitions, support from clinical teams and implementation of teacher training can help to improve childhood experiences for those with CL/P [25]. In caregivers from Canada, the perceived stigma impacted the caregiver-child dynamic; resultantly, this leads to overprotectiveness or heightened sensitivity [26]. Overall, stigmatization and negative perceptions are a common experience for those suffering from CL/P that hinders their own emotional well-being.

Socialization Opportunities for Language Development

Several reports observe that children with CL/P experience delayed expressive language, as showcased through slower sound acquisition and limited sound inventory in early infancy [27-29]. These challenges with speech production experienced by children with CL/P can be attributed to altered oronasal structures, orofacial growth, and learned neuromotor patterns in infancy [27]. Furthermore, speech challenges can be distinguished as obligatory or compensatory [27,30]. Obligatory difficulties are due to structural deformities and cannot

be treated until anatomical changes are first addressed, typically through surgery [27,30]. Alternatively, compensatory difficulties refer to the learned behaviours of children throughout their development based on maladaptive articulatory movements, which include changes in placements of articulation [27]. In cases of compensatory difficulties, these challenges persist even following surgery or structural changes [27]. With this in mind, existing reports state that speech therapy is the leading treatment, as it assists children in learning the placement of articulators and practicing appropriate airflow [27]. Further, it is recommended that these interventions begin as early as possible to improve communication skills and promote children's social development [27]. Beyond speech therapy, early intervention models encompassing language stimulation also promote language and sound production in children with CL/P [31,32]. Such programs, which include play therapy, caregiver-delivered intervention programs, and facilitated caregiver-infant programs, can help promote language and sound production by improving vocabulary and familiarizing children with various phonetics [31,32].

Concerning the relationship between children with CL/P's socialization and SES, current literature reports that lower SES households experience reduced access to speech therapy services, with potential reasons for this disparity including prohibitive out-of-pocket expenses and lack of insurance [33-35]. Furthermore, caregivers from lower SES households may face additional barriers in accessing such language development programs, beyond the costs associated with such programs [36]. These conclusions are from studies performed in North America; while the healthcare systems differ across countries, caregivers from across the globe report similar barriers to accessing such therapies for their children [34,36]. Many barriers exacerbate the financial costs of language programs in lower SES households, such as requesting time off from work, obtaining reliable transportation, arranging childcare for siblings, and direct and indirect costs associated with higher incidences of insurance coverage disruptions [36].

Another consideration is the neighborhood where a child is raised and the social opportunities available [37]. Toddlers raised in more affluent areas are observed to have greater access to educational resources, such as books and toys that facilitate intellectual development, which can help improve their ability to meet age-appropriate language and developmental milestones despite the challenges associated with an orofacial cleft [37]. As well, it is also documented that toddlers raised in more affluent areas likely have greater access to outdoor play spaces, museums, and other enriching activities, which can act as social facilitators for language development [37]. All these factors exemplify other avenues by which SES influences childhood experiences with CL/P [37].

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Access to Medical Care and Interventions

In addition to speech therapy, care for children with CL/P involves a multidisciplinary care team of specialists that work together to devise a treatment plan upon diagnosis [9]. Members may include, but are not limited to, a developmental pediatrician, audiologist, oral surgeon, orthodontist, plastic surgeon, and speech-language pathologist [38]. Managing CL/P is a continual and long-term process with multiple assessments (i.e., physical, hearing, feeding, speech, etc.) and reconstructive surgeries, with a lifetime cost estimated at $101,000 per child across the United States of America [39]. In Canada, the publicly funded healthcare system covers part of the medical expenses for CL/P repair, but this coverage does not include certain procedures and therapies [40]. There are, however, many non-government organizations (NGOs) providing financial aid and resources, such as Operation Rainbow Canada, which offers free reconstructive surgery and related health care [41]. Government programs also exist, like Ontario's Cleft Lip and Palate and Craniofacial Dental Program, assisting families coping with treatment expenses; however, this program has eligibility criteria, requiring patients to be an Ontario resident and OHIP

member, have a CL/P diagnosis, and have sufficient residual craniofacial growth [42]. While existing NGOs and government programs could greatly ease the financial strain of CL/P, stringent and subjective eligibility criteria can still limit accessibility.

Notably, the medical costs associated with CL/P put families of lower SES at a great disadvantage. If CL/P is not treated appropriately in a timely manner, children may experience premature death and life-long difficulties in feeding, speaking, hearing, self-esteem, and psychosocial relationships [43]. The discrepancies with SES naturally create a degree of inequity between children from various SES backgrounds, affecting their socioemotional development and with lasting implications for later life. In fact, research has demonstrated that CL/P is undertreated in low- and middle-income countries due to late diagnosis and a lack of resources, consequently resulting in "extreme social stigma that has resulted in abandonment or infanticide" [44,45]. One study estimated there were "616,655 cases of unrepaired cleft lip and/or palate in 113 low- and middle-income countries in 2014" [46]. Further challenges faced by low-resource countries include lacking safe and sanitary facilities, long travel distances, or reduced specialist expertise. For instance, in South Africa, CL/P cases remain a burden due to a variety of factors, such as a low workforce density of dentists of 0.44 per 10,000 population [47]. The evidently sparse personnel in oral healthcare contributes to why 60% of children with CL/P in South Africa continue to suffer from a lack of care [47]. In addition to insufficient human resources, South Africa also faces a lack of data, increased social stigma, and negative environmental impacts, with areas of greater environmental pollution being linked to CL/P hotspots [47]. Not only do the listed challenges create financial and additional psychological burdens on caregivers, but it also places a heavy emphasis on NGOs. According to Sommerlad, approximately 75% of children with CL/P in low-income countries are treated by NGOs, emphasizing the need for better support and changes in the future focused on long-term sustainability [48]. A proposed method could entail designing training models in low-income countries to manage CL/P [49]. In this way, resources and personnel can be integrated to optimize patient care.

As mentioned, surgery is the immediate treatment option when it comes to CL/P interventions, resulting "in increased self-esteem, self-confidence and satisfaction with appearance" [50]. Furthermore, surgery can be seen as a way to increase physical attractiveness, as physical beauty and social acceptability are common problems faced by individuals with CL/P [50]. At the same time, there is also the possibility of dissatisfaction with surgery since not meeting high expectations could further exacerbate a child's self-satisfaction [50]. In turn, there is not a "one size fits all" for CL/P treatment, and the emphasis should be on the specific needs of the child and family. Ultimately, while costs differ based on an individual's CL/P condition, geographic location, and insurance status, there is nevertheless a financial burden that comes with the long-term care of CL/P that could affect successful medical interventions.

DISCUSSION

Numerous studies have identified how children with CL/P experience more significant difficulties in social environments [51]. Since communication skills play a role in social interaction, articulation errors associated with CL/P may increase the hardships children face in these settings. It has been hypothesized that children with this condition may fear negative judgement from others, "preferring to observe rather than participate actively in conversations" [51]. This concern is further exacerbated by the associated increase of harassment and discrimination, leaving significant potential for lasting sentiments of inferiority. Additionally, the guilt experienced by caregivers is a testament to the societal stigma and misinformation surrounding CL/P. These emotional challenges are compounded by long-term concerns about the child's speech development, educational opportunities, and overall well-being [12]. In turn, while speech difficulties may be the most apparent socioemotional developmental challenge experienced by children with CL/P, there are many other negative impacts that may influence their growth.

Currently, the economic effects of CL/P are not fully understood; however, that does not diminish the importance of examining their costs [52,53]. Families of lower SES often face additional burdens associated with psychological implications, stigma, and financial strain. These barriers could also limit socialization opportunities for children, affecting typical socioemotional development. Caregivers of lower SES may also be at greater risk of neglecting their child due to these increased burdens [54], ultimately affecting attachment styles and emotional regulation. Cleft diagnosis in individuals can also lead to decreased employability in adulthood due to social inequities, such as facing mistreatment in their workplace [55], further perpetuating a cycle of financial stress. Considering these factors, concerns around SES becomes a pertinent issue that needs to be addressed. Currently, government programs and NGOs are in place to assist families with the financial costs of CL/P therapy; however, not only is treatment inaccessible for everyone, but these physical and surgical operations do not address the overlooked social or psychological consequences that children with CL/P often face.

Our review article examined different sources detailing current patterns of the impacts of SES on CL/P; however, there is a possibility for selection bias and oversimplification of the issues. Narrative reviews lack a standardized, comprehensive methodology for study inclusion, so there is an inherent risk that the literature selected may reflect biases. The included studies were also not assessed for quality, furthering how the

conclusions should be drawn with caution. The limitations of narrative reviews can result in an incomplete evaluation of all relevant studies and underrepresent conflicting findings. Nuances may have been missed, particularly in how SES interacts with intersecting factors like geographic location, healthcare access, ethnicity, or cultural stigma, which could all increase the risk of misinterpretation. As nuances are based on researchers' positionalities, transparency with the readers could further address the limitation. Finally, the subjective nature of this article can influence how general conclusions are interpreted and presented. Nevertheless, references were cross-checked, and discussions were held between authors to minimize these limitations to strive for a balanced and reflective summary.

CONCLUSION

Ultimately, this article provides a broad perspective of the issues surrounding SES and CL/P, synthesizing multiple perspectives to provide a general overview. At first, CL/P presents itself as if it only impacts the physical aspects of child development, but the challenges of CL/P impact child development far beyond appearances. With the integration of SES as a factor, potential impacts have risen that may influence typical socioemotional development. This article only discusses a few of the possible challenges associated with SES, and all potential influencing factors associated with families of children with CL/P should be considered together to best support them. More research should be conducted to provide possible alternatives to families of different socioeconomic backgrounds, accessing holistic multidisciplinary support from a team of specialists that best benefits all.

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EXPLORING BARRIERS AND INTERVENTIONS FOR LONG-TERM SOCIAL-EMOTIONAL IMPACTS OF ACQUIRED BRAIN INJURY ON PEDIATRIC PATIENTS IN CANADA: A NARRATIVE REVIEW

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ABSTRACT

Background: Acquired Brain Injury (ABI) refers to brain damage caused by factors such as external trauma or internal infections that occur after birth. ABI is a leading cause of death, disability, and illness in Canada. Pediatric ABI can have various long-term social-emotional impacts, such as lower cognitive abilities, challenges in social interactions, decreased levels of self-esteem and adaptive behaviour, and higher levels of loneliness and antisocial behaviour.

Objective: The objective of this review is to investigate the long-term impacts and implications of moderate to severe ABI on social-emotional development throughout childhood, and the interventions available for pediatric patients.

Methods: This review includes literature from academic databases, including Web of Science, Ovid MEDLINE, and PubMed. Grey literature from reputable sources, including Holland Bloorview Kids Rehabilitation Hospital and CanChild, were also included to provide a holistic view of ABI research. Studies focusing on children ages 6–21 with moderate to severe ABI were prioritized, particularly those conducted in Canadian contexts.

Results: Beyond injury severity and mechanism, caregiver mental health and family functioning influence a child's post-injury trajectory. Interventions addressing social-emotional development typically focus on reintegration into learning and recreation. Persistent challenges include disjointed hospital-to-school transition, insufficient long-term care coordination, and restricted teacher or caregiver training.

Conclusions: This review underscores the need for improved, evidence-based strategies to support the social-emotional development of Canadian children with ABI. Greater collaboration among healthcare providers, educators, and families, alongside more robust longitudinal research, could bridge existing gaps, thereby enhancing continuity of care and outcomes for pediatric ABI populations.

INTRODUCTION

Acquired brain injury (ABI) is a leading cause of death and disability among children in Canada [1]. Based on the 2019 Canadian Health Survey on Children and Youth, 4.4% of children in Ontario ages 1 to 17 years reported experiencing a head injury [1]. ABI is damage to the brain that occurs any time after a person is born. There are two types of ABI: traumatic and non-traumatic [2]. Traumatic brain injury (TBI) refers to a brain injury caused by an external force that either penetrates the skull or is non-penetrating but causes damage from trauma or force [2]. Non-traumatic brain injury (nTBI) refers to damage to the brain due to internal factors, such as a lack of oxygen, tumours, or vessel occlusions [2]. TBI is the most common cause of interruption in typical child development and the leading cause of death in North America in those under the age of 19 [3]. While less common, nTBIs still place a large burden on the healthcare system. In Ontario, Canada, between 2003 and 2010, 17,977 nTBIs requiring care were reported in patients under 19 years [4].

1.1 Severities and Clinical Presentations of ABI

Brain injury severity is a primary factor in predicting the

impact on an individual. The severity of a brain injury is commonly determined by the Glasglow Coma Scale (GCS) score, duration of unconsciousness, and duration of post-traumatic amnesia. Severity is categorized as mild, moderate, or severe. The vast majority (90%) of children who sustain TBI have mild brain injuries, with symptoms typically resolving within days or weeks [2,5]. Children with moderate to severe injuries often experience neurocognitive impairments, challenges with learning new information, deficits in executive function and psychosocial problems [3].

A head injury can be described as focal/localized or diffuse. Focal injury occurs when a specific location is damaged, such as with a stroke where a particular vascular territory is affected. Diffuse injury occurs when more than one area of the brain is damaged, often with acceleration/deceleration forces as well as cerebral edema and pressure effects [6].

1.2 Etiology of Pediatric ABI

Causes of pediatric ABI vary greatly depending on the patient's age and whether the injury is classified as traumatic or non-traumatic [7]. According to the Canadian Institute for Health Information's National Ambulatory Care Reporting System, in children and youth aged 5 to 19 years, the most common causes for TBI-related hospitalizations were sports (44%) and falls (24%) [8]. Other common causes of TBI include motor vehicle collisions, bike-related injuries, and acts of violence [3]. In very young children, non-accidental injury (NAI; previously Shaken Baby Syndrome) is a frequent cause of TBI [3].

According to a 2016 retrospective cohort study on children and youth in Ontario, Canada, with nTBI, the most common nTBI diagnoses were toxic effects of substances, brain tumours, and meningitis [4]. However, patient and clinical characteristics vary depending on the type of nTBI diagnosis. 76% of individuals presenting with toxic effects of substances were adolescents, while 86% of anoxic brain injury cases were infants [4].

1.3 Impact of pABI

Based on a review of children and youth with Brain Injury by CanChild, children with moderate to severe brain injuries experience multiple difficulties in function in the areas of self-care, mobility, cognition, behaviour, and speech and language [9]. The development of persistent behavioural and social disorders is a common post-injury occurrence after pediatric TBI (pTBI), affecting as many as 48% of pTBI survivors [10].

Social-emotional development is an umbrella term that describes individuals' various interpersonal and intrapersonal skills [11]. Social-emotional development entails (1) an individual's understanding of emotional experiences in the self and others, (2) the ability to express emotions in an age-appropriate way, and (3) emotional regulation capacities [11]. Social-emotional development has been found to be central for child and adolescent mental health and can protect against psychopathology and risk across development [12].

An important component of a child's social-emotional development is their participation. Participation, defined by the World Health Organization International Classification of Functioning, Disability and Health as involvement in a life situation, is thought to influence health and well-being [13,14]. Participation occurs in various contexts of a child's life, such as school, play, sport, entertainment, learning, civic life, and religious practice [14]. Therefore, exploring the participation patterns of children and youth with ABI in comparison to typically developing peers can help improve understanding of ABI on a child's social-emotional development.

