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EDITORIAL

Role of iron deficiency anemia in inflammatory bowel disease

Seema Rai

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Abstract

Inflammatory bowel disease (IBD) is a relapsing chronic inflammatory disorder of the small and large gut with rising incidence and prevalence worldwide. Iron deficiency anemia is one of the most common extraintestinal manifestations of IBD, which correlates with the disease activity and tendency to relapse even after successful management. Anemia affects various aspects of quality of life, such as physical, cognitive, emotional, and workability, as well as healthcare costs. The anemia in IBD can be due to iron deficiency (ID) or chronic disease. The relative frequency of ID in IBD is 60%, according to some studies, and only 14% receive treatment. The evaluation of ID is also tricky as ferritin, being an inflammatory marker, also rises in chronic inflammatory diseases like IBD. The review of anemia in IBD patients involves other investigations like transferrin saturation and exploration of other nutritional deficiencies to curb the marker asthenia with which these patients often present. It underscores the importance of timely investigation and treatment to prevent long-term sequelae. We can start oral iron therapy in certain circumstances. Still, as inflammation of the gut hampers iron absorption, an alternative route to bypass the inflamed gut is usually recommended to avoid the requirement for blood transfusions.

Key Words: Colitis; Iron deficiency; Anemia; Inflammation; Ferritin

Core Tip: Iron deficiency is related to many complications in patients with inflammatory bowel disease (IBD) and further increases the mortality and morbidity in this patient group. The effective management of iron deficiency (ID) is essential to improve these patients' lifestyles and health-related complications. ID correlates with the disease activity in IBD and the tendency to relapse even after successful ID therapy. Parenteral iron therapy, a promising avenue, is showing potential in improving the target hemoglobin level in IBD patients.

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INTRODUCTION

Iron deficiency (ID) anemia is a prevalent issue in chronic inflammatory bowel disease (IBD).Three-quarters of patients with IBD suffer from ID anemia. The current definition of anemia to holds for patients with IBD[1]. The mechanism of ID in IBD is multifactorial, and diagnosing and managing ID in such patients is a challenging in such patients. IBD (ulcerative colitis, Crohn's Disease, and inflammatory disease undiagnosed) is characterized by immune-mediated inflammation of the small and large gut that leads to ulceration and bleeding in the intestine[2-4]. IBDs usually involve the whole gut from the mouth to the rectum, Crohn's disease involves the beginning of the small gut up till the start of the large gut and ulcerative colitis from the large gut to the rectum. The prevalence of ID in IBD *as per* a systematic review is 24% and the prevalence is higher in Crohn's disease as compared to ulcerative colitis[5]. The anemia in IBD is unique as it is due to both anemia of chronic disease and ID. The ongoing loss of blood from the inflamed gut mucosa and impaired absorption of iron and vitamin B12 from the inflamed mucosa and other micronutrient deficiency, immune-mediated marrow suppression, drug toxicity (methotrexate), and surgical resection of the duodenum can also lead to impaired absorption, hence leading to depletion of iron stores and therefore ID. Anemia of chronic disease develops due to chronic inflammation, leading to the release of inflammatory cytokines. This increases the production of liver hepcidin which blocks ferroportin-1 and prevents iron release from enterocytes, macrophages and hepatocytes and as a result, iron is sequestrated from erythropoiesis[6,7]. The risk of developing anemia relates to disease activity. The minimum number of investigations required to screen anemia is complete blood count, C-reactive protein, and serum ferritin, which will detect inflammatory flare and ID at an early stage. For patients in remission screening should be done every 6-12 mo, and for patients with active disease screening should be done every 3 mo. The annual vitamin B12 and folic acid screening should be done as and when required[8]. The diagnostic investigations for confirmation of ID are complete blood count, reticulocyte count, serum ferritin, and transferrin saturation, and if more extensive investigations are required vitamin B12, folic acid, and bone marrow examination should be done. The management of ID in IBD is complex, and intravenous iron shows more acceptance and a better rise in hemoglobin and the repletion of iron stores.

PATHOPHYSIOLOGY OF ID IN IBD

Iron is an essential component of hemoglobin in erythrocytes, myoglobin muscle, and enzymes and it accounts for 80% of total body iron. Iron is necessary for oxygen carrying, cellular respiration and cellular proliferation[9]. The daily iron loss is 1-2 mg/day, and this ongoing loss is exaggerated in IBD due to chronic inflammation. ID leads to chronic fatigue, adverse effects on the growing brain, and a negative impact on quality of life[10]. Hepcidin, a 25-amino acid polypeptide that is synthesized primarily in hepatocytes, reduces the iron absorption from the intestine by binding to the only known cellular iron exporter, ferroportin, causing it to be degraded. Therefore, hepcidin is now considered to be the most critical factor controlling iron absorption[11].

The ID in IBD can be absolute or functional. Absolute ID is due to impaired absorption through the inflamed mucosa and chronic blood loss because of dietary restrictions are due to disease, malabsorption, and the effect of drugs being used for the management of the disease[12]. Anemia of chronic disease is due to an increase in hepcidin level. As a polypeptide synthesized in the liver, and it is an acute phase reactant that regulates the plasma iron concentration at the systemic level. The increase in hepcidin is directly related to the release of proinflammatory cytokines like interleukin (IL)-6, IL-7, and tumor necrosis factor-alpha. Hepcidin induces cellular degradation of the ferroportin transporter. This transporter regulates the iron transfer from intracellular to extracellular medium[13]. Hepcidin reduces the absorption of ferrum due to inhibition of divalent metal transport[14]. Transferrin is the main iron carrier protein during inflammation and the inflammatory cytokine -antitrypsin blocks the receptor of transferrin in erythroid progenitor cells, thus inhibiting erythropoiesis.

CONCLUSION

The management of ID in IBD requires continuous monitoring both in terms of clinical signs and symptoms and biochemical investigations. Parenteral therapy should be instituted as soon as possible to avoid the deleterious effect of chronic anemia on quality of life. Parenteral treatment is more effective, faster, and better tolerated by patients with anemia.

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EDITORIAL

Genetic predisposition to childhood cancer

Jelena Roganovic

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Abstract

The etiology of childhood cancer remains largely unknown. Recent evidence suggests that genetic factors play a substantial role in pediatric tumorigenesis. Unlike adult cancers, pediatric cancers typically have a higher prevalence of germline pathogenic variants in cancer predisposition genes. Inherited cancer predisposition syndromes account for approximately 10% of all childhood cancers. Over the years, the diagnosis of cancer predisposition syndromes was based on clinical suspicion prompting referral to a specialized geneticist. However, advances in molecular technologies have led to a shift toward a "genotype-first" approach. Identification of genetic variants related to cancer predisposition enables tailored treatment, improves clinical outcome, optimizes surveillance, and facilitates genetic counseling of the affected child and the family.

Key Words: Cancer; Children; Etiology; Genetics; Cancer predisposition syndromes

Core Tip: Genetic predisposition to childhood cancer has gained increasing attention in recent years as a result of our growing knowledge and advancements in molecular biology. It is estimated that at least 10% of children with cancer have an underlying genetic susceptibility to cancer. Identifying germline pathogenic variants in cancer predisposition genes can be of great importance, both for research studies and clinical implications, including preventive measures, a tailored treatment approach to minimize toxicities, comorbidity evaluation, surveillance and follow-up strategies, comprehensive genetic testing and counseling, psychological support of affected children and their families, and ethical considerations.

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INTRODUCTION

According to the latest Global Burden of Disease Study, 2019, 291300 new cases of childhood cancers (children aged 0-14 years) occurred worldwide in 2019[1]. Cancer in children, although rare, is one of the leading disease-related causes of death in developed countries[1]. The etiology of childhood cancer has been systematically investigated in recent decades but remains largely unclear. Unlike adult cancers, very few environmental risk factors have been associated with cancer risk in children, including ionizing radiation, prior chemotherapy, and parental occupational exposure[2,3]. Due to the early age at diagnosis and the short period of postnatal environmental exposure, it has become increasingly evident that a considerable proportion of pediatric malignancies results from a genetic predisposition. It is estimated that at least 10% of children diagnosed with cancer have inherited cancer predisposition syndrome (CPS)[4]. The most recent studies suggest that this proportion is higher, with germline pathogenic variants in cancer predisposition genes detected in up to 18% of children with cancer[5]. This editorial provides an overview of key aspects of cancer predisposition in pediatric oncology.

TOOL DEVELOPMENT

Identifying children with susceptibility for cancer may lead to modified oncologic treatment in cases of expected syndrome-related increased toxicity or drug resistance as well as intensified screening for early detection of a new cancer. Affected family members may also benefit from appropriate surveillance strategies[6]. Moreover, genetic testing, genetic counseling, and psychological support for the affected children and their families might be warranted.

Due to the potential clinical benefits, it is important for pediatric care providers to become aware of the features of the major inherited CPS. The criteria from Jongmans *et al*[6] and a modified version of these criteria provide a useful framework for identification of children at risk[7-9]. These include: (1) A positive family history of cancer spanning at least three generations [two or more malignancies that occurred in family members before the age of 18 years, including the affected child, a first degree relative (parent or sibling) with cancer < 45 years of age, two or more first or second degree relatives with cancer in the same parental lineage < 45 years, or cancer in a consanguineous family]; (2) Special cancer types and/or cancer features (*e.g.*, childhood onset of an adult type of cancer) known to be strongly associated with CPS; (3) Genetic tumor analysis reveals a defect suggesting germline predisposition (*e.g.*, a pathogenic variant is identified that is known to represent germline cancer predisposition); (4) A child with two or more malignancies (secondary, bilateral, multifocal, synchronous, or metachronous); (5) A child with cancer and obvious nonmalignant signs suggestive of a genetic condition (congenital anomalies, facial dysmorphism, developmental delay and mental impairment, skin anomalies, hematological abnormalities not explained by the current cancer, immune deficiency, and endocrine anomalies); and (6) A child with excessive treatment toxicity.

A child presenting with any of these features should be referred to an experienced clinical geneticist or genetic counselor for further evaluation[7,10]. An updated easy-to-use screening tool, based on the modified Jongmans criteria and useful for the selection of children who may benefit from genetic testing, is shown in Table 1.

HEREDITARY PREDISPOSITION TO CHILDHOOD CANCER

CPS are a heterogeneous group of genetic conditions associated with a significantly increased risk of developing specific tumors at an earlier age. Classic CPS encompass: Neurofibromatosis type 1; Down syndrome; Fanconi anemia; Beckwith-Wiedemann syndrome; Li-Fraumeni syndrome; Louis Barr syndrome (ataxia telangiectasia); Von Hippel-Lindau syndrome; Denys-Drash syndrome; and multiple endocrine neoplasia, among others[8,11]. The main clinical manifestations include: Syndromic features (the most common are facial dysmorphism, skin anomalies, developmental delay, and growth disorders, but not all patients have an overt clinical phenotype, as well as endocrine disturbances, immune or hematological alterations, and solid organ dysfunction); earlier occurrence of specific cancer types; unusual types of cancer; multiple malignancies; familial clustering; and excessive toxicity of anticancer treatments[8,12]. The relationship between cancer and morphological abnormalities has been studied for decades in order to delineate the common critical pathways of embryogenesis and tumorigenesis[13]. In the genetic era, CPS, previously described on the basis of clinical features, have undergone dramatic changes[14].

Most CPS are inherited in an autosomal dominant manner, but in rare instances recessive inheritance and other inheritance patterns are possible. The majority of known cancer predisposition genes are tumor suppressor genes, which require biallelic inactivation to exert their activity. Rarely, proto-oncogenes are activated through germline gain-of-function alterations. The pathophysiology of each CPS varies according to the functions of the altered gene, such as DNA repair, cell proliferation, cell death, or signaling pathways, and according to the molecular mechanisms implicated[4,7]. A growing number of techniques are now available for genetic testing. Next generation sequencing has revolutionized our understanding of the genetic basis of childhood cancer and facilitated omics studies. Whole genome sequencing is the

Table 1 Recognition of genetic predisposition in pediatric cancer patients[6-9]

Characteristics	Conditions
Family history	≥ 2 malignancies occurred in family members before the age of 18 years, including the affected child
	First-degree relative (parent or sibling) with cancer < 45 years of age
	≥ 2 first- or second-degree relatives with cancer in the same parental lineage < 45 years
	Cancer in consanguineous family
Tumor type and/or cancer features known to be strongly associated with cancer predisposition syndrome	
	Adrenocortical carcinoma/adenoma
	ALL (low hypodiploid)
	ALL (ring chromosome 21)
	ALL (Robertsonian translocation 15;21)
	ALL relapse (*TP53* mutated)
	AML (Monosomy 7)
	Basal cell carcinoma
	Botryoid rhabdomyosarcoma of the urogenital tract (fusion-negative)
	Chondromesenchymal hamartoma
	Choroid plexus carcinoma/tumor
	Colorectal carcinoma
	Cystic nephroma
	Endolymphatic sack tumor
	Fetal rhabdomyoma
	Gastrointestinal stromal tumor
	Glioma of the optic pathway (with signs of *NF1*)
	Gonadoblastoma
	Hemangioblastoma
	Hepatoblastoma (*CTNNB1* wildtype)
	Hepatocellular carcinoma
	Infantile myofibromatosis
	Juvenile myelomonocytic leukemia
	Keratocystic odontogenic tumor
	Large cell calcifying Sertoli-cell-tumor
	Malignant peripheral nerve sheath tumor
	Medullary thyroid carcinoma
	Medulloblastoma (SHH activated)
	Medulloblastoma (WNT activated, *CTNNB1* wildtype)
	Medullary renal cell carcinoma
	Medulloepithelioma
	Melanoma
	Meningioma
	Myelodysplastic syndrome
	Myeloproliferative neoplasms (except CML)

	Myxoma
	Neuroendocrine tumor
	Paraganglioma/pheochromocytoma
	Parathyroid carcinoma/adenoma
	Pineoblastoma
	Pituitary adenoma/tumor
	Pituitary blastoma
	Pleuropulmonary blastoma
	Renal cell carcinoma
	Retinoblastoma
	Rhabdoid tumor
	Rhabdomyosarcoma with diffuse anaplasia
	Schwannoma
	Schwannomatosis
	Sertoli-Leydig cell tumor
	Sex cord-stromal tumor with annular tubules
	Small-cell carcinoma of the ovary, hypercalcemic type
	Squamous cell carcinoma
	Subependymal giant cell astrocytoma
	Thyroid carcinoma (non-medullary)
	Transient myeloproliferative disease
Other rare cancers or cancers that typically occur in adults, unusually early manifestation age	
Genetic tumor analysis reveals a defect suggesting germline cancer predisposition	
A child with ≥ 2 malignancies (secondary, bilateral in paired organs, multifocal, synchronous, or metachronous)	
A child with cancer and obvious nonmalignant signs suggestive of a genetic condition	Congenital anomalies
	Facial dysmorphism
	Mental impairment, developmental delay
	Abnormal growth
	Skin anomalies (abnormal pigmentation, *i.e.* ≥ 2 café-au-lait spots, vascular lesions, hypersensitivity to sunlight, benign tumors)
	Immune deficiency
	Endocrine anomalies
A child with excessive treatment toxicity	

ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; CML: Chronic myeloid leukemia; SHH: Sonic hedgehog protein; WNT: Wingless/integrated signaling pathway.

most powerful and comprehensive technique that identifies variants in coding and noncoding regions, detecting up to 85% of cancer-related variants[15,16]. Targeted analysis sequencing, as the name suggests, targets specific regions of the genes known to have strong associations with specific CPS[15,17].

Genomic studies have underscored major differences between pediatric and adult cancers. Pediatric cancers have 14 times fewer somatic alterations than adult tumors, but a higher prevalence of germline pathogenic variants in cancer predisposing genes, except in patients with germline alterations in DNA mismatch repair[15,18,19]. The low overall burden of somatic alterations in pediatric cancer is considered to be related to the embryonal origin of many cancers, dysregulation of developmental pathways, and the short period of exposure to environmental carcinogens[18]. A remarkable heterogeneity of the types of genetic alterations has been discovered in pediatric cancers, including copy

number alterations and structural alterations. The list of cancer predisposition genes associated with CPS is continuing to grow. Some of them are associated with a specific subtype of cancer, whereas germline pathogenic variants in other genes can cause various malignancies. The range of cancers depends on age-specific and tissue-specific predisposition to cancer driver alterations and the biological function of the gene. Moreover, cancer predisposition genes are often associated with cancers that harbor somatic variants of the same gene[20,21]. Selected hereditary syndromes associated with childhood cancers and related genetic alterations are listed in Table 2.

Table 2 Selected cancer predisposition syndromes, associated malignancies and genetic alterations[4,5,7,21]

Cancer predisposition syndrome	Associated malignancy[1]	Genetic alteration
Ataxia telangiectasia	Lymphoma, leukemia	ATM
Beckwith-Wiedemann syndrome	Wilms' tumor, hepatoblastoma, neuroblastoma, rhabdomyosarcoma, adrenocortical carcinoma	IGF-2, CDKN1C
Denys-Drash syndrome	Wilms' tumor	WT1
Diamond-Blackfan anemia	AML, MDS, colon cancer, female genital cancers, osteosarcoma	RPL5, RPL11, RPL35A, RPS10, RPS17, RPS19, RPS24, RPS26
Down syndrome	ALL, AML, MDS, germ cell tumor, retinoblastoma	GATA1, GATA2, IKZF1, JAK2
Familial adenomatous polyposis	Ampullary adenocarcinoma, colorectal cancer, small bowel cancer, stomach cancer, thyroid cancer, pancreatic cancer, hepatoblastoma	APC
Fanconi anemia	AML, MDS, esophageal cancer, head and neck cancer, skin cancer	FANCA, FANCC, FANCG, RAD51C
Gorlin syndrome	Basal cell carcinoma, ependymoma, medulloblastoma, ovarian fibrosarcoma, rhabdomyosarcoma	PTCH1, SUFU, PTCH2
Li Fraumeni syndrome	Adrenocortical carcinoma, ALL, AML, brain tumor, breast cancer, colorectal cancer, neuroblastoma, osteosarcoma, rhabdomyosarcoma, Wilms' tumor	TP53
Multiple endocrine neoplasia type 1	Ependymoma	MEN1
Multiple endocrine neoplasia type 2	Medullary thyroid cancer	RET
Neurofibromatosis type 1	Malignant peripheral nerve sheath tumor, breast cancer, optic glioma, gastrointestinal stromal tumor, JMML, neuroblastoma, embryonal rhabdomyosarcoma	NF1
Neurofibromatosis type 2	Astrocytoma, ependymoma, glioma	NF2
Von Hippel-Lindau syndrome	Clear cell carcinoma, carcinoid, pancreatic islet cell carcinoma, renal cell carcinoma	VHL
WAGR syndrome	Wilms' tumor	WT1

[1]Associated nonmalignant tumors are not included in the list. ALL: Acute lymphoblastic leukemia; AML: Acute myeloid leukemia; JMML: Juvenile myelomonocytic leukemia; MDS: Myelodysplastic syndrome; WAGR: Wilms tumor, aniridia, genitourinary anomalies, and range of developmental delays.

CLINICAL IMPLICATIONS OF GENETIC PREDISPOSITION TO CHILDHOOD CANCER

Identifying children with germline alterations can provide important information for treatment, prevention, surveillance, and genetic counseling. These patients may have increased toxicity to conventional chemotherapy[20,22]. Treatment strategies should, whenever possible, minimize the use of irradiation or alkylating agents that increase the risk of secondary malignancies[18]. There are very few established preventive strategies for children with CPS, such as prophylactic thyroidectomy in children with multiple endocrine neoplasia type 2 and prophylactic colectomy in children with APC-associated polyposis[14]. Focused surveillance protocols can detect early secondary malignancies. They differ between syndromes and integrate imaging (serial ultrasounds, whole-body magnetic resonance imaging) and non-imaging screening elements[5,14,23]. Children and families with a suspected or known CPS should be monitored in specialized centers that provide comprehensive genetic counseling and testing services.

Family medicine and pediatric primary care physicians will likely meet children with major inherited CPS during their practice. Their ongoing role is to recognize signs suggestive of hereditary cancer timely and to refer patients and their families to specialized centers for further evaluation and treatment. Undoubtedly, most cancer predisposition genes are yet to be discovered and characterized. The list of pediatric CPS will steadily grow, and the guidelines for referring children for genetic testing will change over time. Our greater awareness and increasing knowledge of the genetic basis of childhood cancer will have exciting clinical implications in the near future.

CONCLUSION

Genetic predisposition is an important and previously underestimated cause of cancer in children. Studying patients with CPS and underlying mechanisms, by employing comprehensive genomic analyses, is crucial in order to improve preventive strategies, surveillance, adapted treatment, close follow-up, and psychological support of affected children and their families.

FOOTNOTES

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Built environment and childhood obesity

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Abstract

Childhood obesity, an escalating global health challenge, is intricately linked to the built environment in which children live, learn, and play. This review and perspective examined the multifaceted relationship between the built environment and childhood obesity, offering insights into potential interventions for prevention. Factors such as urbanization, access to unhealthy food options, sedentary behaviors, and socioeconomic disparities are critical contributors to this complex epidemic. Built environment encompasses the human-modified spaces such as homes, schools, workplaces, and urban areas. These settings can influence children's physical activity levels, dietary habits, and overall health. The built environment can be modified to prevent childhood obesity by enhancing active transportation through the development of safe walking and cycling routes, creating accessible and inviting green spaces and play areas, and promoting healthy food environments by regulating fast-food outlet density. School design is another area for intervention, with a focus on integrating outdoor spaces and facilities that promote physical activity and healthy eating. Community engagement and education in reinforcing healthy behaviors is necessary, alongside the potential of technology and innovation in encouraging physical activity among children. Policy and legislative support are crucial for sustaining these efforts. In conclusion, addressing the built environment in the fight against childhood obesity requires the need for a comprehensive, multipronged approach that leverages the built environment as a tool for promoting healthier lifestyles among children, ultimately paving the way for a healthier, more active future generation.

Key Words: Non-communicable diseases; Walkability; Playgrounds; Neighborhood green spaces; Safety; Pollution

Core Tip: Prevention of obesity must begin in childhood. Healthy habits and physical activity form the cornerstone. Built environment, the environment in which children grow, play, and eat, must encourage a healthy lifestyle. Studies show critical aspects of the built environment are important for improving children's health and for preventing metabolic diseases.

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INTRODUCTION

Obesity transitioned from being a cosmetic problem to a health condition. A 2021 report from the World Health Organization stated that the prevalence of obesity globally has increased nearly three-fold since 1975[1-6]. This was seen across age groups, with differences observed across geographies[7-10]. Built environment includes homes, schools, urban areas, and access to leisure activities; it has a role in the risk of childhood obesity. Efforts are needed to develop built environments that aid in a healthy lifestyle to prevent diseases later in life.

RISK FACTORS

Although genetics and environmental factors have a role in the pathogenesis, the galloping increase over a short time period points to the overwhelming role of environment. Since childhood obesity is the precursor of obesity in adulthood with its attendant morbidities, prevention is paramount[11]. The first step is to understand the lifestyle factors that lead to obesity, which can then be addressed.

One of the proposed theories for increasing obesity in low-income and middle-income countries is the 'modernization theory.' The 'dependency/world systems theory view' proposes that primarily external structural factors are responsible for the rising obesity trends (*e.g.*, flooding countries with obesogenic, nutrient-poor foods). Fox *et al*[12] compared the dependency theory and modernization theory and found the latter was more likely responsible. Modernization theory states that countries economic progress passes through phases where nutrition transitions occur from a lower calorie, chiefly plant-based diet to a meat and processed food diet that leads to weight gain and attendant comorbidities. There was a global association between urbanization rate and childhood overweight and obesity[12].

These trends were attributed to global economic development, cultural differences, and intergeneration effects of malnutrition in early life. Countries with the most rapid growth shared rapid economic development and social and cultural changes leading to consumption of unhealthy ultra-processed foods. Reversal or stabilization of trends occurred due to governmental interventions as in Denmark[13].

Similarly, increasing sedentary habits resulting from access to electronic gadgets such as mobile telephones, televisions, and computers led to sedentary behavior. Together, increased energy intake and diminished physical activity contributed to the dramatic rise of childhood overweight and obesity[11]. Interventions must address these two factors.

BUILT ENVIRONMENT

Built environment, which refers to the environments that are modified by humans, including homes, schools, workplaces, highways, urban sprawls, accessibility to amenities, leisure, and pollution[14] has a role in influencing both arms of the energy equilibrium. Therefore, attention is increasingly drawn to aspects of built environment that can result in better lifestyle and positive health outcomes[15]. It is significant that obesity in childhood persists into adulthood. A broad-based approach at prevention is essential. Earlier studies showed that the place of living is a strong determinant of obesity. Built environment encompasses the physical built infrastructure in which people live and is a potential area for intervention[16]. It contributes by influencing the broader obesogenic environment, spreading out to the family and sociopolitical environment[17]. Behavioral changes encompass unhealthy diet intake at late hours, watching electronic media with resultant disruption in sleep times, and house, which can lead to adverse metabolic changes[18].

COMPONENTS OF BUILT ENVIRONMENT

A life-course approach to understanding childhood obesity shows key steps for intervention. Trasande *et al*[19] employed it to identify environmental factors encompassing the built environment and chemical environmental agents as correctable factors in preventing obesity. Interventions at the genetic level[20] are not possible yet. The importance of environment in childhood obesity has received focus[21]. Most of the obesogenic environmental factors associated with built environment were related to childhood obesity, including land-use mix, street connectivity, residential density, urban sprawl, access to green space, public transport, bike lanes, sidewalks, neighborhood aesthetics, access to con-

venience stores, supermarkets, grocery stores, full-service restaurants, fast-food restaurants, and fruit and vegetable markets[21]. Some of these factors were consistent on a global basis including greater access to fast-food restaurants in the neighborhood and more fast-food consumption, access to bike lanes and more physical activity, better access to sidewalks and reduced sedentary behaviors, and greater access to green space and less TV screen time.

While early life adverse events result in obesity by the age of 13 years[22], built environment can also affect the quality of life in children[23].

CONCEPT OF BUILT ENVIRONMENT

Built environment encompasses the physical structure as well as the built infrastructure where people live, work, play, learn, travel, and socialize[24]. Both vehicular traffic and environmental pollution are included in the term[16]. The scope has been expanded to include houses, roads, walkways, density, transportation networks, shops, parks, and public spaces as well as activities happening there[25,26].

To determine positive and negative aspects of built environment in children, two parameters are used: Active transport to school refers to walking or bicycling to school every day[26]; and safe routes to school includes provision of a safe and walkable environment that allows children to reach school in an active manner[26].

DETERMINANTS OF BUILT ENVIRONMENT

Ortegon-Sanchez *et al*[27] published a meta-narrative review on the measurement of different features of built environment and child health. In view of the heterogeneity inherent in published studies, a meta-narrative review approach was chosen to systematically review complex topics that were conceptualized and studied in different ways by different research groups[27]. The aim was to provide an understanding of the methods that were employed to study the complex interactions between the built environment and children's physical and mental health. From the major databases (Scopus, MEDLINE, Embase and PSycinfo), 108 studies were included in the analysis. Four broad areas were assessed: Streets; built environment; health; and population.

Objective measurement of physical activity was positively associated with street connectivity, and density of residences, households, and population. It was linked to accessibility as well as objective and perceived closeness to activity. There was a dichotomy between perceived personal safety by the children and their parents.

In contrast, greater time spent in sedentary activities was associated with less walkability. Objective assessment of overweight and obesity were made in 30 studies by using body mass index (BMI). Lower BMI was reported with intersection density, walking paths, parks and play areas, convenience stores, and traffic safety. Higher BMI was related to access to food outlets, perceived risk of crime, and physical incivilities.

Broadly, ten areas were commonly studied: (1) Residential and population density; (2) Street connectivity; (3) Diversity of land-use; (4) Walkability, a composite of the above three factors; (5) Walking infrastructure and perception of street environment; (6) Proximity and accessibility to school and to play spaces; (7) Parks, green areas for physical activities; (8) Perceptions of safety; (9) Motor traffic levels; and (10) Social support and psychosocial factors[27].

Among these, a positive association with children's health was observed with safety, street connectivity, access to play facilities, parks, and land-use diversity. However, there is no one-to-one cause and effect relationship. Different factors can act as enablers or inhibitors, and they interact, resulting in a complex and context-dependent cumulative impact on health measures[27]. This meta-narrative review was built upon the earlier 2010 publication by Galvez *et al*[28] that assessed diet, physical activity, active commuting, walkability, obesity, and neighborhood safety. These associations are in alignment with a recent systematic review using a geographic information system (GIS)[29]. Certain other factors were considered such as aesthetics, and physical activity[30]. The results suggested it is still a work in progress.

GLOBAL STUDIES ON BUILT ENVIRONMENT AND OBESITY

While optimal built environment has its greater potential in preventing obesity at an early age, most previous studies assessed interventions in adults across different geographical regions (Table 1)[31-34].

STUDIES ON CHILDHOOD OBESITY AND BUILT ENVIRONMENT

Europe

In a longitudinal study from Sweden, higher odds of childhood obesity were observed in children from neighborhoods with access to fast-food outlets [odds ratio (OR): 1.14, 95% confidence interval (CI): 1.07-1.22][35]. A cross-sectional study in Wales showed that even after adjusting for deprivation, associations were found between childhood obesity and percentage of land available as accessible open space (OR: 0.981, 95%CI: 0.973-0.989, $P < 0.001$) and density of fast food outlets (OR: 1.002, 95%CI: 1.001-1.004, $P = 0.001$). These risk factors must therefore be addressed[36].

Table 1 Studies on the association of built environment and childhood obesity

Ref.	Publication year	Association with childhood obesity
Sweden[35]	2017	Access to fast food outlets
Wales[36]	2021	Density of fast food outlets
Germany[38]	2020	Access to green spaces
New Zealand[41]	2016	School travel distance, green space
Durham (United States)[42]	2012	Housing location, safety
California (United States)[44]	2018	Green space, safety
New York (United States)[45]	2018	Fast food restaurant density
Montreal (Canada)[46]	2018	Pedestrian friendly areas, fast food outlets
Latin American nations[51]	2023	Urban isolation no association with population density or greenery
Shanghai (China)[57]	2023	Recreational and sports facilities
Bangalore (India)[59]	2019	Neighborhood walkability
Uganda (Africa)[61]	2021	Little relation to environmental characteristics

Similar results were reported from England. There was a statistically significant relationship between the sales of unhealthy foods and the prevalence of overweight and obese children[37]. It was shown that deprivation was positively associated with weight ($P < 0.001$). The non-white population was negatively associated ($P < 0.001$) with overweight and obesity.

Zhou *et al*[38] presented data from Germany (22678 children in 51 administrative areas). Higher spatial availability of greenspace was associated with children's risk of being overweight (OR: 0.989, 95%CI: 0.985-0.994), although this association failed to attain statistical significance (OR: 0.997, 95%CI: 0.992-1.003) after adjusting for other variables.

Oceania

In a review on the status of built environment and childhood obesity from Australia, there was a focus on the role of the built environment in supporting physical activity[39]. The built environments and child health in Wales and Australia (beaches) study incorporated longitudinal quantitative data (surveys, anthropometry, accelerometry, and GIS data) to assess the built environmental influences on children's modifiable risk factors for non-communicable diseases[40].

The urban study from New Zealand studied the associations between neighborhood environment and walking in children[41]. Using GIS, 2016 households were selected from 48 Low-walkability and high-walkability neighborhoods from four cities in New Zealand. Children ($n = 227$) from the selected households wore accelerometers to record their physical activity in the period of 2008-2010. Two aspects were measured: (1) Factors that might affect physical activity and residential environment (school distance, amenities for recreational activity, food outlets, and outlets); and (2) Four audited environmental factors including pedestrian amenities, safety, aesthetics, and local destination. The former were assessed by GIS and the latter by SPACES.

The omni-directional piezo-electric sensor that can measure movements as step and accelerometer counts was worn by the children for 7 d. There was a dichotomy between environmental features and physical activity between school travel and non-school physical activity[41]. During school travel times, more activity was associated when the home distance was 1-2 km from school and the existence of green spaces and attractive streets. Areas with more food outlets showed a negative association with physical activity. These results were different from studies in adolescents for non-school physical activity[41]. The authors advised that parental assurance on safety of children must be addressed when developing built environment.

North America

North Carolina: In 2012, Miranda *et al*[42] studied the association between seven built environment domains and childhood obesity in Durham, North Carolina. Housing damage, property disorder, vacancy, nuisances, and territoriality were linked with the Duke University Medical Center pediatric preventive care visits (2008-2009). Children's overweight and obesity were associated with nuisances and territoriality ($P < 0.05$). Similar associations were observed in adolescents from London[43].

California: In California, the relationship between social and physical environmental attributes of the school environment (within school and neighborhood) and childhood obesity was assessed using random forest and multilevel methods[44]. School obesity prevalence ranged from 0.0% to 75.0% [median of 19.8% (interquartile range = 11.5%) and mean of 19.7% (standard deviation: 7.8%)]. The percentage of socioeconomic disadvantaged ranged from 0.0% to 100.0% [median of 40.2% (interquartile range = 63.9%)]. The most highly ranked built or physical environment variables were distance to the nearest highway and greenness. Others were prevalence of violent crime, socioeconomic disadvantage, and fewer physical education teachers.

New York: Children from New York showed geographic disparities across local regions. The relationship between these differences with built environment was reported by Dwicaksono *et al*[45]. Association of obesity was found with higher fast-food restaurant density (unstandardized coefficient, b = 0.014; $P < 0.05$). Access to food sources was proposed to contribute to regional differences in childhood obesity[45].

Montreal, Canada: In Montreal, Canada, street-level urban design features were shown to shape childhood adiposity [46]. Data were obtained from the Quebec adipose and lifestyle investigation in youth study. The subjects comprised 630 children aged 8-10 years with a history of obesity in the family. Baseline measurements were recorded between 2005 and follow up between 2008 and 2011. Street-level urban designs such as pedestrian aids, physical activity facilities, convenience stores, and fast-food restaurants were shown to be modifiable features to prevent childhood adiposity[46].

New York City: In New York City, the relationship between fifth-grade students' (n = 952) physical activity, psychosocial factors, and neighborhood built environment of the school was assessed[47]. The variables included park access, public transportation density, total crime, and walkability after controlling for age and BMI z-scores. Physical activity in boys was associated with public transportation density (β = 0.375; $P = 0.02$) and negatively associated with total crime (β = -0.216; $P = 0.01$). Frequency of light physical activity in girls was associated with park access (β = 0.188; $P = 0.04$). Built environment characteristics were able to account for 97% of the between-school variation in self-efficacy in walking for exercise in girls[47].

Denver: The relationship between systemic racism and obesity was studied in the Denver metropolitan region. Children aged 4-8 years (n = 250) were drawn from the healthy start cohort. Linear regression models were used to estimate associations between neighborhood features with child BMI z-scores and fat mass percent. A significant association was observed between child BMI and redlining (β: 1.36, 95%CI: 0.106-2.620). There was no association between walkability measures and childhood obesity. Therefore, inclusionary zoning and direct investments in neighborhoods must be assessed and repaired to improve the built environment and thereby children's health status[48].

Longitudinal studies: In 2016, the United States launched a longitudinal analysis of the relationships between early life environment and later obesity among large diverse samples of children. The large sample size and the adoption of standardized methodology enables a refined analyses to identify drivers of childhood obesity[49]. An analysis of 20677 children from the cohorts showed that children from higher-opportunity and lower-vulnerability neighborhoods in early life showed a lower rate of BMI increase and a lower risk of obesity from childhood to adolescence[50].

South America

A cross-sectional analysis of a large group of children (n = 20040) living in 159 cities in six Latin American countries was carried out to assess the association between built and social environment and childhood obesity[51]. This study was important because preschool children were studied, unlike most other reports on school children and adolescents. Up to 97% of the variability was observed between individuals within sub-city units; about 3% of the variance in z-scores of weight for height was attributed to features at the city and sub-city levels. In cities, a greater distance between urban patches (isolation, per 1 standard deviation increase) was associated with lower odds of excess weight (OR: 0.90, 95%CI: 0.82-0.99). There was a significant variation in the prevalence of overweight and obesity (range: 4% to 25%). Cities from Chile had the highest prevalence, while cities in Columbia and Peru had the lowest prevalence. Unlike reports from developed countries, higher levels of urban isolation and education level lowered the odds of excess weight. Similarly, there was no association between excess weight in children and population density, intersection density, and presence of greenery[51]. The difference could be due to increased physical activity and greater perception of safety.

Asia

A scale to determine urban and rural areas was constructed in cities drawn from Asia and Africa (India and Ethiopia), in which built environment was a component[52]. The purpose was to identify factors responsible for geographical differences in the prevalence of non-communicable diseases. This scale was widely employed in the assessment of differences in health conditions[53-55].

China: A recent study from the city of Shanghai in China (2023)[56] showed that neighborhood built environment and outdoor leisure activity opportunities are important influences in the prevalence of obesity of children. Conducive built environment is a modifiable factor to reduce childhood obesity. The neighborhood built environment influenced children's obesity not only directly (β = 0.15, $P < 0.05$) but also through the effect of outdoor leisure activities (β = 0.19, $P < 0.05$) in both boys and girls. A narrative systematic review was published on the impact of built environment and physical activity and obesity in children and adolescents from China (2019)[57]. Sixteen studies revealed a quantitative relationship between built environment and physical activity. Lack of recreational facilities, longer commuting time to sports facilities, and neighborhoods without sidewalks correlated with sedentary behavior[57]. These findings aligned with those from adults and from other countries.

Malaysia: An innovative method was employed to perform a spatial survey on overweight and obesity in Malaysia. The spatial smoothing methods for disconnected regions using split random effects and a common intercept showed a spatial pattern in the prevalence of childhood overweight across districts[58]. Complete BMI and geolocation information was available for 6301 children. The sample size varied widely between districts (0 to 363; median = 28). The national prevalence of overweight (including obesity) was 23.8% (95%CI: 22.2-25.4), the prevalence for boys was 24.5% (95%CI:

22.3-26.9), and the prevalence for girls was 23.0% (95%CI: 21.1-24.9). This study enabled identification of districts with a high prevalence of obesity, with an east to west gradient. Such information allows for corrective measures in precise geographical locations.

India: Devarajan *et al*[59] underlined the importance of modifying the obesogenic environment rather than leaving the responsibility to individuals. Apparently healthy school children from Bangalore (n = 292) aged 6-15 years were stratified, and the walkability index was derived using residential density, street connectivity, and land-use mix environment variables[60]. They concluded that neighborhood walkability may be associated with obesity indices in younger children

Africa

Uganda: A study from Uganda revealed local geographic differences of the association of built environment and physical activity. Nakabazzi *et al*[61] did not find a strong relationship between environmental characteristics and school children's moderate-to-vigorous physical activity. Children's moderate-to-vigorous physical activity was related to the availability of play equipment at home (β = -2.37, P < 0.001; unexpected direction), residential density (β = 2.70, P < 0.05), and crime safety (β = -5.29, P < 0.05; unexpected direction). The sex-specific analyses were inconsistent.

PERSPECTIVE

Traditionally, individuals were blamed for obesity in children for being sedentary. It is now increasingly being realized that environmental factors must be conducive for being physically active, *i.e.* the role of environmental determinants are responsible for health behaviors[57] (Table 2).

Table 2 Aspects of obesogenic environment and related factors[1]

Open spaces for physical activity
Access to unhealthy food outlets
Neighborhood and road safety
Air quality
Travel behavior
Family income

[1]Adapted from Carmo *et al*[72] and Abdollahi *et al*[73].

Encouragingly, interdisciplinary work is carried out to predict the prevalence of physical inactivity. A recent study used spatial machine learning for predicting prevalence of physical inactivity[62]. While it is evident that neighborhood and health are related, there is little information on the relative importance of each component related to activity and the variability across geographic locations. The authors ranked seven socioecological neighborhood aspects to the prevalence of physical inactivity. As a first step, they employed geographical random forest, a nonlinear machine learning regression method to assess the variation and contribution of each predictive factor to physical inactivity. This was followed by its predictive performance being compared with geographically weighted artificial neural networks. The results determined that poverty was the most important determinant and green space the least important to physical inactivity in Chicago [62]. This information could be valuable in designing intervention strategies in other large cities.

POTENTIAL AREAS FOR INTERVENTION

Intervention studies were carried out to assess the impact of targeting school environment, street layout, traffic, and others. Vega-Salas *et al*[63] studied the effect of modifying the food built environments in and around schools from Latin America and the Caribbean. When complemented with nutritional and physical education, environmental intervention can reduce the trend of increasing childhood obesity. The specific effects and pathways of interventions need to be worked out by further studies.

Street-level built environment has a significant effect on health by acting through one's ability to engage in healthy behaviors. There is evidence for improved built environmental factors having a positive impact in deprived areas. Ortegon-Sanchez *et al*[64] published a systemic review on whether these are applicable to high-income countries. Most interventions reported were temporary (*e.g.*, closure of streets to traffic), while a few were permanent changes in street design. Subjects were aged below 18 years from high-income and upper middle-income countries. Outcomes recorded BMI or measures of activities.

The interventions, as mentioned earlier, were temporary and often ad hoc, carried out principally in summer months. Closure of streets were based on community preferences as were the physical activities. Permanent interventions consisted of making streets safe places to play. Although there are numerous factors interacting in improving physical activity, evidence is available that modifying the built environment is an achievable way to improve children's health

both in deprived areas and in children from high-income and upper middle-income countries. Further studies are needed to arrive at the types of changes in the built environment that result in the most significant health improvement[64].

A more comprehensive analysis of determinants that support active travel behaviors was published by Nordbø *et al* [65]. Among the 127 studies that were reviewed, 87.4% were cross sectional; the outcome of active travel was reported in 54. The authors concluded that the following could support active travel behavior: Less traffic; greater safety on roads; infrastructure enabling walking and cycling; shorter distance to facilities; and better walkability.

Evidence has been obtained from disparate and multidisciplinary sources. To contain the epidemic of childhood obesity, focused studies and data synthesis must lead to the employment of practical and effective methods of intervention.

SOLUTIONS TO BENEFIT LOW RESOURCE SETTINGS AND NATIONS

Most of the evidence comes from developed countries, whereas most populations reside in developing countries. How can aspects of built environment be applied to developing nations? It is important considering the increasing prevalence of non-communicable diseases due to urbanization, changes in lifestyle, and socioeconomic transitions; these can be addressed by modifying the built environment.

Planned urban development can prevent overcrowding and provide adequate public space and access to leisure time activities, thereby promoting an active lifestyle. In addition, access to healthy foods and limiting availability of fast foods helps create healthy eating opportunities.

Construction of houses with adequate ventilation that avoid overcrowding and allow access to clean water and sanitation are essential components. Access to public transportation prevents congestion on roads as well as vehicular pollution. The residential areas must be planned to allow green spaces that promote physical activity, reduce stress, and encourage social interactions, all of which mitigate the risk of loneliness (Table 3).

Table 3 Built environment aspects to be addressed in developing nations

Green spaces and provision of spaces for physical activity
Availability and affordability of healthy dietary joints
Pedestrian paths for safe commute
Provision of facilities for playing sports and games
Safe walkability zones to go to school
Development of secure neighborhoods that encourage outdoor activities

These require collaboration and cooperation with both policy makers in the government and the residents of the locality. Implementation faces challenges including financial resources, increasing population, and in some nations political instability. With proper intention, these can all be overcome for the common good. On a broader scale, international funding and cooperation can be sought.

LIMITATIONS OF THE STUDY

The concept of modifying built environment to prevent childhood obesity is still emerging. Most studies were carried out on adults from developed countries. The current study is an attempt to bring the role of built environment to the attention of clinicians. It is a narrative review that gathered recent published studies on the role of built environment in childhood obesity. It also suggested potential ways in which it can be modulated for public good. This can plant the seed for further studies to provide solutions to improve built environment so that non-communicable diseases are prevented.

CONCLUSION

Built environment can be modified to reduce the burden of obesity. Interventions include enhancing active transportation by ensuring safe access to recreational facilities[66-68] and increasing availability of healthy food outlets. Technology can be used to monitor and reduce air pollution, a contributor to obesity[69-71]. These require policy and legislative support, a multi-dimensional challenge. By focusing on creating environments that naturally promote physical activity and healthy eating, we can foster healthier lifestyles for children to lay the foundation for a healthier future.

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FOOTNOTES

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical and laboratory features of juvenile idiopathic arthritis with wrist involvement: Results of a retrospective cohort study

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Abstract

BACKGROUND

Previous studies in the pre-biological era showed an association of wrist inflammation in juvenile idiopathic arthritis (JIA) with progressive disease course, polyarticular involvement and failure of methotrexate treatment.

AIM

To describe features of JIA, associated with wrist arthritis.

METHODS

Data from about 753 JIA patients were included in this retrospective cohort study. The clinical and laboratory features of patients with and without wrist involvement were analyzed.

RESULTS

Wrist involvement was found in oligoarthritis (5.8%), RF(−)/RF(+) polyarthritis (44.9%/15.0%), enthesitis-related arthritis (17.7%), and systemic (58.6%) JIA categories. Unilateral wrist involvement was typical for oligoarthritis patients, bilateral involvement was either equal to that of unilateral involvement or was more frequent in other categories. Wrist arthritis was found to be associated with female sex, a low incidence of uveitis, and more indications of systemic inflammation, including elevated levels of C-reactive protein, erythrocyte sedimentation rate, and platelets, as well as involvement of the cervical spine, temporomandibular, shoulder, elbow, metacarpophalangeal, proximal interphalangeal, distal interphalangeal, hip, ankle, and tarsus arthritis. The number of patients with hip

osteoarthritis and hip replacement was also higher. Wrist arthritis was associated with a lower probability of achieving remission [hazard ratio (HR) = 1.3 (95%CI: 1.0-1.7), P = 0.055], and a higher probability of being treated with biologics [HR = 1.7 (95%CI: 1.3-2.10, P = 0.00009)].

CONCLUSION

Wrist arthritis in JIA patients is a marker of a severe disease course, characterized by more intensive inflammation, unfavorable outcomes, and. requiring more intensive treatment with early administration of biologics. Close monitoring of wrist inflammation with ultrasound and MR assessment with early biological treatment might improve the outcomes.

Key Words: Wrist; Hand; Juvenile idiopathic arthritis; Outcomes; Biologics; Methotrexate

Core Tip: Wrist arthritis has specific symptoms, such as muscle weakness, paresthesia, limited fist function, limited pinch grip, joint deviation, aesthetic complaints, and difficulties in writing, drawing, and working with a knife, pencil, laptop, or other device. The frequency of wrist involvement in juvenile idiopathic arthritis categories was 5.8% in oligoarthritis, 44.9% in RF(−), 15.0% in RF(+) polyarthritis, 17.7% in enthesytis-related arthritis, and 58.6% in systemic. Wrist arthritis was associated with higher inflammation, specific joint involvement (cervical spine, temporomandibular, shoulder, elbow, metacarpophalangeal, proximal interphalangeal, distal interphalangeal, hip, ankle, and tarsus), a lower probability of achieving remission, and a higher probability of being treated with biologics.

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INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most frequent chronic pediatric rheumatic disease and has joint involvement with different prognoses, treatment, and outcomes[1]. Recent data from two national databases indicate that the incidence of JIA in Germany ranges from 34 (29–41) to 60 (53–67) per 100000 patients and the prevalence ranges from 133 (122–145) to 168 (157–179) per 100000 patients. According to the current classification, JIA presents with different categories depending on the number of active joints, the presence of systemic features, and immunological features[1]. The pathogenesis of various JIA categories ranges from autoinflammatory for systemic to autoimmune for RF (+) polyarthritis[3,4]. Treatment includes nonsteroid anti-inflammatory drugs (NSAID), intra-articular corticosteroids, nonbiological (methotrexate, sulfasalazine, leflunomide), and biological disease-modifying antirheumatic drugs (DMARD), and inhibiting various cytokines including tumor necrosis factor and interleukins 1, 6, and 17a[5]. JIA categories, the number of active joints, and specific joint involvement have been described many times as markers of disease course, prognosis, and treatment outcomes[6,7]. Knees, ankles, and wrists are joints that are frequently involved in JIA[6]. Wrist arthritis affects about 25% of JIA patients at the onset of the disease and increases to 40% of patients over the next 5 years[8]. Wrist arthritis can be diagnosed both clinically and with imaging tools. The main clinical signs are pain and swelling with early loss of range of motion[9]. In some patients, wrist arthritis can have a silent course with only limitation of motion detected and subsequent muscle atrophy by the rheumatologist. Sometimes the main complaints are related to weak grip during sports exercises or difficulty with writing. Schoolchildren need more time and breaks during writing. Imaging modalities may show signs of wrist involvement depending on the tool and arthritis duration[10]. Ultrasound and magnetic resonance imaging (MRI) may find effusion and synovial hyperplasia in the early stages and bone marrow edema in MRI, especially in clinically nonmanifest wrist synovitis[11,12]. In some cases with arthritis of the fingers, wrist effusion and bone marrow edema may be found in the absence of clinically evident wrist arthritis[13]. Bone erosions and bone loss are markers of advanced wrist arthritis that might be detected with MRI, computed tomography, or plain X-ray. images [14,15]. Several radiological scores have been applied in JIA and adult rheumatoid arthritis based on plain wrist X-rays [16-18]. Early diagnostic evaluation of wrist arthritis is needed to prevent functional disability and joint damage[19]. The severity of wrist arthritis prompted the American College of Rheumatology (ACR) to include it, along with arthritis of the hip joint and cervical spine, in a separate group in which the use of biological drugs as the first line of DMARD treatment with or without methotrexate may be recommended[20]. We performed our study to describe the clinical features of the patients with wrist arthritis.

MATERIALS AND METHODS

Study design and patient selection

We retrospectively analyzed data from the medical histories of 753 patients between the ages of 2 and 17 who were treated at Saint Petersburg State Pediatric Medical University from 2006-2016. Diagnosis of JIA was made according to the International League of Associations for Rheumatology criteria[21]. The inclusion criteria were: (1) All categories of JIA [21]; (2) A minimum of two observations during at least 2 years in our center; and (3) Wrist arthritis was diagnosed clinically with swelling or pain with limitation of motion. In doubtful cases, the presence of arthritis was confirmed by joint ultrasound (effusion, synovial hyperplasia, and increased Doppler signals from the synovial membrane, erosions) or MRI (effusion, synovial enhancement, erosions). Children with and without wrist arthritis were compared, and having unilateral and bilateral involvement was investigated.

Data collection

Patient evaluation included: (1) Demographic characteristics: Onset age, sex, JIA duration, JIA category, uveitis; (2) Joint assessment: Active joint count, specific joint involvement. In patients with hip involvement, we evaluated the number with hip osteoarthritis and those for whom hip arthroplasty was done; (3) Markers of laboratory and immunological activity. including hemoglobin, white blood cell count, platelets, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antinuclear antibodies (ANA), HLA B27 antigen, and rheumatoid factor (RF); (4) Treatment options including the number of patients who received NSAIDs or oral, high-dose intravenous, or intra-articular injections of glucocorticosteroids in any joints and the cumulative doses, biological and nonbiological DMARDs and the time before biologic administration; and (5) Disease outcomes including achievement of remission and time until remission, developing a significant flare (*i.e.* the flare, followed by change of the current treatment).

Statistical analysis

The sample size was not calculated initially. Statistical analysis was performed with the STATISTICA, version 10.0 (StatSoft Inc., Tulsa, OK, United States). All continuous variables were checked for normality. by the Kolmogorov–Smirnov test. Quantitative variables were reported as medians (Me) and percentiles (25%, 75% for continuous variables, and as absolute frequencies and percentages for categorical variables. Pearson's χ^2 test or Fisher's exact test in the expected frequencies < 5 was used to compare categorical variables. Two quantitative variables were compared using the Mann–Whitney test. The ability of each variable to discriminate patients with wrist arthritis from those without it was evaluated by sensitivity and specificity analysis, and area under the receiver operating characteristic curve were calculated with 95% confidence intervals (CI), and odds ratio (OR) for the detection the best cutoff of continuous variables. Higher values of OR of variables interfere with discriminatory ability. We used the "best" threshold for our data's receiver operating characteristic curve analysis. Survival analysis in each group, with JIA outcomes (treatment with biologics, achievement of the remission) as the event of interest, was estimated the Kaplan–Meier method. The log rank test compared survival curves. Factors significantly associated with the time of JIA outcomes were then tested in a Cox proportional hazards regression model, calculating the hazard ratio (HR) with a 95%CI. A P value of < 0.05 was considered statistically significant.

RESULTS

The patients' demography

The median age at study inclusion was 12.3 (7.9; 16.5) years, had a slight predominance of girls (60.7%) and a relatively long duration of the disease before inclusion [4.3 (1.9; 7.5)] years. The distribution of the JIA categories was oligoarthritis 27.1%, RF-positive and RF-negative polyarthritis 35.2%, psoriatic arthritis 5.3%, enthesitis-related arthritis 24.7%, and systemic arthritis 7.7%. Uveitis was detected in 15.4% of the patients. ANA positivity was 46.1% and RF-positivity was 5.4%.

A total of 86.5% were treated with NSAIDs, 41.7% received intra-articular corticosteroid injections, 20.2% received oral corticosteroids, and 17.9% received pulse therapy. The main nonbiological DMARD was methotrexate in 76.1% of the patients. Sulphasalazine, leflunomide, and cyclosporine A were given to 18.2%, 9.2%, and 46.6% of the patients, respectively. Biological treatment was given to 46.6% of the patients and 64.4% of them achieved remission. A subsequent flare was experienced by 18.3% of the patients.

Characteristics of JIA patients with wrist involvement

Wrist arthritis was present in 204 (27.1%) of the patients, 121 (59.3%) had bilateral, and 83 patients (40.7%) had unilateral wrist involvement. The frequency of wrist involvement in JIA categories was 5.8% in oligoarthritis, 44.9% in RF(−) and 15.0% in RF(+) polyarthritis, 17.7% in enthesytis-related arthritis, and 58.6% in systemic. Wrist arthritis frequently affected girls along with less frequent development of uveitis. Patients with wrist arthritis were shorter and had a smaller body mass index.

Patients with wrist arthritis had more signs of systemic inflammation, *i.e.* higher CRP, ESR, and platelets, and lower hemoglobin levels. Wrist involvement was associated with arthritis involvement of the cervical spine, temporomandibular, shoulder, elbow, metacarpophalangeal, proximal interphalangeal, distal interphalangeal, hip, ankle, and tarsus joints. The number of patients with hip osteoarthritis and hip replacement was also higher in those with JIA and

the time before hip osteoarthritis was longer compared with patients with wrist arthritis. Patients with wrist arthritis required more immunosuppressive treatment with oral and intravenous corticosteroids and had a higher rate of treatment and a higher corticosteroid cumulative dose, more frequent. methotrexate, leflunomide, and cyclosporine A treatment, and less frequent use of sulfasalazine.

Despite the higher proportion of patients with wrist arthritis treated with biologics (predominantly tumor necrosis factor alpha inhibitors), the probability of remission was lower (the percentage of patients who achieved remission was lower and the time to the remission was longer), but flares were rare in patients who achieved remission. The data are shown in Table 1.

Unifactorial analysis revealed that female sex, systemic JIA category, active joints > 9, increased ESR and CRP, and involvement of the specific joints and immunosuppressive treatment with methotrexate, systemic corticosteroids and biologics. were predictors associated with wrist arthritis. The data are in the Table 2.

Comparison of children with unilateral and bilateral wrist arthritis revealed the following differences. Unilateral involvement was more frequently observed in oligoarthritis (4.9% *vs* 1.0%), was about equal in enthesitis-related arthritis (9.1% *vs* 8.6%), and rare in RF-negative (16.2% *vs* 28.7%), and RF-positive polyarthritis (5.0% *vs* 10.0%) and in systemic arthritis (19.0% *vs* 39.7%). The number of patients with uveitis was two times higher in those with unilateral involvement, but the difference was not significant. Laboratory abnormalities included a higher proportion of ANA-positive patients and a lower level of CRP in patients with unilateral wrist involvement. Patients with unilateral wrist involvement required fewer immunosuppressive drugs and had outcomes (remission, flares) similar to those of patients with bilateral involvement. The data are shown in Table 3.

Cox regression analysis found that wrist arthritis was a predictor of a severe disease course. Patients with wrist arthritis had a lower probability of achieving remission (log rank test P = 0.001; HR = 1.3 (95%CI: 1.0-1.7), P = 0.055, Figure 1A), not using biologics (log rank test P = 0.0003; HR = 1.7 (95%CI: 1.3-2.10, P = 0.00009, Figure 1B). Patients with unilateral wrist arthritis had a lower probability of not using biologics (log rank test, P = 0.032; HR = 1.6 (95%CI: 1.03-2.58), P = 0.035).

DISCUSSION

In this study, wrist arthritis was found to be a marker of a severe JIA course. Wrist arthritis was associated with systemic and polyarticular JIA categories, intensive systemic inflammation, an increased number of active joints, higher risk of developing hip osteoarthritis, hip arthroplasty, and intensive treatment. The frequency of wrist involvement ranged from 17%-50% and depended on the distribution of JIA categories in the population and the duration of JIA[6-7]. Several studies have shown an increased frequency of wrist involvement during the disease course[8]. Ulnar and radial deviation of the wrist are the most frequent joint deformities in JIA patients, ranging from 28.6%-50%[22-24]. During a 5 year follow-up observation period, the frequency of wrist involvement increased from 24% at onset to 40%[8]. At the onset of the JIA there were no differences in the frequency of wrist involvement in the persistent-oligo compared to that in polyarticular JIA (19% and 33%, P = 0.272) but in 5 years the difference was significant at 22% *vs* 51%, P = 0.024). Several studies have positioned wrist involvement is as a marker of poor outcomes in JIA[25,26].

Routine clinical assessment of the wrist joint is less reliable than imaging methods, especially MRI, which allow the detection of subclinical synovitis and bone marrow edema[27-29]. The wrist joint was used for the development of a pediatric-targeted MRI scoring system to assess disease activity and damage in juvenile idiopathic arthritis[30]. In JIA patients, synovial thickening and enhancement are particularly present at three anatomical sites, and this information is useful for navigation through MRI of the wrist in search of JIA disease activity[31]. Sometimes clinical examination does not reveal synovitis that is detected by MRI or ultrasound[32-34]. Thermography is a promising tools for detecting mild wrist synovitis, especially if accompanied by ultrasound assessment[35]. MRI scoring was shown to have a poor correlation with laboratory markers of inflammation but it has a strong correlation with the number of swollen joints, physician's global disease activity, and the Juvenile Arthritis Disease Activity Score in 71 joints (JADAS71), confirming the utility of the wrist as a surrogate marker of the total burden of disease activity[30,36,37].

Dynamic contrast-enhanced MRI of the wrist in children with JIA is a relatively new diagnostic tool for the identification of active wrist synovitis[38]. Recently, reference values of sonographic cartilage thickness, bone-capsular distance, and tendon diameter at several joints, including the wrist and hand were provided[39]. The preliminary CARRA MSUS scoring system for assessing arthritis of the pediatric elbow, wrist, and finger joints was recently launched[40]. In the absence of clinically symptomatic inflammation of. the wrist in pediatric patients, contrast-enhanced magnetic resonance imaging revealed juvenile idiopathic arthritis-relevant MRI characteristics that require follow-up observation to determine the clinical significance of this finding[41].

Along with pain, stiffness, and swelling, patients with wrist arthritis may have a set of complaints, *e.g.*, muscle weakness, paresthesia, limited fist function, limited pinch grip, any joint deviation, aesthetic complaints, difficulties in writing, drawing, working with knives, pencils, laptops or other devices[42]. Children with JIA and wrist involvement had higher joint reposition errors than healthy controls for each direction and poorer results than healthy controls in the single hand Purdue Pegboard test, two hand Purdue Pegboard test, hand grip strength, and lateral pinch strength[43]. Some patients needed hand or wrist braces or splints[44].

The abovementioned hand- or wrist-related symptoms were present in 69% of patients, 55% in the hands and. 49% in the wrists. The dominant side was affected most patients (63%) compared to the nondominant hand (53%)[44]. Wrist impairment (predominantly restricted motion) was noted in 30% of the JIA patients, mostly in the dominant hand[44]. Wrist- and hand-related symptoms were mostly observed in RF-negative polyarthritis, compared to other JIA categories

Table 1 Comparative characteristics of patients with juvenile idiopathic arthritis with and without wrist arthritis

Parameters	Whole group, *n* = 753	Wrist arthritis, yes, *n* = 204	No wrist arthritis, *n* = 549	*P* value
Demography				
Sex, females	457 (60.7)	149 (73.0)	308 (56.1)	0.00002
JIA onset age in years Me (25%-75%)	6.0 (3.0-10.4)	5.1 (2.8-9.4)	6.3 (3.0-10.7)	0.064
JIA duration in years Me (25%-75%)	4.3 (1.9-7.5)	5.3 (2.9-8.9)	3.7 (1.7-7.1)	0.00004
Age of the inclusion in the study, Me (25%-75%)	12.3 (7.9-16.5)	13.1 (8.7-17.0)	12.0 (7.4-16.3)	0.032
JIA category				0.000001
Oligoarthritis	204 (27.1)	12 (5.9)	192 (35.0)	
Polyarthritis	265 (35.2)	119 (58.3)	146 (26.6)	
Psoriatic arthritis	40 (5.3)	6 (2.9)	34 (6.2)	
Enthesitis-related arthritis	186 (24.7)	33 (16.2)	153 (27.8)	
Systemic arthritis	58 (7.7)	34 (16.7)	24 (4.4)	
Uveitis	116 (15.4)	15 (7.4)	101 (18.4)	0.0002
Anthropometry				
Height, %, Me (25%-75%)	137 (111-157)	43.1 (17.8-74.4)	56.1 (26.9-78.0)	0.022
Height, SD, Me (25%-75%)	0.11 (-0.7-0.8)	-0.15 (-1.0-0.7)	0.17 (-0.6. 0.9)	0.038
Weight in kg, Me (25%-75%)	31.5 (19.0-50.0)	28.0 (19.5-46.5)	33.0 (19.0-51.5)	0.385
Body mass index, SD, Me (25%-75%)	0.04 (-0.8-0.9)	-0.23 (-1.1-0.8)	0.09 (-0.7-0.9)	0.037
Laboratory				
ANA-positivity	212/460 (46.1)	55/126 (43.7)	157/334 (47.1)	0.713
HLA B27-positivity	100/308 (32.5)	21/75 (28.0)	79/233 (33.9)	0.530
RF-positivity	22/406 (5.4)	7/118 (5.9)	15/288 (5.2)	0.377
ESR, mm/h, Me (25%-75%)	8.0 (3.0-20.0)	12.0 (5.0-29.5)	7.0 (3.0-17.0)	0.000002
C-reactive protein in mg/L, Me (25%-75%)	1.4 (0.2-8.0)	3.3 (0.2-19.5)	1.0 (0.0-6.0)	0.00003
White blood cells as × 10^9/L, Me (25%-75%)	7.1 (5.8-9.4)	7.4 (6.0-9.9)	7.0 (5.8-9.2)	0.056
Platelets as × 10^9/L, Me (25%-75%)	311 (255-388)	342 (278-433)	302 (253-373)	0.00006
Hemoglobin in g/L, Me (25%-75%)	124 (116-132)	121 (105-128)	126 (118-134)	0.000001
Joint involvement				
Wrist arthritis, unilateral	204 (27,1)	83 (40.7)	-	-
Active joints, Me (25%-75%)	6 (3-12)	14 (8-25)	4 (2-8)	0.0000001
Cervical spine	101 (13.4)	62 (30.4)	39 (7.1)	0.0000001
TMJ	43 (5.7)	23 (11.3)	20 (3.6)	0.00006
SCJ	12 (1.6)	6 (2.9)	6 (1.1)	0.072
Shoulder	56 (7.4)	38 (18.6)	18 (3.3)	0.0000001
Elbow	120 (15.9)	74 (36.5)	46 (8.4)	0.000001
MCP	164 (21.8)	96 (47.1)	68 (12.4)	0.000001
PIP	192 (25.5)	109 (53.4)	83 (15.1)	0.000001
DIP	70 (9.3)	37 (18.1)	33 (6.0)	0.0000001
Hip	153 (20.3)	55 (27.0)	98 (17.9)	0.006

Hip osteoarthritis	48/153 (31.4)	24/55 (43.6)	24/98 (24.5)	0.014
Hip prosthetics	16/153 (10.5)	11/55 (20.0)	5/98 (5.3)	0.005
Time before hip osteoarthritis, Me (25%-75%)	5.0 (2.4-9.4)	5.7 (4.5-11.7)	2.3 (1.5-5.9)	0.0009
Sacroiliac	71 (9.4)	15 (7.4)	56 (10.2)	0.232
Knee	535 (72.8)	141 (69.1)	394 (71.9)	0.454
Ankle	323 (42.9)	122 (59.8)	201 (36.6)	0.0000001
Subtalar	62 (8.2)	21 (10.3)	41 (7.5)	0.210
Tarsus	43 (5.7)	20 (9.8)	23 (4.2)	0.003
MTP	98 (13.0)	31 (15.2)	67 (12.2)	0.278
Interphalangeal foot	94 (12.8)	31 (15.2)	63 (11.5)	0.170
Treatment and outcomes				
NSAID	651 (86.5)	172 (84.3)	479 (87.3)	0.295
Any joints IACI	314 (41.7)	77 (37.8)	237 (43.2)	0.180
Oral GCS	152 (20.2)	78 (38.2)	74 (13.5)	0.0000001
GCS pulse therapy	135 (17.9)	67 (33.0)	68 (12.4)	0.0000001
Any GCS treatment	445 (59.1)	142 (69.6)	303 (55.2)	0.0003
Cumulative dose of GCS in mg, Me (25%-75%)	2650 (1000-5000)	3000 (1000-6000)	1750 (900-4000)	0.048
Methotrexate	573 (76.1)	174 (85.3)	399 (72.7)	0.0003
Sulphasalazine	137 (18.2)	28 (13.7)	109 (19.9)	0.053
Leflunomide	7 (9.2)	6 (2.9)	1 (0.2)	0.0005
Cyclosporine A	53 (7.0)	26 (12.8)	27 (4.9)	0.0002
Biologics	351 (46.6)	125 (61.3)	226 (41.2)	0.000001
Time before biologics in years, Me (25%-75%)	4.2 (1,9-7.8)	3.9 (1.5-8.0)	4.3 (2.0-7.6)	0.464
Remission	485 (64.4)	118 (57.8)	367 (66.9)	0.022
Time before remission in years, Me (25%-75%)	3.2 (1.5-6.6)	4.1 (1.8-7.9)	3.0 (1.4-6.1)	0.002
Flare	138 (18.3)	28 (13.7)	110 (20.1)	0.046

Data are *n* (%). ANA: Antinuclear antibodies; DIP: Distal interphalangeal joints; ESR: Erythrocyte sedimentation rate; GCS: Glucocorticosteroids; JIA: Juvenile idiopathic arthritis; IACI: Intraarticular joint injections; Me: Median; MCP: Metacarpophalangeal joints; MTP: Metatarsophalangeal joints; NSAIDs: Nonsteroid anti-inflammatory drugs; PIP: Proximal interphalangeal joints; RF: Rheumatoid factor; SCJ: Sternoclavicular joint; TMJ: Temporomandibular joint.

[44]. Discrepancies between wrist-related complaints and physical fundings were observed in several studies, but the data are contradictory[44,45]. Handwriting problems related to pain are frequently reported by a majority of school-children[42]. Noninvasive testing of hand grip strength with a dynamometer was found to be an independent predictor of disease activity, disability, and quality of life in JIA patients[46].

Wrist involvement was reported to be a clinical biomarker of poor disease prognosis in nonsystemic JIA with plasma biomarkers[47,48]. Bilateral wrist involvement was a marker of poor response to methotrexate therapy[49]. Patients with wrist involvement may have initial treatment with biologicals with or without methotrexate, according to the current ACR recommendations[20]. Tocilizumab may decrease radiographic progression in systemic and polyarticular JIA according to the adapted Sharp-van der Heijde and Poznanski scoring methods[50]. Wrist arthroscopy with synovectomy is considered an option for patients refractory to medical management[51,52]. Early monitoring of wrist involvement with clinical, functional (dynamometer, writing), and radiological (MRI and ultrasound) evaluation can find the subgroup of patients with likely poor outcomes and require earlier initiation of biological treatment. Close monitoring with early medical intervention with physiotherapy and occupational therapy support can improve the outcomes of wrist arthritis.

Limitations

The study has several limitations. The retrospective study cohort, missing data, and differing duration of arthritis

Table 2 Factors associated with wrist involvement in juvenile idiopathic arthritis patients

Parameter	Se	Sp	OR (95%CI)	*P* value
Sex, female	43.9	73.0	2.1 (1.5-3.0)	0.00002
Systemic JIA	16.7	95.6	4.4 (2.5-7.6)	0.0000001
Uveitis	89.1	26.4	0.43 (0.21-0.91)	0.0002
Active joints > 9	69.6	81.1	9.8 (6.8-14.1)	0.000001
Height ≤ 39%	47.1	65.0	1.7 (1.1-2.5)	0.011
BMI ≤ -0.3 SD	49.7	64.1	1.8 (1.2-2.6)	0.004
CRP > 5.9 mg/L	41.0	76.0	2.2 (1.5-3.1)	0.00001
ESR > 11 mm/h	50.5	67.1	2.1 (1.5-2.9)	0.00002
Platelets > 292 × 10^9/L	71.9	46.6	2.2 (1.5-3.1)	0.00001
Cervical spine	30.4	92.9	5.7 (3.7-8.9)	0.0000001
TMJ involvement	11.3	96.4	3.2 (1.7-6.0)	0.00006
Shoulder involvement	18.6	96.7	4.1 (2.3-7.4)	0.0000001
Elbow involvement	36.5	91.6	6.3 (4.1-9.5)	0.000001
MCP involvement	47.1	87.6	6.3 (4.3-9.1)	0.000001
PIP involvement	53.4	84.9	6.7 (4.6-9.5)	0.000001
DIP involvement	18.1	94.0	3.5 (2.1-5.7)	0.0000001
Hip involvement	27.0	83.4	1.7 (1.2-2.5)	0.006
Hip osteoarthritis involvement	43.6	75.5	2.4 (1.2-4.8)	0.014
Hip prosthetics involvement	20.0	94.8	4.7 (1.5-14.2)	0.005
Time before hip osteoarthritis > 3.2 years	95.7	57.1	29.3 (3.3-260.1)	0.0001
Ankle involvement	59.8	63.4	2.6 (1.9-3.6)	0.0000001
Tarsus involvement	9.8	95.8	2.5 (1.3-4.6)	0.003
Treatment with oral GCS	38.2	86.5	4.0 (2.7-5.8)	0.0000001
GCS pulse therapy	33.0	87.5	3.5 (2.4-5.1)	0.0000001
Any GCS treatment	69.6	44.8	3.6 (2.6-5.0)	0.0003
Methotrexate	91.6	16.4	6.7 (3.9-11.5)	0.0003
Biologics	61.3	58.8	2.3 (1.6-3.1)	0.000001
No remission	42.2	66.8	1.5 (1.1-2.0)	0.022
Time before remission > 3.1 years	61.0	53.3	1.8 (1.3-2.5)	0.0006
No flare	86.3	20.1	1.6 (1.01-2.5)	0.046

Data are *n* (%). BMI: Body mass index; CRP: C-reactive protein; DIP: Distal interphalangeal joints; ESR: Erythrocyte sedimentation rate; GCS: Glucocorticosteroids; JIA: Juvenile idiopathic arthritis; MCP: Metacarpophalangeal joints; PIP: Proximal interphalangeal joints.

influenced the study results. Routine clinical assessment of joints may have decrease the number of active joints and influenced study results. The absence of a standardized imaging protocol may have led to missing some cases of wrist arthritis. The above mentioned limitations may have led to underestimation of the study results.

CONCLUSION

Wrist arthritis in JIA patients was a marker of a severe disease course, characterized by more intensive inflammation with unfavorable outcomes, requiring more intensive treatment with early administration of biologics. Close monitoring of the inflammation in the wrist with ultrasound and magnetic resonance assessment with early biological treatment might improve the outcomes.

Table 3 Comparative characteristics of patients with juvenile idiopathic arthritis with unilateral or bilateral wrist involvement

Parameters	Unilateral, *n* = 83	Bilateral, *n* = 121	*P* value
Demography			
Sex, female	65 (78.3)	84 (69.4)	0.160
JIA onset age in years Me (25%-75%)	5.4 (2.9-10.0)	5.0 (2.8-8.9)	0.578
JIA duration in years Me (25%-75%)	4.8 (2.5-7.9)	5.9 (3.0-10.0)	0.231
Age of the inclusion in the study in years, Me (25%-75%)	11.7 (8.4-17.3)	13.7 (8.8-17.0)	0.368
Uveitis	9 (10.8)	6 (5.0)	0.114
Laboratory			
ANA-positivity	31/54 (57.4)	24/72 (33.3)	0.031
HLA B27-positivity	11/33 (33.3)	10/42 (23.8)	0.362
RF-positivity	2/50 (4.0)	5/68 (7.4)	0.720
ESR in mm/h, Me (25%-75%)	11.0 (4.0-30.0)	12.5 (5.0-26.0)	0.746
C-reactive protein in mg/L, Me (25%-75%)	1.5 (0.2-11.6)	4.4 (0.4-36.0)	0.027
White blood cells as × 10^9/L, Me (25%-75%)	7.4 (6.1-9.4)	7.5 (6.0-10.6)	0.416
Platelets as × 10^9/L, Me (25%-75%)	345 (291-419)	335 (263-448)	0.905
Hemoglobin in g/L, Me (25%-75%)	121 (107-128)	121 (105-129)	0.880
Joint involvement			
Active joints, Me (25%-75%)	9 (6-13)	23 (12-34)	0.0000001
Cervical spine	12 (14.5)	50 (41.3)	0.00004
TMJ	4 (4.8)	19 (15.7)	0.016
SCJ	2 (2.4)	4 (3.3)	0.710
Shoulder	5 (6.0)	33 (27.3)	0.0001
Elbow	14 (17.1)	60 (49.6)	0.000002
MCP	29 (34.9)	67 (55.4)	0.004
PIP	36 (43.4)	73 (60.3)	0.017
DIP	10 (12.1)	27 (22.3)	0.062
Hip	12 (14.5)	43 (35.5)	0.0009
Hip osteoarthritis	4/12 (33.3)	9/43 (20.9)	0.371
Hip prosthetics	2/12 (16.7)	9/43 (20.9)	0.744
Time before hip osteoarthritis, Me (25%-75%)	8.2 (4.4-11.7)	5.2 (4.7-10.2)	0.972
Sacroiliac	5 (6.0)	10 (8.3)	0.547
Knee	43 (51.8)	98 (81)	0.000009
Ankle	33 (39.8)	89 (73.6)	0.000001
Subtalar	4 (4.8)	17 (14.1)	0.033
Tarsus	4 (4.8)	16 (13.2)	0.047
MTP	10 (12.1)	21 (17.4)	0.300
Interphalangeal foot	11 (13.3)	20 (16.5)	0.522
Treatment and outcomes			
NSAID	72 (86.8)	100 (82.6)	0.429
Any joints IACI	42 (50.6)	35 (28.9)	0.002
Oral GCS	23 (27.7)	55 (45.5)	0.010

GCS pulse therapy	23 (27.7)	44 (36.4)	0.182
Any GCS treatment	60 (40.7)	82 (59.3)	0.490
Cumulative dose of GCS in mg, Me (25%-75%)	3000 (1000-6000)	3000 (1135-5625)	0.668
Methotrexate	72 (92.8)	102 (84.3)	0.628
Sulphasalazine	12 (14.5)	16 (13.2)	0.801
Leflunomide	1 (1.2)	5 (4.1)	0.235
Cyclosporine A	5 (6.0)	21 (17.4)	0.017
Biologics	41 (49.4)	84 (69.4)	0.004
Time before biologics in years, Me (25%-75%)	5.0 (1.8-8.2)	3.67 (1.1-7.7)	0.187
Remission	48 (57.8)	70 (57.9)	0.998
Time before remission in years, Me (25%-75%)	3.8 (1.8-7.4)	4.2 (1.7-8.6)	0.471
Flare	11 (13.3)	17 (14.1)	0.871

Data are *n* (%). ANA: Antinuclear antibodies; DIP: Distal interphalangeal joints; ESR: Erythrocyte sedimentation rate; GCS: Glucocorticosteroids; JIA: Juvenile idiopathic arthritis; Me: Median; MCP: Metacarpophalangeal joints; MTP: Metatarsophalangeal joints; NSAIDs: Nonsteroid anti-inflammatory drugs; PIP: Proximal interphalangeal joints; RF: Rheumatoid factor; SCJ: Sternoclavicular joint; TMJ: Temporomandibular joint.