This paper aims to investigate the long-term impacts and implications of moderate to severe TBI on social-emotional development throughout childhood, specifically for children and youth ages 6-21. This paper focuses on this age range as it excludes infant-toddler development, which can look markedly different from school-aged children. Additionally, restriction to school-going aged children provides multiple consistent environments, including full-time school, home environments, and healthcare settings in which interventions can be delivered. Furthermore, the paper explores existing interventions available in Canada for pediatric patients with a discussion on current gaps and potential solutions.

METHODS

The research process started with a grey literature consultation of the CanChild and Holland Bloorview Kids Rehabilitation Centre websites, as they are well-known and reputable Canadian organizations focused on treatment and research for children, youth, and adolescents with disabilities, including pABI.

This was followed by a database search on Ovid MEDLINE, Web of Science, CINAHL, and PubMed. Search terms included ABI, pediatric, Canada, long-term, social-emotional, intervention, and their modifiers (Appendix I). Articles were screened based on the following inclusion criteria: (a) the article primarily focuses on children and adolescents from ages 6-21, included under the term 'pediatric', (b) the article focuses on ABI resulting from penetrating and non-penetrating physical trauma, tumours, strokes, and infectious diseases pertaining to the head (ie, encephalitis and meningitis), (c) articles are written or translated in English, and (d) reviews, primary studies, and case studies. Although not part of a strict inclusion or exclusion criteria, Canadian papers were prioritized. As inclusion criteria was limited to Canadian research, the findings provided are likely more applicable to domestic contexts and future interventions and research. However,

sources from the US that were particularly relevant to the aim of this paper were also used tosupplement the research due to the rather limited research in Canada. Studies focusing on infant-toddlers and adults, as well as studies examining acute or short-term impacts and management of pABI, were excluded as they were beyond the scope of the review.

For the purpose of this review, long-term effects of moderate to severe ABI are defined as any impact that persists or manifests after hospitalization. Additionally, social-emotional health and development is defined as the extent to which an individual's understanding, expression and regulation of emotion in both intrapersonal and interpersonal contexts is age-appropriate [11].

3.1 Long-term social-emotional impacts of pABI on patients

pABI affects the child across a multitude of domains, including the social-emotional developmental domain [9]. The long-term social-emotional outcomes of pABI manifests across multiple environments including school, outside-of-school activities, and social settings [14-15]. Difficulties faced by children who sustained a pABI can include academic underachievement, disruptive behaviours, academic exclusion, frustration, lower self-esteem, and social and behavioural difficulties [15].

A survey-based study conducted by Law et. al with the CanChild Institute at McMaster using the Children Assessment of Participation and Enjoyment (CAPE) tool investigated the participation diversity and intensity of 135 children with pABI, comparing them to 354 controls [14]. While inclusion in this study was not limited to moderate-severe ABI, there was no significant difference between the mild and non-mild groups in terms of participation level. The CAPE measure is a valid and reliable assessment tool that examines recreational, active physical, social, skill-based, and self-improvement activities outside of the school environment. The study concluded that children with ABI had a significantly lower participation level across all five activity types and participated with less intensity in recreational, physical, skill-based, and self-improvement activities [14].

Furthermore, children with TBI may have difficulties processing social information and adjusting to social environments. The theory of mind, which is the ability to understand and interpret the thoughts and feelings of others, is an important aspect of social information processing [16]. A study by Hoskinson et al. was conducted at several sites in Canada and the United States, comparing 45 children aged 8-13 against 42 controls. Data was collected using a structural MRI, the Test of Everyday Attention for Children to evaluate executive function, and three measures of various aspects of the Theory of Mind [16]. Additionally, parents rated their child's social and behavioural adjustment using the Behaviour Assessment System for Children-Second Edition. The study's conclusions highlight group differences in performance on theory of mind assessments, with children with severe TBI performing more poorly compared to controls and mild to moderate TBI patients. Additionally, severe TBI patients exhibited lower overall brain volumes in the central executive network, which is foundational to executive functioning. Similarly, they showed reduced right-hemisphere mentalizing network volume. The mentalizing network is thought to support metacognitive tasks and the ability to think about the mental states of others, which is related to the theory of mind [16].

3.2 Barriers in transition to school and work for long-term ABI

Return to school and work posed a significant barrier for adolescents receiving ABI care, as reported by a study by Lindsay et al. This study conducted semi-structured interviews with 10 adolescents with a diagnosis of ABI and 9 of their parents from the Greater Toronto Area, Ontario, Canada to explore the transition of care from pediatric to adult care following a long-term ABI [17]. 7 of the 10 adolescents from the Lindsay et al. study expressed concern over the lack of support provided for transitioning back to school and work [17]. 3 parents also mentioned that more guidance was needed for their children's educational path and in finding meaningful workplace opportunities [17].

The hospital-to-school transition for students following ABI was further investigated in a qualitative systematic review by Hartman et al [18]. Of the 20 articles included in this review, three studies originating from Canada were investigated for this current paper–two papers by Bruce et al. (2008 and 2012) and a paper by Gauvin-Lepage et al. (2010) [19–21]. The two Bruce et al. studies involved a thematic analysis of 20 and 19 participants, respectively, which highlighted the importance of a liaison between the hospitals and schools to ensure a smooth transition for the patients [19–20]. This liaison allows for clear responsibilities of the hospital and school staff, bolstering their confidence to support the student. Additionally, the Gauvin-Lapage et al. study utilized a focus group design with adolescents, parents, and professionals to conclude that social inclusion is a significant factor contributing to smooth transitions [21]. Therefore, interventions must address not only individual accommodations, but also the social surroundings that make up norms and expectations.

3.3 Barriers in transition from pediatric to adult care for long-term ABI

Of the ten adolescents who participated in the Lindsay et al. study, seven had transitioned into adult care, one was on a waitlist, and two were not yet transitioned [17]. Those who have transitioned reported an adequate continuity of care, and that all necessary medical information followed the patient in this transition process [17]. However, these patients also expressed that there

was a significant difference in care that resulted in confusion and discomfort [17]. Although the logistical and administrative aspects of transitions may be well-structured, the patient experience shows that there is work to be done [17]. Three patients found the transition to be significantly challenging, even though they were 'ready' for the transition as deemed by the parents and healthcare workers [17]. Additionally, 3 of the 6 male participants felt that leaving the pediatric system at 18 was too early, as they felt they were too young to be making independent decisions [17]. The sudden change from receiving intensive pediatric care to a broader adult level of care seemed to be the most significant modulator of the transition process [17].

These barriers in the transition from pediatric to adult care have been considered a significant issue within the Canadian healthcare system [22]. A position statement by the Canadian Paediatric Society (CPS) included a call for action to improve the transition to adult care for youth with complex healthcare needs [22]. Within the call for action, the CPS recommended that there should be "flexible age cut-offs between pediatric and adult care services" [22]. Considering that growth and development within the physical, cognitive, moral, and socioemotional domains are individualized, strict age cut-offs–typically 18 in Ontario–are not the most appropriate, highlighting the importance of this recommendation [22]. By introducing systems that ready pediatric patients for adult-level care, patients may find the transition to be more manageable and comfortable [22].

3.4 Interventions and treatments for pABI

Emerging research highlights the need for and benefits of multifaceted treatment and intervention approaches, ranging from occupational therapy (OT) based programs, such as the Pathways and Resources for Engagement and Participation (PREP) intervention protocol created by CanChild, and online interventions such as the TeachABI intervention created and facilitated by Holland Bloorview Kids Rehabilitation Hospital.

The Pathways and Resources for Engagement and Participation (PREP) intervention is a strength-based intervention that focuses on enhancing participation by removing environmental barriers and having OTs support both adolescents and parents through coaching [23]. The PREP intervention includes 5 steps: Make goals, map out a plan, make it happen, measure process and outcomes and move forward [23]. In 2018, a study including 28 adolescents ages 12 to 18 with moderate physical disabilities examined the effectiveness of the PREP intervention in improving participation in community-based activities [23]. Adolescents were recruited from 5 major rehabilitation centres and 2 high schools in Greater Montreal, Quebec [23]. The findings demonstrate that participation can be improved by only changing environmental factors, which provides further evidence to support emerging therapeutic approaches that are "activity-based, goal-oriented, and ecological in nature" [23]. Due to the potential physical consequences of ABI, PREP may be an intervention that is effective for patients who have sustained an ABI.

Another intervention currently being implemented in Ontario is a training program for educators called TeachABI [24]. The TeachABI program is still in development and is intended to be a two-phased course with eLearning and in-person components [24]. A needs assessment conducted to inform the program highlighted gaps in educator training as well as the importance of school-based interventions to effectively accommodate students affected by ABI [24]. Stevens et al. (2021) used a mixed-methods approach, incorporating a survey and workshop to sample educators [24]. From there, they assessed potential resources to support educators and students with ABI in the classroom [24]. A total of 31 stakeholders were recruited, with 27 completing surveys [24]. Survey findings found that 83% of respondents reported being "somewhat knowledgeable" about pABI [24]. They acknowledged that there were significant impacts it can have on the cognitive, physical, and psychological domains in children [24]. Despite this awareness, 65% of participants reported not having experience working directly with students with ABI [24]. Additionally, the majority of participants (61%) reported feeling "not or somewhat comfortable" assisting a student's transition back to school post-ABI [24]. These findings show a disparity, as many educators had some experience working with children with ABI but had low levels of comfort assisting with reintegration post-injury [24]. Results from the workshop identified the need for a 2-part educational course for educators that emphasized building awareness and knowledge about ABI [24].

SCHOOLFirst is an evidence-based and user-driven resource that was co-created by educators, healthcare providers, youth, and families for educators to support students returning to school following a concussion [25]. In the study, educators engaged in a 90-minute workshop that combined a guided walkthrough of the online toolkit with a case-based discussion and completion of a return-to-school planning template [25]. Educators then had ongoing access to the site for classroom use, which is available today to the public. The free, self-paced online toolkit includes short videos, as well as printable planning and tip sheets [25]. This study, which included a survey taken during a concussion education and training workshop was conducted by Holland Bloorview Kids Rehabilitation Hospital and York Region District School Board [25]. Participants included 56 educators, primarily elementary and secondary school teachers, but also school administrators and child and youth workers [25]. Published in 2022, this study evaluated the usability and satisfaction of a return-to-school resource for students following concussion. This study and the associated findings concluded that educators were satisfied with the SCHOOLFirst resource and saw opportunities to use it in the future to support their students post-concussion [25]. Participants said their

overall concussion knowledge, as well as knowledge of how concussions affect the return to school process and available associated resources, increased after the workshop [25]. After the workshop, most participants felt confident in their ability to support students returning to school after a concussion [25].

DISCUSSION

4.1 Summary of the research

Findings from this review suggest pABI can significantly lower participation levels and intensity across all five activity types [15]. Children with TBI exhibited poorer performance in Theory of Mind assessment and a lower overall volume in the central executive and mentalizing networks, impacting executive functioning and metacognitive tasks, respectively [16]. Furthermore, studies exploring the common barriers for pABI patients found that return to school and work posed a large barrier for adolescents receiving ABI care and struggled with the transition between pediatric and adult care [17]. Various programs and resources, including the PREP intervention, TeachABI, and SCHOOLFirst exist to address the long-term social-emotional challenges children and youth living with moderate to severe ABI may experience [23–25].

4.2 Strengths and limitations

This paper presents a novel synthesis of research of the social-emotional impacts of ABI, focusing on research and interventions conducted within Canada.

The literature consistently highlights gaps in treatment coordination, continuity of care, and standardized approaches for pABI [26]. In 2014, Munce et al. highlighted the lack of coordinated, long-term follow-up services for youth with ABI in Ontario [26]. Lack of coordinated services can exacerbate long-term social-emotional challenges for youth, especially during critical transition periods, including back to school or to adulthood [26].

Evidence-based programs including TeachABI and SCHOOLFirst demonstrate the importance of strong partnerships and communication between families and caregivers, educators, and healthcare providers in promoting continuity of care, reducing gaps in knowledge, and ensuring consistent implementation of tailored interventions [24,25] Findings and conclusions drawn from the research studies on TeachABI and SCHOOLFirst highlighted that educators typically have limited formal training on ABI [24,25]. Although many educators understand concussion or ABI symptoms, they often lack the confidence and practical strategies to implement supports and accommodations [25].

There are several limitations associated with these findings. The prioritization of Canadian research highlighted gaps in the recency and depth of local research on social-emotional development. A 2021 prospective cohort study in the United States followed 534 children (including controls) to examine outcomes post-injury and pre-injury factors that may contribute to outcome severity and variance [27]. Similar longitudinal studies such as one conducted by Ryan et al. and systematic reviews like that conducted by Li and Liu synthesize primary studies and recent, high-quality evidence [28,29]. This provides a strong foundation of evidence to understand social-emotional development in relation to ABI within the United States. While geographically close, Canada has a remarkably different education and healthcare system to the United States, necessitating local research on ABI and its impacts on patients and caregivers to effectively inform future interventions and practice. This paper is limited to a smaller pool of evidence describing social-emotional impacts of pABI. Additionally, variability in methodologies, date at which the study was conducted, and the measures of social-emotional development may reduce the generalizability of the findings. Finally, the inclusion of studies only written or translated in English may introduce language bias by excluding relevant studies written in other languages.

4.3 Future research directions

While existing Canadian literature provides valuable insights into the long-term social-emotional impacts of pediatric ABI, there are a few limitations warranting future exploration. Future studies should incorporate longitudinal designs to capture social-emotional developmental changes over time within the Canadian context. This would provide a more comprehensive understanding of the evolving needs of children's long-term social-emotional development with ABI. Additionally, while interventions such as PREP show promise, there remains a lack of large-scale, controlled trials assessing their long-term effectiveness. Future Canadian research should prioritise research designs to assess the sustainability and effectiveness of interventions, ensuring these interventions effectively address the long-term needs of children with ABI.

CONCLUSION

Key influences, including injury severity, family dynamics, and educational support, collectively shape a child's developmental trajectory. Our review indicates when these young individuals re-enter everyday contexts like classrooms, sports, or community activities, they frequently encounter academic and behavioural challenges rooted in deficits with executive functions and social cognition, including theory of mind. Targeted programs like PREP, TeachABI, and SCHOOLFirst can foster more meaningful engagement in daily activities, particularly in school settings, and potentially bolster psychosocial outcomes. These interventions also highlight the need for a multi-stakeholder approach combining school, healthcare,

and family support to address these difficulties, and research consistently note gaps in service coordination and educator training.

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THE ROLE OF RETINOIC ACID IN EXPLAINING THE PREVALENCE OF STRABISMUS FOR CHILDREN WITH FETAL ALCOHOL SPECTRUM DISORDER: A LITERATURE REVIEW

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ABSTRACT

Background: Fetal Alcohol Spectrum Disorder (FASD) encompasses a range of neurodevelopmental conditions caused by prenatal alcohol exposure (PAE), affecting up to 5% of the population. Among its comorbidities, strabismus– a misalignment of the eyes– shows a significantly higher prevalence in children with FASD. Retinoic acid (RA), a metabolite of vitamin A, is crucial for extraocular muscle development. PAE disrupts RA metabolism, potentially mediating the relationship between FASD and strabismus.

Aim: To elucidate the biochemical and physiological pathways linking PAE to strabismus and specifically, focusing on the role of disrupted RA metabolism and its impact on extraocular muscle development and ocular alignment.

Methods: 746 articles relating to strabismus, FASD, and RA were identified using 5 databases. Of these, 67 articles were extracted based on relevance and full-text accessibility.