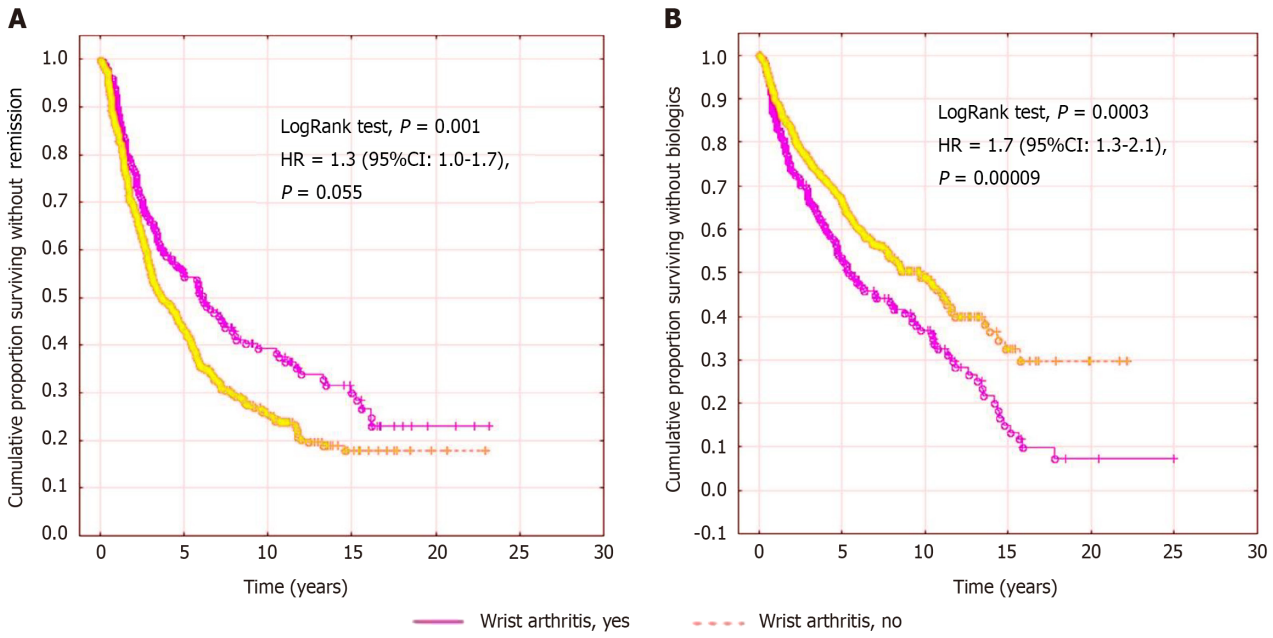

Figure 1 Survival analysis and Cox proportional hazards regression models. A: Cumulative probability of the achievement of the remission in juvenile idiopathic arthritis (JIA) patients with and without wrist arthritis; B: Cumulative probability of requirement in biological treatment in JIA patients with and without wrist arthritis. HR: Hazard ratio.

FOOTNOTES

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ORIGINAL ARTICLE

Observational Study

Evaluation of thyroid profile among children aged 1-15 years with nephrotic syndrome: An observation study

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Abstract

BACKGROUND

The interaction between the kidney and the thyroid is important for normal function of both organs. In nephrotic syndrome, proteinuria leads to loss of several proteins, which in turn causes hypothyroidism.

AIM

To assess the thyroid function in children with nephrotic syndrome.

METHODS

This cross-sectional study was conducted in a tertiary center, Bhopal, from February 2020 to January 2021. Consecutive children aged 1-15 years admitted with nephrotic syndrome (first-time diagnosed and all relapse cases) were included in the study. A thyroid profile was sent along with routine investigations, and thyroid hormone status was assessed in nephrotic syndrome children.

RESULTS

Of the 70 patients, 39 (55.7%) showed abnormal thyroid profiles; 19 (27.1%) had overt hypothyroidism, and 20 (28.6%) had subclinical hypothyroidism. Overt hypothyroidism was seen in 16.1% of newly diagnosed cases, 40% of second relapses, and 2.7% of frequently relapsed cases ($P < 0.001$). The mean serum free T3 and free T4 levels in frequent relapses were 2.50 ± 0.39 ng/dL and 0.78 ± 0.12 ng/dL, respectively, which were significantly lower than in newly diagnosed cases (2.77 ± 0.37 ng/dL and 0.91 ± 0.19 ng/dL, respectively). The mean thyroid-stimulating hormone (TSH) level was significantly higher in frequent relapses 5.86 ± 1.56 μIU/mL) and second relapse (5.81 ± 1.78 μIU/mL) than in newly diagnosed cases (4.83 ± 0.76 μIU/mL) and first relapse cases (4.74 ± 1.17 μIU/mL), ($P < 0.01$).

CONCLUSION
An abnormal thyroid profile was commonly observed in children with nephrotic syndrome, and overt hypothyroidism was more common in frequent relapse cases. Therefore, thyroid screening should be a part of the management of nephrotic syndrome so that hypothyroidism can be detected and managed at an early stage.

Key Words: Nephrotic syndrome; Hypothyroidism; Proteinuria; Children; Steroid-sensitive nephrotic syndrome; Steroid-resistant nephrotic syndrome

Core Tip: In nephrotic syndrome, proteinuria leads to loss of several proteins, which may lead to hypothyroidism. This cross-sectional study was conducted to assess the thyroid function in children with nephrotic syndrome aged 1-15 years. Of the 70 patients, 39 (55.7%) showed abnormal thyroid profiles, 19 (27.1%) had overt hypothyroidism, and 20 (28.6%) had subclinical hypothyroidism. Overt hypothyroidism was seen in 16.1% of newly diagnosed, 40% of second relapses, and 2.7% of frequently relapsed cases ($P < 0.001$). An abnormal thyroid profile was commonly observed in children with nephrotic syndrome, with overt hypothyroidism being more common in frequent relapse cases.

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INTRODUCTION

Nephrotic syndrome is a glomerular disorder characterized by proteinuria greater than 40 mg/m^2/h, a low level of serum albumin (less than 2.5 g/dL), edema, and hypercholesterolemia (serum total cholesterol level greater than 250 mg/dL) [1]. The main proteins to which thyroid hormones bind in the bloodstream are thyroxine-binding globulin (TBG), prealbumin, and albumin. Urinary loss of hormone-binding proteins like transthyretin and TBG, as well as intermediate-sized plasma proteins (size 40–200 kDa) increases the excretion of thyroid-stimulating hormone (TSH) by lowering total T4, which, in turn, causes hypothyroidism[2-4]. In children and adolescents, hypothyroidism may lead to lethargy, weight gain, loss of concentration, and constipation; additionally, it may cause physical and mental retardation in children less than 2 years of age, if left untreated[5].

The thyroid function of children with nephrotic syndrome has been examined in earlier studies[6-8], which revealed a variable incidence of hypothyroidism. The prevalence of nephrotic syndrome in India is estimated to range from 12-16 per 100000, and the annual impact in children ranges from 2-7 per 100000[9]. Compared to Western countries, where the incidence is reported to be 2–3/100000 children, the incidence and prevalence in India are slightly higher (9–10/100000 and 12–16/100000 children, respectively)[7].

Since there were no studies of this kind in central India, we conducted the present study to explore more about this association. Hence, this study aimed to assess thyroid function among patients with nephrotic syndrome aged 1-15 years admitted to a tertiary center in Bhopal from February 2020 to January 2021.

MATERIALS AND METHODS

A cross-sectional observational study was conducted at an academic tertiary care hospital from 1 February 2020 to 31 January 2021 after obtaining approval from the institutional ethical committee.

All new and relapse cases of nephrotic syndrome, aged 1 month to 15 years, who were consecutively admitted to our hospital, were included in the study. Nephrotic syndrome among children was diagnosed as per the International Study of Kidney Disease in Children guidelines: nephrotic range proteinuria with spot urine polymerase chain reaction of > -2, hypoalbuminemia < 2.5 g/dL, hyperlipidemia (serum cholesterol > 200 mg/dL), and edema[10]. Children whose records were not complete and were diagnosed with other renal or systemic diseases causing proteinuria, any known thyroid disorder, or any anti-thyroid/ thyroxine drugs, were excluded from the study.

A detailed clinical history was taken after obtaining informed consent from the parent/legal guardian and a thorough clinical examination was done. Venipuncture was performed after taking proper aseptic precautions, and a morning fasting sample of thyroid profile was taken, along with routine blood tests like complete blood count, liver function test, renal function test, and lipid profile. If there was a delay in the processing of the sample, the sample was stored at 4 °C. The serum levels of free T3, free T4, and TSH were measured with the immunoassay method. A fresh mid-catch morning urine sample was collected in a sterile container for routine microscopic examination.

The diagnosis of nephrotic syndrome requires the presence of edema, massive proteinuria (> 40 mg/m^2/h), hypoalbuminemia (< 2.5 mg/dL), and hyperlipidemia. Corticosteroids are the mainstay of therapy in nephrotic syndrome. Children with a first episode of nephrotic syndrome are likely to have steroid-responsive minimal-change nephrotic syndrome. The Kidney Disease Improving Global Outcome has provided definitions regarding responses to steroid therapy. Response is defined as an attainment of remission within the initial 4 week of corticosteroid therapy. Remission is a urine protein:creatinine ratio of < 0.2 or < 1 + protein on dipstick testing for 3 consecutive days. Relapse is an increase in the first-morning urine protein:creatinine ratio > 0.2 or 2 + or higher on dipstick testing for 3 consecutive days. Frequently relapsing is two or more relapses within 6 months after initial therapy or four relapses in 12 months. Steroid dependence is a relapse during steroid tapering or a relapse within 2 week of discontinuation of therapy. Steroid resistance is the inability to induce remission within 4 week of steroid therapy. All parameters were reviewed for evaluation of the study.

Statistical analysis

All parameters were recorded in a pretested proforma and were reviewed for evaluation of data. Demographic variables were reported as counts and percentages. The statistical tests used were the χ^2 test for analysis of thyroid status in nephrotic syndrome children according to relapse and association of thyroid status with sex, and steroid dependency. An analysis of variance (ANOVA) was used to compare biochemical parameters in nephrotic syndrome cases and compared among newly diagnosed cases and frequent relapse cases. A P value of < 0.05 was considered statistically significant in the analysis. SPSS software version 25 (IBM Corp., Armonk, NY, United States) was used for analysis of the data.

RESULTS

The study was conducted among 70 subjects, of which 58.6% were males. Out of 70 children, 55.7% children had hypothyroidism. Among 39 hypothyroid children, 20 (28.6%) had subclinical hypothyroidism, and 19 (27.1%) had overt hypothyroidism. Most children in our study (47.1%) belonged to the age group of 1-5 years. The demographic profile of the study is presented in Table 1.

Nephrotic syndrome cases were classified based on the occurrence and relapses, and most of the participants (31, 44.3%) belonged to newly diagnosed cases. Children were also classified based on steroid responsiveness, of which 56 (80%) children were steroid responsive. Overt hypothyroidism was seen in 16.1% of cases of newly diagnosed children, and 40% in second relapse cases; this was significantly higher (72.7%) in frequent relapse cases (P < 0.001).

The mean TSH level of study subjects was 5.19 ± 1.32 μIU/mL. Similarly, free T4 levels were significantly decreased in patients with frequent relapse (0.78 ± 0.12 ng/dL) compared to newly diagnosed cases (0.91 ± 0.19 ng/dL) and first relapse cases (0.95 ± 0.11 ng/dL) (Table 2). Other biochemical parameters like glomerular filtration rate (GFR) were lower (59.90 ± 12.10) in frequent relapse cases compared to newly diagnosed cases (69.61 ± 17.79; P < 0.01). We found a positive correlation of serum albumin with free T4 (r = 0.322, P = 0.007). Similarly, serum protein was positively correlated with free T4 (r = 0.369, P = 0.002) (Table 3). There was no significant correlation between serum albumin and serum-free T3 levels. The thyroid status of the study subjects was also assessed based on steroid dependency. Eight (57.1%) children among steroid-responsive subjects, and three (50.0%) among steroid-resistant subjects, had overt hypothyroidism (Table 4).

DISCUSSION

In this observational study, thyroid profiles were estimated in 70 children, out of which 55.7% of children had hypothyroidism. Among these 39 children, subclinical and overt hypothyroidism was noted in 28.6% and 27.1% of the children, respectively. The incidence of abnormal thyroid function among nephrotic syndrome children was like that reported by Singh *et al*[9], who observed elevated TSH levels in 44.51% of nephrotic children. A previous study found a lesser percentage of hypothyroidism (36.3%) among 40 cases of nephrotic syndrome children aged between 1 year to 12 years[11]. Evaluation of thyroid hormone and proper follow-up are essential in nephrotic syndrome children as subclinical hypothyroidism may progress to overt hypothyroidism in 11% of children if appropriate measures are not taken[3].

Most of the children in our study (47.1%) were between the ages of 1 year and 5 years. A similar percentage of hypothyroidism (47.5%) was seen among children of less than 3 years of age in a study by Singh *et al*[9]. We found that nephrotic syndrome and subclinical hypothyroidism were seen more in male children (58.6% and 34.1%, respectively), whereas overt hypothyroidism has equal sex preponderance. Similarly, male preponderance was seen by Hajizadeh *et al* [12] where, out of 104 children with nephrotic syndrome, 41 (67.2%) were males and 20 (32.8%) were females.

In our study, most of the children fell into the category of newly diagnosed cases (44.3%) with a considerably higher mean TSH level among frequent and second relapse cases as compared to newly diagnosed and first relapse cases. Similar findings were reported by Mohamed *et al*[13], who they found that serum levels of free T3 and free T4 were significantly lower, but TSH was higher in relapse patients as compared to remission and control groups. The earlier studies also found a significantly lower concentration of free T4 levels among frequent relapse cases as compared to newly diagnosed cases and first relapse cases[14-16].

Table 1 Demographic details of the study subjects, *n* = 70

Parameters	Number	Percentage
Age group in years		
0-1	2	2.9
> 1 to 5	33	47.1
6-10 y	30	42.8
> 10	5	7.1
Mean age in years	5.88 ± 3.13	
Sex		
Male	41	58.6
Female	29	41.4
Area of residence		
Rural	41	58.6
Urban	29	41.4
Types of nephrotic syndrome		
Newly diagnosed	31	44.3
1st relapse	13	18.6
2nd relapse	15	21.4
Frequent relapse	11	15.7
Thyroid status in study subjects		
Euthyroidism	31	44.3
Subclinical hypothyroidism	20	28.6
Overt hypothyroidism	19	27.1
Response to steroid therapy		
Steroid responsive	56	80
Steroid dependant	8	11.4
Steroid resistant	6	8.6

Table 2 Biochemical parameters in study subjects, *n* = 70

Parameter	Newly diagnosed	1st relapse	2nd relapse	Frequent relapse	*P* value[1]
Free T3	2.77 ± 0.37	2.93 ± 0.16	2.57 ± 0.47	2.50 ± 0.39	0.01
Free T4	0.91 ± 0.19	0.95 ± 0.11	0.84 ± 0.27	0.78 ± 0.12	0.03
TSH	4.83 ± 0.76	4.74 ± 1.17	5.81 ± 1.78	5.86 ± 1.56	< 0.01
GFR	69.61 ± 17.79	69.46 ± 15.20	64.52 ± 13.85	59.90 ± 12.10	< 0.01
T. Cholesterol	398.90 ± 67.25	432.0 ± 48.63	482.13 ± 48.63	476.91 ± 70.74	0.10
TG	411.0 ± 92.72	424.62 ± 82.79	433.07 ± 138.90	500.45 ± 151.38	0.27
LDL	396.64 ± 50.76	415.15 ± 53.30	416.40 ± 67.30	435.82 ± 67.54	0.16

[1]ANOVA test or Kruskal–Wallis H test was used.
GFR: Thyroid-stimulating hormone; LDL: Low-density lipoprotein; TG: Thyroglobulin; TSH: Glomerular filtration rate.

Table 3 Correlation of thyroid function tests with serum albumin and protein

Variable		Free T3	Free T4	TSH
S. albumin	*r* value	0.036	0.322	-0.165
	P value[1]	0.768	0.007	0.172
	n	70	70	70
S. protein	*r* value	0.187	0.369	-0.227
	P value[1]	0.121	0.002	0.059
	n	70	70	70

[1]Spearman correlation coefficient was used.
S: Serum; TSH: Glomerular filtration rate.

Table 4 Association of thyroid status with steroid responsiveness in study subjects, *n* = 70

Thyroid status	Steroid responsive		Steroid resistant	
	Yes	No	Yes	No
Euthyroidism	29 (51.8)	2 (14.3)	1 (16.7)	30(46.9)
Subclinical hypothyroidism	16 (28.6)	4 (28.6)	2 (33.3)	18 (28.1)
Overt hypothyroidism	11 (19.6)	8 (57.1)	3 (50.0)	16 (25.0)
P value[1]	< 0.01		0.29	

Data are *n* (%).
[1]χ^2 test was used.

Nephrotic syndrome is a glomerular disease, where renal damage affects absorption and excretory functions. It results in urinary loss of intermediate-sized plasma proteins and hormone-binding proteins such as TBG, transthyretin, and albumin, leading to a reduction in thyroid hormones causing hypothyroidism. Few studies have found a positive correlation of serum albumin and serum protein with free T4[17,18] which is in line with our study, as we also found a positive correlation of serum albumin ($P = 0.007$) and serum protein ($P = 0.002$) with free T4.

In our study, 11.4% of children were steroid dependent, of which 57.1% were overt hypothyroid and 28.6% were subclinically hypothyroid. A similar study conducted by Marimuthu *et al*[6] concluded that the prevalence of subclinical and overt hypothyroidism was high in idiopathic SRNS, with almost one-third of children having overt hypothyroidism. Since nephrotic syndrome affects the excretory function of the kidneys, GFR is normally lower in frequent relapse cases than in newly diagnosed cases; however, Lo *et al*[18] found no changes in GFR and serum creatinine levels before and after remission among patients with abnormal thyroid function.

The present study has a few strengths and limitations. The way the study participants were categorized based on their thyroid profile, steroid relapse history, and dependence is its strongest point. The main limitations of our study were the small sample size and lack of follow-up of patients. Also, the urine protein creatinine ratio could not be correlated with the thyroid profile.

CONCLUSION

An abnormal thyroid hormone profile was observed in 55.7% of children with nephrotic syndrome, and a higher incidence of overt hypothyroidism was found in frequently relapsing cases. Therefore, screening of thyroid hormone should be a part of the management of patients with nephrotic syndrome.

FOOTNOTES

Author contributions: Kumari P contributed to acquisition and drafting the article; Shrivastava J contributed to drafting the article; Agrawal A contributed to conceptualization and revising the article critically for important intellectual content; Kumari P and Agrawal A contributed to interpretation of data, data analysis; Kumari P and Shrivastava J contributed to the literature review; All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

Institutional review board statement: Approval was obtained from the Institutional Ethical Committee of the Gandhi Medical College, Bhopal (Letter No. ECR/1055/Inst/MP/2018, dated 04/01/2020).

Informed consent statement: The patients were recruited in the study after obtaining informed consent from the parent/legal guardian.

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ORIGINAL ARTICLE

Observational Study

Selenoprotein-p and insulin resistance in children and adolescents with obesity

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Abstract

BACKGROUND

Insulin resistance and obesity present significant challenges in pediatric populations. Selenoprotein P1 (SEPP1) serves as a biomarker for assessing selenium levels in the body. While its association with metabolic syndrome is established in adults, its relevance in children remains underexplored.

AIM

To ascertain SEPP1 blood levels in children and adolescents diagnosed with obesity and to assess its correlation with insulin resistance and adiposity indices.

METHODS

170 children participated in this study, including 85 diagnosed with obesity and an equal number of healthy counterparts matched for age and sex. Each participant underwent a comprehensive medical evaluation, encompassing a detailed medical history, clinical examination, and anthropometric measurements like waist circumference and waist-to-height ratio. Furthermore, routine blood tests were conducted, including serum SEPP1, visceral adiposity index (VAI), and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) level.

RESULTS
Our findings revealed significantly lower serum SEPP1 levels in children with obesity compared to their healthy peers. Moreover, notable negative correlations were observed between serum SEPP1 levels and body mass index, VAI, and HOMA-IR.

CONCLUSION
The study suggests that SEPP1 could serve as a valuable predictor for insulin resistance among children and adolescents diagnosed with obesity. This highlights the potential utility of SEPP1 in pediatric metabolic health assessment and warrants further investigation.

Key Words: Obesity; Childhood obesity; Selenium status; Selenoprotien P1; Insulin resistance

Core Tip: This study investigates the association between serum Selenoprotein P1 (SEPP1) levels and insulin resistance in pediatric obesity. Conducted on 170 children, the study reveals significantly lower SEPP1 levels in obese children compared to healthy peers, with notable negative correlations between SEPP1 levels and adiposity indices such as body mass index, visceral adiposity index, and Homeostatic Model Assessment of Insulin Resistance. The findings suggest SEPP1's potential as a predictor for insulin resistance in pediatric obesity, highlighting its utility in metabolic health assessment. However, further research is needed to determine the temporal relationship between SEPP1 levels and insulin resistance onset in pediatric obesity, emphasizing the importance of continued investigation in this area for clinical practice.

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INTRODUCTION

Obesity among children is a significant global health concern[1]. Various factors contribute to its increasing prevalence, including personal habits, cultural beliefs, genetic predisposition, and environmental influences[2]. In addition to excessive fat accumulation, obesity is characterized by adipose tissue dysfunction, disrupting the regulation of adipocytokines and interfering with insulin action signaling pathways[3]. Insulin resistance (IR) is increasingly common in children and adolescents and is often associated with obesity and metabolic syndrome. Ethnic variations in IR prevalence underscore the importance of considering cardiovascular risks across different racial and ethnic groups, emphasizing the need for preventive strategies due to the lack of established diagnostic criteria for IR in children[4].

Selenoprotein P (SEPP1) is among the 25 human selenocysteine (Sec)-containing proteins[5]. It plays a crucial role in selenium transport to target organs, thereby reducing oxidative stress by delivering protective selenoproteins[6]. Under normal physiological conditions, SEPP1's plasma concentration remains stable, but significant changes occur in certain pathophysiological states[7]. Selenium, an essential nutrient, modulates insulin signaling and impacts carbohydrate and fat metabolism[8]. SEPP1 levels exhibit better predictive accuracy for insulin tolerance compared to fasting blood glucose or HbA1c[9]. Additionally, SEPP1 serves as a biomarker for evaluating selenium status in obesity[10]. However, research on selenium levels in obesity yields inconsistent results regarding selenium status variations among overweight and individuals with obesity and its association with metabolic risk factors[8].

Despite its utility as a selenium status indicator, no research has investigated the relationship between serum SEPP1 concentrations and insulin resistance in children[11]. Addressing this gap, our study aims to explore the link between insulin resistance and selenium status in children with obesity by assessing their serum SEPP1 levels.

MATERIALS AND METHODS

Study design

This cross-sectional comparative study enrolled 170 children from the Clinical Nutrition Unit, Pediatrics Department, Tanta University Hospital, Egypt. The survey was scheduled to be conducted in November 2023. Before recruitment, a thorough a priori power analysis was conducted to ensure an adequate sample size for achieving statistical significance. Ethical approval for the study was obtained from the Ethical Committee of the Faculty of Medicine, Tanta University, Egypt (Registration NO: 36264PR424/11/23). Written consent was obtained from parents or caregivers before enrolling their children in the study.

Study participants

At the onset of the study, 535 medical records of children diagnosed with obesity between January 2021 and November 2023 underwent review. Following contact with families, 62 declined participation. Of the 473 families scheduled for clinic visits, 388 children were excluded based on specific criteria. Eventually, 85 children diagnosed with obesity, according to the World Health Organization's age and sex-specific body mass index (BMI) charts, were enrolled in the study, along with 85 matched healthy controls[12].

The exclusion criteria included children below 6 years or above 16 years of age (n = 57), BMI exceeding -3 standard deviations or ≥ 40 kg/m² (n = 51), underlying endocrine or genetic causes of obesity (n = 30 and 19 respectively), complications impacting SEPP1 levels (such as polycystic ovary syndrome, non-alcoholic fatty liver disease, hypertension) (n = 96), presence of acute or chronic inflammatory processes other than obesity (n = 47), incomplete investigations (n = 43), use of medications affecting selenium status (such as steroids, anticonvulsants, antidepressants) (n = 14), and recent vitamins or minerals supplementation within the last three months (n = 31).

Assessment protocols

Medical history and physical examination: We collected demographic information and obtained family medical history related to obesity, hypertension, or diabetes. A comprehensive physical examination was conducted, which included blood pressure measurements and evaluation for clinical signs of insulin resistance. Anthropometric measurements such as weight, height, BMI, waist circumference, and waist/height ratio were determined and plotted on corresponding growth charts to assess z-scores and centiles. Z-scores indicate how many standard deviations an individual's measurement is from the mean of a reference population. Percentiles rank a measurement's position within a data distribution[13-15].

Laboratory assessment: We conducted a complete blood count, liver function tests, and a comprehensive lipid profile assessment, including serum cholesterol, triglycerides, high-density lipoprotein cholesterol (HDL), and low-density lipoprotein cholesterol (LDL). The lipid profile was analyzed using a fully automatic biochemical analyzer (Beckman, Japan, AU5800). Fasting blood glucose (FBG) was measured using glucose oxidase while fasting insulin levels were obtained through electrochemiluminescence.

Insulin resistance was calculated using the Homeostasis Model Assessment insulin resistance (HOMA-IR) index, employing the formula: HOMA-IR = fasting glucose (mg/dL) × fasting insulin (uIU/mL) / 405. HOMA-IR values exceeding 3.54 are diagnostic for insulin resistance[16]. Additionally, we utilized the visceral adiposity index (VAI) to assess metabolic and fat distribution, aiding in identifying cardiometabolic disease risks and metabolic syndrome. To calculate VAI, the following formulas were employed[17,18]:

$$\text{VAI (males)} = \frac{WC}{39.68+(1.88\times BMI)} \times \frac{TG}{1.03} \times \frac{1.31}{HDL-c}$$

$$\text{VAI (females)} = \frac{WC}{39.58+(1.89\times BMI)} \times \frac{TG}{0.81} \times \frac{1.52}{HDL-c}$$

WC is measured in centimeters, BMI in kg/m², TG and HDL-C in mmol/L[19].

Selenoprotein-P 1 level measurement: The serum levels of SEPP1 were determined utilizing the enzyme-linked immunosorbent assay (ELISA) method with a specific assay kit (Catalog No: DL-SEPP1-Hu, Glory Science, United States). This assay method is tailored to quantify SEPP1 concentrations in human serum samples, with all measurements conducted following the manufacturer's instructions to ensure accuracy and reliability. Fasting blood samples were obtained *via* peripheral venipuncture in the early morning and collected in plain tubes, except for the 2 mL sample designated for complete blood count, which was stored in an EDTA vacutainer tube. Subsequently, centrifugation was performed at 4 °C for 30 minutes at 1000 g to obtain serum samples. The extracted supernatant was stored at -80 °C until further analysis to prevent degradation and maintain SEPP1 stability. SEPP1 levels were quantified through ELISA following the provided assay protocol. The absorbance of the samples was measured spectrophotometrically at a specific wavelength using a microplate reader. A standard curve, generated using known SEPP1 concentrations provided in the assay kit, facilitated the determination of SEPP1 levels in the serum samples. Internal quality control measures were implemented throughout the assay procedure to ensure precision and accuracy. Duplicate measurements were conducted for each sample, and the coefficient of variation between duplicates was monitored to uphold assay reliability.

Statistical analysis

We utilized IBM Corp.'s Statistical Package for Social Sciences version 27 (IBM Corp., Armonk, NY, United States) to conduct statistical analysis. Since our numerical data were not normally distributed, descriptive statistics were presented using the median and interquartile range (IQR: 25th–75th percentiles). Categorical data were expressed as frequencies and percentages. To compare the study and control groups, we employed the non-parametric Mann-Whitney test for non-parametric data analysis. Associations between numerical variables were explored using Spearman's rank-order correlation analysis, while Pearson's χ^2 test was utilized to assess the independence of categorical variables. The performance of SEPP1 in distinguishing participants with and without insulin resistance was evaluated using receiver operating characteristics (ROC) curve analysis. mean ± SD measurements were used for comparative purposes with findings from similar studies in the field. Logistic regression was conducted to assess variables affecting the probability of insulin resistance, while multiple linear regression assessed the effect of potentially relevant variables on SEEP1 levels. A significance level of $P < 0.05$ was applied to determine statistical significance in all analyses conducted.

RESULTS

Figure 1 shows the flow chart of the study, which involved 85 children and adolescents diagnosed with obesity, with a female-to-male ratio of 1.4: 1. The study identified a significant increase in the number of participants with obesity and a positive family history of obesity, diabetes, and hypertension. Among the participants, 48 (56.5%) exhibited acanthosis nigricans, 19 (22.4%) had gynecomastia, 13 (15.3%) presented with acne and hirsutism, and 6 (7%) had striae, buried penis, hip pain, and/or limp. Children with obesity demonstrated higher weight, height, BMI, waist circumference, weight/height ratio, and systolic blood pressure compared to their counterparts without obesity. Table 1 presents the clinical characteristics of the study group.

Among children with obesity, significant increases were observed in serum cholesterol, HDL-C, LDL-C, triglycerides, HOMA-IR, fasting blood sugar, serum insulin concentration, and VAI, as outlined in Table 1. Conversely, serum SEPP1 concentration levels were markedly lower in children with obesity compared to the control group ($P < 0.001$). Additionally, approximately 45.9% of children with obesity and only 5.9% of the control group exhibited insulin resistance based on HOMA-IR > 3.54, as depicted in Table 1.

Table 2 illustrates negative correlations between SEPP1 and several variables, including weight, BMI, waist circumference, weight/height ratio (W/H), W/H ratio centile, VAI, serum insulin, FBG, and HOMA-IR within the group of obese children.

Comparison of serum SEPP1 between obese children with and without insulin resistance showed significantly lower values in those with insulin resistance ($P < 0.001$; Table 3). The purpose of the ROC (Receiver Operating Characteristic) curve analysis in Table 4 is to evaluate the ability of SEPP1 levels to predict obesity in children. The ROC curve helps determine the diagnostic performance of SEPP1 by calculating the Area Under the Curve (AUC), which indicates how well SEPP1 can distinguish between obese and non-obese children. ROC curve analysis indicates that serum SEPP1 significantly predicts insulin resistance in children with obesity, with a ROC AUC of 0.828, 95%CI: 0.724-0.931, $P < 0.0001$. The optimal cut-off value of serum SEPP1 for predicting the presence of insulin resistance was ≤ 7.5, with a sensitivity of 92.3% and specificity of 86.96% (as shown in Table 4 and Figure 2).

The logistic regression analyses in Table 5 aim to identify factors associated with insulin resistance in obese children. Univariate logistic regression identifies potential risk factors individually, while multivariate logistic regression determines the independent effect of each variable when adjusted for other factors. Univariate logistic regression analysis showed a significant association between insulin resistance in obese children (the outcome) and each of age at enrolment, sex, waist circumference, W/H ratio, BMI, and SEEP1 level (all $P < 0.05$). Multivariate logistic regression was conducted using all the variables in the univariate analysis with backward elimination. The variables that were retained within the model included sex, age at enrolment, BMI, and SEEp1 level. Higher age at enrolment and decreased SEEP level were significantly associated with a higher likelihood of insulin resistance. The final model retained sex and BMI, though their P values were above 0.05, as their exclusion from the final model considerably affected the model's performance (Table 5).

Multiple linear regression analysis was conducted to assess the effect of potentially relevant variables on SEEP1 levels in obese children. The results revealed a significant decrease in SEPP1 level with increased total cholesterol, VAI, and HOMA-IR. Meanwhile, SEPP1 levels increased significantly with increased LDL-C, triglycerides, and serum insulin (Table 6).

DISCUSSION

SEPP1, a hepatokine protein produced by the liver, is known for its antioxidant functions and its role in insulin sensitivity and glucose metabolism[20]. However, the relationship between SEPP1 levels and metabolic syndrome, non-alcoholic fatty liver disease, and type 2 diabetes has been a topic of conflicting results in previous studies[21-23]. Despite being a sensitive marker for measuring selenium levels, research on SEPP1 levels among children and adolescents with obesity is scarce. Our study fills this gap by investigating the relationship between SEPP1 and obesity-related parameters, including insulin resistance, in a pediatric population. What sets our research apart is its focus on the pediatric population, a unique angle compared to most existing literature on SEPP1 and metabolic health, which primarily focuses on adults. By studying children, our research provides early insights into how SEPP1 levels correlate with obesity and metabolic disturbances from a young age, which is crucial for early intervention strategies. We also took a comprehensive approach, analyzing multiple obesity-related parameters, including BMI, waist circumference, lipid profiles, and insulin resistance markers, and their association with SEPP1 levels. This comprehensive approach allows us to identify more specific relationships and potential mechanisms linking SEPP1 to metabolic health. Unlike many studies that report absolute values, we utilized Z-scores and percentiles for weight, height, and blood pressure, which provide a more standardized assessment and facilitate comparison across different age groups and populations. Our findings indicate that SEPP1 levels are significantly lower in obese children compared to non-obese controls and are inversely correlated with several obesity-related parameters, such as BMI, waist circumference, and insulin resistance markers. Lower SEPP1 levels may be an early indicator of metabolic dysregulation in obese children.

In our study, we observed significantly higher weight, height, and BMI, along with their corresponding z-scores and waist circumference, weight-height ratio, and related centiles, in children diagnosed with obesity ($P < 0.001$). This finding is consistent with López-Peralta *et al*[24], who suggested that rapid weight gain during early childhood often leads to increased height velocity and advanced bone age. Our analysis also revealed significantly lower SEPP1 levels in children with obesity ($P < 0.001$), with a significant negative correlation between SEPP1 level and adiposity measures such as BMI, waist circumference, and waist-to-height ratio. These results indicate that higher adiposity indices are associated with

Table 1 Characteristics of studied groups, *n* (%)

		Control, *n* = 85	With obesity, *n* = 85	*P* value
Age of enrolment (years)	mean ± SD	10.35 ± 2.33	10.48 ± 2.34	0.743[1]
	Median [IQR]	10.00 [9.00-12.00]	10.00 [8.50-12.00]	
Sex	Male	46 (54.1)	35 (41.2)	0.091[2]
	Female	39 (45.9)	50 (58.8)	
Family history	DM	19 (22.4)	33 (39.3)	0.023[a,3]; 0.002[a,3]; < 0.001[a,3]
	HTN	15 (17.9)	34 (40.0)	
	Obesity	3 (3.6)	42 (49.4)	
weight Z-score (SD)	mean ± SD	0.12 ± 0.72	2.32 ± 0.28	< 0.001[a,3]
	Median [IQR]	0.29 [-0.33 to 0.70]	2.30 [2.10 to 2.42]	
Height Z-score (SD)	mean ± SD	-0.05 ± 0.76	0.78 ± 0.66	< 0.001[a,3]
	Median [IQR]	-0.14 [-0.65 to 0.36]	0.62 [0.24 to 1.40]	
BMI (kg/m^2)	mean ± SD	18.00 ± 2.60	28.32 ± 3.51	< 0.001[a,3]
	Median [IQR]	17.80 [16.00-19.50]	28.40 [25.80-30.50]	
BMI Z-score (SD)	mean ± SD	0.22 ± 0.78	2.24 ± 0.19	< 0.001[a,3]
	Median [IQR]	0.36 [0.00-0.82]	2.20 [2.10-2.36]	
Waist circumference (cm)	mean ± SD	60.44 ± 3.86	88.08 ± 8.71	< 0.001[a,3]
	Median [IQR]	60.00 [57.50-62.00]	86.00 [81.00-94.00]	
Waist circumference (centile)	mean ± SD	38.36 ± 13.27	96.45 ± 2.31	< 0.001[a,3]
	Median [IQR]	43.00 [26.30-49.10]	97.00 [95.80-98.00]	
W/H ratio	mean ± SD	0.43 ± 0.02	0.60 ± 0.04	< 0.001[a,3]
	Median [IQR]	0.43 [0.41-0.44]	0.60 [0.57-0.63]	
W/H ratio (centile)	mean ± SD	33.27 ± 15.93	95.39 ± 3.38	< 0.001[a,3]
	Median [IQR]	30.80 [18.70-50.00]	96.00 [93.60-97.80]	
SBP (centile)	mean ± SD	51.76 ± 13.95	54.89 ± 18.98	0.200[3]
	Median [IQR]	51.00 [46.00-58.00]	55.00 [49.00-61.00]	
DBP (centile)	mean ± SD	53.72 ± 13.45	54.36 ± 14.80	1.000[3]
	Median [IQR]	47.00 [43.00-59.00]	51.00 [48.00-66.00]	
ALT (U/L)	mean ± SD	24.44 ± 3.54	24.75 ± 7.68	1.000[3]
	Median [IQR]	26.00 [22.00-27.00]	24.00 [22.00-26.00]	
AST (U/L)	mean ± SD	22.42 ± 4.20	23.20 ± 5.65	0.300[3]
	Median [IQR]	22.00 [18.00-26.00]	22.00 [19.00-26.00]	
Total cholesterol (mg/dL)	mean ± SD	145.91 ± 14.21	156.86 ± 23.93	< 0.001[a,3]
	Median [IQR]	146.00 [138.00-159.00]	151.00 [143.00-165.00]	
HDL-C (mg/dL)	mean ± SD	48.25 ± 3.88	40.66 ± 3.03	< 0.001[a,3]
	Median [IQR]	47.00 [45.00-50.00]	42.00 [40.00-42.00]	
LDL-C (mg/dL)	mean ± SD	92.71 ± 11.60	101.12 ± 19.68	0.001[a,3]
	Median [IQR]	94.00 [82.00-104.00]	91.00 [85.00-110.00]	
Triglycerides (mg/dL)	mean ± SD	75.65 ± 16.95	109.12 ± 28.24	< 0.001[a,3]
	Median [IQR]	73.00 [60.00-89.00]	103.00 [89.00-115.00]	
VAI	mean ± SD	0.94 ± 0.22	1.70 ± 0.57	< 0.001[a,3]
	Median [IQR]	1.01 [0.76-1.05]	1.63 [1.11-2.20]	

Serum insulin (uIU/mL)	mean ± SD	8.05 ± 2.09	17.23 ± 7.50	< 0.001[a,3]
	Median [IQR]	8.00 [6.20-8.90]	17.20 [11.60-19.70]	
FBS (mg/dL)	mean ± SD	72.04 ± 6.97	81.37 ± 15.21	< 0.001[a,3]
	Median [IQR]	71.00 [68.00-74.00]	80.00 [70.00- 5.00]	
HOMA-IR	mean ± SD	1.42 ± 0.42	3.51 ± 1.85	< 0.001[a,3]
	Median [IQR]	1.40 [1.20-1.60]	3.50 [2.10-4.00]	
SEPP1 (ng/mL)	mean ± SD	70.97 ± 6.49	12.12 ± 10.92	< 0.001[a,3]
	Median [IQR]	69.47 [65.89-77.42]	7.69 [5.82-13.99]	
Insulin resistance	Present	5 (5.9)	39 (45.9)	< 0.001[a,3]
	Absent	80 (94.1)	46 (54.1)	

[1]Mann-Whitney test.
[2]Pearson's χ^2 test for independence of observations.
[3]Adjusted by regression for age at enrollment and sex.
[a]$P < 0.05$.
ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; DM: Diabetes mellitus; FBS: Fasting blood sugar; HDL-C: High-density lipoprotein-cholesterol; HOMA-IR: Homeostasis Model Assessment insulin resistance; HTN: Hypertension; IQR: Interquartile range (25^{th}–75^{th} percentiles; LDL-C: Low-density lipoprotein-cholesterol; SBP: Systolic blood pressure; SD: Standard deviation; SEPP1: Selenoprotien P1; VAI: Visceral adiposity index; W/H ratio: Waist/height ratio.

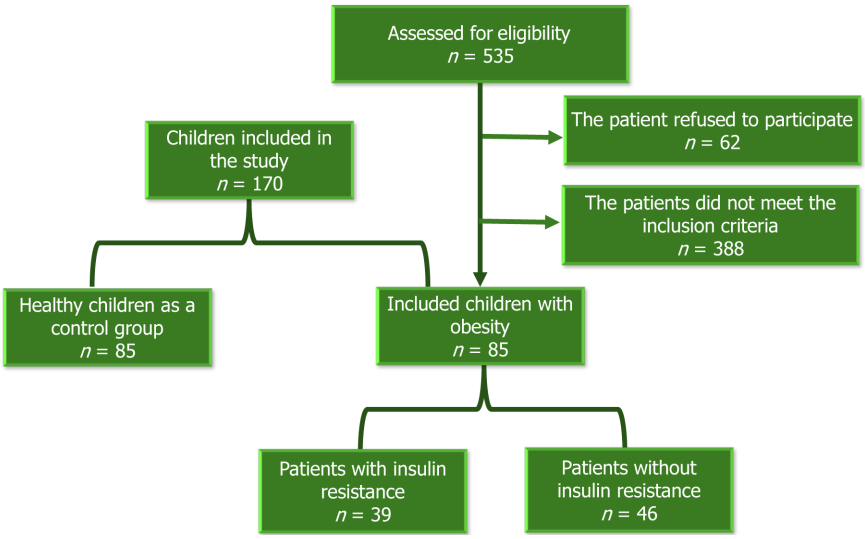

Figure 1 The flow chart of the study.

lower SEPP1 levels. The observed reduction in SEPP1 levels among obese children could be due to increased oxidative stress and inflammation, which are common in obesity and are known to affect SEPP1 expression. SEPP1 is involved in antioxidant defense, and its depletion might reflect an impaired response to oxidative stress in obese individuals[25,26].

Notably, variables like diastolic blood pressure, height, and certain liver enzyme levels did not demonstrate significant associations with SEPP1 levels in this cohort. Ko *et al*[27] similarly reported negative correlations between SEPP1 levels and parameters, including BMI, waist circumference, blood pressure, transaminases, and HOMA-IR. Additionally, studies by Gharipour *et al*[28] and di Giuseppe *et al*[29] reported inverse correlations between SEPP1 levels and BMI and metabolic syndrome. Furthermore, several studies have indicated lower levels of selenium biomarkers in patients with obesity[24,25]. Although our findings differed from those of Chen *et al*[30], Tinkov *et al*[8], and El-kafrawy *et al*[31], who reported higher SEPP1 levels in individuals with obesity, it's important to note that these studies were conducted on adults. Moreover, a meta-analysis of some of these studies reported no significant difference in SEPP1 between patients with obesity and those without[32].

The present study revealed significant correlations between SEPP1 levels and lipid profile markers such as total cholesterol, LDL, and triglycerides. Elevated levels of these lipid components were associated with changes in SEPP1 concentrations. In a meta-analysis, Yu *et al*[32] identified a positive correlation of SEPP1 with LDL cholesterol, although no significant correlation was observed with other glucose and lipid metabolic disease markers. Conversely, Amirkhizi *et al*[33] reported no significant relationship between serum SEPP levels and total cholesterol, LDL cholesterol, and HDL

Table 2 Correlations of serum selenoprotein P1 in children with obesity

	SEPP1 (ng/mL), children with obesity	
	r_s	*P* value
Age of enrolment (years)	-0.098	0.371
weight Z score (SD)	-0.001	0.995
Height Z score (SD)	0.042	0.701
BMI (kg/m^2)	-0.338	0.002[a]
BMI Z score (SD)	-0.044	0.686
Waist circumference (cm)	-0.527	< 0.001[a]
Waist circumference (centile)	-0.183	0.094
W/H ratio	-0.394	< 0.001[a]
W/H ratio (centile)	-0.279	0.010[a]
ALT (U/L)	-0.240	0.027[a]
AST (U/L)	-0.219	0.044[a]
Total cholesterol (mg/dL)	-0.185	0.089
HDL (mg/dL)	0.084	0.443
LDL (mg/dL)	0.076	0.491
Triglycerides (mg/dL)	-0.012	0.916
VAI	-0.252	0.020[a]
Serum insulin (uIU/mL)	-0.223	0.040[a]
FBS mg/dL	-0.258	0.017[a]
HOMA-IR	-0.279	0.010[a]

[a]*P* < 0.05.

ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; FBS: Fasting blood sugar; FE: Fisher's exact test; HDL: High-density lipoprotein; HOMA-IR: Homeostasis Model Assessment insulin resistance; IQR: Interquartile range (25th – 75th percentiles); LDL: Low-density lipoprotein; Max: Maximum; Min: Minimum; NA: Non-applicable; SD: Standard deviation; SEPP1: Selenoprotien P1; VAI: Visceral adiposity index; W/H Ratio: Waist/height ratio; χ^2: Pearson's Chi-square test for independence of observations; Z: Mann-Whitney test; r_s < 0.3: Weak correlation; 0.3-0.7: Moderate; > 0.7: Strong correlation (regardless of the + /- signs); -ve sign: Inverse correlation (one variable increases while the other variable decreases); + ve sign: Direct correlation (both variables decrease or increase together).

Table 3 Selenoprotein P1 level in Insulin and non-insulin resistant children with obesity based on Homeostatic Model Assessment of Insulin Resistance[15]

		Non-insulin resistant, *n* = 46	Insulin resistant, *n* = 39	*P* value
SEPP1 ng/mL	mean ± SD	15.84 ± 12.91	7.73 ± 5.46	< 0.001[1,a]
	Median [IQR]	12.41 [8.00-18.42]	6.26 [5.56-6.73]	

[1]Mann-Whitney test.

[a]*P* < 0.05.

IQR: Interquartile range (25th–75th percentiles); SEPP1: Selenoprotien P1.

cholesterol. Still, they found a significant negative correlation with triglycerides in adult females with polycystic ovary syndrome.

Moreover, in the current study, insulin-related variables, including serum insulin levels and HOMA-IR, exhibited significant associations with SEPP1. Our study found a significant inverse relationship between SEPP1 levels and insulin resistance (HOMA-IR). This aligns with the hypothesis that SEPP1 plays a role in glucose metabolism and insulin signaling. Reduced SEPP1 levels may contribute to impaired insulin action and higher insulin resistance, a key feature of metabolic syndrome[34]. These findings also may suggest that dyslipidemia and insulin resistance may play crucial roles in influencing SEPP1 levels in children with obesity. The VAI is a novel cardio-metabolic risk marker reflecting the distri-

Table 4 Predictive/diagnostic performance of selenoprotien P1 from receiver operating characteristic curve analysis

	Obesity children
AUC	0.828
SE	0.053
95%CI	0.724-0.931
P value	< 0.0001[a]
Cut-off value	≤ 7.5
Sensitivity (%)	92.31
Specificity (%)	86.96
PPV (%)	85.7
NPV (%)	93.0

[a]*P* < 0.05 (testing the null hypothesis AUC = 0.5 against observed AUC).
AUC: Area under the receiver operating characteristics curve; CI: Confidence interval of AUC; NPV: Negative predictive value; PPV: Positive predictive value; SE: Standard error of AUC.

Table 5 Univariate and multivariate logistic regression analysis for variables affecting insulin resistance in the obese group

Independent variables	Univariate regression			Multivariate regression		
	P value	OR	95%CI for OR	*P* value	OR	95%CI for OR
Sex (Male)	0.018[a]	0.399	0.186-0.855	0.106	0.384	0.120-1.224
Age of enrolment (years)	0.046[a]	1.170	1.003-1.366	0.025[a]	1.355	1.038-1.767
Waist circumference (centile)	0.034[a]	1.150	1.010-1.309	_	_	_
W/H ratio (centile)	0.013[a]	1.154	1.031-1.292	_	_	_
BMI Z score (SD)	0.001[a]	18.684	4.415-79.071	0.101	13.458	0.600-301.944
SEEP1 (ng/mL)	0.002[a]	0.837	0.746-0.938	0.007[a]	0.880	0.803-0.966

[a]*P* < 0.05.
BMI: Body mass index; SEPP1: Selenoprotien P1; W/H Ratio: Waist/height ratio; OR: Odds ratio.

bution of abdominal fat and dyslipidemia[17]. Consistent with the findings of El-kafrawy *et al*[31], our results confirmed a significantly higher VAI in children with obesity ($P < 0.001$). Our study also identified a significant negative correlation between SEPP1 level and BMI, waist circumference, W/H ratio, HOMA-IR, and VAI in children with obesity, similar to the findings reported by Ko *et al*[27] and di Giuseppe *et al*[29]. However, El-kafrawy *et al*[31] demonstrated statistically significant positive correlations of SEPP1 with serum insulin concentration, HOMA-IR, and visceral adiposity index in the group with obesity and overweight, along with significant negative associations with waist circumference.

Current research demonstrated that SEPP1 levels could serve as a predictive biomarker for insulin resistance among children with obesity, exhibiting high sensitivity and specificity. The area under the ROC curve indicated strong predictive potential, suggesting that SEPP1 measurements might assist in identifying insulin resistance in this demographic. This study revealed that a SEPP1 value of ≤ 7.5 predicts insulin resistance with 92.31% sensitivity and 86.96% specificity. El-kafrawy *et al*'s study on adults demonstrated an optimal cut-off value of > 5.3 mg/L, with a sensitivity of 71.23% and specificity of 82.35%[31]. Additionally, Zhang *et al*[26] showed that SEPP levels were higher in patients with overweight/obesity and associated with insulin resistance by HOMA-IR and clamp methods. However, they suggested that obesity, rather than insulin resistance, is central to the increase in SEPP. Obesity increases pro-inflammatory cytokines and free radicals, and SEPP1 aids in adipogenesis and guards against oxidative stress. Thus, decreased SEPP1 expression impairs antioxidant protection from ROS, leading to insulin resistance[26,35]. Several hypotheses explain SEPP1 levels in patients with obesity. Obesity alters the gut microbiota (dysbiosis) due to oxidative stress and chronic inflammatory processes, affecting selenium absorption, bioavailability, and status[36]. Hyperactive inflammation also decreases SEPP1 expression and depletes selenoproteins[37-39]. Additionally, Tinkov *et al*[8] found that activation of PPARα/γ during adipogenesis enhances LPR2 expression in the epithelium, linking PPARα/γ activation to the increase in SEPP1 uptake.

The factors influencing SEPP1 levels were further analyzed by multiple linear regression. Our findings indicated that lipid profile components such as total cholesterol, LDL, and triglycerides are significantly associated with SEPP1 levels. Additionally, variables associated with insulin resistance, such as VAI, serum insulin, and HOMA-IR, were significant

Table 6 Multiple linear regression analysis for factors affecting selenoprotien P1 level in children with obesity (*n* = 85)

Variables[1]	B	95%CI	*P* value
DBP	-0.571	-1.313 to 0.171	0.129
Height (cm)	0.077	-2.640 to 2.794	0.955
Waist circumference (cm)	0.414	-4.348 to 5.176	0.863
BMI (kg/m^2)	-0.542	-1.726 to 0.643	0.365
W/H ratio	33.413	-631.753 to 698.579	0.920
ALT (U/L)	-0.100	-0.467 to 0.267	0.589
AST (U/L)	-0.470	-1.005 to 0.066	0.085
Total Cholesterol (mg/dL)	-0.321	-0.526 to -0.117	0.003[a]
HDL (mg/dL)	-0.893	-1.835 to 0.049	0.063
LDL (mg/dL)	0.335	0.089 to 0.581	0.008[a]
Triglycerides (mg/dL)	0.163	0.016 to 0.309	0.030[a]
VAI	-8.340	-15.321 to -1.359	0.020[a]
Serum insulin (uIU/mL)	1.295	0.443 to 2.146	0.003[a]
HOMA-IR	-6.224	-9.685 to -2.764	0.001[a]

[1]Every variable was adjusted for other variables in the table.

[a]*P* < 0.05.

B: Regression coefficient. ALT: Alanine transaminase; AST: Aspartate aminotransferase; BMI: Body mass index; DBP: Diastolic blood pressure; DM: Diabetes mellitus; FBS: Fasting blood sugar; HDL: High-density lipoprotein; HOMA-IR: Homeostasis Model Assessment insulin resistance; HTN: Hypertension; IQR: Interquartile range (25th–75th percentiles); LDL: Low-density lipoprotein; SEPP1: Selenoprotien P1; VAI: Visceral adiposity index, W/H ratio: Waist/height ratio.

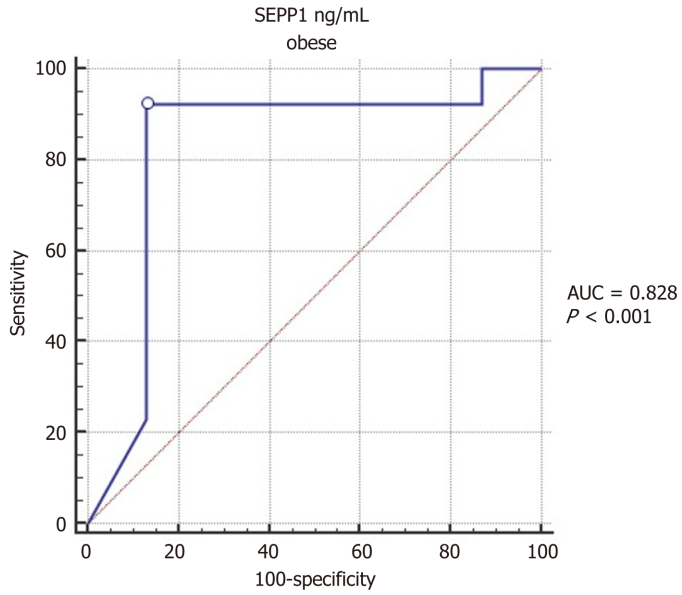

Figure 2 Receiver operating characteristic curve analysis of selenoprotein P1 as predictor for insulin resistance in children with obesity.
AUC: Area under the curve; SEPP1: Selenoprotein P1.

predictors influencing SEPP1 concentrations. As SEPP1 reflects selenium status in the body, and selenium is known to affect the activity of insulin-antagonistic phosphatases, SEPP1 could potentially reflect the insulin resistance status of the body. Conversely, in diabetes, dysregulated carbohydrate metabolism may impact plasma selenium and SEPP1 levels because hepatic biosynthesis of SEPP1 is suppressed by insulin and stimulated under hyperglycemic conditions[40]. Moreover, SEPP1 levels can predict the response to the oral hypoglycemic effects of metformin, offering the potential for tailoring the treatment of insulin resistance and diabetes[41].

Given the strong association between SEPP1 levels and insulin resistance, SEPP1 could serve as a biomarker for the early identification of children at risk for developing metabolic disorders. Early detection allows for timely interventions, which are critical in preventing the progression of obesity-related complications. Further research exploring the underlying mechanisms and longitudinal studies investigating the dynamic changes in SEPP1 levels in response to interventions could provide deeper insights into its role in metabolic health among children with obesity. While our study suggests that SEPP1 levels are inversely correlated with obesity and insulin resistance, it is essential to acknowledge that the literature on SEPP1 concentrations in obesity is not uniform. Different studies have reported varying results, which may be attributed to differences in study populations, methodologies, and the specific parameters measured. Our research adds to this growing body of evidence by providing data from a pediatric population that has been less studied than adults.

Our findings indicate that SEPP1 could be a valuable biomarker for assessing metabolic health, particularly in identifying insulin resistance. However, several factors may explain why SEPP1 is not yet widely used in clinical practice. SEPP1 is a relatively novel biomarker in the context of metabolic disorders. More extensive research and validation studies are required to establish its utility and reliability compared to traditional markers such as fasting insulin, glucose, and HOMA-IR. The measurement of SEPP1 levels requires specific assays that may not be readily available in all clinical settings. Developing standardized, accessible, and cost-effective methods for SEPP1 measurement is crucial for its widespread adoption. Current clinical guidelines for diagnosing and managing metabolic disorders predominantly rely on well-established markers. Incorporating SEPP1 into these guidelines will require robust evidence from large-scale studies and consensus among healthcare professionals.

Study limitations

It's important to remember that the study was limited to a specific demographic region and had a particular sample size. This means that the results may not apply to other populations, limiting the generalizability of the findings. Also, since it was a cross-sectional study, it only provided a snapshot of associations at a single time, making it difficult to establish causal relationships or determine the directionality of observed associations between SEPP1 levels and metabolic parameters. In addition, despite efforts to control participant selection, there could be inherent biases due to exclusion criteria or recruitment methods that could influence the representation of specific subgroups within the study population. Additionally, the study relied on specific assays and measurement techniques to quantify SEPP1 levels and other metabolic parameters, which could affect the strength of the findings. Conducting the study within a single institution might limit the diversity of the population, potentially overlooking variations present in a more extensive and diverse setting. Despite efforts to control for various variables, unaccounted confounding factors or variables not included in the analysis could influence the observed associations. It's also important to note that the study didn't have longitudinal data, which could have provided a clearer understanding of the dynamic nature of the relationships between SEPP1 levels and associated metabolic parameters over time.

Recommendations

This study emphasizes the need for longitudinal investigations spanning diverse populations to validate the observed associations between SEPP1 levels and metabolic indices among children and adolescents with obesity. Long-term studies could unravel the temporal dynamics of SEPP1 alterations and their role in metabolic health progression. Deeper mechanistic studies are warranted to elucidate the underlying pathways linking SEPP1 with obesity-related metabolic disturbances. Investigating how SEPP1 is intricately involved in adiposity-related insulin resistance could provide pivotal mechanistic insights. Considering the predictive potential of SEPP1 for identifying insulin resistance, further research should explore its clinical applicability as a diagnostic biomarker in routine pediatric care. Establishing standardized cutoff values and validation in larger cohorts could enhance its utility in clinical practice. Engaging in interventional trials targeting SEPP1 levels could offer novel therapeutic avenues. Exploring interventions that modulate SEPP1 expression or selenium status may help attenuate metabolic disturbances in children and adolescents with obesity.

Public health efforts focusing on nutritional strategies to optimize selenium intake and maintain adequate SEPP1 levels may play a preventive role in mitigating metabolic risks among the pediatric population at risk of obesity-related complications. Emphasizing education for healthcare providers regarding the role of SEPP1 in pediatric metabolic health could aid in early screening, diagnosis, and personalized interventions for children and adolescents at risk of metabolic dysregulation. These recommendations aim to stimulate further research and translate the findings into tangible clinical and public health strategies, ultimately contributing to enhanced metabolic health outcomes among children and adolescents with obesity.

CONCLUSION

This study underscores the intricate interplay between SEPP1 levels and metabolic indices among children and adolescents diagnosed with obesity. The investigation revealed a significant inverse correlation between SEPP1 concentrations and adiposity indices, including BMI, waist circumference, and waist-to-height ratio. A noteworthy association was also established between SEPP1 and insulin resistance, indicating its potential as a predictive biomarker. The observed reduction in SEPP1 levels among children with obesity, coupled with its significant negative correlation with markers of adiposity and insulin resistance, suggests a potential role for SEPP1 in the pathophysiology of metabolic disturbances in this demographic. Notably, SEPP1 emerged as a promising predictor of insulin resistance, displaying high sensitivity and specificity, with implications for early identification and intervention strategies.

Moreover, the study highlighted associations between SEPP1 levels and lipid profile components, specifically total cholesterol, LDL, and triglycerides. These findings underscore the multifaceted relationship between SEPP1 and metabolic factors, indicating its potential as a reflective biomarker for assessing metabolic health. While providing valuable insights, this study acknowledges certain limitations inherent in its cross-sectional design and sample characteristics. Longitudinal studies with diverse populations and refined measurement techniques are warranted to validate these associations and elucidate the dynamic nature of SEPP1 in relation to metabolic health among children and adolescents with obesity. Understanding the intricate associations between SEPP1 and metabolic parameters holds promise for delineating novel avenues for early detection, targeted interventions, and tailored management strategies for mitigating metabolic dysregulation among this vulnerable population.

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FOOTNOTES

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Data sharing statement: The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

STROBE statement: The study was done according to and aligned with the STROBE guidelines, and detailed observational study reporting was ensured. The STROBE checklist is attached.

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ORIGINAL ARTICLE

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Quieting the neonatal intensive care unit: A quality improvement initiative

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Abstract

BACKGROUND

The neonatal intensive care unit (NICU) is vital for preterm infants but is often plagued by harmful noise levels. Excessive noise, ranging from medical equipment to conversations, poses significant health risks, including hearing impairment and neurodevelopmental issues. The American Academy of Pediatrics recommends strict sound limits to safeguard neonatal well-being. Strategies such as education, environmental modifications, and quiet hours have shown to reduce noise levels. However, up to 60% of the noises remain avoidable. High noise exposure exacerbates physiological disturbances, impacting vital functions and long-term neurological outcomes. Effective noise reduction in the NICU is crucial for promoting optimal neonatal development.

AIM

To measure the sound levels in a NICU and reduce ambient sound levels by at least 10% from baseline.

METHODS

A quasi-experimental quality improvement project was conducted over 4 mo in a 20-bed level 3 NICU in a tertiary care medical college. Baseline noise levels were recorded continuously using a sound level meter. The interventions included targeted education, environmental modifications, and organizational changes, and were implemented through three rapid Plan-Do-Study-Act (PDSA) cycles. Weekly feedback and monitoring were conducted, and statistical process control charts were used for analysis. The mean noise values were compared using the paired *t*-test.

RESULTS

The baseline mean ambient noise level in the NICU was 67.8 dB, which decreased to 50.5 dB after the first cycle, and further decreased to 47.4 dB and 51.2 dB after subsequent cycles. The reduction in noise levels was 21% during the day and 28%

at night, with an overall decrease of 25% from baseline. The most significant reduction occurred after the first PDSA cycle (mean difference of −17.3 dB, $P < 0.01$). Peak noise levels decreased from 110 dB to 88.24 dB after the intervention.

CONCLUSION
A multifaceted intervention strategy reduced noise in the NICU by 25% over 4 months. The success of this initiative emphasizes the significance of comprehensive interventions for noise reduction.

Key Words: Quality improvement; Noise pollution; Preterm care; Sound measurement; Plan-Do-Study-Act

Core Tip: In our neonatal intensive care unit study, we addressed the problem of high noise levels that can negatively affect the health and development of neonates. We implemented a multifaceted approach of targeted education, environmental modifications, and organizational changes. As a result, we reduced the noise levels by up to 25% over 4 mo. Although we did not assess clinical outcomes, our study provides a foundation for future research and emphasizes the need to maintain optimal noise levels for the well-being of neonates.

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INTRODUCTION

The neonatal intensive care unit (NICU) is a critical care environment for preterm infants who require specialized medical attention. However, the NICU is also a noisy environment that harms neonate health. Noise refers to any unwanted sound that hampers performance and triggers a stressful physiological and psychological response[1]. Some noise sources are continuous sounds from monitors, ventilators, alarms, infusion pumps, incubators, and conversations between doctors, staff and family[2]. Studies show that the average noise levels in NICUs range from 7 to 120 dB[3]. Exposure to loud noise has been implicated in both short- and long-term complications in neonates[3]. The American Academy of Pediatrics (AAP) recommends a sound limit below 45 dB in NICU[4]. The AAP also stated that the sound level should not exceed 50 dB for 10% of the measurement period, and the maximum sound level should not exceed 65 dB[5]. Hearing loss may result from high-intensity sounds damaging the cochlear cilia. Neonates are passive consumers of harmful noise which makes them more susceptible to its damaging effects[2]. Preterms are more vulnerable because of central nervous system immaturity and decreased autonomic and self-regulatory abilities, and exposure to loud sounds has been attributed to poor neurodevelopment and growth[2,3]. Hearing impairment is diagnosed in 2% to 10% of preterm infants, compared to 0.1% in the general pediatric population[3]. Although neonates benefit from noise reduction, it is not clear how to effectively lower the noise level in NICUs. A study by Mackenzie and Galbrun[6] in 2007 on noise reduction in hospitals estimated that up to 60% of the noises could be avoidable. Recent evidence shows that educational training, environmental modifications, and the implementation of quiet hours significantly impact noise reduction[1,7,8]. High-level sound exposure was shown to increase blood pressure, hypoxic episodes, apnea, bradycardia, disturbed sleep, muscle tone, and intracranial pressure. It also influenced the neuroendocrine and immune systems[1,5,8]. Increased oxygen need and caloric consumption are also more pronounced in preterms[2]. Infants cannot self-stabilize, which can have a lasting impact on neurological development that results in attention deficit, hearing disorders, speech and language disorders, and delays[8]. Thus, we conducted this study with the objectives of measuring the sound levels in our NICU and reducing ambient sound levels by at least 10% from baseline.

MATERIALS AND METHODS

The study was conducted at the NICU, Department of Pediatrics at Subbaiah Institute of Medical Sciences (SUIMS), Shimoga, India. It is a 20-bed level 3 NICU with an open bay system. The patient care team consists of two main consultants, four residents, two interns, and twelve nurses. The nurses and residents work in shifts, with shift changes at 8 am and 8 pm.

This quasi-experimental quality improvement initiative (QI) project was conducted over 4 mo, from December 9, 2023, to March 18, 2024, after obtaining ethical clearance from the Institutional Ethics Committee. We included all healthcare workers involved in caring for NICU babies, including SUIMS support staff working in the NICU, as well as caretakers of the neonates. Noise levels were recorded using a sound level meter (Mastech MS 6701 rs 232/data logger) with a range of

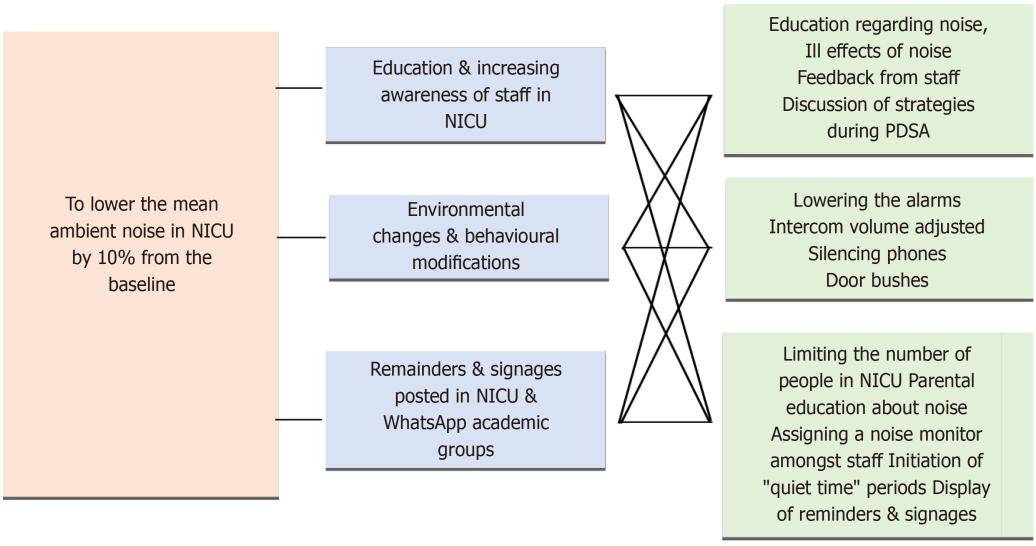

Figure 1 Key driver diagram. NICU: Neonatal intensive care unit; PDSA: Plan-Do-Study-Act.

30-130 dB. Decibel readings were obtained continuously, with one reading recorded every 5 s from the NICU cubicle. The device was placed in the NICU, centrally located, and attached to a desktop. The device recorded data that was checked daily and saved in Excel format. NICU baseline mean noise level was obtained during morning and night shifts over 2 wk. The Institute for Healthcare Improvement model for improvement was used as the framework for this project, and interventions were tested using rapid Plan-Do-Study-Act (PDSA) cycles. A multifaceted intervention strategy was applied. The first PDSA cycle of 2 wk consisted of targeted education of the healthcare providers, including nursing staff, consultants, residents, interns, support staff and patient caretakers. The patient caretakers were briefed in the local language, Kannada. Multiple short sessions were conducted on what noise is, its sources, the ill effects of noise, and ways of reducing it. Following the first cycle, the sound was recorded for 1 wk. The second PDSA cycle of 2 wk consisted of environmental modifications like changing alarm settings, placing reminder signs to maintain silence and silencing the mobile, *etc*, both in English and Kannada, and implementation of a quiet period of one h per day between 8 am and 9 am. Following the second cycle, the sound was recorded for 1 wk. The third PDSA cycle of 2 wk included increasing the quiet period to 2 h per day, from 8 am to 9 am and 7 pm to 8 pm. A departmental policy was implemented to ensure that handovers and discussions during rounds were made away from the main cubicle. Additionally, a limit was placed on the number of people allowed inside the NICU at any time until 10. The security guard at the entrance was given a register to make a note of the 11th person entering the NICU, and we addressed them. One consultant, two residents and one nurse were chosen as spies to ensure adherence to regular feedback. During these cycles, weekly feedback on the mean noise level was provided to the healthcare team. A power point presentation was done in the classroom before starting each PDSA cycle to introduce the cycle and allow questions about doubts and to give feedback. The newborn caretakers were also addressed in a way that was appropriate to their understanding. The mean noise levels during the day and night shifts and peak noise levels were calculated during each PDSA cycle. The average noise levels were calculated for 2 wk after three PDSA cycles. Regular reminder messages using WhatsApp were sent to the healthcare team. The standards for quality improvement reporting excellence 2.0 guidelines for reporting were followed. The key drivers of our study are shown in Figure 1.

Statistical analysis

Descriptive statistics were used to summarize the weekly noise levels and peak noise measurements recorded throughout the study period. Weekly mean noise levels and peak noise levels were calculated for both day and night shifts, providing an overview of the ambient noise environment within the NICU.

Control chart analysis was employed to visually represent the mean noise level over time [1]. Control charts are essential for understanding and communicating data in healthcare improvement efforts. They are statistically rigorous and user-friendly, enabling researchers to make data-driven decisions in quality improvement studies[9]. Statistical process control charts, generated using QI Macros software (Know Ware International, Inc., Denver, CO, United States), were used to monitor changes in noise level and identify any significant shifts or trends. Control limits, including the upper control limit (UCL) and lower control limits (LCL), representing three standard deviations above and below the average, and the upper warning limit (UWL) and lower warning limit (LWL), representing two standard deviations above and below the average noise, respectively, were calculated to establish boundaries within which noise levels were expected to fluctuate under normal process conditions.

Comparison of baseline noise levels and those observed during and after the implementation of intervention cycles was conducted to assess the effectiveness of noise reduction strategies. The paired *t*-test was used to determine the significance of any observed changes in noise level after the PDSA cycles. A significance level of = 0.05 was adopted to evaluate statistical significance. All data were analyzed with SPSS, version 29.0 (IBM Corp., Armonk, NY, United States).

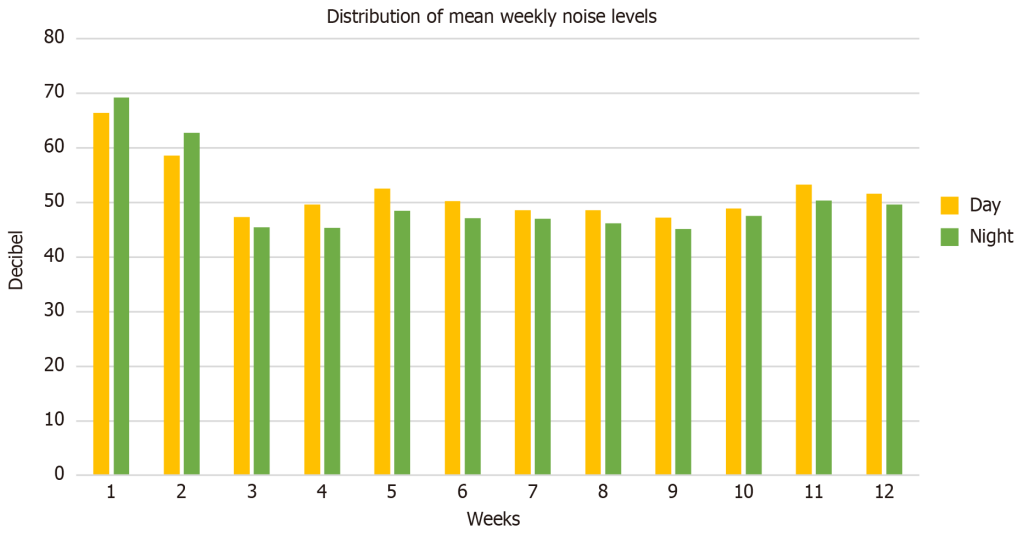

Figure 2 Hourly average noise level during the day and at night.

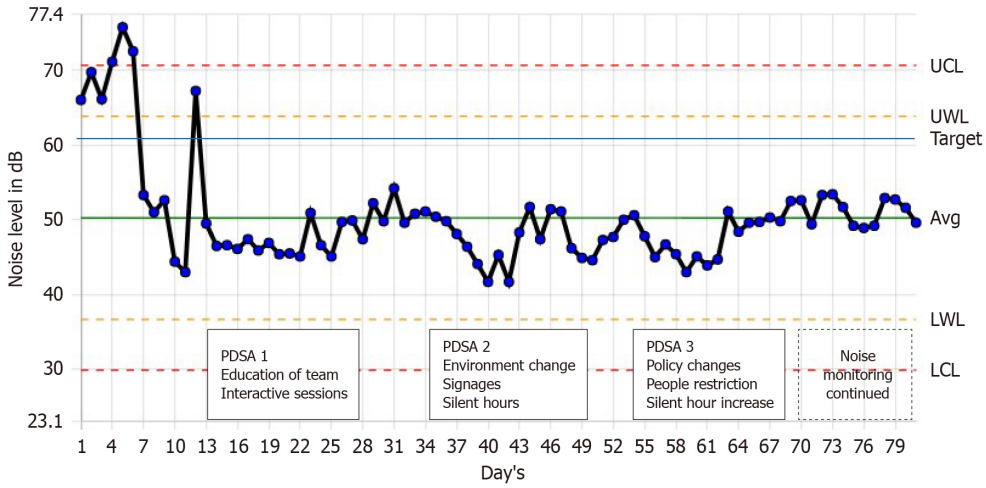

Figure 3 Control chart of the daily average ambient noise level. Avg: Average; dB: Decibel; LCL: Lower control limit; LWL: Lower warning limit; PDSA: Plan-Do-Study-Act; UCL: Upper control limit; UWL: Upper warning limit.

RESULTS

The baseline mean ambient noise level in the NICU was 66.4 dB during the day and 69.2 dB at night, with a 24 h average of 67.8 dB. At the end of the first PDSA cycle, the mean noise levels were 52.6 dB in the day and 48.5 dB at night with a 24 h average of 50.5 dB. At the end of the second cycle, the mean noise levels were 48.6 dB during the day and 46.2 dB at night with a 24 h average of 47.4 dB. At the end of the third cycle, the day and night mean noise levels were 53.3 dB and 50.4 dB, respectively at the end of 1 wk, and 52.4 dB and 50 dB at the end of 2 wk. The 24 h average noise level was 51.2 dB at the end of 2 wk after the third PDSA cycle (Figure 2). With the implementation of interventions in successive PDSA cycles, the mean noise levels in the NICU decreased from baseline by 21% during the day and by 28% at night, with a 24 h reduction of 25% at the end of three cycles. Successive noise reductions were achieved over 4 mo (Figure 3). From the control charts during the first PDSA cycle, it can be seen that the noise levels were within the UCL and LCL. However, during the last few days of the post-PDSA monitoring wk, the noise was noted to cross the UWL (Figure 4A). During the second PDSA cycle, the noise levels were noted to hit the LWL twice, but afterward it remained within the UWL and LWL (Figure 4B). In the third PDSA cycle, the noise level was well within the UWL and LWL, including the monitoring wk post-PDSA cycle (Figure 4C). Significant reductions in noise levels were observed after PDSA 1 (mean difference = −17.3 dB, P = 0.00054) and from Baseline to PDSA 2 (mean difference = −20.4 dB, P < 0.001). However, the change from PDSA 1 to PDSA 2 was not statistically significant (mean difference −3.1 dB, P = 0.053). Notably, there was a significant increase in noise level from PDSA 2 to PDSA 3 (mean difference 4.4 dB, P = 0.0097), resulting in a net reduction from Baseline to PDSA 3 (mean difference = −15.9 dB, P = 0.001) (Table 1). The noise peaks also decreased from 110 dB in the baseline period to 88.24 dB at the end of three PDSA cycles (Figure 5). The most significant drop in the peak noise level was noted during the first PDSA cycle, after which the peak noise levels stabilized, and no further drop was noted.