Results: PAE disrupts RA metabolism through competitive inhibition, reducing RA production by up to 87% and altering RA receptor expression. These disruptions may contribute to the development of strabismus by impairing the formation of extraocular muscles and the cerebellum, as supported by findings from both animal models and human studies under FASD-like conditions.

Conclusion: The disrupted RA metabolism caused by PAE provides a plausible explanation for the increased prevalence of strabismus in children with FASD. Further research into genetic and epigenetic markers could enhance clinical assessments and promote earlier diagnosis and intervention, especially for regions with higher FASD prevalence. Understanding these mechanisms is crucial for optimizing medical interventions and mitigating the severity of outcomes following PAE.

INTRODUCTION

1.1 Fetal Alcohol Spectrum Disorder

Fetal Alcohol Spectrum Disorders (FASD) encompass a range of conditions caused by alcohol consumption during pregnancy. Although the prevalence of FASD in North America was historically estimated to be 1% of the population, including in a meta-analysis from 2016, more recent estimates indicate upwards of 5% [1–6]. This increase may be partly due to ascertainment/diagnostic bias, considering its significant growth in attention and therefore diagnosis of FASD. However, considering the worldwide increases in alcohol consumption, there may be some truth to these increases [7–9]. The well-established condition under this spectrum, Fetal Alcohol Syndrome (FAS), requires the presence of three characteristics for a clinical diagnosis: characteristic facial dysmorphology, clinically significant impairments in three domains of the central nervous system (CNS), and prenatal or postnatal growth impairment [10–12]. Unfortunately, this excludes children affected by alcohol in-utero but were otherwise categorized as undergoing 'typical development' due to the absence of characteristic FAS features. To address this, the 5th edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) proposed a new clarifying term for diagnosis

associated with in-utero alcohol exposure, termed Neurobehavioral Disorder Associated With Prenatal Alcohol Exposure (ND-PAE) [13–15]. This term encompasses the full range of developmental disabilities associated with exposure to alcohol in-utero even in the absence of physical atypicalities, and is one this review will focus on. A proposed criterion of ND-PAE includes "more than minimal exposure to alcohol during gestation", defined as consuming more than 13 alcoholic drinks per month of pregnancy or more than 2 alcoholic drinks in one sitting [14]. Additional criteria include exhibition of impaired neurocognitive functioning, impaired self-regulation, and impaired day-to-day adaptive functioning, all of which must be present during childhood. Considering the lack of physical dysmorphologies used to diagnose FAS, ND-PAE is often categorized as a hidden disorder, making it difficult to accurately diagnose [6,16–18]. This characteristic of ND-PAE–or FASD in general–calls for supplementary diagnostic tools to strengthen a diagnosis. For the purposes of this review, the term 'FASD' will be used predominantly, as 'ND-PAE' is a fairly new term that has not been fully implemented nor integrated into the field.

1.2 Strabismus

The eye consists of six extraocular eye muscles that control movement. The six muscles are the superior rectus (elevation), inferior rectus (depression), medial rectus (adduction/medial movement), lateral rectus (abduction/lateral movement), superior oblique (intorsion/medial rotation), and inferior oblique (extorsion/lateral rotation). Strabismus is an eye condition whereby ocular alignment is not achieved due to issues related to eye muscles [19,20]. The global prevalence of childhood strabismus varies from 1.5–3%, by factors such as age and ethnicity, with South Ethiopia reporting up to 17.9% [21–27]. The high prevalence in regions like Ethiopia aligns with the similarly high rates of FASD cases in South African populations, highlighting the possible role of ethnicity and social determinants of health on these conditions [28,29]. The four classifications of strabismus and the resulting physical manifestations are highlighted in Table 1, alongside a diagram of the eye muscles in Figure 1 [30,31].

Classification	Result	Affected Muscle(s)
Esotropia	Eye turned inward	Overaction of *medial rectus* Underaction of *lateral rectus*
Exotropia	Eye turned outward	Overaction of *lateral rectus* Underaction of *medial rectus*
Hypertropia	Eye turned upward	Overaction of *superior rectus* OR *inferior oblique* Underaction of *lateral rectus* OR *superior oblique*
Hypotropia	Eye turned downward	Overaction of *inferior rectus* OR *superior oblique* Underaction of *superior rectus* OR *inferior oblique*

Table 1. Strabismus classifications and affected eye muscles

Current statistics show a robust relationship between FASD and strabismus [16,32–34]. In a cross-sectional, observational study performed by Kavitha et al., researchers revealed that 15.97% of children without

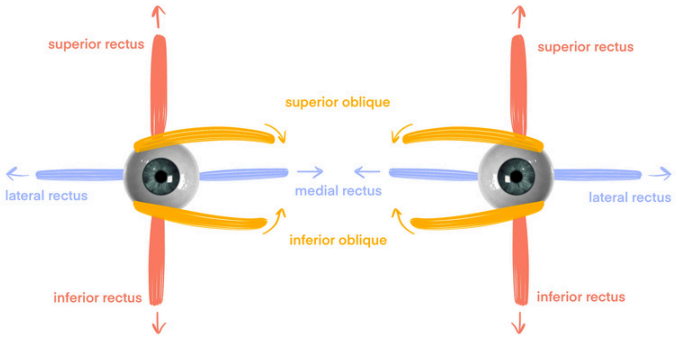

Figure 1. Muscles of the Eye

FASD had strabismus, whereas 41.49% of children with FASD had strabismus [35,36]. In one of their papers, Strömland et al. stated that alcohol was what significantly affected ocular abnormalities, like strabismus [37]. This review attempts to identify how alcohol contributes to this relationship in an effort to explain the significant correlation between FASD and strabismus.

METHODS

Multiple databases, namely Ovid MEDLINE, Ovid EMBASE, Web of Science, JSTOR, and PubMed were used to search for published academic articles in reputable journals. The majority of relevant literature was derived from Ovid as they yielded the most results. To provide an accurate review of the literature, grey literature and searches performed outside of databases were limited to the greatest extent possible unless deemed necessary for certain sections. Three clusters of keywords were used, including any associated abbreviations, truncations, and wildcards to refine the search: 1:['strabismus' OR 'cross eye'], 2:['fetal alcohol spectrum disorder' OR 'fetal alcohol syndrome' OR 'prenatal alcohol exposure'], and 3:['vitamin A' OR 'retinol' OR 'retinoic acid']. Full-text accessible articles both written and translated in English, were included. The initial searches across the databases (n=746) were condensed (n=486) by removing duplicates. Title and abstracts were screened for relevance. Studies exploring eye conditions besides strabismus were excluded, as it was beyond the scope of this review. 67 studies were ultimately selected and synthesized to inform the review, as illustrated in Figure 2.

RESULTS

3.1 Alcohol and its association with FASD

Although the dosage, timing, and duration of alcohol exposure to the prenatal environment may alter the extent of damage, it is unclear how each of these factors directly causes an outcome. Pregnant individuals are therefore strongly discouraged from consuming any amount of alcohol throughout a pregnancy. Unfortunately, the global prevalence of alcohol consumption during

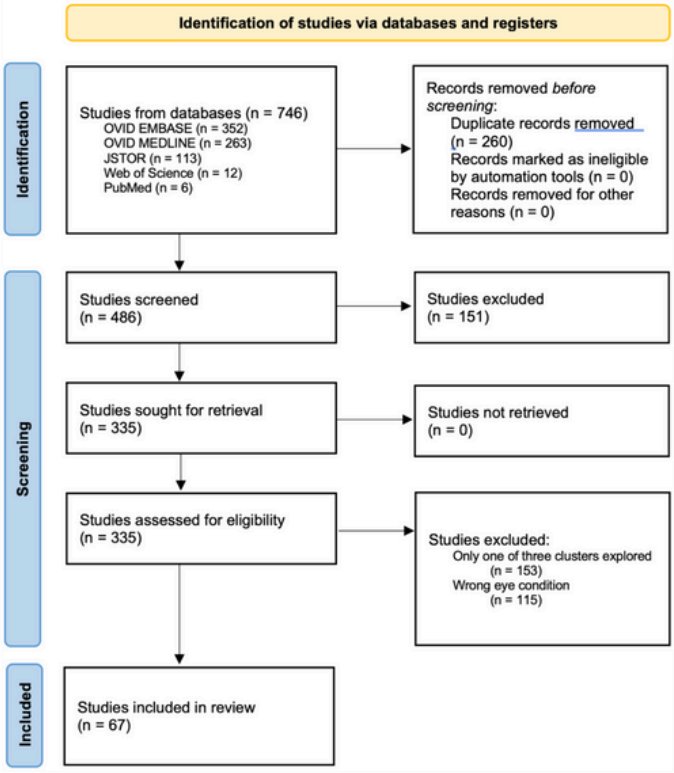

Figure 2. PRISMA flow diagram

pregnancy was estimated to be 9.8% as reported by a 2017 meta-analysis [38]. Alcohol is able to readily cross the placenta to reach the fetus, affecting fetal development [6]. In a prospective longitudinal study, researchers revealed that alcohol consumption also changes the expression of certain genes related to the growth and production of red blood cells (erythropoiesis) and blood vessels (angiogenesis), and iron homeostasis in the fetus [39]. The interference with these systems compromises proper fetal growth and neurodevelopment [40–42].

3.2 Alcohol and its association with retinoic acid levels

Retinol, commonly known as Vitamin A, was found to be a potential mediator of this relationship. The presence of alcohol arrests retinol metabolism, which may ultimately contribute to strabismus. Retinol, when metabolized, becomes Retinoic Acid (RA) using retinaldehyde as an intermediate (Figure III) [43,44]. RA regulates transcription factors, mediates embryogenesis and differentiation, develops the eye and its muscles, and acts as a morphogen that shapes the developing eye [44,45]. This metabolism is done by the enzyme Retinaldehyde Dehydrogenase (RDH). Alcohol is a potential molecule that is hypothesized to interrupt this interaction, as the ethanol in alcohol competitively inhibits RDH to convert ethanol into acetic acid instead of retinol into RA [46–48]. This is due to the similar molecular structures of retinol and ethanol. Another possible mechanism is the downregulation of the retinoic acid receptor β (RARβ) via ethanol [49–50]. Ethanol was found to change the expression of RARβ mRNA, possibly inferring that even if retinol were effectively

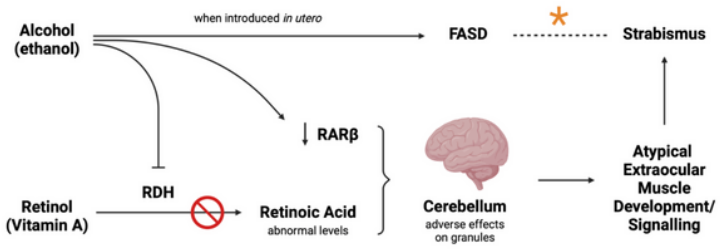

Figure 3. Visual Relationship between FASD and Strabismus (denoted by the dotted line)

converted to RA in the presence of ethanol, RA may not be able to induce adequate downstream effects due to the limited receptors.

Although the biochemical mechanism is still hypothetical, the impact of ethanol on RA levels is well-supported by the literature. Molotkov *et al*. recorded an 87% reduction in RA production when ethanol was introduced in mice, which is a significant drop [51]. Furthermore, Gray *et al*. demonstrated that, in an *in-vitro* experiment, the adverse effects of alcohol in development could be ameliorated by introducing RA into the culture [52]. Another study using rats demonstrated that alcohol consumption in pregnant mice not only decreased RA levels but increased retinol levels in the fetal heart [53]. This further supports the potential mechanism of retinol metabolism being inhibited by the presence of ethanol, therefore causing a build-up of retinol. This accumulation of retinol is also harmful to the fetus, as it is linked to developmental defects in the CNS [54–56]. In fact, a cross-sectional study found that 19% of children with FASD exhibited significantly elevated serum levels of retinol [57]. The researchers concluded these children may have a completely altered retinol metabolism, meaning the effects of prenatal alcohol exposure on a fetus' micronutrient balance may have sustained effects throughout child development. It is interesting to note that prenatal exposure to alcohol could also result in a significantly deficient serum vitamin A level, which then could also lead to developmental defects in the CNS, as presented in a case study by Goez *et al*. [58]. Perhaps this means that there is an optimal level of retinol and RA for typical development, and deviations from this optimum can have adverse effects on CNS development.

3.3 Retinoic acid levels and its association with strabismus

It has been established that ethanol exposure in the prenatal environment causes dysfunctional development of the CNS, contributing to outcomes like FASD. Of the CNS, the cerebellum, specifically the cerebellar granules, were most affected when animal models were exposed to third trimester-equivalent ethanol exposure [59]. Abnormal levels of RA, both excessive and deficient, were shown to also significantly impact cerebellar granules [60,61]. A study by Comai et al. demonstrated that RA plays a predominant role in initiating the establishment of extraocular muscles, which are

necessary for the fine displacement of the eyeball [62]. Problems and trauma to the extraocular muscles cause ocular motility disorders, like strabismus [63]. The cerebellar granules play a crucial role in eye coordination, and damage in this area can cause outcomes like strabismus. In fact, strabismus is one of the characteristic clinical features of an autosomal recessive disorder that causes degeneration of the cerebellar granules, called 'Primary Degeneration of the Granular Layer of the Cerebellum' [64]. A study by Kumar et al. confirms this relationship, as they demonstrated that high levels of ethanol affect RA receptor expression, impairing the survival and differentiation of cerebellar granules [49]. Furthermore, a systematic review of magnetic resonance imaging (MRI) studies of brains in subjects exposed to alcohol prenatally found that the physical cerebellar volume was consistently smaller when compared to controls [65–67]. In addition, lesions of the cerebellar vermin in three monkeys caused esodeviation, a loss of comitancy, and defects in phoria adaptation, which are all examples of ocular misalignments that are closely associated with strabismus [68,69]. Accordingly, it can be inferred that the cerebellum has a prominent role in ocular alignment, and therefore in preventing strabismus.

RA contributes significantly to the intricate processes of embryonic development, serving as a vital signaling molecule governing cellular differentiation and morphogenesis. An experimental research study conducted by Kahana et al. highlights the mediating behavior of RA in extraocular muscle (EOM) organization in zebrafish, supporting data from relative mammalian models [70]. Specifically, RA is observed to support the regulation of neural crest-derived periocular mesenchyme (POM), the tissue surrounding the optic cup, directing the formation of EOM-associated connective tissues [62]. The precise organization and structural integrity of EOMs, mediated by RA signaling, are essential for maintaining eye alignment during embryonic development and ensuring proper binocular vision. Consequently, disruptions in the RA signaling pathway can have profound consequences, leading to conditions impacted by the misarrangement of EOM, such as strabismus.

In a zebrafish model of FASD, Marrs et al. showed that the extent of FASD manifestations caused by ethanol could be alleviated by retinoic acid [71]. This further supports the hypothesis that retinoic acid, or the lack thereof, has a role in both strabismus and FASD, making it a prominent mediator of this relationship.