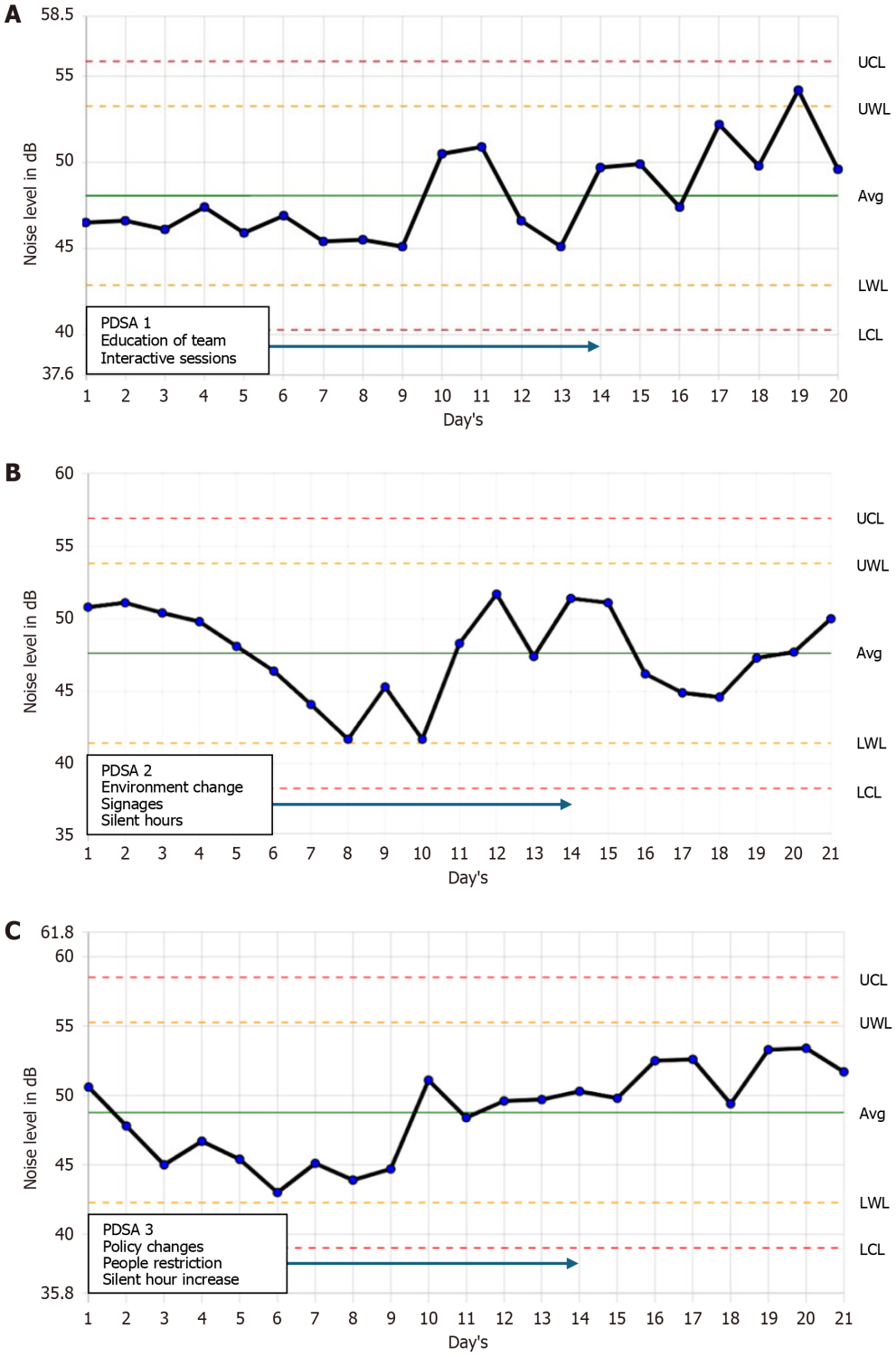

Figure 4 Control chart of the daily average ambient noise level. A: Plan-Do-Study-Act (PDSA) cycle 1; B: PDSA cycle 2; C: PDSA cycle 3. Avg: Average; dB: Decibel; LCL: Lower control limit; LWL: Lower warning limit; UCL: Upper control limit; UWL: Upper warning limit.

DISCUSSION

The 24 h average baseline noise level in our NICU was 67.8 dB, which decreased to 50.5 dB after our first cycle and to 47.4 dB and 51.2 dB after the next two cycles. There was a significant reduction after the first cycle but little change in subsequent cycles. This QI initiative resulted in a 24 h average noise reduction of 25% over 4 mo. The peak noise level decreased by 17% from baseline. The most substantial change occurred during the initial PDSA cycle, indicating the effectiveness of targeted education and early environmental modifications.

This result was achieved with a multifaceted intervention strategy including targeted education sessions for healthcare providers and caretakers, environmental modifications such as adjusting alarm settings and implementing quiet periods, and organizational changes to limit the number of individuals in the NICU at any given time. These interventions were

Table 1 Comparison of change in mean noise levels after each Plan-Do-Study-Act cycle

Noise level	Mean difference in 24-h mean noise	*t*-test statistic	*P* value
Baseline to PDSA 1	-17.3	6.7	< 0.01[a]
PDSA 1 to PDSA 2	-3.1	2.4	0.053
PDSA 2 to PDSA 3[1]	4.4	-3.7	< 0.01[a]
Baseline to PDSA 2	-20.4	6.2	< 0.01[a]
Baseline to PDSA 3	-15.9	5.9	< 0.01[a]

[a]*P* < 0.01.
[1]Significant increase in noise.
PDSA: Plan-Do-Study-Act.

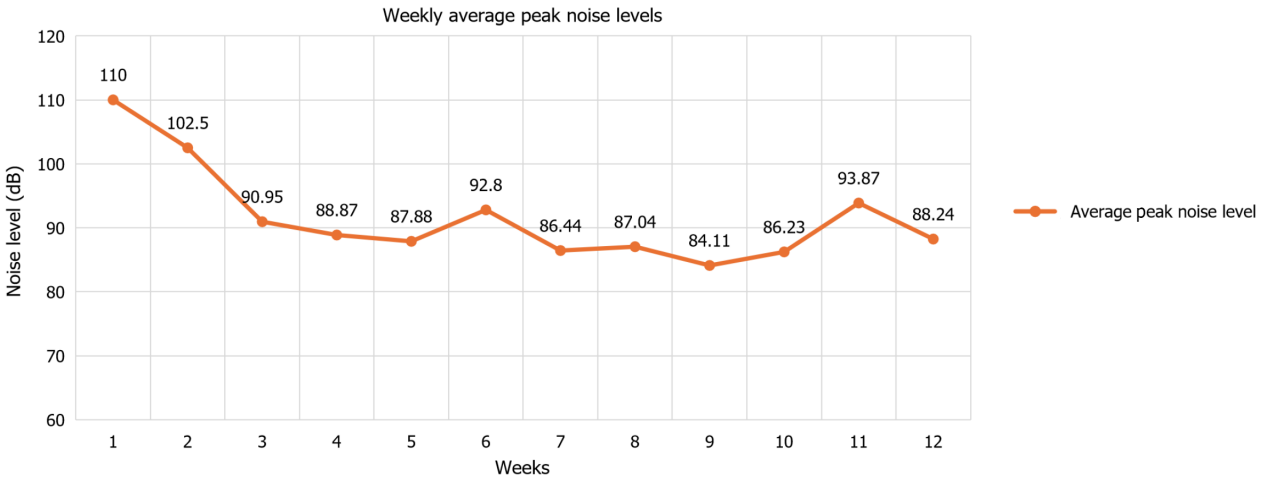

Figure 5 Run chart of weekly average peak noise level.

implemented progressively over three PDSA cycles, with weekly feedback from the healthcare team.

We employed continuous monitoring of noise levels using a sound level meter and implemented the Institute for Healthcare Improvement model for improvement as our framework. Ahamed *et al*[1], used targeted education, behavioral, and environmental modifications to decrease the noise level in their NICU over 4 PDSA cycles. Similar quality improvement initiatives were used by Chawla *et al*[7], who achieved a 20% reduction from baseline noise level. A pilot project over a shorter 11 wk period found a 13.7% reduction in noise levels using education and silent hour implementation[8].

Accurate sound estimation requires a class 1 or 2 device, but considering financial constraints, we used a Mastech (MS 6701 rs 232/data logger) sound level meter, which has a rating of IEC 651 and the ANSI S1.4 type 2 American standard for sound level meter performance, which has been used earlier[10,11].

During the targeted education sessions, we were surprised to learn that our nursing staff was unaware of the ill effects of noise. Their active participation in asking questions helped us. We also gathered some valid inputs from the senior faculty, who helped us plan the study.

Our study underscores the importance of implementing comprehensive interventions to address noise pollution in the NICU setting. By involving various stakeholders and using iterative improvement cycles, we successfully achieved our aim of reducing noise levels within the NICU. Moreover, our findings suggest that sustained efforts and ongoing monitoring are essential for maintaining optimal noise levels and ensuring the well-being of neonates in intensive care settings.

In addition to noise reduction, our study also helped with team building and coordination among the stakeholders, especially the nursing staff and residents.

Our study has some limitations. We did not assess the impact of noise reduction on clinical outcomes. The noise meter was placed only in the main NICU cubicle, and because of technical reasons, it was not rotated between the out born NICU areas. We had no control over the biomedical team visiting for equipment checks, which led to noise. Hospital renovation work adjacent to the NICU area led to increased peak levels during the 11th wk of our study. Owing to a technical issue, we lost data for 1 d during the first PDSA cycle. Because of the Hawthorne effect, it was noted that during data collection times, the staff would become hypervigilant. This bias was limited by continuous sound monitoring over 24 h. Though we achieved our target of a 10% reduction in noise level, we were far from reaching the AAP recommendation. Though the study duration was short, it serves as a pilot study to achieve AAP noise level targets. Future research

could explore these associations to elucidate additional benefits of noise reduction interventions in NICU settings.

CONCLUSION

Our study demonstrates the feasibility and effectiveness of implementing a multifaceted intervention strategy to reduce noise levels within the NICU. By addressing this critical issue, we aim to improve the quality of care and enhance outcomes for preterm infants undergoing intensive medical treatment.

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FOOTNOTES

Author contributions: Rangaswamy DR and Kamble N conceptualized and designed the study, coordinated and supervised data collection, drafted the initial manuscript, and reviewed and revised the manuscript; Veeramachaneni A designed the data collection instruments, collected data, conducted the initial analyses, and reviewed and revised the manuscript; All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work; Rangaswamy DR is the Guarantor for this paper.

Institutional review board statement: This study was reviewed and approved by the Ethics Committee of Subbaiah Institute of Medical Sciences [Approval number: IEC-SUIMS/70Nov/23].

Informed consent statement: Waiver of consent was granted by the IEC.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

Data sharing statement: Dataset available from the corresponding author upon reasonable request at rajatadri93@gmail.com. Participants consent was not obtained, in line with no participant-related data being collected and with the dataset containing sound values.

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ORIGINAL ARTICLE

Observational Study

Perception, use of social media, and its impact on the mental health of Indian adolescents: A qualitative study

Vishnu V Taddi, Ravshish K Kohli, Pooja Puri

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Abstract

BACKGROUND

Mental illness is a health challenge faced by adolescents that has grown worse after the Coronavirus disease 2019 pandemic. Research on social media and young people's mental health has recently increased, and numerous studies have examined whether frequent use of social media is linked to issues such as anxiety, stress, depression, eating disorders, insomnia, frustration, feeling alone, and externalizing problems among adolescents. This influence of social media on adolescents' lives is clear, with many platforms like Facebook, Instagram, and YouTube playing an important role in daily interactions and self-expression. Even though social media offers numerous benefits, such as connectivity and information sharing, excessive usage can have detrimental effects on mental health, particularly among adolescents.

AIM

To study the impact of social media on the mental wellbeing of adolescents, and the associated potential dangers in India.

METHODS

A total of 204 adolescents aged 14 years to 23 years were included in the study. This study explored the intricate relationship between social media usage and adolescent mental health in India. The study employs a cross-sectional survey design to capture a snapshot of adolescent mental health and social media usage patterns. Data collection involved administering structured questionnaires and the analysis utilized quantitative methods, including descriptive statistics.

RESULTS

Excessive use of social media is correlated with increased stress, anxiety, and depression. Adolescents engage in compulsive behaviors such as scrolling in the middle of the night, which negatively impacts their mental and physical health, and leads to significant sleep disruption. Findings from the study aim to provide insights into the current state of adolescent mental health and inform strategies to

promote positive wellbeing in the Indian population.

CONCLUSION
The study underscores the need for further research to better understand the complex interplay between social media and adolescent mental health, and need for effective strategies to combat online harassment.

Key Words: Adolescents; Anxiety; Cyberbullying; Depression; Mental health; Social media

Core Tip: Mental illness is one of the health challenges that adolescents face these days, and it has grown worse after the Coronavirus disease 2019 pandemic. Research on social media and regarding the metal health of young people has increased recently. Numerous studies have examined whether frequent use of social media is linked to issues such as anxiety, stress, depression, eating disorders, insomnia, frustration, feeling alone, and externalizing problems among adolescents. The pervasive influence of social media on adolescents' lives is evident, with platforms like Facebook, Instagram, and TikTok playing a central role in daily interactions and self-expression. While social media offers numerous benefits, including connectivity and information sharing, excessive usage can have detrimental effects on mental health, particularly among adolescents. This study explores the intricate relationship between social media usage and adolescent mental health in India. The study employs a cross-sectional survey design to capture a snapshot of adolescent mental health and social media usage patterns. Data collection involved administering structured questionnaires and the analysis utilized quantitative methods, including descriptive statistics. Findings from the study aim to provide insights into the current state of adolescent mental health and inform strategies to promote positive wellbeing in this population. Additionally, the study underscores the need for further research to better understand the complex interplay between social media and adolescent mental health.

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INTRODUCTION

In the digital age, social media has become an integral part of everyday life, significantly influencing how individuals interact, communicate, and perceive the world. This phenomenon is particularly pronounced among adolescents, a group characterized by their adaptability to new technologies and platforms. In India, the proliferation of smartphones and affordable internet has accelerated social media usage, making it a ubiquitous presence in the lives of young people.

Adolescents, during their formative years, are especially susceptible to external influences, and social media can play a pivotal role in shaping their perceptions, behaviors, and mental health. While social media offers numerous benefits, such as enhanced connectivity, access to information, and opportunities for self-expression, it also poses potential risks. These risks include exposure to cyberbullying, unrealistic comparisons, addiction, and other mental health challenges[1]. With the number of adolescents effectively taking an interest in these digital communities, social media has, in its very foundation, changed the way that we interact with one another and with the world around us. With that in mind, to begin with, social media, at its very core, has benefits that have transformed the way we communicate, learn, and are entertained.

Social media usage among Indian adolescents has seen exponential growth in recent years. Platforms such as Facebook, Instagram, WhatsApp, and TikTok (before its ban) are immensely popular. According to a report by the Internet and Mobile Association of India (IAMAI), over 65% of internet users in India are between the ages of 12 years and 29 years, highlighting the significant presence of adolescents online (IAMAI, 2020). The primary motivations for social media use among adolescents include staying connected with friends and family, entertainment, and information seeking. A study by Sharma and Vyas[2] revealed that Indian adolescents often use social media to gain social validation and as a platform for self-expression. This desire for validation can sometimes lead to excessive use and dependence on social media.

Social media can have positive effects on adolescent mental health by providing platforms for support and community building. For instance, online support groups and mental health awareness pages can offer adolescents a sense of belonging and reduce feelings of isolation[3]. Furthermore, creative expression through social media can enhance self-esteem and personal growth. However, the negative impacts of social media on mental health are more frequently documented. Studies indicate a strong correlation between excessive social media use and symptoms of anxiety, depression, and loneliness among adolescents[4]. Factors contributing to these outcomes include cyberbullying, social comparison, and sleep disruption.

Positive impacts

Support networks: Longitudinal studies highlight the role of social media in maintaining support networks, particularly for adolescents dealing with mental health issues. A study by Singh and Gupta[5] found that adolescents who engaged with online support groups reported sustained improvements in their mental health over a 2-year period.

Self-esteem and identity formation: Social media platforms provide spaces for self-expression and identity exploration. Over time, this can lead to increased self-esteem and a stronger sense of identity, especially for those who receive positive feedback and support from peers[6].

Negative impacts

Increased anxiety and depression: Longitudinal data consistently show a correlation between high social media use and increased levels of anxiety and depression. A study by Farooq *et al*[7] followed adolescents over 3 years and found that those who spent more than 3 h per day on social media were more likely to report symptoms of depression and anxiety.

Cyberbullying: The incidence of cyberbullying has been tracked over time, with longitudinal studies indicating a rising trend. Victims of cyberbullying often experience long-term psychological effects, including increased anxiety, depression, and lower self-esteem[8].

Social comparison and body image issues: Adolescents frequently compare themselves to idealized images on social media, leading to negative body image and low self-esteem. A longitudinal study by Sharma[9] found that exposure to such content over a prolonged period exacerbates these issues, particularly among female adolescents.

Addiction and behavioral changes

Social media addiction: Longitudinal studies indicate that social media addiction can develop over time, with adolescents increasingly prioritizing online interactions over real-life engagements. This can lead to sleep disturbances, academic decline, and social isolation[10].

Behavioral shifts: Prolonged exposure to social media can result in behavioral changes, such as increased impulsivity and decreased attention span. A study tracked adolescents over 4 years and observed a decline in academic performance and face-to-face social interactions among heavy social media users[11].

Forensic analysis of the impact of social media on the mental health of Indian adolescents

A forensic analysis of the mental health of adolescents due to social media involves a comprehensive examination of the available evidence, research findings, and case studies to understand the complex relationship between social media usage and mental wellbeing. It involves five basic steps, which are detailed as follows.

Data collection: Provide an overview of the increasing prevalence of social media usage among adolescents globally and the growing concern about its potential impact on mental health. Discuss the importance of forensic analysis in understanding and addressing these issues[12].

Identification of key factors: (1) Duration and frequency of social media use; (2) Types of platforms and activities engaged in quality of online interactions and social support; (3) Exposure to cyberbullying, harassment, or negative content; (4) Comparison and self-esteem issues arising from social media use; and (5) Effects of excessive screen time on sleep patterns and overall wellbeing.

Assessment on impact on mental health: Investigate the impact of social media use on the mental health of Indian adolescents. Identify both positive effects (*e.g.*, social support, information access) and negative effects (*e.g.*, cyberbullying, social comparison, sleep disturbances). Examine how these effects vary across different demographic groups and socioeconomic backgrounds.

Evaluation of intervention strategies: Assess the effectiveness of existing intervention strategies designed to mitigate the negative effects of social media on adolescent mental health. This may include school-based programs, parental guidance initiatives, mental health support services, and platform-specific measures implemented by social media companies[13].

Legal and ethical considerations: Discuss legal and ethical implications related to social media use among adolescents, including privacy concerns, data protection, online safety regulations, and the responsibility of social media platforms in safeguarding user wellbeing[14,15].

MATERIALS AND METHODS

Study population and data

A variety of questionnaires that reflect the emotional wellbeing of the individual and are correlated with social media usage were administered. Consent was provided by adolescents aged 14 years to 23 years, to a total of 204 participants. The Google forms with questionaries were distributed through different social media platforms to collect the information from the target population of adolescents.

Inclusion criteria: (1) Individuals under 23 and above 14; (2) Individuals who are active users of at least one social media platform (*e.g.*, Facebook, Instagram, Twitter, Snapchat, YouTube, *etc*), for a period of time; and (3) Individuals who are proficient in the language in which the survey is conducted.

Exclusion criteria: (1) Individuals who are under 14 and above 23; (2) Individuals who are not an active user of social media or have not used social media in the past 6 months; (3) Individuals who are not proficient in the survey language; and (4) Individuals undergoing treatment for severe mental health issues.

Sample size: A total of 204 adolescents aged 14 years to 23 years were included in the study.

Data collection: Data were collected through structured questionnaires assessing social media usage (hours per day, platform preference) and mental health outcomes (using standardized scales for depression, anxiety, and self-esteem).

Statistical analysis

The study adopted a cross-sectional survey design, and data was analyzed using quantitative methods. A correlational analysis was utilized to reveal relationships between use of social media and wellbeing of Indian adolescents.

RESULTS

A total of 204 responses were received. The participation of females *vs* males according to age is depicted in Table 1. The percentage of female participants was very high compared to male participants; the age of the participant was high, between 20 years to 23 years, and most respondents used social media for 2–3 h per day. The values are shown in Figure 1A and B, emphasizing the increasing rate of social media usage by adolescents and the effect which the excessive screen time may cause on psychological wellbeing. A very high percentage of adolescents in the study experienced sleep disturbances due to late-night social media usage, as depicted in Figure 1B. All these findings highlight the requirement for focused interventions aimed at encouraging good social media habits and the reduction of negative impacts of digital media exposure on adolescents' mental wellbeing. Among the 204 adolescents surveyed, a high percentage of participants felt pressure to maintain an image on social media platforms, as shown in Figure 1C and D. In total, 29.4% of the respondents strongly agreed with the statement that they were forced to adhere to society's perceived norms of attractiveness, success, and popularity that are transmitted *via* digital platforms. Also, 27% of participants agreed moderately with a statement showing the omnipresent effect of social media on young people's self-perceptions and identity formations. These findings explain the crippling effect of social media on adolescents' mental health and the negative implications that are associated with the comparison culture and unattainable beauty standards of online platforms. With a very high percentage of adolescents having been negatively influenced in self-esteem and body image, as indicated in Figure 1D, the urge to project the perfect online personality increases feelings of inadequacy, anxiety, and low self-esteem among vulnerable people, which may lead to a myriad of mental health problems. On balancing online and offline life, a large percentage among the surveyed adolescents reported having difficulties. It is clear that 21.6% strongly agree and 38.2% moderately agree with the statement, as shown in Figure 1E. The findings indicate that there is a critical problem among young people when it comes to finding limits between digital engagement and real-world interaction. Not being able to attain a balance between online and offline activities might have serious implications for the mental health and general wellbeing of adolescents.

Most adolescents responded that they have felt anxiety or stress related to their participation in social media. It was observed that 18.6% strongly agree and 36.3% moderately agree that they have felt pressure related to the number of followers, likes, or comments they get on social media, as shown in Figure 1F. A high percentage of adolescents do not post their opinions on social media because they do not want to be judged or criticized. Herein, 24% of total respondents strongly agree, and 29.4% moderately agree, as shown in Figure 1G.

DISCUSSION

The increasing adoption and changing patterns of social media use among Indian adolescents highlight the rapid integration of these platforms into their daily lives. As platforms evolve and new ones emerge, adolescents' engagement with social media continues to grow. This trend is driven by several factors, including greater accessibility to smartphones and the internet, the dynamic nature of social media platforms, and the intrinsic motivation for social interaction and self-expression.

The shift in platform preferences from Facebook to more visually oriented platforms like Instagram and Snapchat indicates a preference for more engaging and interactive content. This change reflects broader global trends and suggests that Indian adolescents are not isolated in their digital behaviors, but are part of a global youth culture. Adolescents' motivations for using social media have expanded beyond mere connectivity to include content creation, information consumption, and participation in online communities. This shift signifies a deeper integration of social media into various aspects of adolescents' lives, from leisure activities to information sourcing. The pressure of continuous availability and excessive usage of social media has generated concerns regarding the adverse impacts of digital media exposure such as increased stress, anxiety, and depression among excessive users. Moreover, these findings indicate the addictive nature of social media platforms as many youths were addicted to compulsive behaviors like midnight

Table 1 Demographic data according to distinct age group

Variable	Statement	Percentage
Sex	Male	46.1
	Female	48
	Prefer not to say	5.9
Age in years	14-16	16.2
	17-19	33.8
	20-23	50
Average time spend on social media in h	< 1	19.6
	2–3	32.
	4–5	28.4
	> 5	19.1
	12	0.5

scrolling, which badly affects their mental and physical health, and they prefer online connections and communications over in-person social contact[16].

These findings explain the crippling effect of social media on adolescents' mental health and the negative implications that are associated with the comparison culture and unattainable beauty standards in online platforms[17]. Digital immersion and excessive screen time may take away time that should be spent with face-to-face socialization, physical activity, and other offline activities necessary for healthy development[18]. The data results reveal an alarming aspect of the pervasive influence of social media metrics on the mental wellbeing of adolescents. It shows that the quest for online validation and approval is a major source of stress and anxiety for young people[19]. Perhaps social media, emphasizing metrics like the number of followers, likes, and comments, brings feelings of inadequacy, comparison, and self-doubt among adolescents, who incessantly assess their worth and popularity from such measures[9,20]. Thus, the impact that social media exerts on readiness to voice thoughts and opinions by adolescents in online spaces is highlighted. Because of the fear of being judged or criticized, a barrier to self-expression emerges, which constrains people from voicing their viewpoints or makes them conform to the prevalent norms and expectations[21].

The fear of social backlash or ostracism of online reputation leads people to withhold self-expression and opinions. This is the fear of being judged on social media, acting like a pernicious factor for the mental health of adolescents because of self-censorship, social anxiety, and loss of self-confidence[22,23]. It influences adolescents to have more pro-mainstream opinions or just avoid controversial topics; limiting the number of perspectives and discourses within online communities. Indeed, 16.7% strongly agree and 28.9% agree with the opinion that this has happened to them, as shown in Figure 1H. These results show how often cyberbullying persists in digital spaces and why proactive measures against this major problem are important[24]. Cyberbullying includes all forms of harassment, intimidation, and abuse that happen through digital channels like social media platforms, messaging applications, and online forums[25]. Victims of cyberbullying often meet a list of negative repercussions, including psychological distress, social exclusion, and decreased self-esteem. That this proportion of adolescents reported having faced cyberbullying suggests that preventing and addressing online harassment should be at the heart of strategies. Combating cyberbullying requires the collaboration of schools, parents, and digital platforms to promote digital literacy, create a culture of empathy and respect, and support victims. Educating young minds and adolescents about responsible online behavior, encouraging bystanders to act, and reporting cyberbullying incidents are the major ways to make a safer digital environment. Additionally, 27% strongly agree and 37.3% agree that they have seen someone being cyberbullied on social media; this proves how social media is becoming a dangerous place for young minds and adolescents, as shown in Figure 1I. These facts, on the whole, present general evidence that pervasive effects of social media on youth demand targeted interventions that promote healthier online habits and minimize debilitating effects of the medium. These include digital health through healthy use, authentic self-expression, resilience to online pressures, and ways of countering cyberbullying in an effective manner, to keep the young generation healthy in body and mind amidst the digital era.

Development of AI-powered monitoring tools

Artificial intelligence (AI)-powered tools that monitor social media usage patterns and identify early signs of mental health issues need to be developed.

AI-driven personalized interventions

The effectiveness of AI-driven personalized mental health interventions delivered through social media platforms needs to be determined.

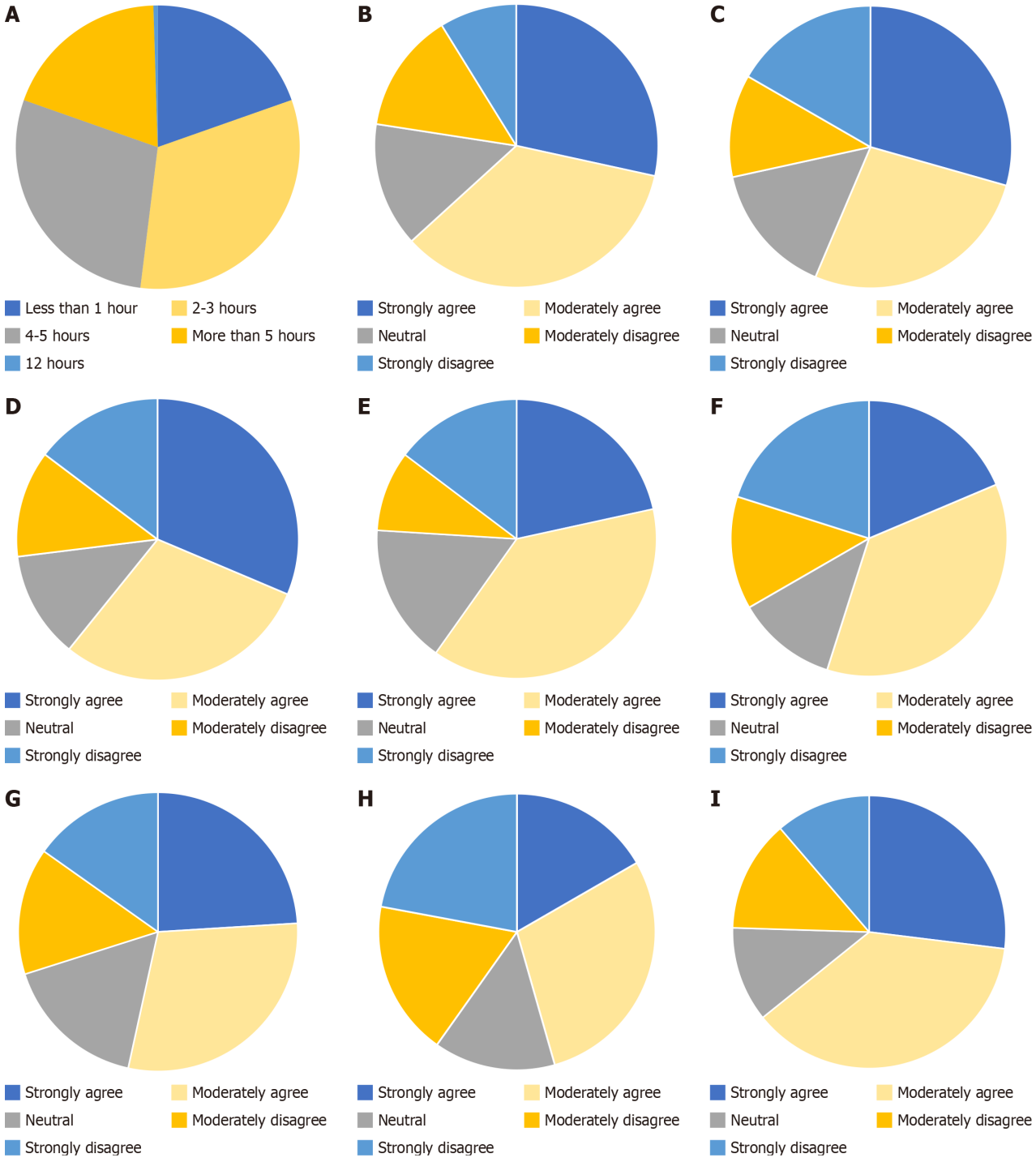

Figure 1 Data distribution. A: Time spent on social media; B: Sleep disturbance; C: Under-pressure scenario due to social media; D: Negative influence of social media on self-esteem; E: Challenging balance online and offline; F: Feeling of anxiety or stress due to followers, likes, or comments; G: Fear of being judged or criticized on social media; H: Cyberbullying on social media; I: Witness instances of cyberbullying on social media.

Sentiment analysis for early detection

Research should be conducted on the use of sentiment analysis to detect negative emotional states in social media posts and provide timely support.

AI-enhanced cyberbullying prevention

AI systems need to be developed to detect and prevent cyberbullying on social media platforms.

Virtual mental health assistants

The use of AI-powered virtual mental health assistants that provide immediate support and resources to adolescents experiencing distress should be explored.

CONCLUSION

The relationship between social media use and mental health among Indian adolescents is multifaceted. It is essential to recognize both the positive and negative aspects of social media, and to adopt strategies to mitigate potential harm while maximizing the benefits. This includes promoting digital literacy, fostering healthy online behavior, providing mental health support services, and encouraging balanced use of social media platforms. Additionally, further research is needed to understand the specific cultural and contextual factors influencing the impact of social media on the mental wellbeing of Indian adolescents.

FOOTNOTES

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SYSTEMATIC REVIEWS

Pulse oximetry in pediatric care: Balancing advantages and limitations

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Abstract

BACKGROUND

Pulse oximetry has become a cornerstone technology in healthcare, providing non-invasive monitoring of oxygen saturation levels and pulse rate. Despite its widespread use, the technology has inherent limitations and challenges that must be addressed to ensure accurate and reliable patient care.

AIM

To comprehensively evaluate the advantages, limitations, and challenges of pulse oximetry in clinical practice, as well as to propose recommendations for optimizing its use.

METHODS
A systematic literature review was conducted to identify studies related to pulse oximetry and its applications in various clinical settings. Relevant articles were selected based on predefined inclusion and exclusion criteria, and data were synthesized to provide a comprehensive overview of the topic.

RESULTS
Pulse oximetry offers numerous advantages, including non-invasiveness, real-time feedback, portability, and cost-effectiveness. However, several limitations and challenges were identified, including motion artifacts, poor peripheral perfusion, ambient light interference, and patient-specific factors such as skin pigmentation and hemoglobin variants. Recommendations for optimizing pulse oximetry use include technological advancements, education and training initiatives, quality assurance protocols, and interdisciplinary collaboration.

CONCLUSION
Pulse oximetry is crucial in modern healthcare, offering invaluable insights into patients' oxygenation status. Despite its limitations, pulse oximetry remains an indispensable tool for monitoring patients in diverse clinical settings. By implementing the recommendations outlined in this review, healthcare providers can enhance the effectiveness, accessibility, and safety of pulse oximetry monitoring, ultimately improving patient outcomes and quality of care.

Key Words: Pulse oximetry; Oxygen saturation; Monitoring; Advantages; Limitations; Challenges; Recommendations; Clinical practice; Non-invasive; Children

Core Tip: For clinicians utilizing pulse oximetry in practice, it's essential to remember several key considerations. Firstly, ensure proper sensor placement on well-perfused areas. Minimize motion artifacts by securing the sensor snugly but not too tightly. Establish baseline oxygen saturation levels and consider patient-specific factors like age and medical conditions. Continuous monitoring is crucial in high-risk patients. Regularly maintain and calibrate equipment, replacing sensors as needed. Educate caregivers on the importance of pulse oximetry and proper usage. Lastly, readings should be accurately documented in patient records. By adhering to these core tips, healthcare providers can optimize the effectiveness of pulse oximetry monitoring and enhance patient care.

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INTRODUCTION

Pulse oximetry, a cornerstone in modern pediatric healthcare, swiftly and noninvasively offers clinicians invaluable insights into a patient's oxygenation status and is considered the "fifth vital sign"[1]. In the pediatric setting, where oxygen saturation (SpO_2) levels hold profound implications for respiratory function and overall well-being, pulse oximetry is a vital tool in the armamentarium of healthcare providers. It plays a crucial role in assessing respiratory function and oxygenation status in children of all ages, from neonates to adolescents[2]. This technology has revolutionized the management of pediatric patients by providing real-time data on oxygen levels, enabling timely intervention and improved patient outcomes. It is used in many pediatric conditions, such as monitoring respiratory status, assessment of oxygenation during procedures, screening for congenital heart defects, monitoring sleep-disordered breathing, and home monitoring for conditions that need more than usual care[3]. Pulse oximetry operates on the spectrophotometry principle, which measures light absorption by oxygenated and deoxygenated hemoglobin molecules in the blood. The pulse oximeter emits two wavelengths of light, typically red and infrared, through a translucent part of the patient's body, such as a finger, toe, or earlobe[4]. Oxygenated hemoglobin absorbs more infrared light, while deoxygenated hemoglobin absorbs more red light. By analyzing the ratio of absorbed light at these wavelengths, the pulse oximeter calculates the SpO_2 level, expressed as a percentage ($\%SpO_2$)[5].

However, as with any diagnostic modality, understanding its advantages and limitations is paramount to its effective utilization and interpretation. Understanding the technology and its limitations is vital to avoid unnecessary testing due to erroneous readings[6]. This review article is not just a theoretical exploration of pulse oximetry in pediatric care. It is a practical guide that aims to equip clinicians with the knowledge to utilize and interpret pulse oximetry in their daily practice effectively. This article provides a nuanced understanding of its utility in pediatric practice by comprehensively exploring pulse oximetry principles, clinical applications across various pediatric conditions, and inherent advantages in

enhancing patient care. Moreover, this systematic review critically examines the limitations and challenges associated with pulse oximetry use in pediatrics, including factors that may impact the accuracy and reliability of readings. By addressing these considerations, clinicians can confidently navigate pulse oximetry interpretation complexities, ensuring optimal patient management and clinical decision-making. Ultimately, this systematic review underscores the pivotal role of pulse oximetry in pediatric healthcare while emphasizing the importance of maintaining a discerning approach that acknowledges its strengths and limitations. By striking this delicate balance, clinicians can harness the full potential of pulse oximetry to improve outcomes and enhance the quality of care for pediatric patients worldwide.

MATERIALS AND METHODS

Literature searching

In conducting this systematic review, a thorough search of electronic databases, including PubMed/MEDLINE, Embase, Scopus, and Google Scholar, was conducted from inception to May 11, 2024, employing a combination of Medical Subject Headings terms and keywords relevant to pulse oximetry monitoring in pediatric patients. Additionally, reference lists of pertinent articles and reviews were manually scrutinized to identify any additional relevant studies. Studies meeting the following criteria were included: (1) Focus on pulse oximetry monitoring in pediatric populations; (2) Address the advantages, limitations, challenges, or guidelines for effective use of pulse oximetry; (3) Published in English; and (4) Available as full-text articles. Two independent reviewers screened the titles and abstracts of identified articles, with subsequent full-text reviews for potentially eligible studies.

Data resources

Data from included studies were extracted using a standardized form, encompassing study characteristics, participant demographics, intervention or exposure details, outcomes assessed, and key findings. The narrative synthesis approach was employed to summarize findings, identify themes, and organize data descriptively. Quality assessment of included studies was conducted using appropriate tools based on study design, with any limitations or biases discussed within the review.

RESULTS

The systematic review identified 231 relevant studies meeting the inclusion criteria. Figure 1 shows the flow chart of the article (106 research articles, 86 review articles, 8 systematic reviews and meta-analyses, 10 case reports, 9 letters to the editors, 6 guidelines, 3 editorials, and 3 books). These studies encompassed a range of topics related to pulse oximetry monitoring in pediatric patients, including its advantages, limitations, challenges, and guidelines for effective use. The results were categorized into several key themes to facilitate comprehensive analysis and synthesis.

Advantages of pulse oximetry

The literature highlighted pulse oximetry's advantages, including its noninvasive nature, real-time feedback on SpO_2 levels and pulse rate, early detection of hypoxemia, suitability for various medical procedures, portability and versatility, user-friendliness, continuous monitoring capabilities, integration into telemedicine platforms, and cost-effectiveness.

limitations and challenges

Conversely, limitations and challenges identified encompassed motion artifacts, poor peripheral perfusion, ambient light interference, nail polish or acrylic nails, skin pigmentation, intravascular dyes, hemoglobin variants, carbon monoxide (CO) poisoning, changes in altitude and barometric pressure, delayed measurement compared to arterial blood gas analysis, false alarms, and alarm fatigue syndrome.

Guidelines for effective use

Guidelines for effective pulse oximetry use in pediatric patients emphasized proper sensor placement, establishment of baseline SpO_2 levels, continuous monitoring, consideration of patient factors, regular equipment maintenance, alternative sensor sites for patients with poor perfusion, minimizing patient movement, staff education, and accurate documentation. Overall, the results underscored the importance of pulse oximetry monitoring in pediatric care while highlighting the need to address its limitations and challenges to optimize its effectiveness.