DISCUSSION

The relationship between FASD and strabismus is an important one. Although the relationship is multifaceted, elucidating these relationships can help healthcare providers, such as optometrists, ophthalmologists, and pediatricians, to accurately diagnose and inform patients of potential comorbidities. An example of this relationship in practice is the application of the FASD eye code (see below). As alluded to earlier, FASD is a hidden disorder, meaning that FASD cannot be diagnosed with a single test. There are also currently no standardized tools for FASD [72]. Instead, diagnosis is based on a combination of evidence, including the FASD eye code, whereby four vision assessments, one of them being strabismus, are completed to supplement a diagnosis. This complementary diagnostic tool for FASD was developed in 2021 by Aring *et al.*, which was demonstrated to have 38–52% sensitivity and 95–100% specificity [73,74]. Although the low sensitivity means that many true FASD cases will be missed (false negatives), its high specificity means that a positive result can be useful in ruling in FASD. Whilst the FASD eye code is helpful in theory, its practical adoption remains limited due to its novelty and the relatively low prevalence of FASD. It may be interesting to see if the FASD eye code will be implemented more effectively in regions where FASD and strabismus are significantly more prevalent, like Africa [1–6,28,29].

Clinically, these findings between FASD and strabismus highlight the importance of preventative counselling for pregnant individuals and families, particularly regarding the risks associated with PAE. Healthcare providers should receive education on the effects of disrupted RA metabolism, and its role in ocular abnormalities such as strabismus in children with FASD. Enhanced screening protocols and early intervention strategies could help reduce the developmental impact and improve long-term outcomes for affected individuals.

Moreover, incorporating FASD-related ocular conditions into medical education curricula would significantly enhance the ability of healthcare providers to identify and manage these cases effectively. Further, policy-level interventions could reinforce clinical practices by advocating for the integration of ocular screening in routine pediatric assessments. Together, these initiatives may lead to more standardized diagnostic procedures, improving both the accuracy and timeliness of FASD diagnosis and intervention.

While clinical and policy-level strategies are essential, understanding the broader genetic, environmental, and epigenetic contexts remains critical for fully addressing the complexities of FASD and strabismus. Maternal hypovitaminosis A, characterized by vitamin A deficiency, has been linked to various ocular malformations during embryonic development. The type and severity of these malformations depend on the stage of pregnancy during which the deficiency occurs [76]. Since ocular development is vulnerable to both vitamin A deficiency and PAE, findings from research in these areas may be transferable, offering deeper insights into external influences on eye development. Within the context of FASD, further research could explore how the timing and severity of alcohol exposure influences the manifestation of FASD comorbidities, such as abnormal

eye developments. It could be possible that the severity of PAE at different stages of gestation could result in a spectrum of abnormalities, ranging from complete deformation of the eyes to conditions like strabismus [77].

The nuances in the relationships between FASD and strabismus highlight its multifaceted nature. Ethanol and its effect on retinoic acid deficiency cannot be concluded as the sole factor that correlates the two. Genetic or environmental factors may predispose a child to these conditions, both pre- and post-natally, while others may possess protective factors [78]. On the other hand, epigenetic changes (alteration in gene expression without DNA sequence modification) induced by PAE could play a critical role in shaping the development of FASD and strabismus [79–81]. For example, a study by McKay *et al*. investigated the presence and expression of resilience alleles, which could serve as potential factors that protect against PAE-driven RA deficiency [78]. The role of genetic and epigenetic variables must be further explored to deepen our understanding of these complex relationships. Identifying and evaluating potential genetic and epigenetic biomarkers could then provide valuable tools for the clinical assessment of children with PAE. This could promote earlier diagnosis of FASD, enabling timely interventions and improved care. However, these areas remain underexplored, with some aspects yet to be investigated.

It is important to acknowledge the limitations that may hinder the strength of the literature review conducted. Firstly, the methodological approach of this study included papers exclusively published in the English language, narrowing the full scope of research that may provide relevant publications in other languages. Additionally, the heterogeneity in study designs, including sample populations, could limit the generalizability and comparability of findings. Many of the findings discussed are derived from animal models or in vitro studies, which warrant caution when applying these findings to human populations. Furthermore, future systematic reviews and meta-analyses could benefit from a more inclusive approach and rigorous quality assessment protocols to better validate the conclusions drawn in this review. Finally, although this review offers potential in explaining the relationship between FASD and strabismus, future research can focus on experimenting with these findings directly, drawing more conclusive results for this field of research.

CONCLUSION

Ultimately, the relationship between FASD and strabismus is complex, with disrupted RA metabolism highlighting the intricate interplay between PAE and ocular developmental outcomes. PAE significantly impacts RA metabolism, reducing its availability and altering receptor expression. This impairs the development of extraocular muscles and the cerebellum, leading to ocular misalignment. In support, evidence from animal models display the works of these mechanisms, explaining the prevalence of strabismus in children with FASD. Advancing the understanding of these multifactorial relationships is crucial for enabling early diagnosis and optimizing medical interventions. Further research should focus on investigating genetic and epigenetic biomarkers that elucidates and links the various factors outlined in Figure I. This could lead to the development of more robust assessment tools, mitigating the severity of outcomes following PAE.

Beyond advancing clinical understanding, public health initiatives may play a crucial role in reducing the prevalence and severity of FASD and its associated conditions, like strabismus. Raising awareness about the risks of PAE, alongside provision of additional support and education for at-risk populations, could significantly reduce the incidence of these outcomes. Additionally, implementing screening programs for early detection of FASD in high-prevalence regions could enable timely interventions, alleviating some of the downstream comorbidities. Collaboration between researchers, healthcare providers, and policymakers is essential to integrate these findings into effective prevention and care strategies, ultimately improving outcomes for affected children and their families.

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A REVIEW ON THE RELATIONSHIP BETWEEN MATERNAL ENVIRONMENT AND PEDIATRIC ALL INITIATION AND PROGRESSION: THE ROLE OF EARLY-LIFE EPIGENETIC MODIFICATIONS

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer, yet its etiology remains incompletely understood, particularly regarding the interplay between genetic, epigenetic, and environmental factors. This review explores how early-life epigenetic modifications contribute to ALL initiation and progression, with a focus on maternal influences. Unlike genetic mutations, epigenetic changes are reversible and shaped by environmental exposures, making them critical in leukemia risk and prognosis.

Maternal folate levels and metabolic conditions can alter fetal DNA methylation, influencing hematopoietic development. Folate provides methyl groups necessary for maintaining genomic stability, and its deficiency during pregnancy can lead to DNA hypomethylation, disrupting gene regulation and potentially fostering leukemogenesis, the process by which normal hematopoietic cells transform into malignant leukemia cells. Similarly, maternal diabetes, through hyperglycemia and insulin-like growth factor 1 overproduction, induces oxidative stress and epigenetic changes that may predispose offspring to ALL.

Epigenetic alterations, such as DNA methylation changes, can have distinct signatures linked to prognosis and therapeutic response. These findings highlight their potential as early biomarkers and targets for intervention. However, the field lacks longitudinal studies tracking epigenetic changes from birth to diagnosis.

By integrating research on maternal environmental factors and leukemia-associated epigenetic modifications, this review underscores the need for further investigation into potential pathways linking maternal exposures to epigenetic programming and subsequent leukemogenesis. Understanding these mechanisms could improve early detection, predict prognosis, and inform targeted therapies for pediatric ALL.

ABBREVIATIONS

Epigenetic signatures are abbreviated as the following:
i.e. H3K9me3: histone 3, lysine 9, trimethylation

INTRODUCTION

Acute lymphoblastic leukemia (ALL) is the most commonly diagnosed cancer in children [1]. ALL occurs when immature lymphoid stem or progenitor cells replicate uncontrollably, undergoing clonal proliferation. These malignant cells use more resources and take up more space in the patient's bone marrow, preventing healthy stem cells from maturing properly [2]. As a result, blood cell counts decrease leading to a range of symptoms including tiredness, bruising, swollen lymph nodes, and pain. Approximately 80% of childhood cases of ALL involve B-cell progenitor cells (B-ALL) [1].

The majority of pediatric ALL cases do not have well-established causes but may result from a genetic and/or environmental factors, such as familial cancer syndromes [1]. Several mutations have been identified in ALL subtypes defined by the World Health Organization (WHO) classification of leukemia [2]. These mutations

often involve aberrant activity of transcription factors, chromosomal gains or losses, and hyperactivity of tyrosine kinase genes, affecting growth, metabolism, and differentiation. Less commonly, genetic mutations may be inherited from parents and increase the child's risk of cancer. For instance, Li-Fraumeni syndrome occurs when a child inherits a mutated version of the TP53 tumor suppressor gene, increasing their risk of leukemia [3]. However, mutations are often acquired, developing after conception. Lifestyle-related risk factors such as body weight, physical exercise, tobacco use, and diet play a larger role in adult cancers but have a limited influence on childhood cancers as it takes several years for these factors to influence risk [4]. Ultimately, the cause of the majority of mutations in childhood ALL remain unknown, are thought to arise from chance mutations in lymphoblasts, which are mutations that occur randomly and without external influence [5].

Beyond genetic mutations, growing evidence highlights the role of epigenetic modifications in pediatric cancers [6]. Epigenetics is an emerging and evolving field of research which refers to heritable changes in gene expression that occur without altering the underlying DNA sequence [7]. Unlike inherited genetic mutations, epigenetic changes can be reversible [7]. These changes are regulated by mechanisms such as DNA methylation and histone modification, as well as microRNAs (miRNA), which influence how genes are expressed or silenced [7]. Epigenetic processes are crucial for normal development, but their dysregulation can contribute to cancer initiation and progression [8]. In pediatric ALL, epigenetic modifications can influence key processes such as cell differentiation, proliferation, and apoptosis. Typical hematopoietic cell development relies on precise regulation and control of these modifications. During leukemogenesis, these may also be deregulated. These epigenetic alterations may be triggered by environmental exposures in early life, such as maternal diet, environment, or toxic substances, potentially contributing to the initiation and progression of leukemia. Understanding the role of early-life epigenetic modifications in pediatric ALL offers valuable insights into disease mechanisms and can help inform therapeutic interventions and treatment.

While epigenetic mechanisms are well-documented at the time of ALL diagnosis, their potential role in predisposing children to the disease or contributing to its early development remains underexplored and not yet established [9]. The following review will investigate maternal environmental factors that contribute to early-life epigenetic changes. Then, it will demonstrate how these epigenetic changes are implicated in the initiation and progression of pediatric ALL. Through this exploration, the review will highlight potential mechanisms linking early-life epigenetic changes to increased susceptibility to pediatric ALL. Early-life is defined as the prenatal period.

METHODS

A comprehensive search was conducted concerning epigenetics, environmental influences, and their implications in pediatric ALL. Databases used included OVID, PubMed and ScienceDirect. Our inclusion criteria encompassed several study types such as systematic reviews, prospective and retrospective studies. However, case studies were excluded from our search to explore broader trends rather than focused examples. The literature included came from regions in North America, Europe and Asia as epigenetics involvement in pediatric ALL is an emerging field, resulting in a limited amount of research focused in North America alone. Thus, this article pulled from a variety of sources to have a well-rounded understanding of the relationship between epigenetics and pediatric ALL and produce more rigorous evidence-based conclusions.

ENVIRONMENTAL FACTORS

While there are several environmental factors that have been associated with the risk of developing childhood ALL, this review will focus on maternal folate intake, maternal diabetes, and maternal diet. The selection of these factors was based on their consistency in recent epidemiological studies, their biological relevance in fetal development and immune function, and the availability of peer-reviewed literature. With this refined scope, we aim to provide a detailed analysis of how these factors may influence the development of ALL in children.

3.1 Folate

Maternal folate intake plays an important role in DNA methylation. Folate is involved in the 1-carbon metabolism pathway. A metabolic pathway which utilizes folate as a carrier to synthesize methyl group donors [10]. This pathway specifically generates S-adenosylmethionine (SAM), a universal methyl donor integral methylation reaction such as histone and DNA methylation [10]. In this process, dietary folate is metabolized into 5-methyltetrahydrofolate (5-methylTHF) and subsequently converted into tetrahydrofolate (THF), a coenzyme. THF is used to produce 5,10-methyleneTHF and then 5-methylTHF via the methylenetetrahydrofolate reductase (MTHFR) enzyme. This reaction provides remethylation of homocysteine into methionine, a precursor of SAM [11]. As illustrated in Figure 1, limited folates as a methyl group source can disrupt the maintenance of proper methylation processes leading to genomic DNA hypomethylation [12]. A study examined the link between maternal folate intake and ALL [13]. They analyzed bone marrow from children with ALL and saliva from their mothers. By assessing genetic variations in folate metabolism and DNA methylation patterns,

researchers found that some leukemia cases exhibited abnormal DNA hypermethylation in genes regulating cell growth. Since folate influences DNA methylation, these findings suggest that maternal folate status during pregnancy may contribute to epigenetic changes in utero, potentially increasing ALL risk in offspring [13].

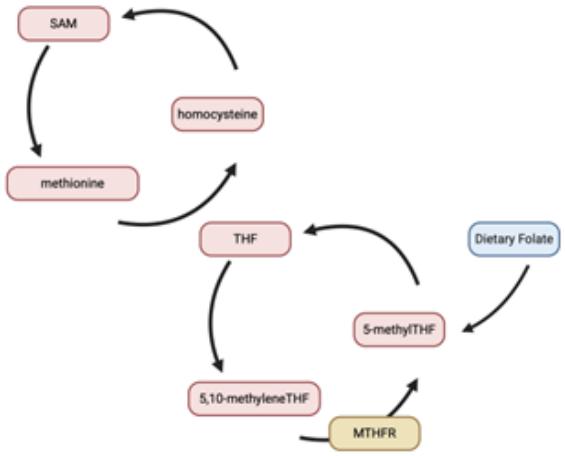

Figure 1. 1-carbon metabolism pathway: Adapted from [10,11]

3.2 Diabetes

Maternal diabetes has been identified as one of the numerous in-utero factors associated with an increased risk of childhood ALL [14]. This risk is linked to two categories of maternal diabetes: pregestational diabetes mellitus and gestational diabetes mellitus (GDM). Several primary and secondary studies have explored this relationship.

A register-based study conducted in Denmark by Søegaard et al. examined this association in children born between 1996 and 2015 [14]. The findings revealed that children of mothers with pregestational diabetes had a 2.91-fold higher risk of developing ALL, with the strongest associations observed in genetic subtypes such as ETV6-RUNX1-positive and high-hyperdiploidy. GDM also elevated the risk, although to a lesser extent, with a 1.75-fold increase compared to children of non-diabetic mothers. No significant association was found between paternal diabetes and the risk of ALL. However, higher birth weight, a common outcome in babies of mothers with diabetes, was loosely associated with an increased risk of ALL, particularly in children of mothers with pregestational diabetes, but not in those of mothers with gestational diabetes [14].

A recent study by Marcoux et al. conducted a retrospective cohort study of 1 million children born between 2006 and 2019 in Quebec, Canada, to assess the risk of childhood cancer following exposure to GDM [15]. The study found an increased risk of childhood cancers, with leukemia showing the strongest association. The findings suggested that children exposed GDM during pregnancy had a 1.74-fold increase in the risk of developing ALL within the first two years of life compared to children who were not exposed to GDM [15].

The association between GDM and childhood cancer is thought to be driven by maternal hyperglycemia and hyperinsulinemia [16]. Hyperglycemia is associated with the production of reactive oxygen species, which can cause DNA damage in fetal cells, potentially increasing cancer risk later in life. GDM also alters fetal growth through overproduction of insulin (IGF-1), which promotes cellular growth. Elevated insulin levels are associated with fetal macrosomia (higher birth weight), and have been linked to a greater risk of leukemia, particularly ALL. Hematopoietic cells may be especially sensitive to high IGF-1 levels, increasing the risk of blood cancers [15].

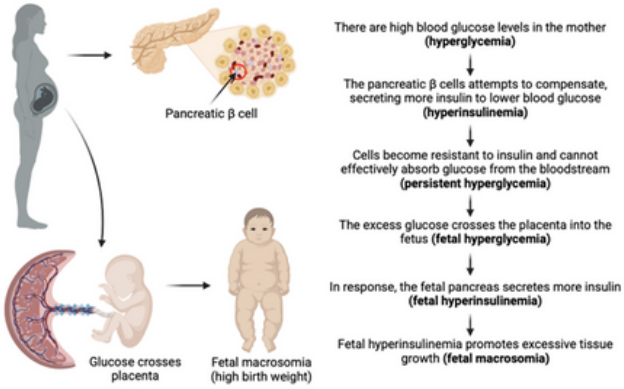

Figure 2. The mechanism of GDM: Adapted from [17]

3.3 Diet

The maternal diet shapes the risk of a child developing ALL. Two key systematic reviews have examined this relationship, revealing both protective and harmful effects of certain foods and nutrients.

Several foods have protective effects, such as certain fruits, vegetables, protein sources, folic acid, and multivitamins [18,19]. Children whose mothers eat a diet rich in fruits and vegetables during pregnancy may have a lower risk of developing ALL. Foods abundant in antioxidants such as carotenoids, vitamin A, and vitamin C, help prevent DNA damage. Glutathione is an antioxidant tripeptide found in meat and vegetables. It plays a key role in cellular functions such as cell differentiation, proliferation, and apoptosis. These processes help promote DNA repair and maintain cellular health, potentially lowering the risk of leukemogenesis [19]. The decreased risk of ALL associated with the maternal use of vitamin formulations as supplements can be explained by the capacities of the components, including folate and iron, to protect against oxidative damage to lipids, lipoproteins and DNA [19].

In contrast, some foods may have harmful effects, such as caffeine. Maternal coffee consumption, more than two cups per day, is linked to an increased risk of childhood ALL [19]. Caffeine can inhibit Topoisomerase I and Topoisomerase II, which are nuclear enzymes that solve the topological problems associated with DNA replication, transcription, recombination and chromatin remodeling. This can potentially cause DNA damage and increased leukemia risk.

MECHANISMS

This review explores DNA methylation, histone modifications, and miRNAs as they are among the most well-studied epigenetic mechanisms with established roles in gene regulation and relevance to leukemia [7,8].

4.1 DNA Methylation

DNA methylation is a key epigenetic mechanism that can contribute to the initiation and progression of many cancers, including pediatric ALL by altering gene expression patterns crucial for normal hematopoiesis [9]. In particular, aberrant methylation can disrupt cellular differentiation and tumor suppression, potentially driving leukemogenesis.

DNA methylation involves the addition of methyl groups to cytosine residues in CpG dinucleotides, often leading to transcriptional silencing of critical regulatory genes [20]. One of the most extensively studied forms of aberrant DNA methylation in ALL is the hypermethylation of CpG-rich regions, known as CpG islands (CGIs), which are commonly found in gene promoter regions. A review by Nourlund & Syvänen revealed that ALL cells consistently exhibit higher levels of methylation at CpG sites within CGIs compared to both normal bone marrow cells and cells in remission [21]. This means that the hypermethylation of CGIs is associated with the disease. This modification can silence tumor suppressor genes and differentiation factors, contributing to malignant transformation [21].

DNA methylation patterns are largely established during early embryogenesis and are influenced by genetic and environmental factors [9,22]. Hence, the prenatal period represents a critical window for the establishment of DNA methylation patterns which can influence disease susceptibility. Specifically, emerging evidence suggests that aberrant methylation patterns associated with pediatric ALL may originate in utero [9]. For example, a study by Nickels et al. examined twins discordant for ALL and identified differential DNA methylation at birth, using archived neonatal blood spots [9]. They identified that DNA hypomethylation may contribute more generally to ALL risk. Thus, these epigenetic alterations may occur prenatally and precede disease onset, supporting the hypothesis that early-life methylation changes may serve as a priming event for leukemogenesis, predisposing hematopoietic cells to malignant transformation later in life.

Beyond general DNA methylation dysregulation, specific methylation markers associated with pediatric ALL have been detected years before clinical diagnosis, suggesting a role in disease initiation. One well-documented example is the hypermethylation of VTRNA2-1, a gene involved in cellular mechanisms like Protein Kinase R-mediated cell death and immune regulation [23]. A large-scale birth cohort study analyzing neonatal blood spots found that VTRNA2 -1 hypermethylation was detectable at birth in infants who later developed ALL [23] . This study, as well as Nickels et al. [9] , provide evidence that this epigenetic alteration occurs in utero rather than as a secondary consequence of leukemia progression. Hypermethylation of this gene was significantly associated with reduced VTRNA2 -1 expression and worse survival outcomes in pre-B ALL patients [23] . These findings were validated across multiple independent populations and ethnicities and remained stable across different tissues, suggesting a consistent and reproducible early-life methylation signature . An epigenetic signature refers to a gene-specific, genome-wide DNA methylation pattern. Further, longitudinal follow-up of leukemia patients revealed a dynamic pattern: VTRNA2 -1 hypermethylation was elevated at leukemia diagnosis, normalized during remission, and increased again at relapse. This links it to disease progression. Beyond VTRNA2 -1, other genes have also been identified as exhibiting aberrant DNA methylation in pediatric ALL, contributing to leukemogenesis. T hese findings highlight the prognostic value of epigenetic signatures. Genome-wide analyses have revealed a distinct DNA methylation signature in leukemic bone marrow, characterized by hypermethylation of genes such as TCF3 [24] , EGR4 [25] , and BTG4 [26] . These genes are integral to B-cell differentiation, cell cycle regulation, and apoptosis; their silencing promotes the dysregulation of hematopoiesis and survival of leukemic blasts.

Overall, these findings indicate that aberrant DNA methylation may precede and contribute to leukemogenesis, and that once leukemia has been established, DNA methylation continues to influence its aggressiveness and progression.

4.2 Histone Modifications

Histones are recognized for their integral role in DNA packaging where they can be modified to promote or deter transcription of specific genes [8]. Negatively charged DNA wraps around positively charged histone proteins made from lysine and arginine residues. Post-translational modifications are highly specific, most often involving epigenetic changes such as methylation or acetylation at lysine residues. For instance, the following epigenetic changes suppress gene expression; H3K9me3, H3K27me3, while H3K4me3, H3K9ac, H3K14ac, H3K79me have been shown to promote gene expression [8]. The control of key enzymes balance these changes. For methylation, there are histone lysine methyltransferases (HMTs) and histone lysine demethylases (HDMs). For acetylation, there are histone acetyltransferases (HATs) and histone deacetylases (HDACs). Ultimately, research shows that the etiology of ALL may be influenced by gain or loss of function mutations of epigenetic modifying genes thus causing irregulated histone marks and subsequent malignancy [8]. The following paragraphs will discuss specific histone modifications, involving both histone acetylation

and methylation, and their mechanism of action in ALL.

4.2.1 Histone Acetylation

Several genes and proteins may be responsible for histone acetylation in ALL [27].
Loss of function mutations to the CREB binding protein (CREBBP) gene have been shown in B-ALL. The CREBBP contains HAT activity, particularly with H3K18 [27]. When this gene is mutated, oftentimes in relapsed cases, there is transcriptional dysregulation of targets including glucocorticoid responsive genes [27,28]. A 2015 next-generation sequencing study of childhood ALL found a larger incidence of CREBBP alterations in high hyperdiploidy cases of B-ALL, the most common subtype of ALL in children [29]. Moreover, a study by Gao et al. suggests that low CREBBP expression can be associated with adverse long-term risk factors in pediatric ALL and that it is an indicator of worse prognosis [30].

Additionally, several HDAC proteins have been demonstrated to be more highly expressed in ALL cases in comparison to healthy bone marrow [30]. A global loss of histone h4 acetylation has been commonly shown in pediatric B-ALL where favourable prognosis is associated with preserved acetylation [31]. Additionally, one study examining 94 pediatric ALL cases found that higher expression of HDAC7 and HDAC9 genes resulted in worse prognosis [30]. Thus, HDAC inhibitors have become appealing pharmaceutical targets to prevent relapse. Furthermore, protocadherin 17 protein coding gene is a tumour suppressor gene that may be involved in ALL. Repression of deacetylation has been shown to upregulate this gene's transcription, thus making this a potential therapeutic mechanism to treat ALL [32].

4.2.2 Histone Methylation

Histone methylation occurs when a methyl group is added to histone proteins, which can either activate or repress gene expression, depending on the specific histone residue [33]. Histone methylation may be involved in the KMT2A rearrangement B-ALL [34]. This is the most prevalent B-ALL subtype among children, accounting for 70% of infant leukemias [35]. KMT2A is a H3K4, HMT protein that activates transcription of mapped genes [35]. When this gene is rearranged it commonly results in fusion proteins. These fusion proteins can interact with epigenetic regulators, subsequently dysregulating gene expression [36]. For example, histone 3 lysine 79 methyltransferase (DOT1L), may be recruited by MLL-fusion proteins causing overexpression of the HOXA homeobox gene [27,33]. This can result in leukemia as this gene is normally tightly regulated by hematopoietic progenitors.

Furthermore, a study by Jaffe et al. found that t(4;14) translocation induces NSD2 mutations, commonly among those with the ETV6-RUNX1 fused gene B-ALL subtype [36]. NSD2 is HMT of H3K36 [8]. Normally, H3K36 is unmethylated, whereas the epigenetic signature involving NSD2 mutations demonstrates increased H3K36me2 and lower levels of unmodified H3K36. Additionally, a whole genome sequencing of 12 cases of T-ALL, highlighted loss of function mutations in the genes that encode for components of the polycomb repressor complex 2 (PRC2), thus demonstrating this gene's tumour suppressing role [8]. As PRC2 contains H3K27 methyltransferase activity, when its expression is altered, the subsequent expression of the genes it acts on changes [37]. Studies have shown that PRC2 loss of function mutations are associated with activation of the IL7R/JAK/STAT pathway, leading to uncontrolled cell growth in T-ALL [37].

4.3 MiRNA

MiRNAs are small non-coding RNAs which play a role in regulating gene expression [38,39]. They can do this through sequence-specific binding to mRNA to promote or hinder its translation. These RNA molecules can be around 22 nucleotides long which can negatively control target gene expression post-transcriptionally. Currently, there are about 460 known human miRNAs [39]. Most MiRNAs are transcribed from DNA sequences into primary miRNAs which are then processed into precursor miRNAs, and ultimately into mature miRNAs. miRNAs can act as tumour suppressor genes as well as oncogenes [38-40]. Differentially expressed miRNAs have been seen to be associated with the initiation and progression of childhood ALL [38-40].

Oncogenic miRNAs (oncomiRs) have been seen to be involved with the progression of childhood ALL [41]. OncomiRs can promote leukemogenesis by downregulating tumor suppressor genes, enhancing oncogenic pathways [40]. There are many OncomiRs that exist, for example miR- 55 is a well-characterized oncomiRs, often overexpressed in childhood ALL patients. As seen in figure 2 miR-155 promotes ALL progression through inhibiting Casitas B-lineage lymphoma (CBL), a protein that plays a role in reducing proliferation and enhancing apoptosis of ALL cells [41]. miR-155 additionally has been seen to inhibit function of ZNF238, a tumor suppressor [41,42]. As such overexpression of miR-155 can increase cell proliferation in ALL cells [43]. miR-155 is just one type of oncomiR that plays a role in the initiation and progression of ALL specifically by promoting increased cell proliferation in ALL cells.

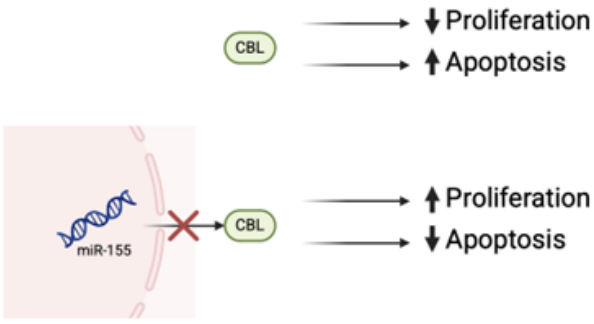

Figure 3. miR-155 promotes ALL progression by inhibiting CBL, thus leading to increased proliferation and decreased apoptosis of ALL cells. Adapted from [42]

DISCUSSION

This review underscores the growing recognition of early-life epigenetic modifications as key contributors to the initiation and progression of pediatric ALL. While previous research has focused heavily on genetic mutations, emerging evidence highlights the role of DNA methylation, histone modifications, and miRNA dysregulation in shaping the leukemic epigenome [8]. These alterations can silence tumor suppressor genes, disrupt normal hematopoiesis, and promote leukemogenesis [8]. Notably, epigenetic changes can be influenced by prenatal environmental exposures, suggesting that ALL susceptibility may, in part, be established in utero [8,9,13,14].

One of the most compelling findings is the influence of maternal factors on the epigenetic regulation of ALL risk. Studies have linked maternal folate intake and diabetes to differential DNA methylation patterns in offspring, with potential implications for disease susceptibility [13]. Maternal folate depletion has been associated with altered methylation of genes implicated in leukemogenesis, whereas maternal diabetes has been linked to increased ALL risk [13]. While these associations provide important insight, the precise mechanistic pathways remain unclear. Further research is needed to determine how these maternal exposures drive specific epigenetic modifications and whether interventions targeting these pathways could reduce disease risk.

Beyond environmental influences, aberrant DNA methylation is a hallmark of pediatric ALL [9,21]. The hypermethylation of CpG islands in tumor suppressor genes has been detected at birth in infants who later develop ALL, indicating that epigenetic changes may precede ALL onset [23]. Similarly, histone modifications contribute to leukemogenesis, as mutations in histone-modifying genes, including CREBBP and NSD2, disrupt transcriptional regulation [8,27]. The overexpression of HDACs in ALL has also been linked to poor prognosis, supporting the rationale for HDAC inhibitors as potential therapeutic targets [30]. Furthermore, dysregulated miRNAs, such as miR-155, drive leukemic cell proliferation by downregulating tumor suppressor pathways, reinforcing the significance of post-transcriptional gene regulation in ALL pathogenesis [40-43].

Overall, this review bridges two critical aspects of pediatric ALL research;demonstrating how maternal environmental factors can drive early-life epigenetic changes and how these modifications, in turn, influence both the incidence and prognosis of the disease. By integrating evidence from recent studies, this review highlights potential connections linking maternal exposures to epigenetic changes and subsequent leukemogenesis and emphasizes the need for further longitudinal investigations.

LIMITATIONS

Several key challenges remain. A major limitation of current research is the reliance on associative and retrospective studies, which makes it difficult to establish causal relationships such as between early-life epigenetic modifications and ALL onset. While some methylation patterns have been detected at birth, more research needs to be done to confirm that these changes are primary drivers of leukemogenesis. Future studies should aim to confirm the direct role of specific epigenetic modifications in disease initiation. There were also a limited number of longitudinal studies tracking epigenetic changes from birth through leukemia diagnosis. In our review, Ghantous et al., a prospective birth cohort study, emerges as one of the first and most comprehensive studies of its kind in pediatric ALL research [23]. This study not only demonstrates that specific epigenetic markers are detectable at birth, but more notably tracks their stability and changes over the course of the disease. Other included studies have provided valuable insights by comparing epigenetic differences at birth (for instance, in twins discordant for ALL) [9], yet they do not offer the same serial follow-up across multiple disease stages. The lack of longitudinal studies highlights the urgent need for more research to track how early-life epigenetic changes develop over time and drive the onset of leukemia.