DISCUSSION

Historical perspective

The invention of pulse oximetry reflects a success story of the continuous and successive collaboration of scientists spanning over a century and a half. In the mid-19th century, German scientists like Friedrich Ludwig Hunefeld (1840) from Germany and Felix Hoppe-Seyler (1864) began unraveling the mysteries of blood oxygenation[7]. Their discoveries laid the groundwork for the Irish-English mathematician and physicist George Gabriel Stokes in 1864 to investigate how

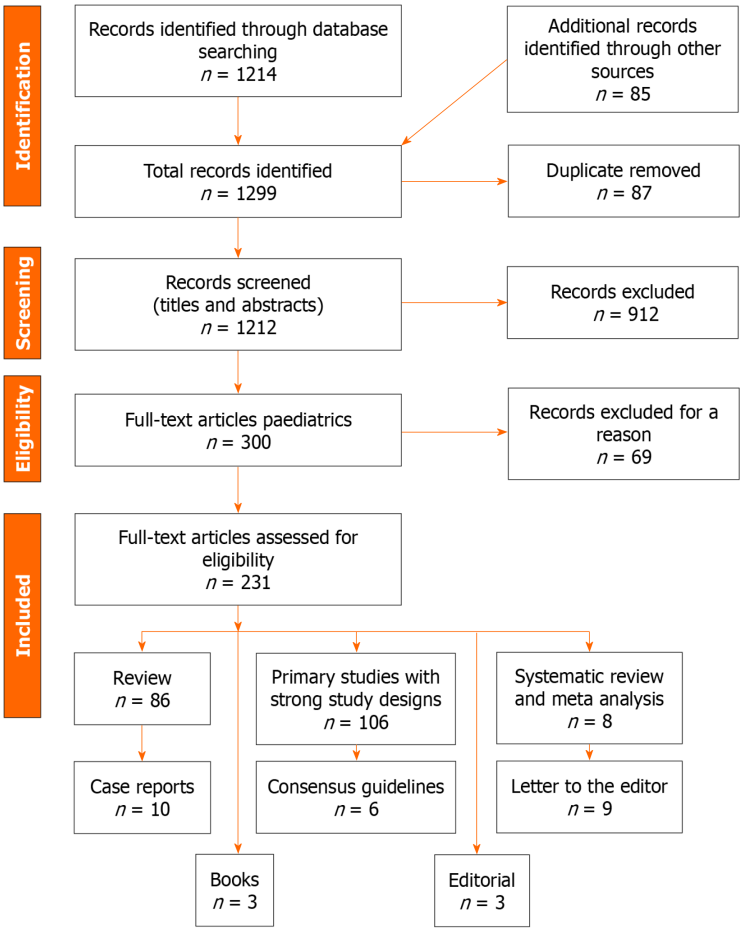

Figure 1 Flow chart of the study.

oxygen interacts with hemoglobin in the bloodstream. Through experiments, Stokes and Hoppe-Seyler determined that hemoglobin binds to oxygen, leading to changes in blood color[8]. Despite this breakthrough, measuring blood oxygen levels remained a challenge until the development of the modern pulse oximeter, which revolutionized medical monitoring.

In 1935, German physician Karl Matthes developed a rudimentary pulse oximetry device to measure blood oxygenation through light. This device, attached to a patient's earlobe, detects the presence of oxygenated and deoxygenated hemoglobin, which easily shines through a patient's blood without taking a blood sample. The device detected oxygenated and deoxygenated hemoglobin using green and red-light wavelengths. Matthes later found red infrared light to be more effective. Despite its innovation, Matthes's device was challenging to calibrate and provided saturation trends rather than precise values[9]. In the 1940s, American inventor and physiologist Glenn Millikan created the first practical and portable oximeter, primarily for World War II pilots flying at high altitudes. This device used a technique called "ear oximetry", which involved placing a sensor on the earlobe to measure SpO_2 in arterial blood. However, Millikan's device could only measure static oxygen levels without advanced technology, offering a limited understanding of the pilot's condition. Millikan's original oximeter design lacked the crucial element of ensuring sufficient blood volume in the ear[7]. Recognizing this oversight, Dr Earl Wood of the Mayo Clinic substantially enhanced the device between 1948 and 1949. He ingeniously devised a method using pneumatic pressure to increase blood flow into the ear, improving accuracy and reliability for real-time readings. Wood's innovative earpiece was a key component of his advanced oximetry system, which gained prominence through advertising in the 1960s[10].

In 1964, surgeon Robert Shaw from San Francisco enhanced the oximeter sensor by incorporating additional 8 wave lengths of light, surpassing the two utilized by Matthes's original design. Shaw's innovation expanded the device's capability with eight light wave lengths, enabling more comprehensive data collection for calculating oxygenated blood levels[11]. This advancement marked the creation of the first ear oximeter, which provided absolute readings. In 1970, Hewlett Packard introduced the first commercial oximeter based on Shaw's design. Despite being expensive and cumbersome, Shaw's oximeter demonstrated the viability of pulse oximetry principles for commercialization. Hewlett Packard's commercialization of the eight wave length ear oximeter paved the way for the availability of pulse oximetry devices in medical settings[12].

In the 1960s, Japanese scientist Takuo Aoyagi discovered that the ratio of red to infrared light absorption could be used to estimate arterial blood SpO_2. Between 1972 and 1974, while investigating methods to enhance arterial blood flow measurement devices, he uncovered a breakthrough relevant to pulse oximetry. He realized that arterial blood oxygenation levels could be determined by monitoring the heart's pulse rate. Aoyagi's principle led to the development

of the Oximeter OLV-5100 by Nihon Kohden in 1975, recognized as the world's first modern ear pulse oximeter utilizing pulse oximetry based on his discovery[13]. Despite initial commercial setbacks, Aoyagi's insight eventually gained recognition. Minolta launched the first fingertip pulse oximeter, OXIMET Met 1471, in 1977, followed by pulse oximeters from Nellcor and Biox Technology in the 1980s. By 1987, Aoyagi was celebrated as the inventor of modern pulse oximetry devices, advocating for non-invasive continuous monitoring technology in patient care. This principle has been embraced by modern pulse oximetry devices, which are now efficient and painless for patients, reflecting Aoyagi's visionary approach to healthcare technology[14].

Over the years, pulse oximetry technology has continued to evolve. Early pulse oximeters were large, bulky, and primarily used in operating rooms and critical care settings. Technology advancements led to the miniaturization of pulse oximeters, making them more portable and suitable for use outside hospital settings. This allowed for greater flexibility in monitoring pediatric patients, both in hospitals and at home[15]. One of the key advancements in pediatric pulse oximetry was the development of sensors specifically designed to be used for infants and children. These sensors are smaller and often include adhesive attachments to secure them to a child's finger, toe, or other appropriate site. Continuous improvement in sensor technology, sophisticated algorithms, and signal processing techniques have increased pulse oximeters' accuracy and reliability, even in challenging pediatric populations with low perfusion or motion artifacts[16]. As a standard tool for assessing oxygenation and respiratory function across diverse medical conditions, pulse oximeters seamlessly integrate into patient monitoring systems, facilitating continuous tracking alongside vital signs like heart and respiratory rates. This integration heightens patient safety and enables early detection of respiratory issues in patients with a wide range of medical conditions. With the rise of telemedicine and remote patient monitoring technologies, pulse oximeters have assumed greater significance in pediatric care. Parents and caregivers can now monitor children's SpO_2 levels at home, guided by healthcare providers, facilitating timely interventions as needed [17]. Figure 2 shows the timeline for the discovery and invention of pulse oximetry.

Principles of pulse oximetry

Pulse oximetry is a non-invasive method for monitoring blood SpO_2 by measuring the ratio between oxygenated and deoxygenated hemoglobin. It operates on a sophisticated understanding of hemoglobin's behavior in response to oxygen and light. Hemoglobin is a specific blood protein responsible for carrying oxygen; every gram of hemoglobin can carry 1.34 mL of oxygen[18]. Hemoglobin exhibits positive cooperativity. When one oxygen molecule binds to one of hemoglobin's four binding sites, it increases the affinity for oxygen in the remaining sites. This property leads to a sigmoidal oxygen dissociation curve, facilitating rapid lung oxygen loading and efficient offloading in oxygen-deficient tissues. Hemoglobin exists in two forms: Taut (T), the deoxygenated form with low oxygen affinity, and relaxed (R), the oxygenated form with high oxygen affinity[19]. These configurations result in different electromagnetic absorption properties, influencing how hemoglobin interacts with light. Pulse oximeters capitalize on these differences in light absorption between the T and R configurations[20].

The technique involves shining light through a translucent part of the body, typically a fingertip or earlobe, and measuring the amount of light absorbed by oxygenated and deoxygenated hemoglobin (Figure 3). Pulse oximeters utilize electronic processors and light-emitting diodes (LEDs) that emit light at specific wavelengths, typically red (with a wave length of 660 nm) and infrared (with a wavelength of 940 nm)[21]. These wavelengths are chosen because they correspond to the absorption peaks of oxygenated and deoxygenated hemoglobin. Oxygenated hemoglobin absorbs more infrared light and allows more red light to pass through, while deoxygenated hemoglobin absorbs more red light and allows more infrared light to pass through. The LEDs turn on and off quickly, switching between red and infrared light about thirty times every second[20]. The oximeter measures how much light goes through (doesn't get absorbed). These measurements change over time because there's more blood in the arteries when the heart beats. The oximeter shows how much of the light is from the arteries by comparing the lowest and highest light readings. This helps it measure just the arterial blood. The processor then calculates the red-to-infrared light ratio, which shows how much oxygen is in the blood[22]. Following the Beer-Lambert law, the processor uses this ratio and a special table to determine the SpO_2 level based on how much light gets absorbed. This law describes the relationship between the concentration of a substance in a medium and the amount of light absorbed by that substance[23]. In pulse oximetry, the absorption of light by hemoglobin is proportional to its concentration in the blood. By measuring the absorption of light at specific wavelengths, the pulse oximeter can determine the ratio of oxygenated hemoglobin to total hemoglobin and calculate the SpO_2 level[24]. Pulse oximeters come in two main types: Transmittance devices and reflectance devices. Transmittance pulse oximeters, the more common type, operate by transmitting light through a body part like a fingertip or ear. The amount of oxygen in the blood affects how much light is absorbed by the tissue. A light detector on the opposite side of the probe measures the unabsorbed light, and a microprocessor computes the blood SpO_2[25]. Reflectance pulse oximeters, on the other hand, are placed on the skin surface and measure the light reflected off the tissues rather than passing through them. This reflected light's absorption is then used to determine SpO_2 levels. It's worth noting that designing reflectance devices to perform effectively is inherently more challenging[26].

The pulsatile nature of arterial blood flow allows for the differentiation between arterial and venous blood. During each cardiac cycle, arterial blood volume increases, leading to a temporary increase in the amount of light absorbed by the pulsatile arterial blood[27]. By detecting these fluctuations in light absorption, pulse oximeters can isolate arterial blood and provide accurate SpO_2 readings. The raw light absorption data collected by the pulse oximeter undergoes sophisticated signal processing algorithms to filter out noise and motion artifacts[28]. These algorithms analyze the amplitude and frequency of the pulsatile signal to extract SpO_2 information accurately. These algorithms are formulated based on SaO_2 measurements in healthy volunteering individuals who inhale various oxygen concentration blends, and typically, each manufacturer develops their specific algorithms. Signal processing techniques are crucial for obtaining reliable measurements, particularly in challenging conditions such as low perfusion or motion interference[29]. The SpO_2 value

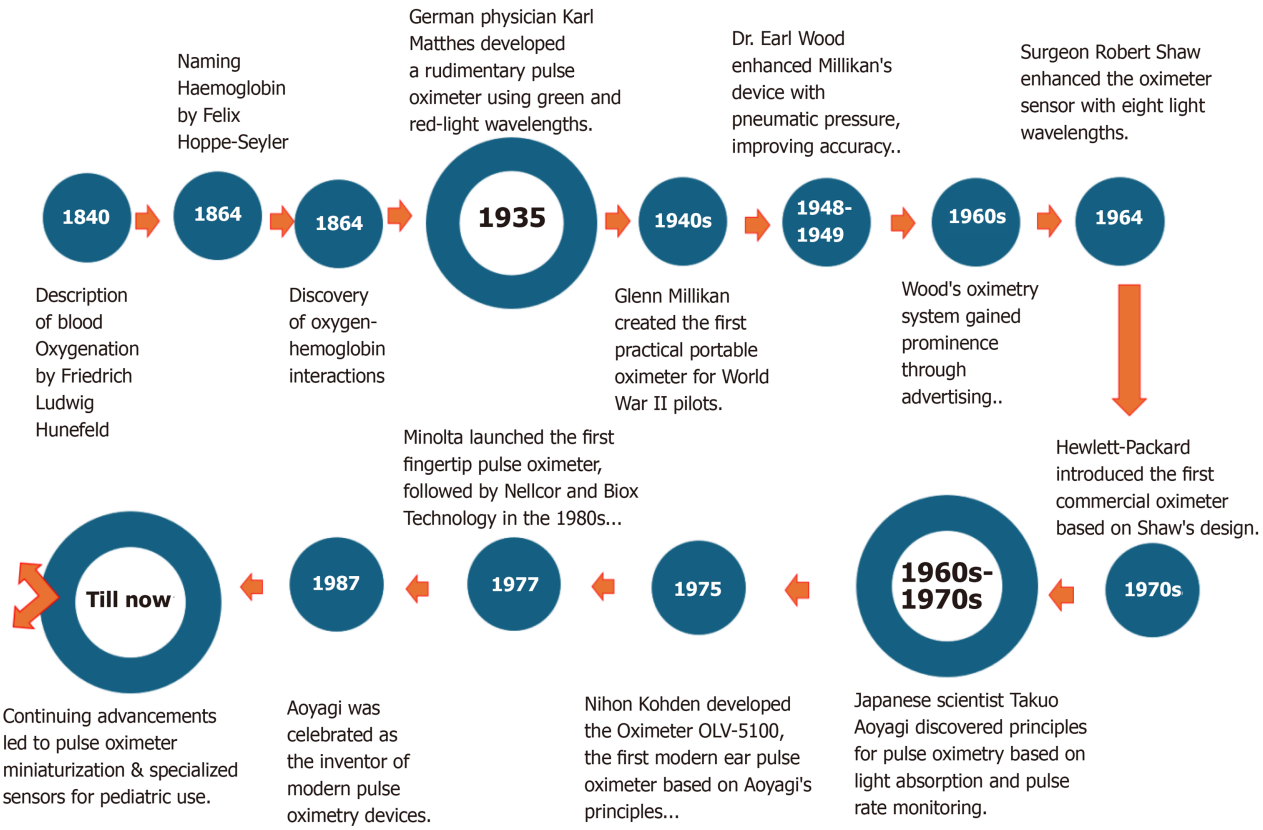

Figure 2 The Timeline for the discovery and invention of pulse oximetry.

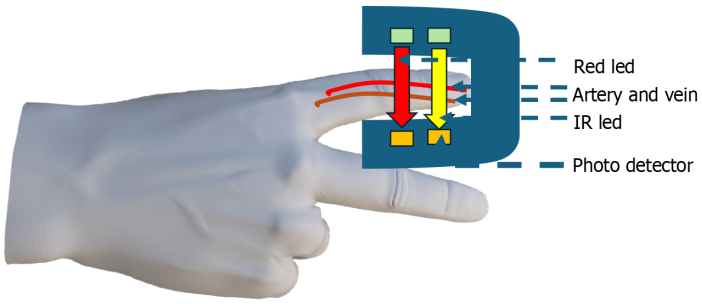

Figure 3 The pulse oximeter idea. The oximeter has a light-emitting diode on one end, and there is a phototransistor on the opposite end of the oximeter. Light-emitting diodes alternately emits red and infrared light, and part of the light will be absorbed after it passes through red blood cells in the blood vessels of the finger.

shown reflects the average of readings taken over the preceding 3 to 6 seconds, while the information is refreshed at intervals of 0.5 to 1.0 seconds. However, pulse oximeters require periodic calibration to ensure accuracy. Calibration involves comparing the oximeter's readings to a reference standard and making adjustments as necessary[30]. Factors such as ambient light, skin pigmentation, and device performance can affect the accuracy of pulse oximetry measurements, highlighting the importance of regular calibration procedures[31]. Therefore, pulse oximetry operates based on three main principles: Difference in light absorption by oxygenated and deoxygenated hemoglobin, pulse modulation of arterial blood flow, and sophisticated signal processing techniques. Using these three principles, pulse oximeters provide clinicians with real-time information about a patient's oxygenation status, facilitating timely interventions and improving patient care[1]. Clinicians should realize that when there is decreased hemoglobin concentration, such as in anemia, there is a decrease in total O_2 content of the blood but no change in the O_2 saturation; hence, oximetry is not an effective test to evaluate oxygen status in the presence of anemia or polycythemia[32].

Special considerations of pulse oximetry in pediatric age

Several considerations are specific to pulse oximetry in pediatric patients. Children have smaller fingers and earlobes than adults. Therefore, specialized sensors designed for pediatric use are necessary to ensure proper fit and accurate readings. These sensors are often smaller in size and may include adhesive attachments to secure them to the child's finger, toe, or other appropriate site[33]. Children, especially infants and toddlers, may be more prone to movement

during monitoring, which can introduce motion artifacts and affect the accuracy of pulse oximetry readings[34]. Careful positioning of the sensor and minimizing patient movement can help mitigate this issue. Skin pigmentation can vary widely among children, which may affect the accuracy of pulse oximetry readings. Darker skin tones can absorb more light, potentially leading to lower readings. Healthcare providers should be aware of this factor and consider appropriate adjustments or alternative monitoring sites if necessary[35].

Pediatric patients, particularly neonates and infants, may have lower peripheral perfusion compared to adults, making it challenging to obtain reliable pulse oximetry readings. In such cases, choosing a monitoring site with better perfusion or using pulse oximetry in conjunction with clinical assessment can help ensure accurate monitoring[36]. Pediatric pulse oximeters may require specific calibration settings tailored to the age and size of the patient population they are intended for. Healthcare providers should ensure that pulse oximeters used in pediatric settings are appropriately calibrated to obtain accurate readings[37]. When interpreting pulse oximetry readings in pediatric patients, healthcare providers should consider factors such as the child's age, clinical condition, and baseline SpO_2 levels[38]. Contextualizing the SpO_2 readings within the overall clinical picture is essential for accurate assessment and appropriate intervention. Although pulse oximetry is a valuable tool for assessing oxygenation, it has many considerations in pediatric patients[39]. Therefore, healthcare providers must be mindful of the unique considerations associated with monitoring children of varying ages and sizes. Attention to sensor size and placement, motion artifacts, skin pigmentation, perfusion, calibration, and clinical interpretation is essential for obtaining accurate and reliable pulse oximetry readings in pediatric settings. Table 1 shows some of the challenges that may face using pulse oximetry in children and how to overcome them.

Preferred placement sites for pulse oximetry probe in pediatric age

For accurate pulse oximetry readings in children, choosing the right probe placement site is crucial. In neonates, the preferable placement sites are palm of the hand followed by the sole of the foot if a reading on the palm is difficult. Some studies suggest alternative sites like the wrist or ankle in neonates, but the palm and sole are generally preferred due to better accuracy. In infants and children, the finger (index finger is the preferable one, followed by the thumb, middle finger, and the great toe), nose, earlobe, and forehead are preferable sites for pulse oximetry probe placement[40,41]. These areas have a higher vascular density than other regions, such as the chest wall, making them suitable for accurate SpO_2 measurements. The choice of probe placement site depends on the clinical circumstances, and some trial and error may be necessary to find the optimal site for placement foreach patient[1]. For example, in patients with hypotension orvasoconstriction, the ear and forehead may be more reliable as these areas are less likely to have vasoconstriction than the fingers in response to catecholamines. In hypothermia, where secondary vasoconstriction occurs, the forehead probe is more reliable than the finger probe[42,43].

There are two main types of pulse oximeter probes used in pediatric patients: Reusable clip probes and single-patient adhesive probes[1]. Reusable clip probes are advantageous for their rapid deployment, ease of sampling different body sites, and cost-effectiveness, especially in outpatient settings where multiple patients are monitored sequentially with one probe[44]. On the other hand, single-patient adhesive probes offer advantages such as potentially lower transmission of infections, secure placement in patients with excessive movement, and the ability to monitor sites other than the fingers, nose, ears, and forehead. These adhesive probes are particularly useful for continuous monitoring of SpO_2[45].

It is important to ensure that the probe is placed correctly on a well-perfused site. The two parts of the probe (the light emitter and the light sensor) need to be opposite each other to get an accurate reading. The probe should fit snugly but comfortably on the chosen site, avoiding excessive pressure that could restrict blood flow. In addition, the probe should not be placed on a constricted area, such as a finger with a band age or an infant's mitten[46]. If the signal quality is poor, try shining a light on the fingertip to improve signal strength. Minimize movement during measurement to prevent interference with the readings. When using the foot for neonates or infants, secure the probe to prevent dislodging[47]. Commercially available wraps or securing methods designed for pulse oximetry on the foot can be helpful. Even after selecting the appropriate probe type, false SpO_2 readings may still occur due to various factors and medical conditions [48].

For all age groups, it's important to follow general tips to ensure accurate pulse oximetry readings. When placing the probe, ensure it fits snugly but comfortably on the chosen site, avoiding excessive pressure that could restrict blood flow. If the signal quality is poor, try shining a light on the fingertip to improve signal strength[49]. Minimize movement during measurement to prevent interference with the readings. These tips and careful consideration of clinical circumstances help optimize pulse oximetry monitoring in pediatric patients and individuals of all ages (Table 2).

Clinical application and utilization of pulse oximetry in pediatric diagnosis and monitoring

Pulse oximetry is crucial in pediatric diagnosis and monitoring, offering a non-invasive and real-time assessment of SpO_2 levels in children. This technology has become indispensable in various clinical settings, from neonatal intensive care units (NICUs) to general pediatric wards, emergency departments, and outpatient clinics (Table 3).

Fetal and neonatal care

In neonatal care, pulse oximetry can continuously monitor SpO_2 during delivery in preterm infants, term neonates, and those with respiratory distress syndrome (RDS), congenital heart defects, or other respiratory conditions. Early detection of hypoxemia allows for prompt intervention, such as supplemental oxygen therapy or adjustments in ventilatory support, to optimize oxygenation and prevent hypoxic injury[50].

Fetal pulse oximetry: Fetal pulse oximetry, a technique healthcare providers use to monitor SpO_2 levels in a fetus's blood during labor and delivery, is crucial in assessing the fetus's well-being. It provides real-time information about fetal oxygenation status, allowing for prompt intervention if necessary[51]. A specialized sensor is placed on the fetus's scalp

Table 1 The challenges facing using pulse oximetry in children and how to overcome them

Problem	Suggested solution
Children have smaller fingers and earlobes	Use specialized sensors designed for pediatric use. These are smaller in size and may include adhesive attachments to secure them properly on the child's finger, toe, or other appropriate site
Increased risk of movement during monitoring	Ensure careful positioning of the sensor and minimize patient movement during measurement to prevent motion artifacts that could affect the accuracy of pulse oximetry readings
Variation in skin pigmentation	Be aware that darker skin tones can absorb more light, potentially leading to lower readings. If necessary, consider appropriate adjustments or alternative monitoring sites to account for skin pigmentation differences
Lower peripheral perfusion in pediatric patients	Choose a monitoring site with better perfusion or use pulse oximetry in conjunction with clinical assessment to ensure accurate monitoring, especially in neonates and infants
Specific calibration settings for pediatric oximeters	Ensure that pulse oximeters used in pediatric settings are appropriately calibrated to obtain accurate readings, with calibration settings tailored to the age and size of the patient population
Consideration of clinical factors in interpretation	Contextualize SpO_2 readings within the overall clinical picture, considering the child's age, clinical condition, and baseline oxygen saturation levels for accurate assessment and appropriate intervention

SpO_2: Oxygen saturation.

Table 2 The preferred placement sites for pulse oximeter probes in neonates, infants, and children

Age group	Preferred placement sites
Neonates	The palm of the hand (preferred)
	Sole of the foot (if palm reading is difficult)
	Wrist
	Ankle
Infants	Finger (index finger preferred, followed by thumb, middle finger, and great toe), nose, earlobe, forehead
Children	Finger (index finger preferred, followed by thumb, middle finger, and great toe), nose, earlobe, forehead

or another appropriate location within the birth canal to measure oxygen levels in the fetus's blood. During labor, the fetus depends on a constant supply of oxygen from the mother's blood through the placenta[52]. Any complications during labor, such as umbilical cord compression, placental insufficiency, or prolonged labor, can lead to fetal distress or hypoxia, which can compromise oxygen delivery to the fetus. Fetal pulse oximetry, with its ability to detect changes in fetal oxygenation, enables healthcare providers to monitor oxygen levels continuously and take immediate action[53].

Fetal pulse oximetry is a valuable tool that can be used in conjunction with other fetal monitoring methods, such as electronic fetal heart rate monitoring, to assess the overall condition of the fetus during labor. This combined approach allows healthcare providers to make timely decisions regarding interventions, such as administering oxygen to the mother, changing her position, or proceeding with a cesarean delivery if fetal distress is detected[54]. However, it is important to note that fetal pulse oximetry has limitations. It may not be suitable for all pregnancies or labor situations due to factors such as the position of the fetus, the presence of meconium, and certain maternal conditions, which may affect the accuracy and reliability of the readings. Additionally, fetal pulse oximetry is not routinely used in all labor and delivery settings[55]. It may be reserved for cases where fetal well-being is questioned or other inconclusive monitoring methods. However, the clinical effectiveness of fetal pulse oximetry is still a subject of debate[56]. For example, Bloom *et al*[57] discovered that monitoring fetal SpO_2 does not correlate with decreased cesarean delivery rates or improved neonatal outcomes. On the other hand, East *et al*[58] found that employing fetal pulse oximetry to assess fetal well-being during labor led to a statistically significant decrease in operative interventions for non-reassuring fetal status compared to solely utilizing conventional cardiotocograph monitoring. This decrease occurred without any significant variance in neonatal outcomes. However, Peek *et al*[59] claimed that Bloom *et al*[57] failure to interpret the results of fetal pulse oximetry may be the cause of their findings. He also expected a higher rate of cesarean sections when using fetal pulse oximetry. He suggested having clear guidelines for intrapartum use of fetal pulse oximetry. Despite these limitations, fetal pulse oximetry remains a valuable tool in the array of fetal monitoring techniques, aiding in the comprehensive assessment of fetal health during labor and delivery[52].

Newborn screening for critical congenital heart disease: Pulse oximetry screening is recommended and integrated into routine newborn screening protocols to detect critical congenital heart disease (CCHD) in many healthcare facilities worldwide. Newborns undergo pulse oximetry screening at 24 to 48 hours of life or before discharge from the birthing facility to detect potentially life-threatening heart defects early[60]. The screening involves comparing the SpO_2 readings between the upper and lower extremities to identify significant differences that may indicate underlying heart defects. Specific cutoff values for SpO_2 are used to interpret the screening results. Pulse oximetry readings in neonates can

Table 3 Clinical indications of pulse oximetry in neonates, infants, and children

Clinical application	Description
Neonatal indications	
Fetal and neonatal care	Pulse oximetry can continuously monitor oxygen saturation during delivery and in neonates with respiratory distress syndrome, congenital heart defects, or other respiratory conditions
Newborn screening for CCHD	Pulse oximetry screening detects CCHD in newborns by comparing SpO_2 readings between the upper and lower extremities, indicating the presence of heart defects
RDS	Pulse oximetry assesses oxygenation and monitors respiratory status in preterm infants with RDS, guiding oxygen therapy and evaluating response to treatment
BPD	Pulse oximetry monitors oxygenation and respiratory status in infants with BPD, guiding oxygen therapy, detecting complications, and assessing response to interventions
Apnea of prematurity	Pulse oximetry detects oxygen desaturation events associated with apnea in premature infants, allowing for prompt intervention and monitoring of respiratory status
PPHN	Pulse oximetry assesses oxygenation and monitors response to treatment in infants with PPHN, guiding oxygen therapy and evaluating the effectiveness of interventions
Neonatal methemoglobinemia	Pulse oximetry may underestimate O_2 saturation in neonatal methemoglobinemia, prompting further investigation and monitoring of response to treatment
Postoperative care	Pulse oximetry monitors O_2 saturation levels in neonates after surgery, facilitating early detection of respiratory compromise & guiding interventions for optimal recovery
Infancy and childhood indications	
Children with respiratory illnesses	Pulse oximetry is essential for managing respiratory illnesses in children. It aids in assessing oxygen saturation levels and the severity of the condition, monitoring oxygen therapy effectiveness, tracking treatment response, and guiding clinical decisions. It provides valuable insights into conditions like pneumonia, bronchiolitis, and asthma exacerbations
Assessment of circulatory status	Pulse oximetry is significant in evaluating circulatory status in children. It allows for the early detection of circulatory compromise and guides interventions to restore perfusion and prevent organ dysfunction. It also provides real-time feedback on treatment effectiveness, particularly in cases of shock or hypovolemia
Monitoring during anesthesia and sedation	Pulse oximetry is crucial for monitoring children during anesthesia and sedation. It enables continuous assessment of SpO_2 levels and pulse rate. It aids in the early detection of respiratory depression, airway obstruction, and hypoxemia, ensuring patient safety during procedures requiring anesthesia or sedation
Management of sleep disorders	Pulse oximetry is instrumental in managing childhood sleep disorders such as OSA or central sleep apnea. It facilitates screening, assesses severity, monitors treatment effectiveness, and detects complications. It also enables home monitoring, leading to early treatment failure or disease progression detection
Evaluation of trauma and critical care	Pulse oximetry assists in the rapid assessment of oxygenation status in children with trauma or critical illness, aiding in the early detection of hypoxemia and respiratory compromise. It provides continuous monitoring during critical care interventions and facilitates timely escalation of care
Home monitoring	Pulse oximetry is valuable for monitoring various childhood disorders at home, including respiratory conditions, congenital heart diseases, neurological disorders, and neonatal complications. It enables early detection of abnormalities, prompts medical attention, and enhances accessibility to healthcare services when integrated with telemedicine technologies

BPD: Bronchopulmonary dysplasia; CCHD: Critical congenital heart disease; OSA: Obstructive sleep apnea; PPHN: Persistent pulmonary hypertension of the newborn; RDS: Respiratory distress syndrome; SpO_2: Oxygen saturation.

indicate the presence of CCHD through several key indicators[61]. By measuring SpO_2 levels simultaneously in the right hand and foot, pulse oximetry can reveal significant differences in saturation between the upper and lower extremities, suggesting impaired oxygenation or cardiac shunting characteristic of CCHD[62]. Additionally, low SpO_2 levels, reflected by SpO_2 readings below the normal range, may signify hypoxemia associated with certain types of CCHD. Clinical cyanosis, coupled with low SpO_2 readings, further supports the diagnosis of severe hypoxemia in neonates with critical heart defects[63].

A hyperoxia-hyperventilation test can differentiate the cardiac cause of central cyanosis from the pulmonary cause in a sick newborn. This test typically involves a series of steps. Initially, an arterial blood gas sample is obtained while the neonate is breathing room air to establish baseline oxygenation levels. Subsequently, the patient is administered 100% oxygen (FiO_2) for a duration of 10 minutes[64]. A repeat arterial blood gas is then performed to evaluate the response to oxygen therapy, specifically looking for an increase in the partial pressure of oxygen (PaO_2) to greater than 150 mmHg. If the hypoxia is attributed to a respiratory cause, such as RDS, the PaO_2 is expected to rise above the threshold of 150 mmHg with supplemental oxygen. However, in cases where hypoxia is secondary to a congenital cardiac lesion, such as a right-to-left cardiac shunt, the PaO_2 may not significantly increase despite high levels of supplemental oxygen[65]. Alternatively, many physicians use pulse oximetry to monitor SpO_2 levels before and after administering 10 minutes of 100% FiO_2. If, after this period, the SpO_2 remains below a certain threshold (typically 95%, although some references suggest 85%), it suggests that central cyanosis is likely due to an intracardiac shunt. This sequential evaluation aids in distin-

guishing between respiratory and cardiac causes of neonatal hypoxia, facilitating appropriate management and intervention[66].

Pulse oximetry can help the clinician expect the presence of ductal-dependent lesions in the neonates. Pulse oximetry measures SpO_2 at two different sites: Pre-ductal (typically the right hand) and post-ductal (either foot). In normal circulation, there is a minor difference in SpO_2 between these two sites due to the mixing of oxygenated and deoxygenated blood in the systemic circulation[67]. However, in ductal-dependent CCHD, this difference can be significant. In ductal-dependent lesions, such as hypoplastic left heart syndrome or critical aortic stenosis, oxygenated blood from the placenta preferentially flows through the patent ductus arteriosus to reach the descending aorta[68]. As a result, SpO_2 is higher in the pre-ductal site (right hand) compared to the post-ductal site (lower extremities)[69]. Conversely, the lower extremities receive deoxygenated blood, leading to lower SpO_2 levels post-ductal. This discrepancy in SpO_2 between the pre-ductal and post-ductal sites, known as "differential cyanosis", is highly suggestive of ductal-dependent CCHD[70]. Infants with ductal-dependent lesions may present with cyanosis and hypoxemia due to inadequate oxygen delivery to the body. Pulse oximetry readings may reveal lower SpO_2 levels in the post-ductal site, reflecting impaired systemic perfusion and oxygenation[71].

In the transposition of the great arteries, the aorta and pulmonary artery are switched, causing oxygen-rich blood to be pumped back to the lungs instead of the body. This results in cyanosis and hypoxemia shortly after birth. Pulse oximetry screening in newborns can detect lower SpO_2 levels, often showing a significant difference in saturation between the upper and lower extremities. This discrepancy alerts healthcare providers to the possibility of transposition of the great arteries or other forms of CCHD, prompting further diagnostic evaluation and timely intervention[72]. Tetralogy of Fallot (TOF) is a congenital heart defect characterized by four abnormalities in the heart's structure, including a ventricular septal defect, pulmonary stenosis, overriding aorta, and right ventricular hypertrophy. In infants with TOF, SpO_2 levels may be lower than normal due to decreased pulmonary blood flow and the mixing of oxygenated and deoxygenated blood[73]. Pulse oximetry screening can detect hypoxemia and cyanosis, indicating inadequate blood oxygenation. Additionally, pulse oximetry readings may reveal SpO_2 discrepancies between the upper and lower extremities, reflecting the presence of a significant shunt associated with TOF[74].

Monitoring the response to interventions, such as oxygen therapy or prostaglandin infusion, allows for dynamic assessment of cardiac function and pulmonary circulation in neonates suspected of having CCHD. Continuous monitoring facilitates the identification of trends in SpO_2, enabling early recognition of deteriorating cardiac status and prompt intervention[75]. Pulse oximetry is a valuable tool for detecting CCHD in neonates by assessing SpO_2 discrepancies, hypoxemia, and response to interventions, leading to timely diagnosis and management of these critical conditions[76].

Neonates with abnormal pulse oximetry screening results undergo additional diagnostic tests, such as echocardiography, to confirm or rule out the presence of CCHD. Early detection of CCHD allows prompt referral to pediatric cardiology services for a comprehensive evaluation and timely intervention if necessary[77]. Pulse oximetry screening for CCHD has led to the early detection of heart defects in newborns, enabling timely interventions that can improve outcomes and reduce morbidity and mortality associated with undiagnosed CCHD. Identifying infants with CCHD before they become symptomatic allows for proactive management and appropriate planning for medical and surgical interventions[78]. While pulse oximetry screening has proven effective, it is not foolproof, and false-positive and false-negative results can occur. Factors such as low birthweight, prematurity, transient physiological changes, and technical issues with the screening process can affect the accuracy of the results[79]. Healthcare providers should be aware of these limitations and use clinical judgment to interpret screening results in the context of the individual patient's clinical presentation.

RDS: Preterm infants are at risk of developing RDS due to immature lung development and surfactant deficiency. RDS in newborns, also known as hyaline membrane disease, is a condition characterized by inadequate lung development and surfactant deficiency, leading to respiratory distress shortly after birth[80]. While pulse oximetry alone can not definitively diagnose RDS, it plays a vital role in assessing oxygenation and monitoring respiratory status in affected infants. Infants with RDS often present with hypoxemia due to impaired gas exchange in the lungs[81]. Pulse oximetry allows for continuous non-invasive monitoring of SpO_2 levels in these infants. Lower-than-normal SpO_2 readings indicate inadequate oxygenation and may prompt further evaluation for RDS. Infants with RDS frequently require supplemental oxygen to maintain adequate SpO_2 levels[82]. Pulse oximetry is used to titrate oxygen therapy, ensuring that SpO_2 levels are within the target range while avoiding hyperoxia or hypoxia. Monitoring SpO_2 trends helps healthcare providers adjust oxygen therapy as needed based on the infant's respiratory status[83]. Pulse oximetry is valuable for assessing the response to treatment interventions in infants with RDS. Initiating interventions such as supplemental oxygen, nasal continuous positive airway pressure, or mechanical ventilation aims to improve oxygenation and respiratory function [84]. Monitoring SpO_2 levels before and after treatment can gauge the effectiveness of interventions and guide further management decisions. Infants with RDS are at risk of developing complications such as respiratory failure, pneumothorax, or bronchopulmonary dysplasia (BPD)[85]. Pulse oximetry facilitates early detection of worsening respiratory status or the onset of complications by monitoring changes in SpO_2 levels and providing real-time feedback to healthcare providers. Serial measurements of SpO_2 over time allow for longitudinal monitoring of respiratory status and oxygenation trends in infants with RDS[86]. Continuous pulse oximetry monitoring provides valuable information on the infant's response to treatment, disease progression, and readiness for weaning off supplemental oxygen support[87].

BPD: BPD is a chronic lung disease that primarily affects premature infants who require mechanical ventilation and oxygen therapy for an extended period. While pulse oximetry alone cannot definitively diagnose BPD, it is a valuable tool in assessing oxygenation and monitoring respiratory status in affected infants[88]. Infants with BPD often have ongoing

respiratory issues and may become oxygen-dependent and require supplemental oxygen to maintain adequate SpO_2 levels. Continuous pulse oximetry monitoring is used to titrate oxygen therapy, ensuring that SpO_2 levels are within the target range while minimizing the risk of hyperoxia or hypoxia. Pulse oximetry allows for continuous monitoring of SpO_2 trends over time[89]. In infants with BPD, fluctuations in SpO_2 levels may indicate changes in respiratory status, disease progression, or response to treatment. Healthcare providers use these trends to adjust oxygen therapy and assess the effectiveness of interventions. Infants with BPD are at increased risk of respiratory distress episodes, such as apnea, desaturation, or bradycardia[90]. Pulse oximetry provides real-time monitoring of SpO_2 levels during these episodes, allowing for prompt intervention and management to stabilize the infant's respiratory status. Infants with BPD may exhibit instability in oxygenation, with fluctuations in SpO_2 levels during periods of activity, feeding, or respiratory distress[91]. Pulse oximetry helps identify episodes of oxygen desaturation or instability, guiding healthcare providers in optimizing respiratory support and monitoring the infant's response to interventions. Serial measurements of SpO_2 over time enable longitudinal monitoring of respiratory status and oxygenation trends in infants with BPD[92]. Continuous pulse oximetry monitoring provides valuable information on the infant's respiratory stability, response to treatment, and readiness for weaning off supplemental oxygen support as the disease resolves[93].