Additionally, mechanistic/functional studies are needed to determine how maternal factors, such as diet and metabolic conditions, modulate the epigenome and induce specific epigenetic changes in hematopoietic stem cells. This would help establish that maternal factors contribute to leukemia risk specifically via induction of epigenetic changes.

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IMPACT OF SIGHT LOSS ON THE SOCIAL-EMOTIONAL DEVELOPMENT OF CHILDREN AND ASSOCIATED INTERVENTIONS

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ABSTRACT

Sight loss, which includes a range of conditions from partial vision loss to complete blindness, can significantly impact a child's social-emotional development. Social-emotional development refers to a child's ability to understand and manage their feelings, which is essential for navigating social situations and forming healthy relationships. While much research has focused on the physical and cognitive aspects of sight loss, little has been written about its social-emotional effects, making it important to examine how sight loss affects this domain of development. This review explores the various impacts of sight loss on the social-emotional development of children, including its effect on attachment styles and the ability to socialize and form relationships. Interventions such as infant massage, International Classification of Functioning, Disability, and Health (ICF) Framework, and providing an individualized support system for children with sight loss attempt to address these issues. By reviewing these interventions, this paper seeks to identify effective strategies for mitigating the impact of sight loss on the social-emotional development of children and discusses the importance of their implementation. Through synthesizing current research, this paper aims to deepen understanding and inform strategies to promote positive social-emotional outcomes for children with sight loss.

POSITION STATEMENT

We acknowledge that our engagement with this research is shaped by our positionality. As sighted, able-bodied, undergraduate students from North America, our perspectives are influenced by our academic background, cultural context, and access to specific sources. While we strive for a comprehensive analysis, we recognize that our viewpoint is inherently shaped by these factors.

INTRODUCTION

A child's social-emotional development involves understanding, regulating, and expressing emotions, as well as recognizing and responding to the emotions of others. Sight loss can impact this development, making it more challenging to navigate social situations and form healthy relationships [1]. Social-emotional development fosters important life skills, such as effective communication, the ability to express empathy, and the capacity to self-regulate and practice self-care when needed [1]. Healthy social-emotional development allows children to form secure attachments to parents and build friendships with their peers. These interpersonal relationships provide a sense of safety, support, and belonging, all of which are foundational for overall well-being and mental health [2]. Vision, a key sensory modality, plays an integral role in social-emotional development by providing critical cues such as facial expressions and body language, which help facilitate social engagement and emotional understanding [3,4].

According to the World Health Organization's International Classification of Diseases 11 (ICD-11; VV10), visual impairment is defined as a presenting visual acuity (VA) in the better eye worse than 3/60, with blindness representing the most severe form of impairment. Functional low vision includes individuals with VA less than 6/18 up to light perception, alongside limitations in visual fields [4]. Notably, although visual impairment is a common term found in literature, according to the Canadian National Institute for the Blind

(CNIB) inclusive language guidelines, using terminology such us “impairment” or “deficit” focuses negatively on sight loss and is not preferred [5]. As such, for the purposes of this review, the terminology “sight loss” will be used hereon-out when discussing individuals with sight loss and/or blindness.

This paper explores the impact of sight loss on the social-emotional development of children, examining key developmental stages from before school-age to school-age and outlining interventions currently utilized by children with sight loss. For the purposes of this article, development was divided into two stages—“before school-age” (0-3 years) and “school-age” (4+ years)—to reflect the distinct differences in a child’s social environments and interactions. Here, “school” refers specifically to formal schooling in Ontario, which includes a free two-year kindergarten program for children aged 4 and 5 [6]. While attendance only becomes mandatory at age 6, age 4 is used here as a typical marker for the start of the “school-age” period. By synthesizing current research, this paper aims to deepen understanding and inform strategies to promote positive social-emotional outcomes for children with sight loss.

METHODS

Articles, either written or translated into English, were eligible for inclusion in this review. A preliminary literature review was conducted on Google Scholar as an introduction to the available literature. The databases PubMed, Ovid, SAGE Journals, and Web of Science were consulted to gather relevant information. Searches included terms related to sight loss, early childhood, infancy, adolescence, school-aged children, social-emotional development, and interventions. Primary studies and reviews were included in the research. Exclusion criteria consisted of studies involving blind children with additional disabilities to reduce confounding variables which could affect the interpretation of outcome specific to blindness. These excluded conditions including deaf-blindness, traumatic brain injury (TBI), acquired brain injury (ABI), and cerebral palsy.

IMPLICATIONS OF SIGHT LOSS: BEFORE SCHOOL-AGE CHILDREN

Sight loss in infant-toddlers profoundly impacts social-emotional development, as vision is a key modality for communication and interaction [3]. Without visual input, they face challenges in expressing emotions, engaging in social exchanges, and forming secure attachments, encouraging a deeper understanding of their unique needs [3,4]. One notable limitation of research is its predominant focus on the child’s interaction with the mother, often excluding mention of paternal interactions.

3.1 Emotional Expression and Recognition

Infants with sight loss display a limited repertoire of expressive behaviors compared to sighted infants. For instance, a study looking at the responses of blind infants to their mothers versus strangers found that blind infants’ social smiles, a critical marker of early emotional development, are less frequent and often elicited by auditory or tactile stimuli rather than visual cues [7]. This delay in expressive behaviors can hinder the reinforcement of caregiver interactions and may affect the reciprocal nature of emotional exchanges [7]. A study conducted in 2022 using a parental questionnaire to assess emotion regulation in children with sight loss found that blind children, aged 9-12 months old exhibit lower composite scores for emotion regulation compared to their sighted peers of the same age, emphasizing the developmental challenges posed by the lack of visual input [8]. Moreover, blind infants struggle with nuanced expressions of emotions such as fear or avoidance, which are often less discernible without visual cues. This limitation may reduce the frequency and immediacy of maternal responses, further compounding developmental delays [7].

3.2 Social Interaction

One of the significant challenges for blind infants is initiating and sustaining social interactions. Sighted infants often rely on visual cues to coordinate their behaviors with their social environment, enabling them to attract attention and engage in reciprocal interactions. Blind infants, however, face difficulties in recognizing when they have their caregiver’s attention, often resulting in fewer self-initiated interactions, which is a marker of motor difficulties [7]. This reduced initiative is compounded by their limited ability to observe and imitate facial expressions, a cornerstone of early communication and social bonding. The concept of dialogue, where infants learn that their actions elicit predictable responses from caregivers, is also delayed in blind infants. This delay stems from their restricted opportunities to experience consistent visual feedback, making it harder for them to develop intentionality and reciprocity in their interactions [7].

3.3 Maternal Role and Environmental Influence

The role of a caregiver is particularly pivotal for blind infants. Mothers of infants who are blind often face challenges in interpreting their child’s subtle behavioral cues and adapting their responses accordingly. This difficulty can result in either overprotective or inconsistent caregiving practices, which impacts the development of a secure attachment style [7]. Attachment refers to a specific aspect of the relationship between a child and their caregiver, aimed at ensuring the child's safety, security, and comfort. It involves the child using the caregiver as a secure base for exploration and as a haven for protection and emotional support

when needed [8]. Research emphasizes the importance of maternal sensitivity and the need for specialized interventions to support caregivers in fostering reciprocal interactions and promoting the infant's social-emotional growth [7,8].

3.4 Attachment and Seperation Anxiety

The development of attachment behaviors, such as separation anxiety, where an infant feels uneasy when away from their caregiver, is influenced by an infant's ability to perceive and conceptualize the presence of caregivers [9]. Blind infants show a delayed onset of separation anxiety which may be linked to their slower development of cognitive prerequisites, such as object permanence, or the ability to know an object exists even when not directly observed [10]. Unlike sighted infants, who visually track the departure and return of caregivers, blind infants rely on auditory and tactile cues, making it harder for them to conceptualize their caregiver's absence and develop separation anxiety [7].

INTERVENTIONS: BEFORE SCHOOL-AGE CHILDREN

While knowledge of interventions for early childhood social-emotional development, particularly in improving parental attachment and social skills in blind infants, remains limited, several approaches have shown promise.

4.1 Infant Massage

One such intervention is a therapeutic practice called infant massage, where parents and caregivers massage their baby's body to foster bonding and improve their infant's sense of comfort within the parent-child relationship [11]. A structured approach to the massage is provided by the International Association of Infant Massage (IAIM) protocol, which guides parents through gentle strokes and techniques tailored to the baby's developmental stage and needs [11]. For infants with sight loss, massage(s) can compensate for the absence of visual cues, such as eye contact, smiling and positive affect, and attunement, all of which are important for developing secure attachment. Attunement involves the caregiver's sensitive response to the infant's needs, allowing the infant's brain to receive the nurturing input necessary for healthy development [12]. By being attentive to the infant's cues and responding appropriately through massage, parents can demonstrate to their infant that their emotional needs will be met. This tactile communication shows the infant that their caregiver is present and responsive, reinforcing feelings of comfort and safety [13]. At an early stage, this practice supports the development of skills such as communication through verbal tone, touch, and empathy, which help validate the child's feelings and trust [13,14]. A longitudinal study examined the effects of infant massage on maternal confidence and responsiveness, using standardized scales such as the Parenting Stress Index and the Maternal Confidence Scale. The resultsshowed that regular infant massage significantly improved maternal confidence and responsiveness, enhancing the parent-infant relationship and promoting positive social-emotional development [14].

4.2 Parent-focused Programs

Another early intervention includes programs and resources designed specifically for parents to facilitate stronger bonds with their infants affected by sight loss. In 2003, the United Kingdom's central government launched the Early Support program to educate families of children with disabilities on the best practices to promote healthy development [15]. As part of the initiative, the Developmental Vision teams at Great Ormond Street Hospital (GOSH) created the Developmental Journal for Babies and Children with Visual Impairment [15], a guide tailored towards supporting parents and caregivers in navigating their child's developmental journey. The Developmental Journal includes a comprehensive list of expected developmental steps in children with sight loss who are up to 36 months old, providing families with a framework to track progress and adapt their parenting styles to the child's individual needs [15]. By offering structured guidance to help parents better understand their child's developmental progress and challenges, the journal strengthens the bond between caregiver and child [15]. Parents are encouraged to actively participate in their child's development through activities that promote effective communication, shared discovery, and joint attention. These include interactive games with sound-emitting, textured toys, as well as sensory exploration exercises that guide the child's hand to identify objects. Such activities are important for building trust, emotional security, and secure attachment [15].

IMPLICATIONS OF SIGHT LOSS: SCHOOL-AGED CHILDREN

A child's transition into formal schooling is a critical period for their cognitive and social-emotional development. During these years, children form meaningful relationships with peers, develop self-awareness, explore their identity, and refine their emotional regulation—all of which contribute to overall well-being and future success [16,17]. It has been found that children with sight loss may experience challenges related to social aspects of their school life, such as having limited involvement in school activities [18] and lacking positive social interactions with their sighted peers and teachers [19]. Undoubtedly, lacking exposure to various experiences that help children build their social-emotional competency puts children with sight loss at a disadvantage compared to their sighted peers.

Measuring social-emotional development in school-aged children often relies on measurements such as school belonging, self-esteem, and social relationships with

peers and teachers. These various indicators can be correlated to Bronfenbrenner's ecological model, which considers how various systems interact with the child's nature to influence their development [20]. As seen in Figure 1 [refer to appendix], the ecological model depicts how there are a multitude of forces that impact the child at different levels based on how the child interacts with them. The model conceptualizes human development by depicting how it can be influenced by a child's nested environmental systems [21]. As such, when considering the experiences of a school-aged child, it is critical to account for the various factors that directly and indirectly shape how they interact with their environment.

5.1 Microsystems & Mesosystem

A child's social-emotional development is influenced by their direct environments, or microsystems, including family, school, and peer relationships. In school aged children, peer relationships and feeling a sense of belonging at school are particularly important as they directly influence the self-esteem and academic inclusion of children [22]. Notably, it has been found that the severity and visibility of a child's visual disability can influence their self-esteem. For example, adolescents with severe sight loss often report a stronger sense of school belonging which is speculated to be because they have accepted their condition and are more willing to seek support [23]. In contrast, those with moderate impairments may try to hide their disability from their typically developing peers with the fear that their needs may not be understood, leading to social isolation and lower self-esteem [22,23]. In addition to these findings, the use of specialized equipment for sight loss has also been discussed as a factor impacting social inclusion for students due to internalized shame and feeling as if they stand out amongst their peers [24]. According to the Canadian National Standards for the Education of Children and Youth Who are Blind or Visually Impaired, developing skills with assistive technology and orientation and mobility is essential for the development of body and spatial awareness as well as directionality [25]. These skills are not only critical for a child's safety but can also increase the probability that the student will be actively involved in age-appropriate activities with their peers [25].

The next system that can influence social-emotional development in children is the mesosystem which are the interactions between the microsystems. Importantly, it has been suggested that social support from teachers, parents, and other care providers can act as protective factors against social emotional development challenges for children [26]. By supporting children to learn how to identify when peers are trying to initiate social engagement or facilitating lessons on how to understand nonverbal signals and social cues from others, children with sight loss can be better equipped to form relationships with others [26].

5.2 Exosystem

The exosystem indirectly influences a child's experiences, such as school policies, teacher training, or parental work environment. Notably, the Ontario Human Rights Commission has indicated that children in the province face a variety of barriers in education, including physical inaccessibility, a lack of individualization, and negative attitudes and stereotypes [27]. These barriers can act as significant hindrances to a child's social-emotional development as they can result in feelings of isolation and low self-esteem [23].

5.3 Macrosystem & Chronosystem

Societal and cultural norms within the macrosystem can influence children with sight loss, particularly as negative societal perceptions and cultural biases towards disability can lead to internalized stigma [27]. A lack of knowledge among educators, staff, and students can make it difficult for students with disabilities, potentially feeling ashamed, which could lead to social withdrawal, influencing social-emotional development. Over time, within the chronosystem, significant events may take place in society, which can change the trajectory of a child's social-emotional development, depending on its influence. For example, the current age of technology offers students with visual disabilities several resources that can help them with their academic learning, social relationships, and physical navigation within the world [28]. However, it also creates a space for online bullying and economic barriers due to the price of technology [29,30]. These various forces can influence a child's experiences within the world, ultimately indirectly also influencing their development.

INTERVENTION: SCHOOL-AGE CHILDREN

6.1 The Evolution of Disability Perspectives & ICF Framework

The understanding of disability, especially sight loss, has evolved over time [31]. Historically, rehabilitation followed the medical model, focusing on anatomical issues and isolated skills [27]. However, in the 1970s, the social model emerged, viewing disability as a result of societal barriers rather than individual limitations. In 2007, the World Health Organization's International Classification of Functioning, Disability, and Health (ICF) unified both perspectives, emphasizing active participation in all aspects of life, including education, social interactions, and community activities [31]. This integrated approach forms the foundation for the development of interventions designed to address the social-emotional needs of school-aged children with vision loss, ensuring they are supported not only in their academic pursuits but also in their social inclusion and emotional well-being [31].