Apnea of prematurity: Apnea of prematurity (AOP) is a common condition characterized by episodes of breathing pauses in premature infants. While pulse oximetry alone cannot definitively diagnose AOP, it plays acritical role in monitoring respiratory status and detecting apnea-related oxygen desaturation events[94]. Infants with AOP may experience oxygen desaturation during apneic episodes due to decreased respiratory effort or airflow obstruction. Pulse oximetry continuously monitors SpO_2 levels in these infants, allowing healthcare providers to detect and quantify episodes of oxygen desaturation associated with apnea. While pulse oximetry primarily measures SpO_2, it can indirectly signal the presence of apnea by detecting associated oxygen desaturation events[95]. A sudden decrease in SpO_2 levels below the normal range may indicate the onset of an apneic episode, prompting further evaluation and intervention. Apnea episodes in premature infants often coincide with bradycardia and oxygen desaturation. Pulse oximetry, in conjunction with heart rate monitoring, helps identify apnea-bradycardia events by detecting simultaneous decreases in SpO_2 and heart rate[96]. These events are suggestive of apnea and warrant clinical intervention. Continuous pulse oximetry monitoring provides real-time feedback on SpO_2 levels, allowing healthcare providers to assess respiratory status and response to interventions[97]. Monitoring SpO_2 trends over time helps identify apnea and oxygen desaturation patterns, guiding treatment decisions and adjustments in respiratory support. Infants with AOP may require supplemental oxygen to maintain adequate oxygenation during apneic episodes. Pulse oximetry enables titration of oxygen therapy to target SpO_2 levels, ensuring optimal oxygenation while minimizing the risk of hyperoxia or hypoxia during apnea events[98].

Persistent pulmonary hypertension of the newborn: Persistent pulmonary hypertension of the newborn (PPHN) is a life-threatening condition characterized by elevated pulmonary vascular resistance and right-to-left shunting of blood, resulting in hypoxemia. While pulse oximetry alone cannot definitively diagnose PPHN, it plays a crucial role in assessing oxygenation and monitoring response to treatment[70]. Infants with PPHN typically present with severe hypoxemia due to impaired oxygenation secondary to pulmonary hypertension. Pulse oximetry continuously monitors SpO_2 levels, allowing healthcare providers to promptly detect and quantify the degree of hypoxemia[99]. Persistent low SpO_2 readings despite oxygen therapy may raise suspicion for PPHN. Oxygen therapy isa cornerstone of management for PPHN, aimed at improving oxygenation and alleviating hypoxemia. Pulse oximetry provides real-time feedback on SpO_2 levels, enabling healthcare providers to assess the effectiveness of oxygen therapy and titrate supplemental oxygen to target SpO_2 levels[100]. Serial measurements of SpO_2 over time help monitor SpO_2 trends in infants with PPHN. Pulse oximetry allows healthcare providers to assess the stability of oxygenation, detect fluctuations in SpO_2 levels, and evaluate the response to interventions such as oxygen therapy, vasodilator therapy, or mechanical ventilation[101]. Pulse oximetry helps differentiate hypoxemia associated with PPHN from other causes, such as RDS, pneumonia, or congenital heart defects. The characteristic pattern of hypoxemia in PPHN, often refractory to oxygen the rapyalone, may raise suspicion for the condition. Infants with PPHN may require intensive care management, including mechanical ventilation, inhaled nitric oxide therapy, and hemodynamic support[102]. Pulse oximetry allows for continuous monitoring of SpO_2 levels during treatment, guiding adjustments in therapy and assessing the infant's response to interventions[103].

Neonatal methemoglobinemia: Neonatal methemoglobinemia is a condition characterized by elevated levels of methemoglobin, a form of hemoglobin that cannot bind oxygen effectively. While pulse oximetry is generally reliable for detecting SpO_2 levels in the presence of normal hemoglobin, it may underestimate SpO_2 in the presence of methemoglobinemia[104]. Methemoglobin absorbs light differently than oxygenated or deoxygenated hemoglobin, leading to altered light absorption patterns[105]. Pulse oximeters may inaccurately measure SpO_2 in the presence of methemoglobinemia, resulting in lower-than-actual readings. Despite oxygen therapy, persistent low SpO_2 readings may prompt further investigation for methemoglobinemia[106]. Some advanced pulse oximeters off era feature known as methemoglobin pulse oximetry, which specifically measures the percentage of methemoglobin in the blood. Methemoglobin pulse oximetry readings can provide additional information about the presence and severity of methemoglobinemia in neonates[107]. In neonates with unexplained cyanosis or persistent hypoxemia despite adequate oxygen therapy, clinicians may suspect methemoglobinemia as a possible underlying cause. Pulse oximetry findings and clinical assessment and history can raise suspicion for methemoglobinemia and prompt further diagnostic evaluation, such as blood gas analysis or co-oximetry[108]. Treatment of neonatal methemoglobinemia typically involves the administration of methylene blue or exchange transfusion to reduce methemoglobin levels and improve oxygen-carrying capacity. Pulse

oximetry can monitor the response to treatment, with increasing SpO_2 levels indicating successful reversal of methemoglobinemia[109].

Postoperative care: Neonates undergoing surgical procedures, such as congenital heart or abdominal surgeries, require close monitoring of SpO_2 levels during the postoperative period[110]. Pulse oximetry is used to assess respiratory status, detect hypoxemia, and monitor for complications such as atelectasis, pneumothorax, or airway obstruction. Continuous SpO_2 monitoring facilitates early detection of postoperative respiratory compromise and guides interventions to optimize oxygenation and ventilation[4].

Case study: Management of a neonate with RDS.

Patient background: A full-term neonate is admitted to the NICU with respiratory distress shortly after birth. The infant was delivered *via* emergency cesarean section due to fetal distress during labor.

Clinical presentation: Upon admission, the neonate exhibits tachypnea (respiratory rate of 70 breaths per minute), nasal flaring, and intercostal retractions. Initial assessment reveals cyanosis of the extremities. The infant's SpO_2 on room air is 82%.

Pulse oximetry monitoring and management: Continuous pulse oximetry monitoring is initiated using a neonatal-specific pulse oximeter with appropriate sensor placement on the infant's right hand. The pulse oximeter displays fluctuating SpO_2 readings between 80% and 88%, indicating intermittent hypoxemia despite supplemental oxygen therapy *via* nasal cannula at 2 liters per minute.

Clinical decision-making: Based on pulse oximetry readings and clinical assessment, the NICU team adjusts the oxygen therapy to maintain SpO_2 levels between 88% and 92%, aiming to balance oxygenation while avoiding hyperoxia. Frequent bedside assessments, including periodic blood gas analysis, confirm the effectiveness of therapy adjustments in improving the infant's oxygenation status.

Outcome: Over the next 24 hours, the neonate's respiratory distress gradually improves. Pulse oximetry continues to guide oxygen therapy adjustments, ensuring optimal SpO_2 levels without compromising respiratory function. The infant is weaned off supplemental oxygen successfully by the third day of admission, and pulse oximetry monitoring is continued intermittently to monitor respiratory status during feedings and sleep.

Conclusion: This case study highlights the critical role of pulse oximetry in managing RDS in neonates. By providing continuous, non-invasive monitoring of SpO_2 levels, pulse oximetry guided timely interventions and optimized oxygen therapy, contributing to improved clinical outcomes and ensuring the safe transition from NICU to regular nursery care. This case study exemplifies how pulse oximetry is used in clinical practice to monitor and manage oxygenation in neonates with respiratory distress, demonstrating its practical application and impact on patient care.

Infants and children care

Children with respiratory illnesses: Pulse oximetry plays a vital role in managing respiratory illnesses in children, providing valuable insights into their SpO_2 levels and respiratory status. This non-invasive monitoring technique allows healthcare providers to promptly assess oxygen levels, particularly in conditions like pneumonia, bronchiolitis, and asthma exacerbations, where hypoxemia can occur. Detecting hypoxemia early enables timely interventions to improve oxygenation and prevent complications[111]. In pediatric respiratory illnesses, pulse oximetry serves several key purposes. Firstly, it helps gauge the severity of the condition by indicating the extent of hypoxemia. Low SpO_2 levels may signal respiratory distress or failure, guiding decisions regarding the need for hospitalization, intensive care, or advanced respiratory support like non-invasive ventilation[112]. Additionally, pulse oximetry is crucial for monitoring the effectiveness of oxygen therapy. Healthcare providers can adjust oxygen flow rates by regularly assessing SpO_2 levels to optimize delivery while avoiding oxygen toxicity[113]. Moreover, pulse oximetry aids in tracking the response to treatment. Changes in SpO_2 levels over time can indicate the efficacy of interventions such as bronchodilators, corticosteroids, or antibiotics, helping clinicians tailor management strategies accordingly[114]. In emergency departments or hospital settings, pulse oximetry readings help make decisions regarding discharge or continued hospitalization. Stable SpO_2 levels may suggest readiness for discharge, while persistent hypoxemia may necessitate further observation or treatment[115].

SpO_2 is a sensitive marker for assessing disease severity in conditions characterized by ventilation/perfusion mismatch, such as asthma exacerbations, acute bronchiolitis, chronic lung disease of prematurity, and pneumonia[116]. Conversely, in cases of proximal airway obstruction (*e.g.*, acute laryngotracheitis, vocal cord dysfunction, or foreign-body aspiration), SpO_2 may not reliably reflect disease severity. Hypoxemia in such instances primarily arises from hypoventilation, leading to elevated $PaCO_2$ levels[117]. Consequently, patients may not exhibit significantly low SpO_2 readings, as a SpO_2 below 90% typically corresponds to a $PaCO_2$ level of over 80 mmHg, according to the alveolar gas equation[18]. It is important to recognize that concurrent diffuse peripheral airway obstruction (*e.g.*, laryngotracheobronchitis) may contribute to ventilation/perfusion mismatch and decrease SpO_2 levels. However, in this scenario, hemoglobin desaturation signifies a secondary physiological phenomenon rather than the disorder's primary mechanism[118].

Pulse oximetry facilitates home monitoring for children with chronic respiratory conditions like asthma or cystic fibrosis. Portable pulse oximeters allow parents or caregivers to assess a child's SpO_2 levels regularly, especially during respiratory symptom episodes[3]. Abnormal readings prompt timely medical evaluation and intervention, enhancing the

management of chronic respiratory conditions. While pulse oximetry is widely used for continuous SpO_2 monitoring in infants and children, its routine use in acute respiratory illness is not universally recommended[86]. The American Academy of Family Physicians advises against continuous pulse oximetry unless the child requires supplemental oxygen. Continuous monitoring has been associated with increased admission rates and longer hospital stays, highlighting the need for judicious use based on clinical assessment[119]. However, pulse oximetry is still an invaluable tool in managing respiratory illnesses in children. It provides real-time information on oxygenation status and guides clinical decision-making. By incorporating pulse oximetry into comprehensive care protocols, healthcare providers can optimize outcomes for pediatric patients with respiratory conditions[120].

Assessment of circulatory status: Pulse oximetry, a precise and accurate tool, plays a significant role in assessing circulatory status in children. It provides valuable information about tissue perfusion and oxygen delivery. By measuring SpO_2 levels in the blood, pulse oximetry enables healthcare providers to confidently evaluate the adequacy of circulatory function in pediatric patients[121]. In children with circulatory compromise, such as shock or hypovolemia, pulse oximetry can detect changes in tissue oxygenation early, allowing for prompt intervention to restore perfusion and prevent organ dysfunction[122]. Additionally, pulse oximetry can help monitor the response to interventions to improve circulatory status, such as fluid resuscitation or vasopressor therapy. By continuously monitoring SpO_2 levels, pulse oximetry provides real-time feedback on the effectiveness of treatment strategies, guiding further management decisions [123]. Overall, pulse oximetry is a valuable tool in assessing circulatory status in children, aiding in the early detection of circulatory compromise and facilitating timely interventions to optimize patient outcomes[124].

Monitoring during anesthesia and sedation: Pulse oximetry is crucial in monitoring children during anesthesia and sedation, providing a continuous and non-invasive assessment of SpO_2 levels and pulse rate. For instance, in a recent case, a child undergoing anesthesia experienced a sudden drop in SpO_2 levels, immediately detected by the pulse oximeter. This allowed the healthcare team to intervene promptly and prevent a potential crisis[125,126]. This monitoring technique is essential for ensuring the safety and well-being of pediatric patients undergoing anesthesia or sedation procedures. During anesthesia or sedation, there is a risk of respiratory depression, airway obstruction, and hypoxemia, particularly in children, due to their unique physiological characteristics and vulnerability[127]. Pulse oximetry allows healthcare providers to detect changes in SpO_2 levels early, enabling prompt intervention to prevent hypoxemia-related complications such as tissue hypoxia, organ dysfunction, or cardiac arrest[128]. The continuous monitoring of SpO_2, a precise assessment tool, helps anesthesia providers assess the adequacy of ventilation and oxygenation throughout the procedure. Any decline in SpO_2 can indicate airway compromise, hypoventilation, or respiratory depression, prompting immediate corrective measures such as airway repositioning, oxygen supplementation, or assisted ventilation[129].

Furthermore, pulse oximetry aids in titrating the delivery of supplemental oxygen during anesthesia or sedation. However, it's important to note that pulse oximetry may not always accurately reflect the patient's true oxygenation status, especially in certain clinical conditions[66]. By closely monitoring SpO_2 levels, healthcare providers can adjust oxygen flow rates to maintain optimal oxygenation while minimizing the risk of hyperoxia-associated adverse effects, such as absorption atelectasis or oxygen toxicity[130]. In addition to oxygenation monitoring, pulse oximetry provides valuable information about the child's cardiovascular status through continuous pulse rate monitoring. Changes in pulse rate can indicate hemodynamic instability, cardiovascular depression, or adverse drug reactions, prompting further assessment and intervention as needed[131]. Generally, pulse oximetry is not only an indispensable tool for ensuring the safety and effective management of children undergoing anesthesia or sedation, but it also proves to be a cost-effective investment[132]. By facilitating real-time monitoring of SpO_2 and pulse rate, pulse oximetry enhances the detection of respiratory and cardiovascular compromise, allowing for timely intervention and optimization of patient outcomes, thereby reducing the need for more expensive interventions or treatments[133].

Management of sleep disorders: Pulse oximetry plays a significant role in managing childhood sleep disorders, particularly in conditions such as obstructive sleep apnea (OSA) or central sleep apnea[134]. It is a valuable screening tool for sleep-disordered breathing. It allows healthcare providers to assess SpO_2 levels during sleep and detect abnormalities indicative of sleep apnea, such as recurrent oxygen desaturation events orthose associated with apnea or hypopnea episodes[135]. Additionally, pulse oximetry provides essential information about the severity of sleep-disordered breathing in children by quantifying the frequency and magnitude of oxygen desaturation events and guiding treatment decisions and interventions[136]. Moreover, it is instrumental in monitoring the effectiveness of treatments such as continuous positive airway pressure therapy, adenotonsillectomy, or weight management by assessing the response to treatment and adjusting management strategies accordingly[137]. Pulse oximetry also helps identify complications associated with childhood sleep disorders, such as nocturnal hypoxemia, hypercapnia, or cardiac arrhythmias, prompting further evaluation and management[138]. Furthermore, portable pulse oximeters enable home monitoring of SpO_2 levels, allowing parents or caregivers to track overnight SpO_2 trends and detect abnormalities suggestive of sleep-related breathing disturbances. This home monitoring facilitates early detection of treatment failure or disease progression, leading to timely medical intervention and improved outcomes for children with sleep-related breathing disturbances [139].

Evaluation of trauma and critical care: Pulse oximetry, a crucial tool, is instrumental in the evaluation of children with trauma and those in need of critical care[140]. In trauma cases, it aids in rapidly assessing oxygenation status, providing immediate insight into the child's respiratory function. By measuring SpO_2 levels, pulse oximetry helps identify hypoxemia, a condition that may result from respiratory compromise due to traumatic injuries such as chest trauma, pneumothorax, or airway obstruction. The early detection of hypoxemia is vital, as it allows for initiating prompt interventions to optimize oxygenation and prevent secondary complications[141]. Additionally, pulse oximetry assists

healthcare providers in monitoring respiratory status during critical care interventions, such as intubation, mechanical ventilation, or oxygen therapy[142]. Continuous monitoring of SpO_2 levels enables real-time assessment of treatment efficacy and early detection of respiratory deterioration or airway compromise, prompting timely adjustments to the management plan[143]. Moreover, pulse oximetry aids in the detection of potential complications associated with trauma or critical illness, including respiratory failure, acute RDS, or sepsis. By providing continuous SpO_2 monitoring, pulse oximetry facilitates the timely identification of deteriorating respiratory function or oxygenation status, allowing for prompt escalation of care and initiation of lifesaving interventions[144]. Therefore, pulse oximetry enables healthcare providers to be proactive and vigilant, making timely assessments of oxygenation status and facilitating appropriate interventions to optimize patient outcomes.

Home monitoring: Pulse oximetry is an important tool for monitoring various childhood disorders at home[38]. It provides valuable information about SpO_2 levels non-invasively, especially in children with chronic respiratory disorders like asthma, cystic fibrosis, or BPD. By regularly monitoring SpO_2 levels at home, parents or caregivers can assess the child's respiratory status, particularly during episodes of coughing, wheezing, or shortness of breath[3]. Abnormal readings can alert them to seek medical attention promptly. Pulse oximetry is also useful for children with sleep-related breathing disorders like OSA[145]. Continuous overnight oximetry monitoring helps identify episodes of oxygen desaturation during sleep, which is a characteristic of OSA. Parents or caregivers can record and report these findings to healthcare providers for further evaluation and management[146].

Children with congenital heart diseases, such as cyanotic heart defects, may need ongoing monitoring of their SpO_2 levels at home. Pulse oximetry enables parents or caregivers to detect any fluctuations in SpO_2, which could indicate worsening heart function or complications. Early abnormalities detection allows prompt medical attention and intervention[147]. Some neurological disorders, such as seizures or neuromuscular diseases, can affect respiratory function and oxygenation. Pulse oximetry monitoring at home helps assess the child's respiratory status during periods of increased risk, such as seizures or respiratory muscle weakness[148]. Abnormal SpO_2 levels may indicate the need for immediate intervention or adjustment of treatment. Premature infants or those with a history of neonatal complications may also require home monitoring of their SpO_2 levels to detect episodes of desaturation or apnea[149]. Pulse oximetry allows parents or caregivers to closely monitor the infant's respiratory status, particularly during sleep or periods of illness. Any deviations from normal SpO_2 levels can prompt medical evaluation and intervention. Regular pulse oximetry monitoring at home allows for early detection of abnormalities, facilitating timely intervention and improved management of the child's condition[150].

Pulse oximetry, integrated with telemedicine technologies, offers an innovative approach to home monitoring of childhood disorders. Caregivers can remotely share real-time pulse oximetry data with healthcare providers through telemedicine platforms, allowing for continuous monitoring and timely intervention[151]. This integration enhances the accessibility of healthcare services, especially for families living in remote areas or with limited access to specialized medical facilities. Additionally, telemedicine consultations enable healthcare providers to interpret pulse oximetry readings remotely, guiding treatment adjustments or further diagnostic steps as needed[152]. The combination of pulse oximetry with telemedicine enhances the effectiveness of home monitoring, improving the management of various childhood disorders and promoting better health outcomes[153].

Case study: Management of an infant with bronchiolitis

Patient background: A 6-month-old male infant is brought to the pediatric emergency department by his parents due to worsening cough, wheezing, and increased respiratory effort over the past two days. The infant was born full-term without complications and had no significant medical history.

Clinical presentation: Upon assessment, the infant appears anxious and breathes rapidly with nasal flaring and chest retractions. Auscultation reveals bilateral wheezing and diminished breath sounds in the lower lung fields. The infant's initial SpO_2 on room air is 88%.

Pulse oximetry monitoring and management: Continuous pulse oximetry monitoring is initiated using a pediatric pulse oximeter with a sensor placed on the infant's right index finger. The pulse oximeter displays SpO_2 readings fluctuating between 86% and 92% during periods of rest and drops to 82% during coughing episodes.

Clinical decision-making: Based on pulse oximetry readings and clinical assessment, the pediatric team administered supplemental oxygen *via* nasal cannula at two liters per minute to maintain SpO_2 levels above 92%. Serial pulse oximetry measurements guide the titration of oxygen therapy to ensure adequate oxygenation without over-oxygenating the infant.

Outcome: Over the next 24 hours, the infant's respiratory distress improves with oxygen therapy. Pulse oximetry monitoring continues to guide clinical decisions, including adjusting oxygen flow rate during periods of activity and sleep. The infant successfully transitions to room air after demonstrating stable SpO_2 levels above 94% for several hours.

Conclusion: This case study illustrates the use of pulse oximetry in managing respiratory distress in infants with bronchiolitis. By providing real-time feedback on SpO_2 levels, pulse oximetry facilitated the timely initiation and adjustment of oxygen therapy, optimizing respiratory support and contributing to the infant's clinical improvement. This example demonstrates how pulse oximetry is integral in managing respiratory conditions in infants, ensuring appropriate oxygenation and guiding the rapeutic interventions based on continuous monitoring of SpO_2 levels.

Diseases and conditions that need specific consideration when using pulse oximetry

Anaemia: Pulse oximetry plays a crucial role in monitoring patients with anemia. While pulse oximetry provides valuable information about SpO_2, it's essential to understand its limitations in the context of anemia. In patients with anemia, the reduced hemoglobin levels can affect the accuracy of SpO_2 readings[1]. Since hemoglobin is responsible for carrying oxygen, lower hemoglobin concentrations mean less oxygen is available to bind to. As a result, pulse oximeters may report lower SpO_2 values even if the oxygen-carrying capacity of the available hemoglobin is normal[24]. Additionally, in severe cases of anemia where tissue oxygen delivery is compromised, pulse oximetry may underestimate the severity of hypoxemia. This discrepancy occurs because pulse oximeters measure the SpO_2 of hemoglobin within the blood vessels but may not accurately reflect tissue oxygenation[154].

Clinicians should interpret pulse oximetry readings in patients with anemia cautiously and consider other clinical indicators such as respiratory rate, heart rate, and clinical symptoms to accurately assess the overall oxygen status[155]. In cases of uncertainty or severe anemia, arterial blood gas analysis may be necessary to determine the PaO_2 and assess tissue oxygenation more directly[156]. Despite its limitations, pulse oximetry remains a valuable tool for monitoring patients with anemia, especially in conjunction with other clinical assessments. By providing real-time information about SpO_2, pulse oximetry helps guide clinical decision-making and ensures timely interventions to optimize patient care[157].

Polycythemia: Polycythemia is a condition characterized by excess red blood cells in the bloodstream. Using pulse oximetry in patients with polycythemia presents certain challenges and considerations. Polycythemia can affect the accuracy of pulse oximetry readings due to changes in blood viscosity and oxygen-carrying capacity[158]. In individuals with polycythemia, the increased number of red blood cells can result in higher hemoglobin levels, potentially leading to falsely elevated SpO_2 readings on pulse oximetry and decreased oxygen affinity to hemoglobin[159]. This is because pulse oximeters measure the percentage of oxygenated hemoglobin in the blood, and the higher hemoglobin levels in polycythemia can skew these readings[154]. Furthermore, the increased viscosity of the blood in polycythemia may affect peripheral perfusion, which can also influence pulse oximetry measurements. Reduced peripheral perfusion can result in slower capillary refill times. It may lead to inaccurately low SpO_2 readings on pulse oximetry, particularly in extremities where the probe is typically placed[160]. Healthcare providers must be aware of these potential limitations when interpreting pulse oximetry readings in individuals with polycythemia. Clinicians may need to consider alternative methods of assessing oxygenation in these patients, such as arterial blood gas analysis, particularly if there are concerns about the accuracy of pulse oximetry readings[161]. Pulse oximetry can differentiate polycythemia vera from secondary erythrocytosis, as normal SpO_2 is one of the major criteria of polycythemia vera[162]. However, patients with polycythemia vera could have low SpO_2 due to other causes of hypoxia[163].

Metabolic derangement: Pulse oximetry is invaluable in assessing patients with acid-base disorders, providing essential information about SpO_2 levels. However, it's important to understand how acid-base disturbances can influence pulse oximetry readings and interpretation. Acidosis, whether respiratory or metabolic, can significantly impact pulse oximetry readings. One notable effect is the left shift of the oxygen is sociation curve, where hemoglobin's increased affinity for oxygen may yield higher saturation levels despite tissue hypoxia[164]. Additionally, acidosis can induce peripheral vasoconstriction, reducing blood flow to extremities and potentially affecting the accuracy of SpO_2 measurements[165]. Changes in hemoglobin affinity due to acidosis may further complicate readings, with severe cases impairing oxygen binding, potentially resulting in lower saturation levels[166]. Respiratory compensation mechanisms to correct acid-base imbalances may also influence pulse oximetry readings through alterations in respiratory rate and depth[167]. Moreover, acidosis-induced changes in tissue perfusion can lead to tissue hypoxia, which may not always be reflected in SpO_2 measurements due to factors like peripheral vasoconstriction[168]. Consequently, clinicians should interpret pulse oximetry readings cautiously in the context of acidosis, considering other clinical parameters for a comprehensive assessment of oxygenation status.

On the other hand, respiratory or metabolic alkalosis can also impact pulse oximetry readings, albeit indifferent ways than acidosis. In alkalosis, the oxygen dissociation curve shifts to the right, causing hemoglobin to have a decreased affinity for oxygen[169]. This shift can result in lower saturation levels detected by pulse oximetry, even in adequate tissue oxygenation. Additionally, alkalosis may induce peripheral vasodilation, increasing blood flow to extremities and potentially affecting SpO_2 measurements[170]. Changes in respiratory rate and depth associated with respiratory compensation for alkalosis may also influence pulse oximetry readings, like acidosis[171]. Furthermore, alterations in tissue perfusion due to alkalosis-induced vasodilation may impact SpO_2 readings, with increased blood flow potentially leading to higher saturation levels being detected[172]. Overall, clinicians should consider these effects of alkalosis when interpreting pulse oximetry readings, ensuring a comprehensive assessment of oxygenation status alongside other clinical parameters.

Cardiac arrhythmia: Arrhythmia can affect pulse oximetry readings by causing irregular blood flow in the arteries, leading to fluctuations in the pulsatile signal detected by the oximeter[173]. This irregularity can result in inaccurate SpO_2 measurements, as the oximeter may have difficulty distinguishing between arterial and venous blood pulsations[174]. Moreover, arrhythmias like atrial fibrillation can cause rapid and irregular heartbeats, further complicating the interpretation of pulse oximetry readings[175]. In such cases, healthcare providers may need to rely on alternative methods for assessing oxygenation status, such as arterial blood gas analysis, to obtain more accurate measurements.

Certain modifications or considerations may be necessary to ensure accurate readings when using pulse oximetry in patients with arrhythmias. One common approach is to use pulse oximeters with advanced signal processing algorithms designed to filter out noise and motion artifacts more effectively[176]. These algorithms can help mitigate the effects of irregular pulsations caused by arrhythmias and improve the accuracy of SpO_2 measurements. Additionally, some pulse

oximeters may offer specific settings or modes tailored for use in patients with arrhythmias. These settings may adjust the device's sensitivity or filtering parameters to accommodate irregular heart rhythms better and optimize signal detection [177].

Healthcare providers should also monitor the quality of the pulse oximetry wave form displayed on the device. Irregular or inconsistent waveforms may indicate poor signal quality, which could lead to unreliable SpO_2 readings, particularly in patients with arrhythmias[174]. While pulse oximetry remains a valuable tool for monitoring oxygenation in patients with arrhythmias, healthcare providers should be aware of its limitations and consider supplementary assessments, such as clinical evaluation and arterial blood gas analysis, when necessary to ensure comprehensive patient care[178].

Hypothermia: Hypothermia poses challenges and can significantly affect accurate pulse oximetry readings due to its impact on peripheral perfusion and tissue oxygenation[42]. When the body temperature drops below normal levels, peripheral vasoconstriction occurs as a physiological response to conserve heat, reducing blood flow to the extremities. This decrease in peripheral perfusion can result in weaker pulsatile signals detected by the pulse oximeter, potentially leading to inaccurate readings of SpO_2[179].

Furthermore, hypothermia can also affect the oxygen dissociation curve, altering hemoglobin's affinity for oxygen [180]. As body temperature decreases, hemoglobin's affinity for oxygen increases, making it more difficult to release oxygen to the tissues. This shift in the oxygen dissociation curve can lead to falsely elevated SpO_2 readings on pulse oximetry, as hemoglobin may hold onto oxygen more tightly than usual, even in tissues experiencing oxygen deprivation [181].

In clinical practice, healthcare providers should be cautious when interpreting pulse oximetry readings in hypothermic patients, considering both false highs and false lows. To mitigate the effects of hypothermia on peripheral perfusion, local rubbing or heating of cold extremities before applying the probe may temporarily improve perfusion in infants. However, for hypothermic patients, monitoring with a forehead probe is an alternative option[182]. Furthermore, new-generation pulse oximeters are equipped with signal extraction algorithms designed to perform better in low-perfusion states, enhancing their accuracy in hypothermic patients[183]. Occasionally, supplemental assessments, such as arterial blood gas analysis, may be necessary to assess oxygenation status in these patients accurately. These advancements help healthcare providers obtain more reliable SpO_2 measurements in challenging conditions such as hypothermia[184].

Jaundice: Jaundice typically does not significantly affect pulse oximetry readings, as bilirubin absorbs light at a different spectrum (around 450 nm) than that used by pulse oximeters[185]. This characteristic enables the reliable use of pulse oximetry for monitoring jaundiced patients, including neonates. However, in cases of severe hemolytic jaundice, patients may also exhibit elevated levels of carboxyhemoglobin, which can potentially cause inaccurate pulse oximetry readings [1]. Additionally, falsely low SpO_2 values have been reported in rare instances of bronze baby syndrome, although this phenomenon is uncommon. Low SpO_2 is due to excessive bilirubin accumulation in the skin, which can interfere with accurately detecting arterial blood SpO_2 by the pulse oximeter[186]. Overall, pulse oximetry remains a valuable tool for monitoring patients with jaundice, with minimal interference from bilirubin levels in most cases.

Exposure to electromagnetic fields: Exposure to electromagnetic fields, particularly from sources such as electrosurgical cauterization units and cellular phones, can potentially interfere with the accuracy of pulse oximetry readings. This interference may result in erroneous SpO_2 readings[187]. Additionally, during magnetic resonance imaging, standard pulse oximetry sensors may not be suitable due to the risk of interference with image quality and the potential for thermal injury caused by the heating of the sensor[188]. Therefore, special pulse oximetry devices equipped with fiberoptic technology are recommended during magnetic resonance imaging procedures to mitigate these risks and ensure accurate SpO_2 monitoring without compromising patient safety[189]. Table 4 summarizes the diseases or conditions, the problems they pose to pulse oximetry, and potential solutions to address these challenges.

Advantages of pulse oximetry: Pulse oximetry, a non-invasive medical technology, offers numerous advantages across various clinical settings due to its ability to measure SpO_2 levels in the blood and pulse rate accurately and continuously [190]. One of the primary advantages of pulse oximetry is its non-invasive nature. Unlike arterial blood gas sampling, which requires invasive procedures and carries some risks, pulse oximetry involves placing a sensor on a patient's skin, typically on a finger, toe, or earlobe[191]. This makes it well-tolerated by patients, including infants and children, and reduces the risk of complications associated with invasive monitoring techniques. In addition, pulse oximetry provides real-time feedback on a patient's SpO_2 levels and pulse rate[192]. This allows healthcare providers to continuously monitor changes in oxygenation status, enabling prompt intervention if SpO_2 levels drop below the normal range. Real-time monitoring is particularly crucial in critical care settings, where rapid detection of hypoxemia or changes in respiratory status can be lifesaving[193].

Pulse oximetry facilitates the early detection of hypoxemia, a condition characterized by low oxygen levels in the blood. By continuously monitoring SpO_2 levels, healthcare providers can identify hypoxemia before clinical symptoms become apparent, allowing timely intervention to improve oxygenation and prevent complications associated with inadequate tissue oxygen delivery[194]. Pulse oximetry is valuable during various medical procedures, including anesthesia, sedation, and surgery. It helps anesthesia providers assess a patient's oxygenation status throughout the procedure, detect changes in SpO_2 levels early, and optimize ventilation and oxygenation to prevent hypoxemia-related complications. Similarly, pulse oximetry aids in monitoring patients undergoing sedation or procedural sedation, ensuring their safety and well-being during the procedure[126,195].

Modern pulse oximeters are portable and versatile, allowing their use in various clinical settings, including hospitals, ambulatory care facilities, and even home healthcare settings. Portable pulse oximeters are battery-operated and

Table 4 The diseases or conditions, the problems they pose to pulse oximetry, and potential solutions to address these challenges

Disease/condition	Problem with pulse oximetry	Solution
Anaemia	Reduced accuracy of SpO_2 readings due to lower hemoglobin levels affecting oxygen saturation	Interpret readings cautiously, consider other clinical indicators, and perform arterial blood gas analysis for severe cases
Polycythaemia	Falsely elevated SpO_2 readings due to increased hemoglobin levels and altered blood viscosity	Be aware of potential inaccuracies and consider alternative assessment methods, such as arterial blood gas analysis
Metabolic derangement	Shifts in the oxygen dissociation curve and peripheral vasoconstriction can affect SpO_2 readings	Interpret readings cautiously, consider other clinical parameters, and be aware of acidosis-induced left shifts or alkalosis-induced right shifts
Cardiac arrhythmia	Irregular blood flow causes fluctuations in pulsatile signal, leading to inaccurate readings	Use pulse oximeters with advanced signal processing algorithms, monitor waveform quality, and consider alternative assessments such as arterial blood gas analysis
Hypothermia	Reduced peripheral perfusion and altered oxygen dissociation curve affecting SpO_2 accuracy	Apply local heating to improve perfusion, use pulse oximeters with enhanced low-perfusion algorithms, and consider supplemental assessments
Jaundice	Minimal interference from bilirubin with pulse oximetry readings, though COHb may cause inaccuracies	Monitor for COHb levels in severe cases; rely on pulse oximetry for most jaundiced patients
Electromagnetic field	Interference with pulse oximetry readings from sources such as electrosurgical units and cellular phones	Use fiberoptic pulse oximetry during MRI procedures to minimize exposure to electromagnetic fields

COHb: Carboxyhemoglobin; MRI: Magnetic resonance imaging; SpO_2: Oxygen saturation.

lightweight, making them convenient in emergency medical services settings, outpatient clinics, and remote locations where access to traditional monitoring equipment may be limited[196]. Pulse oximeters are user-friendly devices that require minimal training for healthcare providers to operate effectively. They typically feature simple interfaces and intuitive displays that provide clear and easy-to-interpret readings of SpO_2 levels and pulse rate. This ease of use enhances their accessibility and utility in diverse healthcare settings[197].

Pulse oximetry enables continuous monitoring of SpO_2 and pulse rates, allowing healthcare providers to track changes in a patient's respiratory status over time. Continuous monitoring is particularly beneficial in critical care settings, where patients may require close observation for extended periods, such as during mechanical ventilation or recovery from surgery[198]. With advancements in telemedicine and remote patient monitoring technologies, pulse oximetry can now be integrated into telehealth platforms, allowing for remote monitoring of patients' SpO_2 levels and pulse rate from a distance. Remote monitoring enables healthcare providers to remotely assess patients' respiratory status, provide timely interventions, and optimize patient care without needing in-person visits[199]. Pulse oximetry is a cost-effective monitoring tool that provides valuable clinical information at a relatively low cost compared to other monitoring techniques, such as arterial blood gas analysis. Its affordability and widespread availability make it accessible to healthcare providers in diverse healthcare settings, including resource-limited settings where access to advanced monitoring equipment may be limited[1].

Causes of limited wide-use of pulse oximetry, especially in the developing world

Despite the significant potential benefits of pulse oximetry in low- and middle-income countries (LMICs), several challenges hinder its widespread use. One major barrier is the limited availability of supplemental oxygen, which is necessary for treating hypoxemia, as identified through pulse oximetry screening and as a potential lifesaver[200]. In many low-resource settings, healthcare facilities struggle to maintain a reliable oxygen supply due to logistical and infrastructural constraints. This shortage of oxygen not only undermines the effectiveness of pulse oximetry as a diagnostic tool but also compromises the ability to provide life-saving treatment to hypoxemic patients[201].

Moreover, the initial cost of pulse oximeters and ongoing maintenance and support requirements pose significant financial challenges for healthcare systems in LMICs[197]. The high upfront expenses for procuring pulse oximeters and the need for periodic replacement of components such as probes and batteries can strain already limited budgets, often leaving healthcare providers with difficult choices. Additionally, technical barriers, including faulty equipment and inadequate training of healthcare personnel, further impede the effective use of pulse oximetry in resource-limited settings[202,203]. Provider misconceptions and lack of awareness about the importance of pulse oximetry also contribute to its underutilization. Many healthcare providers in LMICs may not fully appreciate the value of pulse oximetry in diagnosing hypoxemia and guiding treatment decisions[111]. This lack of understanding can lead to a reluctance to incorporate pulse oximetry into clinical practice and may result in missed opportunities for early intervention[204].

Addressing these challenges requires a comprehensive approach that includes urgent policy changes and substantial investment in healthcare infrastructure. Governments and international organizations must prioritize the integration of pulse oximetry into national healthcare policies and guidelines, ensuring access to both the devices and the necessary oxygen therapy[205]. Training programs should be implemented to educate healthcare providers about the benefits of pulse oximetry and how to utilize the technology in clinical practice effectively[206]. Furthermore, research efforts should focus on developing cost-effective solutions tailored to the unique needs of LMICs[207]. This may involve the develop-

ment of more robust and affordable pulse oximeter models and innovations in oxygen delivery systems to improve accessibility and reliability[15]. Collaborative initiatives between public health agencies, academic institutions, and private sector partners can help drive progress in this area and ultimately improve healthcare outcomes for children in LMICs[208].

Limitations and challenges of pulse oximetry

Pulse oximetry has revolutionized the monitoring of SpO_2 levels and pulse rate in healthcare settings, offering a non-invasive and convenient method for assessing respiratory status[153]. However, like any medical technology, pulse oximetry has its limitations and challenges that healthcare providers must be aware of to interpret its readings accurately. Understanding these limitations is essential for ensuring the appropriate use of pulse oximetry and avoiding misinterpretation of data. Below, we discuss some key limitations and challenges associated with pulse oximetry in clinical practice[209]. Motion artifacts can affect the accuracy of pulse oximetry readings, particularly in patients who are restless, agitated, or experiencing involuntary movements. Pediatric patients, especially infants and toddlers, are often restless and may move frequently[179]. Motion artifacts can interfere with the pulse oximeter's ability to detect pulsatile blood flow accurately, leading to erroneous readings. Proper sensor placement and minimizing patient movement can help mitigate this challenge[210]. Inpatients with poor peripheral perfusion, such as those with hypotension, hypothermia, or vasoconstriction, pulse oximetry may not accurately reflect their true SpO_2 levels. Pediatric patients, particularly those with circulatory compromise or peripheral vascular disease, may have poor peripheral perfusion[211]. Inadequate perfusion can affect the pulsatile component of the signal detected by the pulse oximeter, resulting in inaccurate readings and delaying appropriate interventions. Careful assessment of perfusion status and consideration of alternative monitoring methods may be necessary in these cases[212].