6.2 Social Awareness & Inclusion Strategies for Children with Vision Loss

Children with vision loss often face challenges in developing social awareness and skills due to their reduced access to non-verbal cues, such as facial expressions and body language. Embedding opportunities for social interaction within everyday classroom activities is emphasized as a means to provide children with vision loss meaningful experiences that foster self-awareness and peer engagement [31].

Strategically planning these environments allows for incidental learning and positive peer interactions, addressing the difficulties children with low vision face in learning through imitation [27]. Thoughtfully designed classroom layouts, such as those implemented at elementary schools in Northern Ontario and the Greater Toronto Area, prioritize clear, unobstructed pathways, consistent furniture placement, and accessible seating arrangements to help children confidently navigate and locate objects. For example, teachers ensured that students with sight loss were seated closer to the front of the classroom for better access to the whiteboard and instructional materials while avoiding isolation [32]. Additionally, seating students in pairs rather than groups facilitated social inclusion while accommodating their unique needs. Classroom adaptations such as taped-down wires, tactile markers, and Braille-labeled objects further enhance navigation and engagement, ensuring that specialized equipment and support staff facilitate rather than hinder peer interactions in an inclusive learning environment [32].

6.3 Tailored Educational Approaches & School Belonging

Educators emphasize that relying on a one-size-fits-all approach may not effectively support inclusion and well-being, particularly for students with unique challenges [32]. Instead, they advocate for adaptable strategies that accommodate diverse learning needs [32]. Educational systems should embrace diverse approaches that honor individuality and create meaningful engagement opportunities tailored to each child's unique strengths and needs. Fostering understanding among sighted peers is necessary, as it encourages positive social interactions and reduces barriers to inclusion [23]. In doing so, children with low vision are able to develop relationships and greater confidence in social settings. School belonging plays a pivotal role in shaping the self-esteem and emotional well-being of students with vision impairments. Students who feel valued and included are more likely to exhibit higher levels of self-confidence, resilience, and emotional stability [23]. Conversely, a lack of belonging can exacerbate feelings of isolation and hinder social-emotional development. Teacher and parental social support serve as protective factors against social-emotional challenges, such as isolation and difficulty developing social skills. Additionally, peer-focused interventions, such as collaborative activities between students with low vision and their sighted peers, have been shown to improve social behaviours and foster stronger connections within the classroom [23].

6.4 Structured Activities for Skill Development & Individualized Support System

Structured activities offer children with low vision opportunities to develop specific social-emotional and social skills in a supportive environment. Small group sessions involving storytelling, games, and discussions are effective in helping children practice skills such as expressing emotions, resolving conflicts, and initiating conversations [23,31]. These activities create positive interactions among sighted peers, promoting understanding and collaboration while simultaneously enhancing the development of critical social competencies and creating a more inclusive classroom atmosphere [23,31]. Additionally, individualized support, such as one-on-one mentoring and counseling, is crucial in addressing specific social-emotional needs that group settings may not effectively manage. These sessions can focus on building self-esteem, coping with feelings of isolation, or developing tailored social skills [33]. Furthermore, programs such as buddy systems and "circle of friends" utilize peer networks to provide natural support and promote inclusion. These strategies leverage the strength of peer relationships to help children feel more connected and supported in their social environments [33].

DISCUSSION

The findings in this review highlight various discrepancies in social-emotional development across developmental stages for children with sight loss. From infancy through school age, children with visual loss face unique challenges in emotional expression, social interaction, attachment, and impulse control, all of which contribute to developmental disparities when compared to their sighted peers. The existing literature offers limited insight into the social-emotional disparities between sighted children and those with low vision. As such, further research is needed to understand how these differences impact long-term developmental outcomes.

Despite the interventions identified, without clear implementation strategies, the gaps in developmental trajectories will persist. Future research should focus on developing comprehensive, evidence-based programs that integrate social-emotional learning with assistive technology and inclusive education practices. By addressing the unique barriers children with sight loss face and implementing targeted interventions, educators, caregivers, and policymakers can work collaboratively to close the developmental gap between children with sight loss and their sighted peers. This would not only foster emotional well-being and social competence but also pave the way for greater inclusion and long-term success for children with sight loss.

LIMITATIONS

Several limitations must be considered. This review is limited to published studies in North America and the United Kingdom, meaning its findings apply to the Canadian context, and relevant unpublished data may have been overlooked. Variability in sample sizes, methodologies, and outcome measures across studies contributes to significant heterogeneity, restricting the generalizability of the findings. It is also important to acknowledge that these interventions are not accessible to all children, particularly those in low-resource settings where specialized services and support may be limited. Addressing these limitations through further research will help ensure that interventions are both effective and widely applicable.

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APPENDIX

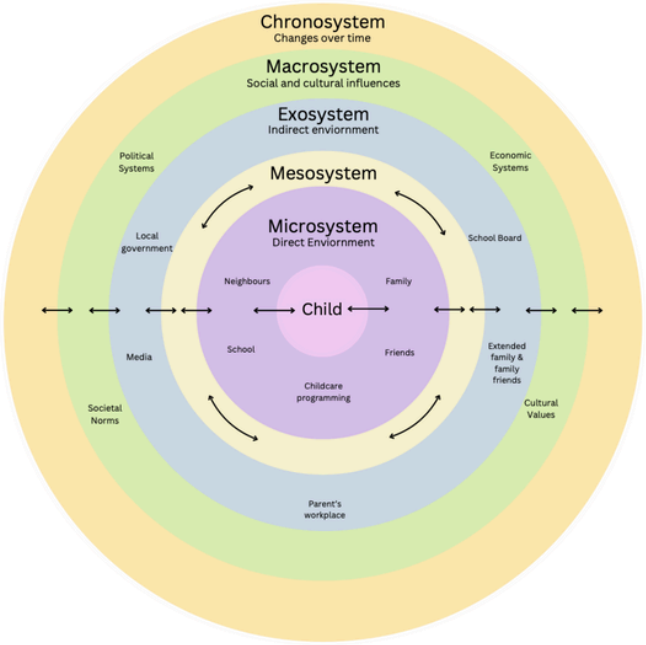

Figure 1: Bronfenbrenner's Ecological Systems Model

Photo description: There are five circles, each representing a different system as outlined by Bronfenbrenner. The circles are in ascending order, each getting slightly bigger than the one before. In the center there is a pink circle, of which is the smallest, that has the text 'child'. Moving outwards there is a slightly larger purple circle titled 'microsystem'. Within this circle there are several terms that depict a child's direct environment including 'Neighbours', 'family', 'school', 'friends', and 'childcare programming'. The next circle is yellow and is slightly larger than before. Within the picture there are four arrows that follow the shape of the circle.

A LITERATURE REVIEW OF CAREGIVER RISK FACTORS FOR ADOLESCENT SUBSTANCE USE

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ABSTRACT

Background: Adolescent substance use is a significant public health concern in Canada, with rates of alcohol use reaching 75%, and both cannabis and tobacco use reaching 26%, in Ontario schools. This behaviour poses serious health risks, including dependence, neurocognitive deficits, and mental health challenges. Caregiver influence plays a critical role in shaping adolescent substance use. Currently, there remains a gap in the literature regarding prevention and intervention strategies tailored to at-risk youth that specifically consider caregiver-related risk factors.

Objective: To identify evidence-based parental risk factors for adolescent substance use, to inform future prevention and intervention strategies.

Methods: 420 studies were identified from an initial search for studies related to adolescent (defined as aged 10-19) substance use and parents.

Results: 11 unique parental risk factors for adolescent substance use were identified. Low parental monitoring (24) and prenatal substance exposure (20) had the greatest number of studies and the largest compiled study populations. Seven risk factors were related to the parent-child relationship, such as low parental support and high parental permissiveness. Interparental conflict and parental substance use were also identified as significant risk factors. Three parent-child relationship factors, low parental punishment, low parental communication, and harsh parenting, had few but recent studies, indicating they may be emerging research topics in parent-child dynamics.

Conclusion: This review identified several caregiver-related factors commonly associated with adolescent substance use, including prenatal substance exposure, low parental monitoring, and poor parent-child communication. While findings suggest these factors may interact in complex ways, further research is needed to clarify how they contribute to risk and how they might inform the development of supportive, family-centered prevention efforts.

INTRODUCTION

The use of substances such as alcohol and cannabis among adolescents in Canada remains prominent, despite gradual declines in areas such as tobacco. Responses from the province-wide Ontario Student Drug Use and Health Survey indicated that up to 60% of students in grades 7–9 reported using various substances at some point in their lives [1]. In Ontario specifically, 75% of grade 12 students reported lifetime alcohol use, 26% reported lifetime cannabis use, and 26% reported lifetime nicotine use [1]. These patterns highlight the continued relevance of addressing substance use during adolescence, a critical period for physical, socioemotional, and cognitive development [2]. Early initiation of substance use (which we defined as any consumption of a substance regardless of duration) is associated with an increased likelihood of dependence and long-term health consequences [3]. Substance-abusing youth are at higher risk than nonusers for mental health issues, including major depressive disorders, anxiety disorders, and personality disorders [4]. Additionally, early substance use can lead to neurocognitive deficits, such as impaired memory, hindered academic performance, and decreased cognitive control [3]. These risks underscore the importance of identifying and mitigating factors that contribute to substance use during this vulnerable stage of development.

Parental influence is widely recognized as a key factor in

adolescent substance use. Research has consistently shown that caregiver behaviors, attitudes, and styles can shape an adolescent's risk of substance use [5]. For example, parental substance use is strongly linked to higher rates of adolescent substance use. Contrastingly, authoritative parenting, marked by high involvement and communication, is associated with a lower risk of adolescent substance use [6][7]. Despite this substantial body of research, there is a lack of standardization in how parental influence is measured. Studies vary in their focus, examining an array of factors such as parental monitoring (which we defined as the process by which parental knowledge may be enhanced), communication, and attitudes toward substances. This variability in research focus underscores the need for more unified approaches to studying parental influences.

Given the critical role caregivers—including parents, guardians, or anyone who has a primary role in looking after the child— play in shaping adolescent behavior and the complex interplay of factors involved, this review seeks to compile existing research on the primary risk factors related to the caregivers of at-risk children. By exploring the available literature, we aim to provide a clearer understanding of the pathways through which caregivers' parenting styles, genetic factors, and substance use contribute to adolescent substance use, offering insights to inform prevention and intervention strategies.

METHODS

1.1 OVID Medline Search

This literature review was conducted via a search of the Ovid MEDLINE. The search string in Ovid MEDLINE are listed on Appendix 1.

1.2 Inclusion/Exclusion Criteria

The search process and the inclusions/exclusions at each stage are detailed in Figure 1. The initial search was conducted on January, 2025. 421 search results were imported into the software Covidence, with duplicates automatically identified and removed.

Studies were eligible if they:

- Reported on caregiver for factors that the study defined as risks for adolescent substance use, to assess relationship between caregiver-related behaviours/factors and adolescent substance use.
- Any form of adolescent adolescent substance use.
- Included Adolescents (aged 10-19).
- Were a prospective observational study.
- Set in North America to control for cultural similarity.

The exclusion criteria included:

- n> 50 , to ensure sufficient sample size for study.
- Systematic reviews.
- Articles published prior to 1980, due to vast differences in substance use prior to 1980, specifically pertaining to marketing and general impression of smoking [45].

1.3 Study Selection & Exclusion Process

After screening 420 articles by title and abstract, 94 studies remained for full-text screening. Of these, 63 were excluded for the following the following eight reasons: outdatedness (1 article); abstract-only paper (12 articles); conducted outside of North America (10 articles); focusing on outcomes unrelated to research question (8 articles); wrong comparator (5 articles); wrong intervention (6 studies); wrong study design (12 articles); sample size (n<50) (1 article). Ultimately, 31 articles were included in this review (appendix 2).

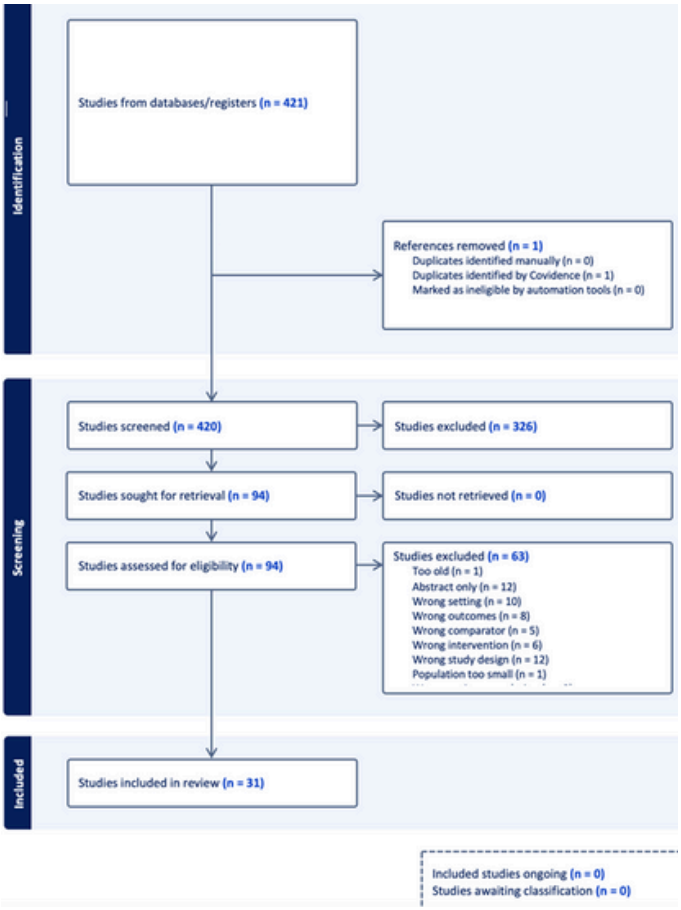

Figure 1. PRISMA Flow Diagram

RESULTS

The literature review revealed variance in both the number of studies and the number of participants associated with parental risk factors. We identified 11 unique variables. Prenatal substance exposure and low parental monitoring were the most extensively researched risk factors, with 24 and 20 studies, respectively, and were associated with the largest participant samples (44,633 and 45,307 participants). There was also significant evidence connecting parental substance use, poor parent-child relationships, low parental knowledge, low parental support, interparental

conflict, and high parental permissiveness to adolescent substance use, though to a lesser extent. In contrast, low parental punishment, low parental communication, and harsh parenting were each examined in only one study and involved similarly small participant samples of less than 1,000. These patterns suggest a robust background of evidence and research interest in parental risk factors with a few emerging topics–the three least researched factors were all published within the last seven years.

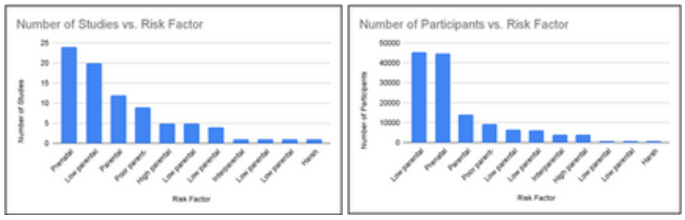

Figure 2. Study & Participant Distribution Across Parental Risk Factors

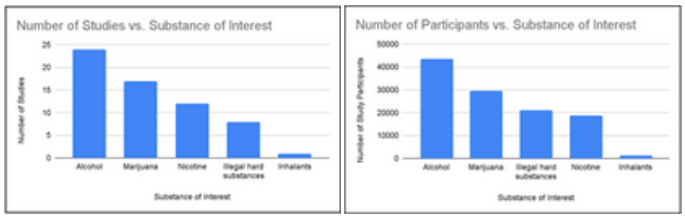

Figure 3. Study & Participant Distribution Across Various Substance Classifications

Findings from the literature review identify alcohol and marijuana as the most studied substances, included in 24 and 17 studies respectively, with the largest participant samples at 43,424 and 29,703. In contrast, nicotine was included in 12 studies and had a smaller pooled participant sample size of 18,649 when compared to alcohol and marijuana.

DISCUSSION

This literature review identified prenatal substance exposure and low parental monitoring as leading contributors to adolescent substance use risk. Prenatal substance (alcohol, cocaine, cigarette) exposure is consistently associated with adolescent externalizing behaviors, such as fighting, bullying, or vandalism, and impulsivity [41]. These behaviors lead to an increased likelihood of initiating substance use [40].

Parental monitoring, the actions taken by a caregiver to determine their child's whereabouts, also plays a key role in mediating adolescent substance engagement [41]. Low parental monitoring is connected to a greater association with deviant peers and risk-taking behaviors [42]. It is also positively associated with other parental risk factors identified in this study [43]. Our research found that this process can be impaired by parental substance use, poor parent-child relationships, and limited parental communication [17,19,23,36,38]. This interconnectedness highlights the cumulative nature of these risk factors, where one vulnerability in the parent-child dynamic may amplify the effects of others. Other major risk factors were related to the nature of the parent-child relationship, with the exception of interparental conflict. Although not directly related to the child, interparental conflict likely interferes with many typical processes that improve the parent-child relationship and lead to increased parental support and knowledge [34]. For instance, heightened conflict between parents can reduce the time and emotional resources available to engage with the child, potentially leaving them more susceptible to external influences such as peer pressure.

It also aimed to identify major research interests and developing topics within parent-child dynamics. Prenatal substance exposure is likely the most researched due to the simplicity of exposure measurement and extensive hospital records. Conversely, we believe low parental monitoring to be so commonly associated with adolescent substance use due to its comorbidity with other risk factors, acting as a pathway for increased risky behavior and peer deviance. This review also identified three emerging topics of research in parent-child dynamics. Low parental punishment, low parental communication, and harsh parenting all produced p-values lower than 0.05 in their respective studies and were all conducted within the last seven years. These emerging topics suggest growing research interest in more nuanced parenting behaviours and their influence on adolescent substance use. Identifying low parental punishment as a risk factor challenges growing notions that reduced discipline is inherently protective by avoiding harsh parenting [25][33]. Cox et al. identified that it may fail to establish clear boundaries and expectations, leading to an increase in adolescent autonomy without adequate guidance [25]. Conversely, over-disciplining through harsh parenting is also a potential risk factor as it may contribute to externalizing behaviours and rebellion, increasing susceptibility to substance use [44]. Parental communication is another emerging topic, representing a growing emphasis on a bilateral relationship between parents and their children [25]. This process may empower adolescents and increase their autonomy without diminishing parental knowledge or monitoring [25].

Parental factors associated with adolescent substance use are deeply interwoven. As we identify key risk factors, it is important to maintain a holistic lens to design interventions and support at-risk families. No individual factor stands alone, and the parent-child relationship is defined by constantly changing interactions and dynamics as children grow and develop. For example, low parental monitoring may stem from broader issues such as parental stress or substance use. Similarly, poor parent-child relationships can exacerbate other risk factors, such as low parental communication or support, which creates a feedback loop that increases the risk of adolescent substance use.

The distribution of research across substances of interest also provided valuable insights into social trends

surrounding substance use in North America. Alcohol and marijuana were the most studied substances. The abundance of research surrounding these topics reflects significant public health concerns regarding their widespread use and impact among adolescents. The focus on marijuana is particularly notable given its recent legalization in Canada, while alcohol remains widely socially accepted. These findings indicate an abundance of statistically significant studies that connect adolescent substance use to parental risk factors, highlighting the need for further research investigating the roles parents can play in adolescent substance use and how they may be supported.

Further, nicotine was the third most researched substance. Its lower inclusion in research may reflect the decline in traditional tobacco use in Canada since the 1960s, as the dangers of smoking became more widely recognized [39]. However, despite this decline, nicotine use remains prevalent among adolescents due to the rise of new, popularized methods such as vaping and e-cigarettes [40]. These methods have gained significant traction among youth, which may explain the continued concern and need for research into their usage patterns and associated risks [40]. The shifting landscape of nicotine consumption underscores the importance of ongoing monitoring and the development of tailored prevention strategies to address these emerging trends.

LIMITATIONS

Methodologically, some limitations include the extraction process and quality assessment for articles. Firstly, while every other stage of the screening phase requireds two author consensus in order to be included/excluded from the study, data extraction requireds only one reviewer. While data extraction is often more objective than the prior two phases, it could have been beneficial to include more reviewers during data extraction to come to a consensus on the data being withdrawn.

FUTURE DIRECTIONS

This review demonstrated areas where there is potential for further research and analysis. For instance, there is a significant lack of studies originating from Canada, and many studies from the United States were highly regional. Nation-wide studies could be useful in collecting more data regarding the effects of caregiver risk factors in different areas of North America. Furthermore, there is limited study on inhalants, another area where potential for further research lies, especially with the growing usage of e-cigarette products in adolescent populations.

CONCLUSION

The unique contribution of this review was as an open-ended, systematic data synthesis of parental risk factors associated with adolescent substance use. It compiled a list of key factors that may be targeted through caregiver-focused interventions and potential future topics of research. Caregivers should be included in future research on adolescent substance use, and their key role in mediating adolescent substance use risk should be reflected in national primary prevention strategies and family-based interventions.

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APPENDIX

Search Number	Ovid MEDLINE Searches	Results
1	"Adolescent substance use".mp.	1581
2	"Adolescent alcohol use".mp.	829
3	"Teenage drug use".mp.	18
4	"Adolescent cannabis use".mp.	283
5	"Youth marijuana use"".mp.	38
6	"Adolescent tobacco use".mp.	210
7	"Adolescent cigarette use".mp.	35
8	"Adolescent electronic cigarette use".mp.	14
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8	2941
10	"Parental identification and response".mp.	1
12	"Parental maltreatment".mp	57
13	"Parental style".mp.	154

Appendix 1. OVID MEDLINE Search String

14	Parenting.mp.	38826
15	"Family Stress".mp.	1465
16	Maternal.mp.	402621
17	Paternal.mp	32149
18	"Parental drug use".mp.	85
19	"Parental practices".mp	315
20	"Parenting behaviors".mp.	215
21	"Family structure".mp.	4387
22	"Parent-child relationship".mp.	2258
23	Prenatal.mp	214200
24	10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	595688
25	9 and 24	426

Appendix 1. OVID MEDLINE Search String (continued)

Study ID	Country	Study design	Unique Population Characteristics*	Total number of participants	Adolescent age at assessment**	Risk factors	Adolescent substance use measures
Brody 1993	United States	Cross sectional study		80	(11,15]	High parental permissiveness; Poor parent-child relationship; Prenatal substance exposure; Low parental monitoring	Illegal hard substances; Marijuana; Alcohol
Anderson 1994	United States	Cross sectional study		489	(13,20]	Prenatal substance exposure; Low parental support	Illegal hard substances; Marijuana; Alcohol
Bogenschneider 1998	United States	Cross sectional study		1227	(13,19]	Prenatal substance exposure; Low parental monitoring	Illegal hard substances; Marijuana; Inhalants
Simons-Morton 2005	United States	Cohort study		2453	(11,16]	High parental permissiveness; Parental substance use; Prenatal substance exposure; Low parental monitoring	Alcohol
Walden 2007	United States	Cohort study		1,514	(10,13]	Parental substance use; Prenatal substance exposure	Nicotine; Illegal hard substances; Marijuana; Alcohol
Herman-Stahl 2008	United States	Cross sectional study		7910	(12,17]	Prenatal substance exposure; Low parental monitoring	Illegal hard substances; Marijuana; Alcohol
Branstetter 2009	United States	Cohort study		200	(14,17]	High parental permissiveness; Poor parent-child relationship; Low parental monitoring	Marijuana; Alcohol
Luk 2010	United States	Cross sectional study		1308	(15,17]	Poor parent-child relationship; Prenatal substance exposure; Low parental monitoring	Nicotine; Marijuana; Alcohol
Bahr 2010	United States	Cross sectional study	Race; Gender; Geography	4983	(12,19]	Parental substance use; Prenatal substance exposure; Low parental monitoring; Low parental support	Alcohol
Abar 2014	United States	Cross sectional study	Race	5419	(12,15]	Low parental knowledge; Poor parent-child relationship; Prenatal substance exposure	Marijuana; Alcohol
Minnes 2014	United States	Cohort study		358	(12,16]	Prenatal substance exposure	Nicotine; Illegal hard substances; Marijuana; Alcohol
Rioux 2016	Canada	Cohort study		209	(15,16]	Low parental monitoring	Alcohol
DeGenna 2016	United States	Cohort study		456	(16,17]	Low parental knowledge; High parental permissiveness; Parental substance use; Prenatal substance exposure; Low parental monitoring; Low parental support	Nicotine
Choi 2017	United States	Cohort study		784	(14,16]	Poor parent-child relationship; Prenatal substance exposure	Nicotine; Alcohol
Kelly 2017	United States	Cross sectional study		117	(13,18]	Prenatal substance exposure; Low parental monitoring	Alcohol
DeGenna 2017	United States	Cohort study		784	(16,17]	Parental substance use; Prenatal substance exposure	Nicotine
Diggs 2017	United States	Cohort study		215	(18,20]	Low parental knowledge; Poor parent-child relationship; Parental substance use; Prenatal substance exposure; Low parental monitoring	Alcohol
Rusby 2018	United States	Cohort study		400	(13,15]	Poor parent-child relationship; Parental substance use; Low parental monitoring	Marijuana; Alcohol
Yoon 2018	United States	Cross sectional study	Race; Gender; SES	685	(12,15]	Poor parent-child relationship; Prenatal substance exposure; Low parental monitoring	Nicotine; Illegal hard substances; Marijuana; Alcohol
Epperson 2018	United States	Cohort study	Race; Ethnicity	1536	(15,17]	Parental substance use; Prenatal substance exposure; Low parental monitoring	Nicotine
Cox 2018	United States	Cohort study		848	(15,18]	Parental substance use; Other: low parental punishment, low parental communication	Alcohol
Hill 2018	United States	Cohort study		363	(13,20]	Poor parent-child relationship; Parental substance use; Prenatal substance exposure; Low parental support	Marijuana
Voce 2020	United States	Cross sectional study		1056	(14,19]	High parental permissiveness	Alcohol
Sartor 2020	United States	Cohort study	Race; Gender; SES	1,869	(8,18]	Low parental monitoring; Other: parental involvement	Nicotine
Zheng 2021	Canada	Cohort study		842	(13,18]	Prenatal substance exposure; Low parental monitoring; Harsh parenting	Alcohol
Paige 2022	United States	Cohort study		338	(11,17]	Parental substance use; Poor parent-child relationship	Nicotine; Marijuana; Alcohol
Bray 2022	United States	Cohort study	Race; Gender	4067	(14,19]	Prenatal substance exposure; Low parental monitoring; Interparental conflict	Alcohol
Pelham 2023	United States	Cohort study		8,780	(10,17]	Prenatal substance exposure; Low parental monitoring	Nicotine; Illegal hard substances; Marijuana; Alcohol
Larroulet 2021	United States	Cross sectional study		263	(14,19]	Parental substance use; Prenatal substance exposure	Marijuana
Parlette 2022	United States	Cross sectional study		132	(12,20]	Low parental knowledge; Prenatal substance exposure; Low parental monitoring	Marijuana; Alcohol
Clinchard 2024	United States	Cohort study	SES	237	(13,18]	Low parental knowledge; Prenatal substance exposure; Low parental monitoring	Nicotine; Marijuana; Alcohol

*Unique population characteristics identifies studies that looked at specific populations that did not represent the general population.
**The square bracket indicates the second value being non-inclusive of the study population.

Appendix 2. Population & Assessment Information of Included Studies; *this appendix compiles the study characteristics extracted from our search. Unique population characteristics refer to studies that targeted a specific population.*

MCMASTER CHILD HEALTH CONFERENCE

10th Annual McMaster Child Health Conference

The McMaster Child Health Conference is an annual symposium for stakeholders, faculty, and students from multiple disciplines to discuss issues, policies, and novel research relevant to child health and development. For their 10th year, the conference invited the Hamilton community to explore the theme “Caring for the Future: Addressing Chronic Illness in Pediatric Populations” at McMaster University on March 22nd, 2025. Keynote speakers and workshop leaders covered a range of topics, including the transition from pediatric to adult care, and the lived experience of patients with chronic illness.

MCMASTER CHILD HEALTH CONFERENCE

The Association Between Childhood Neighbourhood Crime Exposure and Atherosclerosis Burden; A Retrospective Cohort Study in the city of London, Ontario.

ADITYA SIKAND, JOY CHOWDHURY, UTKARSH CHAUDHRY, MELISSA TIANQI WANG, NOAH KIM, SHAHBHANO MIRZA, ARDAVAN BEHROUZ, DR. DR. MAHMOUD REZA AZARPAZHOOH

[1]STROKE PREVENTION AND ATHEROSCLEROSIS RESEARCH CENTRE, WESTERN UNIVERSITY

According to the World Health Organization, 85% of premature deaths are associated with cardiovascular health, which relate to environmental stressors. Through observing the neighbourhood crime rates of patients during childhood at the SPARC cardiovascular clinic, we can observe associations between the stressors of living in areas with a high crime rate and atherosclerosis. Our study is a retrospective cohort study that examines crime rates in the city of London, Ontario and pairs them with patients that lived in that area during their childhood. We hope that this study will provide more insight towards creating healthy living environments for children.

Community Clinician Management Patterns of Childhood Dyslipidemia

KATHERINE N. TOM[1], NATASHA DESILVA[2], ALICIA POLACK[3], KARISHMA SINGH[1], CHARLES KEOWN-STONEMAN[4], JONATHON MAGUIRE[4], CATHERINE BIRKEN [3], DR. PETER D. WONG[3]

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Childhood dyslipidemia refers to abnormal blood lipid levels in children and increases risk for cardiovascular disease in adulthood. Our goal was to describe how primary care physicians manage childhood dyslipidemia. We reviewed the medical records of otherwise healthy children with abnormal blood lipid levels. We wanted to see how many physicians engaged in each management practice such as informing families, repeating bloodwork and making referrals to specialists. We found that physicians rarely identified abnormal lipid levels or started early management. Our results would support increasing awareness about recent guidelines for childhood dyslipidemia screening and management to improve patient care.

MCMASTER CHILD HEALTH CONFERENCE

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ABOUT THE JOURNAL

The Child Health Interdisciplinary Literature and Discovery (CHILD) Journal was created by students in the Child Health Specialization (CHS) of the Bachelor of Health Sciences Program at McMaster University.

Managed by third-year students in the specialization as part of the course curriculum, with guidance from CHS Instructors and Facilitators, the journal aims to showcase the work of students within the specialization.

The focus of The CHILD is to showcase the in-depth knowledge, collaborative projects, talents and ideas of CHS students. Students in their third year of the specialization lead the development and publishing process with support from CHS alumni. Articles include perspective and opinion pieces, reviews, and general commentaries. Students in all years of the Child Health Specialization are invited to contribute work highlighting a range of topics in child health and development.

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