Ambient light, including sunlight or artificial light sources, can interfere with pulse oximetry readings by affecting the accuracy of the sensor's photodetectors. Ambient light interference can result in erroneous readings or signal loss, compromising there liability of pulse oximetry measurements, particularly in brightly lit environments[22]. Nail polish, acrylic nails, or other nail enhancements can interfere with light transmission through the nail bed, affecting the accuracy of pulse oximetry readings. These substances may block or scatter light, leading to inaccurate measurements of SpO_2 levels and pulse rate[213]. Skin pigmentation, particularly dark skin pigmentation, can attenuate the transmission of light through the skin, potentially affecting the accuracy of pulse oximetry readings. The absorption of light by melanin can interfere with the sensor's ability to detect SpO_2 accurately. In patients with dark skin tones, pulse oximeters may underestimate SpO_2 levels, leading to misinterpretation of the patient's respiratory status[214,215]. Certain medical conditions or interventions may involve the administration of intravascular dyes, such as methylene blue or indocyanine green. These dyes can interfere with the absorption of light by hemoglobin, affecting the accuracy of pulse oximetry readings. Healthcare providers should consider the presence of intravascular dyes when interpreting oximetry readings in pediatric patients[216].

Pediatric patients may have hemoglobin variants, such as fetal hemoglobin, which can affect the accuracy of pulse oximetry readings. Pulse oximeters are calibrated based on the absorption spectra of adult hemoglobin, and variations in hemoglobin types can lead to discrepancies in SpO_2 measurements[217,218]. Pulse oximetry may produce falsely elevated SpO_2 readings in patients with CO poisoning. This is because pulse oximeters cannot distinguish between oxygen and CO bound to hemoglobin, leading to overestimating SpO_2 levels and masking the presence of CO toxicity[219]. Altitude and barometric pressure changes can affect the accuracy of pulse oximetry readings, particularly in high-altitude environments or during air travel. Reduced atmospheric pressure at higher altitudes may result in lower SpO_2 readings, even without true hypoxemia, leading to misinterpretation of the patient's respiratory status[220].

Pulse oximetry provides a continuous but delayed measurement of SpO_2 levels compared to arterial blood gas analysis. This delay may result in a lag time between changes in a patient's respiratory status and the detection of these changes by pulse oximetry, potentially delaying the initiation of appropriate interventions[184]. Pulse oximetry may occasionally trigger false alarms, particularly during periods of patient movement, inadequate sensor placement, or technical issues with the device. False alarms can disrupt clinical workflow, lead to unnecessary interventions or investigations, and decrease healthcare provider confidence in pulse oximetry readings[221]. Overall, while pulse oximetry is a valuable monitoring tool in healthcare, healthcare providers need to recognize its limitations and challenges and interpret its readings in conjunction with clinical assessment and other diagnostic modalities for optimal patient care[114].

Alarm fatigue syndrome

Alarm fatigue syndrome is a condition when healthcare providers become desensitized to alarm signals because of frequent exposure to false or non-actionable alarms. This can cause delayed responses or missed critical events[222]. In pulse oximetry, alarm fatigue can occur when the device generates excessive alarms, whether due to technical issues, patient conditions, or environmental factors[221]. False alarms may result from motion artifacts, poor signal quality, improper sensor placement, or fluctuations in patient physiology, such as arrhythmias or hypoperfusion. These false alarms can lead to healthcare providers ignoring or disabling alarms, which could compromise patient safety[179,223].

Several strategies can be implemented to address alarm fatigue syndrome in pulse oximetry. First, healthcare facilities should establish alarm management protocols to prioritize clinically relevant alarms and reduce unnecessary alarms. This may involve adjusting alarm thresholds based on patient characteristics and clinical context and implementing alarm delay features to minimize transient alarms[224]. Additionally, regular maintenance and calibration of pulse oximetry equipment can help prevent technical issues contributing to false alarms. Healthcare providers should also receive education and training on properly using and interpreting pulse oximetry alarms to ensure appropriate responses[34].

Furthermore, advancements in technology, such as the development of smart alarm systems and signal processing algorithms, aim to improve the specificity of alarms and reduce alarm fatigue[225]. These systems utilize artificial intelligence and machine learning to analyze physiological data and distinguish between true clinical events and artifacts, reducing the frequency of false alarms[226]. Addressing alarm fatigue syndrome in pulse oximetry requires a multi-faceted approach involving technology, education, and protocol development to enhance patient safety and optimize alarm management practices[227].

Guidelines for effective pulse oximetry

Table 5 summarizes the guidelines for effective use of pulse oximetry. Effective monitoring of pulse oximetry in pediatric patients is crucial to assess their oxygenation status accurately and guide clinical management. The pulse oximeter sensor should be placed on a well-perfused area such as the finger, toe, or earlobe, depending on the child's age and size[86]. The sensor should be secured snugly but not too tightly to prevent motion artifacts and ensure optimal signal quality. Establishing a baseline SpO_2 level for each patient is essential to facilitate the interpretation of subsequent readings[192]. Age, baseline respiratory status, and underlying medical conditions should also be considered while determining the expected SpO_2 range[3].

Continuous pulse oximetry monitoring can promptly detect changes in SpO_2, especially in critically ill or high-risk pediatric patients. It provides real-time feedback on oxygenation status and enables timely intervention if necessary[133]. SpO_2 levels, respiratory rate, heart rate, level of consciousness, and skin color are crucial factors while monitoring a patient's condition. Minimizing patient movement, ensuring proper sensor placement, and using immobilization techniques or sedation as appropriate, particularly during procedures or in agitated pediatric patients, can reduce motion artifacts and enhance signal quality[228].

Regular monitoring of pulse oximetry equipment is necessary to ensure its proper functioning. Any technical issues should be addressed promptly, and the equipment should be calibrated according to the manufacturer's guidelines[229]. Sensors should be replaced as needed to maintain accuracy and reliability. For pediatric patients with poor peripheral perfusion or compromised circulation, alternative sites for sensor placement, such as the forehead or palm, can improve signal quality and accuracy[33]. Monitoring the trends in SpO_2 over time is more important than relying solely on individual readings. Tracking changes in SpO_2 levels during interventions such as oxygen therapy or respiratory treatments can help evaluate treatment efficacy and response[230].

Parents, caregivers, and healthcare staff should be educated about the importance of pulse oximetry monitoring and proper sensor placement. They should be trained to interpret oximetry readings and recognize signs of respiratory distress or hypoxemia[197]. Lastly, documenting pulse oximetry readings, relevant clinical information, and interventions in the patient's medical record is crucial. Accurate records help track changes in oxygenation status, monitor treatment response, and facilitate communication among healthcare providers[231]. By following these practical guidelines, healthcare providers can optimize the effectiveness of pulse oximetry monitoring in pediatric patients, leading to improved patient outcomes and better quality of care.

Limitations of the study

While this review on pulse oximetry provides valuable insights into its advantages, challenges, and guidelines for effective use, several limitations must be considered. Firstly, the scope of the review may not encompass all aspects of pulse oximetry due to the complexity and vastness of the topic, potentially overlooking certain limitations or emerging issues. Additionally, publication bias could skew the findings, favoring studies with positive results and neglecting others. The review's date range may also limit its inclusiveness of recent pulse oximetry technology and research advancements. Furthermore, the generalizability of the review's conclusions may be limited by variations in healthcare settings, patient populations, and clinical practices. The quality of included studies, bias in selection criteria, and language bias could further impact the reliability and validity of the review's findings. Additionally, heterogeneity among included studies and potential conflicts of interest among authors may introduce interpretation uncertainties. Lastly, incomplete accounting for confounding factors and limitations of secondary data analysis could affect the robustness of the review's conclusions. Despite these limitations, acknowledging and addressing these potential biases and uncertainties is essential for interpreting the review's findings accurately and guiding future research efforts in pulse oximetry.

Recommendations

Based on the insights gleaned from this review study on pulse oximetry, several specific recommendations emerge to optimize its utility and mitigate challenges in clinical application.

Advancing technological innovation: Further research is urgently needed to explore cutting-edge technologies and methodologies in pulse oximetry. This research should aim to overcome current limitations, such as motion artifacts and inaccuracies, in patients with compromised peripheral perfusion. Investing in studies assessing the efficacy and reliability of pulse oximetry across diverse patient demographics and clinical scenarios can yield evidence-based guidelines for optimal utilization.

Education and training initiatives: It is paramount to prioritize education and training on pulse oximetry for healthcare professionals, caregivers, and patients. Specific training programs should emphasize correct sensor placement, interpretation of oximetry data, and appropriate responses to alarm signals. These initiatives are crucial for fostering proficiency and awareness, which is essential for improved patient outcomes.

Table 5 General guidelines for effective use of pulse oximetry

Guideline	Details
Sensor placement	Place on well-perfused areas (finger, toe, earlobe) based on the child's age and size
Sensor securement	Secure snugly but not too tightly to prevent motion artifacts and ensure optimal signal quality
Establish baseline	Establish a baseline oxygen saturation level for each patient to interpret subsequent readings accurately
Considerations	The expected oxygen saturation range should be determined based on age, baseline respiratory status, and underlying medical conditions
Continuous monitoring	Continuous monitoring should be used in critically ill or high-risk patients to promptly detect changes in oxygen saturation
Additional parameters	Monitor respiratory rate, heart rate, level of consciousness, and skin color alongside oxygen saturation levels
Minimizing artifacts	Minimize patient movement, ensure proper sensor placement, and use immobilization techniques or sedation as needed to reduce motion artifacts
Equipment maintenance	Regularly monitor and address technical issues and calibrate equipment according to manufacturer's guidelines
Sensor replacement	Replace sensors as needed to maintain accuracy and reliability
Alternative sites	Alternative sensor placement sites (forehead or palm) should be used for patients with poor peripheral perfusion or compromised circulation
Trend monitoring	Monitor trends in oxygen saturation over time rather than relying solely on individual readings
Education	Educate parents, caregivers, and healthcare staff about the importance of pulse oximetry and proper sensor placement
Documentation	Document pulse oximetry readings, relevant clinical information, and interventions in the patient's medical record
Optimization	Every effort should be made to optimize pulse oximetry monitoring effectiveness, improving patient outcomes and care quality

Healthcare infrastructure and resource allocation: Healthcare systems and policymakers should allocate resources to enhancing pulse oximetry infrastructure. This includes ensuring access to supplemental oxygen, procuring reliable pulse oximetry equipment, and implementing maintenance protocols. Overcoming logistical and financial barriers to pulse oximetry adoption, particularly in resource-constrained settings, is crucial for expanding its reach and efficacy in clinical practice.

Promoting interdisciplinary collaboration: Fostering interdisciplinary collaboration among researchers, clinicians, engineers, and industry stakeholders is imperative for driving innovation in pulse oximetry technology. Collaborative endeavors can lead to the development of novel sensor designs, advanced signal processing algorithms, and telemonitoring solutions. These innovations are essential for addressing existing limitations and effectively meeting evolving healthcare needs.

Continuous surveillance and quality assurance: Continuous surveillance and evaluation of pulse oximetry practices are vital for ensuring accuracy, reliability, and safety in clinical settings. Implementing stringent quality assurance protocols, including regular audits, performance assessments, and feedback mechanisms, can identify areas for improvement and support ongoing quality enhancement efforts.

By embracing these specific recommendations, healthcare stakeholders can enhance the effectiveness, accessibility, and reliability of pulse oximetry monitoring. This proactive approach ultimately advances patient care outcomes and ensures the optimal use of pulse oximetry in clinical practice.

CONCLUSION

This comprehensive review underscores the pivotal role of pulse oximetry in modern healthcare while illuminating its limitations, challenges, and potential solutions. Pulse oximetry is a cornerstone technology for non-invasive SpO_2 and pulse rate monitoring, offering invaluable real-time feedback crucial for timely clinical interventions. However, the review elucidates various factors that can compromise the accuracy and reliability of pulse oximetry readings, including motion artifacts, poor peripheral perfusion, ambient light interference, and patient-specific factors such as skin pigmentation and hemoglobin variants. Despite these challenges, the study provides actionable recommendations to optimize pulse oximetry utilization, encompassing technological advancements, education, healthcare infrastructure, interdisciplinary collaboration, and quality assurance practices. By embracing these recommendations, healthcare stakeholders can harness the full potential of pulse oximetry, ensuring its efficacy, accessibility, and safety across diverse clinical settings. Ultimately, this review serves as a call to action for continuous innovation, education, and quality improvement efforts to enhance pulse oximetry monitoring and advance patient care worldwide.

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FOOTNOTES

Author contributions: Al-Beltagi M, Saeed NK, Bediwy AS, and Elbeltagi R contributed to this review exploring pulse oximetry in pediatric care; Al-Beltagi M, Saeed NK, and Elbeltagi R conceptualized and designed the review with Al-Beltagi M specifically proposing, designing, and conducting the search in electronic databases, as well as synthesizing the included studies' findings; Al-Beltagi M, Saeed NK, and Bediwy AS screened studies, extracted data, and contributed to the analysis and interpretation of the results; Al-Beltagi M and Saeed NK made crucial and indispensable contributions to the project, qualifying them as co-first authors of the review; Al-Beltagi M and Elbeltagi R played important and indispensable roles in this manuscript, Elbeltagi R provided oversight and guidance throughout the review process, as well as contributing to the interpretation of the results and drafting the manuscript; furthermore, Al-Beltagi M and Elbeltagi R collaborated closely in synthesizing the findings, identifying specific use of pulse oximetry in pediatric care, and discussing the clinical implications of the results. This collaboration between Al-Beltagi M and Elbeltagi R was crucial for the completion and publication of this review, which aims to enhance our understanding of the use of pulse oximetry in pediatric care and its clinical implications.

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Decoding the genetic landscape of autism: A comprehensive review

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Abstract

BACKGROUND

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition characterized by heterogeneous symptoms and genetic underpinnings. Recent advancements in genetic and epigenetic research have provided insights into the intricate mechanisms contributing to ASD, influencing both diagnosis and therapeutic strategies.

AIM

To explore the genetic architecture of ASD, elucidate mechanistic insights into genetic mutations, and examine gene-environment interactions.

METHODS
A comprehensive systematic review was conducted, integrating findings from studies on genetic variations, epigenetic mechanisms (such as DNA methylation and histone modifications), and emerging technologies [including Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 and single-cell RNA sequencing]. Relevant articles were identified through systematic searches of databases such as PubMed and Google Scholar.

RESULTS
Genetic studies have identified numerous risk genes and mutations associated with ASD, yet many cases remain unexplained by known factors, suggesting undiscovered genetic components. Mechanistic insights into how these genetic mutations impact neural development and brain connectivity are still evolving. Epigenetic modifications, particularly DNA methylation and non-coding RNAs, also play significant roles in ASD pathogenesis. Emerging technologies like CRISPR-Cas9 and advanced bioinformatics are advancing our understanding by enabling precise genetic editing and analysis of complex genomic data.

CONCLUSION
Continued research into the genetic and epigenetic underpinnings of ASD is crucial for developing personalized and effective treatments. Collaborative efforts integrating multidisciplinary expertise and international collaborations are essential to address the complexity of ASD and translate genetic discoveries into clinical practice. Addressing unresolved questions and ethical considerations surrounding genetic research will pave the way for improved diagnostic tools and targeted therapies, ultimately enhancing outcomes for individuals affected by ASD.

Key Words: Autism spectrum disorder; Genetics; Epigenetics; Clustered Regularly Interspaced Short Palindromic Repeats-Cas9; Gene-environment interactions; Personalized medicine

Core Tip: This review synthesizes current knowledge on the genetic and epigenetic factors contributing to autism spectrum disorder (ASD). It highlights the complexity of ASD's genetic architecture and the role of epigenetic mechanisms such as DNA methylation and non-coding RNAs in disease pathogenesis. Emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats-Cas9 and advanced bioinformatics are pivotal for advancing our understanding of ASD. Collaborative research efforts are crucial for integrating diverse disciplines and international data, aiming to translate genetic insights into personalized therapies. Addressing unresolved questions and ethical considerations will be essential for maximizing the clinical utility of genetic discoveries in improving outcomes for individuals with ASD.

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INTRODUCTION

Autism spectrum disorder (ASD) is a multifaceted neurodevelopmental condition marked by a heterogeneous array of symptoms that can significantly influence social interaction, communication, and behavioral patterns[1]. The term "spectrum" underscores the extensive variability in the severity and manifestation of symptoms among affected individuals. The cardinal features of ASD encompass deficits in social communication, engagement in repetitive behaviors, and a restricted range of interests. Specifically, individuals with ASD experience challenges in both verbal and non-verbal communication, have difficulty interpreting social cues, and encounter obstacles in forming and sustaining relationships[2]. They also display repetitive activities, stereotyped movements, adherence to specific routines, and intense preoccupations with particular topics or activities (Figure 1). The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5), delineates the diagnostic criteria for ASD, emphasizing persistent deficits in social communication and interaction coupled with restrictive and repetitive behavioral patterns, interests, or activities[3].

Globally, ASD is estimated to affect approximately 1 in 100 children, though prevalence rates exhibit considerable variation across different countries and studies. In the United States, data from the Centers for Disease Control and Prevention indicate that about 1 in 36 children were diagnosed with ASD as of 2020[4]. This rising prevalence is likely attributable to enhanced awareness, expanded diagnostic criteria, and improved diagnostic methodologies. Epidemiological data also reveal a marked gender disparity, with ASD being approximately four times more prevalent in boys than in girls[5]. Emerging research, however, suggests that females with ASD may be underdiagnosed or diagnosed later, possibly due to distinct symptomatology that differs from their male counterparts[6].

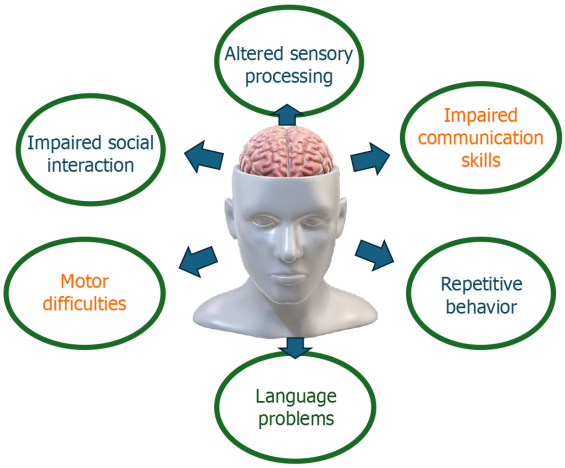

Figure 1 The main clinical manifestations of autism spectrum disorder.

ASD has profound implications for both affected individuals and their families. Children with ASD frequently exhibit developmental delays in speech, language, and motor skills. These children often necessitate individualized educational programs and support services to achieve academic success[7]. Social interaction difficulties can lead to social isolation and challenges in forming and maintaining peer relationships. Additionally, individuals with ASD have higher incidences of co-occurring medical and psychiatric conditions, such as anxiety, depression, attention-deficit/hyperactivity disorder (ADHD), and other mental health disorders[8]. Adults with ASD face significant hurdles in securing and maintaining employment, with many experiencing underemployment or unemployment. A considerable number of adults with ASD require varying degrees of support to live independently, with some necessitating lifelong care. Families of individuals with ASD frequently endure high levels of stress, anxiety, and emotional strain[9]. The financial burden associated with therapies, medical care, special education, and supportive services can be substantial. Parents and caregivers often struggle to balance care responsibilities with professional and other family obligations, leading to reduced work hours or workforce withdrawal[10].

The economic impact of ASD is substantial, encompassing both direct costs, such as medical care and special education, and indirect costs, including lost productivity. In the United States, the lifetime cost of caring for an individual with ASD is estimated to range from $1.4 to $2.4 million[11]. The increasing prevalence of ASD imposes significant demands on healthcare systems to deliver diagnostic, therapeutic, and support services. Educational institutions require additional resources and specialized staff to address the unique needs of students with ASD. Furthermore, heightened awareness of ASD has spurred policy changes and advocacy efforts to enhance service provision, fund research initiatives, and promote inclusive practices[12].

This review aims to synthesize current research findings on the genetics of ASD. This comprehensive systematic analysis seeks to elucidate the intricate interplay between genetic factors, environmental influences, and phenotypic heterogeneity in ASD. By examining the latest advances in genomic technologies, such as whole-genome sequencing (WGS) and genome-wide association studies (GWAS), the review aims to identify and understand the genetic risk factors associated with ASD. Additionally, it explores emerging insights into gene-environment interactions, epigenetic mechanisms, and the role of rare and De novo mutations (DNMs) in the etiology of autism. This synthesis of research findings is intended to inform future research directions and therapeutic strategies, contributing to a deeper understanding of the genetic architecture of ASD and ultimately aiding in developing more effective interventions and support mechanisms for individuals affected by this complex disorder.

MATERIALS AND METHODS

This review utilized a systematic approach to synthesize and analyze existing literature on the genetic underpinnings of ASD. A systematic literature search was conducted using multiple electronic databases, including PubMed, Scopus, Web of Science, and Google Scholar. The search spanned articles published till June 2024 to capture the most recent and relevant studies. Key search terms included "Autism Spectrum Disorder," "genetics," "whole-genome sequencing," "exome sequencing," "copy number variations," "epigenetics," "gene-environment interactions," "de novo mutations," and "genetic architecture." Boolean operators (AND, OR) were employed to refine and expand the search results. Specific inclusion and exclusion criteria were established to ensure the included studies' relevance and quality. Inclusion criteria ensured the studies were peer-reviewed, focused on human genetics in ASD, and published in English. We excluded non-peer-reviewed articles, animal studies, unavailable full texts, or articles not published in English.

Relevant data, including study objectives, methodologies, key findings, and conclusions, were extracted from the selected articles. The extracted data were organized into thematic categories to facilitate a structured synthesis of the information. These categories included advances in genomic technologies (*e.g.*, WGS, exome sequencing), the role of copy number variations (CNVs), gene-environment interactions, epigenetic mechanisms, therapeutic implications and person-

alized medicine, current and future therapies, research challenges, and future directions.

The quality of the included studies was assessed using standardized criteria adapted from the Critical Appraisal Skills Programme checklist. This evaluation considered factors such as study design, sample size, methodology robustness, and the relevance of findings to the research questions. Studies were rated as high, moderate, or low quality, and only high and moderate-quality studies were included in the final synthesis to ensure the reliability of the conclusions. As this study is a literature review, no primary data collection involving human subjects was conducted. Therefore, ethical approval was not required. However, ethical considerations were considered by ensuring the inclusion of ethically conducted studies and appropriately citing all sources.

RESULTS

The comprehensive systematic review identified 356 articles that met the inclusion criteria: 130 research articles, 202 review articles, 4 meta-analyses, 7 systematic reviews, 7 case reports, 2 editorials, and 4 commentaries (Figure 2). Our review of genetic research in ASD has elucidated key findings across several domains, highlighting the complexity and diversity of the disorder. Numerous risk genes have been identified, including *CHD8*, *SHANK3*, and *MECP2*, which play critical roles in synaptic function, neural development, and chromatin remodeling. Notably, studies have shown aberrant DNA methylation patterns, such as hypermethylation of the *MECP2* gene, linked to environmental influences like prenatal stress and toxins, contributing to neural anomalies in ASD. Histone modifications, including changes in acetylation and methylation states, disrupt chromatin structure and gene expression, particularly in genes associated with neural connectivity and plasticity. Additionally, dysregulation of non-coding RNAs, such as microRNAs, impacts the regulation of genes crucial for neural development and synaptic function, further contributing to ASD pathology.

These genetic insights are revolutionizing therapeutic strategies, shifting towards personalized medicine approaches. Tailoring behavioral interventions like Applied Behavior Analysis (ABA) and social skills training based on genetic profiles can address specific deficits more effectively. Pharmacological treatments, including antipsychotics and selective serotonin reuptake inhibitors (SSRIs), are increasingly guided by genetic profiling to enhance efficacy and minimize side effects. Nutritional interventions, such as gluten-free and casein-free diets, are also being personalized based on genetic predispositions related to metabolic processes, improving gastrointestinal and behavioral symptoms in individuals with ASD.

Future therapies are on the horizon, driven by genetic and epigenetic research advancements. Gene therapy targeting specific genetic abnormalities, such as *CHD8* or *SHANK3* mutations, holds promise for correcting or mitigating these genetic disruptions. Epigenetic therapies, including DNA methylation modulators and histone deacetylase inhibitors, aim to reverse abnormal chromatin states and restore normal gene expression patterns. Emerging technologies like Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-Cas9 enable precise genetic modifications to study and potentially correct mutations, while advanced bioinformatics tools analyze extensive genomic data to identify novel genetic variants and risk genes. Single-cell RNA sequencing (scRNA-seq) provides insights into cellular heterogeneity in the brain, and brain organoids offer a model for studying the impact of genetic and environmental factors on neural development.

Collaborative research is crucial for advancing our understanding and treatment of ASD. Multidisciplinary collaborations integrate expertise from genetics, neuroscience, psychology, bioinformatics, and clinical medicine, enhancing research outcomes and facilitating the translation of findings into clinical practice. International collaborations and pooling resources and data from diverse populations enhance studies' statistical power and generalizability. Addressing ethical and practical considerations, such as the accessibility and privacy of genetic testing, is essential for integrating genetic insights into routine clinical care.

DISCUSSION

Overview of ASD

ASD is characterized by various symptoms affecting social interactions, communication, and behavior. Patients with ASD have verbal and nonverbal communication challenges, including difficulties in spoken language and nonverbal cues such as eye contact, facial expressions, and gestures[13]. They also have social reciprocity challenges, including difficulty engaging in reciprocal social interactions, sharing interests and emotions, and initiating or responding to social overtures. In addition, they have trouble developing, maintaining, and understanding relationships, including challenges in adapting behavior to suit various social contexts and forming friendships[14].

Patients with autism commonly suffer from repetitive behaviors and restricted interests. They engage in repetitive actions such as hand-flapping, rocking, or spinning. Additionally, they suffer from insistence on sameness, inflexible adherence to routines, or ritualized verbal or nonverbal behavior patterns[15]. They also have highly restricted, fixated interests with an intense focus on specific topics or objects, often abnormal in intensity or focus. They also have sensory sensitivities with over-reactivity to sensory input, such as an unusual interest in sensory aspects of the environment (*e.g.*, lights, sounds, textures)[16].

The DSM-5 outlines specific criteria for diagnosing ASD, divided into two main categories. The first category involves persistent deficits in social communication and social interaction. These deficits manifest in various ways: Social-emotional reciprocity issues, such as an abnormal social approach, failure of normal back-and-forth conversation,

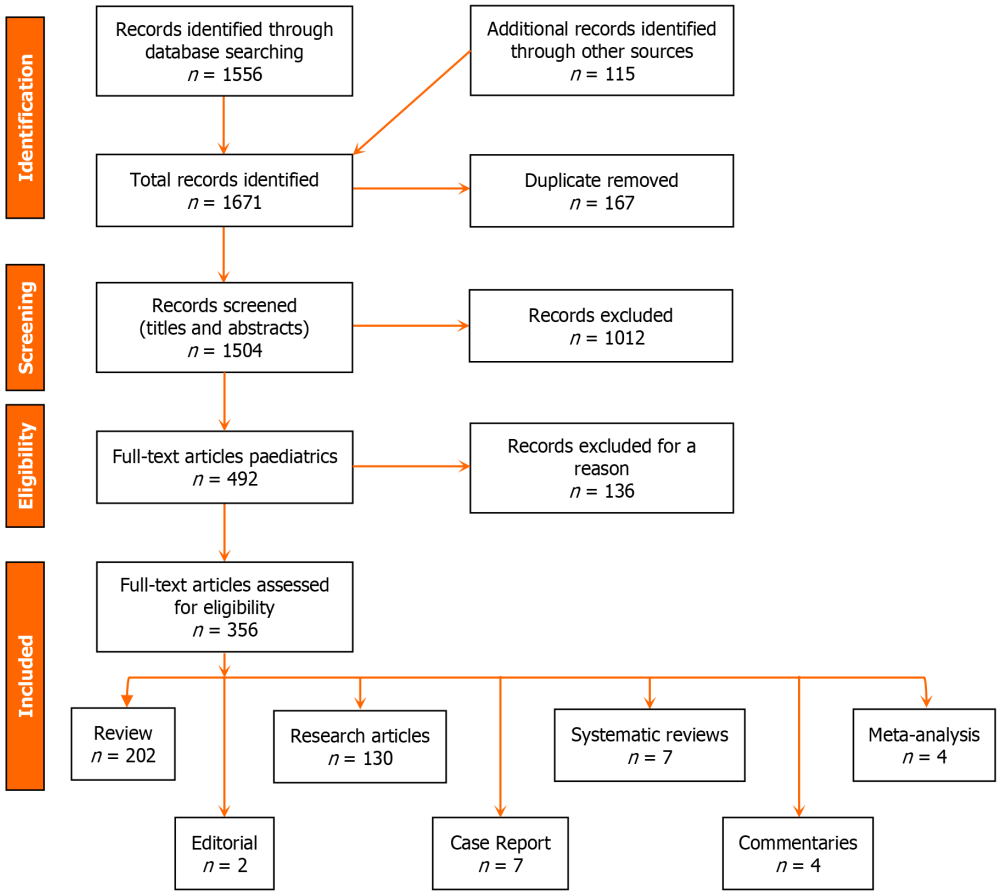

Figure 2 The study flow chart.

reduced sharing of interests or emotions, and failure to initiate or respond to social interactions[17]. There are also deficits in nonverbal communicative behaviors used for social interaction, including poorly integrated verbal and nonverbal communication, abnormalities in eye contact and body language, difficulties in understanding and using gestures, and a lack of facial expressions and nonverbal communication[18]. Lastly, there are deficits in developing, maintaining, and understanding relationships, including difficulty adjusting behavior to suit different social contexts, challenges in sharing imaginative play or making friends, and a general absence of interest in peers[19].

In addition to the core diagnostic criteria, the DSM-5 specifies that symptoms of ASD must be present in the early developmental period. However, they may not become fully apparent until social demands exceed the individual's limited capacities or may be masked by learned strategies later in life[20]. Furthermore, these symptoms must cause clinically significant impairment in social, occupational, or other important areas of current functioning. The disturbances observed should not be better explained by intellectual disability or global developmental delay. While intellectual disability and ASD often co-occur, a comorbid diagnosis requires that the social communication impairments be disproportionate to the general developmental level[21].

Overview and phenotypic heterogeneity of autism

ASD is marked by symptoms affecting social interactions, communication, and behavior. Patients face verbal and nonverbal communication challenges, including difficulties with spoken language, eye contact, facial expressions, and gestures. They struggle with social reciprocity, engaging in reciprocal interactions, sharing interests and emotions, and responding to social overtures. Additionally, they struggle to form and maintain relationships, adapt behavior to various social contexts, and form friendships[13,14]. Repetitive behaviors and restricted interests are common in autism. Patients engage in repetitive actions like hand-flapping and insist on sameness, adhering inflexibly to routines. They often have highly focused, intense interests in specific topics or objects and exhibit sensory sensitivities, reacting strongly to sensory inputs like lights, sounds, and textures[15,16].

The DSM-5 outlines two main diagnostic criteria categories for ASD: Deficits in social communication and social interaction and restricted repetitive behaviors and interests[17-19]. Social communication deficits include social-emotional reciprocity, nonverbal communication, and relationship development and maintenance[17-19]. Symptoms must be present early in development, cause significant impairment in functioning, and not be better explained by intellectual disability or global developmental delay. Intellectual disability and ASD often co-occur, but a comorbid diagnosis requires that social communication impairments exceed general developmental levels[20,21].

ASD isn't a one-size-fits-all condition. ASD is renowned for its phenotypic heterogeneity, which refers to the wide variability in the manifestation of symptoms and traits among individuals with the disorder. Variations in core symptoms, abilities, and motor skills, along with factors like sex and co-existing conditions, create a spectrum of experiences[22]. This heterogeneity encompasses a broad range of social, communicative, and behavioral challenges, making everyone's experience with autism unique. This phenotypic variability is due to the complex interplay of genetic, environmental, and biological factors[23]. Genetic factors include DNMs, inherited genetic variants, CNV, and epigenetic modifications. Environmental factors encompass prenatal exposures, perinatal events, and postnatal influences such as early childhood experiences and exposure to toxins[24]. Biological factors involve improper synaptic morphology and function, differences in brain structure and function, and imbalances in neurotransmitter systems. Co-occurring conditions, such as intellectual disability and other neurodevelopmental and psychiatric disorders, also contribute to variability in symptom presentation and severity[25]. Gender differences also play a role in phenotypic variability in patients with autism. Self-injurious behavior is more frequent in women than men with autism. Males with autism are more likely to have more severe language difficulties than females with autism[26].

Developmental trajectories, including the age of onset and progression of symptoms, along with the development of adaptive skills, further influence the heterogeneity of ASD[27]. Additionally, gene-environment interactions and epigenetic changes play crucial roles in shaping the manifestation of ASD traits. This clinical heterogeneity imposes a substantial challenge to the proper diagnosis and management of patients with autism. It also may reflect the genetic variability present in patients with ASD[28]. Individuals with ASD exhibit diverse levels of difficulty in engaging in reciprocal social interactions. Some may struggle with basic social conventions like making eye contact or recognizing social cues, while others might struggle to share interests or emotions. These challenges can include difficulties in initiating and sustaining conversations, understanding jokes or sarcasm, and recognizing social cues[29]. The ability to form and maintain relationships varies greatly. Some individuals may have profound difficulties in making and keeping friends, while others might develop meaningful relationships but find navigating the nuances of social interactions challenging. Problems with social reciprocity and forming relationships can lead to social isolation and challenges in peer interactions[30].

There is significant variability in verbal communication abilities among those with ASD. Some individuals may be nonverbal or have limited speech, while others may have extensive vocabulary but struggle with pragmatic language use, such as understanding idioms and metaphors or engaging in back-and-forth conversations[31]. Difficulties with nonverbal communication are common and can include challenges in understanding and using body language, facial expressions, and gestures. This can affect the ability to interpret others' emotions and intentions, leading to miscommunications and social misunderstandings. Patients with autism show variable behavioral challenges[32]. These behaviors manifest in various forms, including repetitive movements (*e.g.*, hand-flapping, rocking), ritualistic behaviors (*e.g.*, strict adherence to routines), and intense focus on specific interests (*e.g.*, deep knowledge about a particular subject). The intensity and nature of these behaviors can vary widely among individuals. These behaviors can be coping mechanisms or ways to express excitement, stress, or other emotions. While some individuals may exhibit mild repetitive behaviors, others may have behaviors that significantly interfere with daily activities[33].

Many individuals with ASD have atypical responses to sensory stimuli. This can include hyper-reactivity (*e.g.*, being overwhelmed by loud noises or bright lights) or hypo-reactivity (*e.g.*, seeming indifferent to pain or extreme temperatures). These sensory issues can significantly impact daily functioning and quality of life. Many individuals with ASD have a strong preference for routine and predictability[34]. Changes in routine can cause significant distress and anxiety. Higher rates of co-occurring conditions such as anxiety, depression, ADHD, epilepsy, and gastrointestinal issues are common in individuals with ASD. These conditions can compound the challenges faced by individuals with autism, adding to the complexity of managing their overall health and well-being[35].

Studying the phenotypic heterogeneity of ASD and its biological basis is crucial for several reasons. It helps to identify and understand genetic risk factors that specify specific pathways and mechanisms underlying the disorder's behavioral deficits. It also improves diagnostic accuracy by assisting clinicians to recognize and diagnose the disorder more precisely, thus ensuring that individuals receive the appropriate support and interventions[36]. This understanding enables the development of personalized treatment plans tailored to the unique social, communicative, and behavioral challenges faced by each individual with autism. Enhanced knowledge of phenotypic diversity also leads to better support systems in educational and workplace settings, creating more inclusive environments. Understanding this heterogeneity provides essential information for families and caregivers for practical support and advocacy, helping them manage daily challenges and set realistic expectations[37]. Additionally, research into the phenotypic variability of ASD informs public health policies and funding priorities, ensuring resources are allocated effectively to meet the diverse needs of the autism community. This research also provides insights into the underlying biological, genetic, and environmental factors contributing to ASD, potentially leading to early diagnosis and new therapeutic targets. Moreover, increasing awareness of ASD's diverse manifestations helps reduce stigma, fostering greater acceptance and inclusion in society[38].

Genetic architecture of autism

The genetic architecture of ASD is highly complex, with more than 100 genes implicated in its pathogenesis. ASD is considered a highly polygenic disorder, which is influenced by multiple genes, each contributing a small effect. The combined effect of many genetic variants, both common and rare, creates a cumulative risk of developing ASD[39]. This polygenic risk model helps explain the broad spectrum of ASD phenotypes and the variability in symptom severity and presentation. Genetic susceptibility to ASD refers to the increased likelihood of developing the disorder based on an individual's genetic makeup[40]. This susceptibility is influenced by various genetic factors (Figure 3), including common genetic variants with small effects, rare genetic variants with large effects, DNMs, and CNVs augmented with the gene-

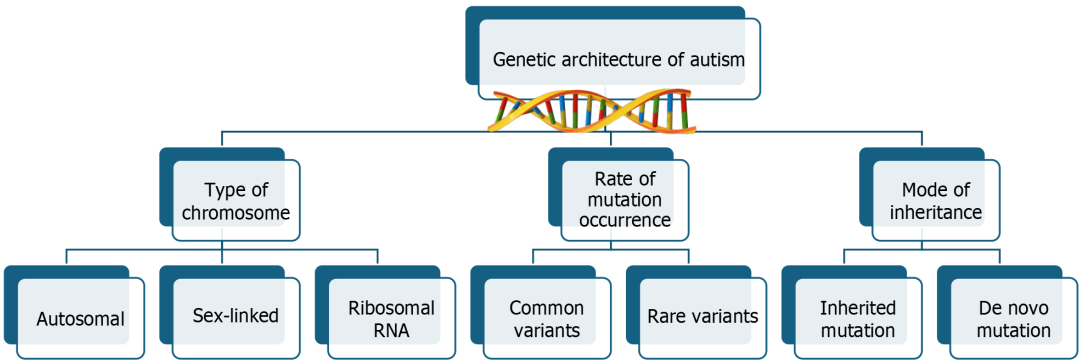

Figure 3 Simple diagrammatic presentation of the genetic architecture of autism.

environment interactions and epigenetic factors effects, which can contribute to the risk of ASD either individually or through complex interactions[41].

Common genetic variants: These genetic variants are relatively frequent variations in the DNA sequence frequently found in the general population and contribute modestly to the risk of developing ASD. Each common variant typically has a small effect on ASD risk, but collectively, they can significantly contribute to genetic susceptibility[42]. These variants are often single nucleotide polymorphisms (SNPs) identified through GWAS. These studies involve scanning the genomes of many individuals to find genetic markers associated with ASD[43]. These studies have identified several SNPs that are more common in individuals with autism compared to those without the disorder. In addition, risk alleles are specific versions of genetic variants that increase the likelihood of developing ASD. While each risk allele contributes only slightly to ASD risk, the presence of multiple risk alleles can have a substantial impact[44].

A polygenic score, also known as a polygenic risk score, is a measure that aggregates the effects of many genetic variants to estimate an individual's genetic predisposition to a particular trait or disorder, such as ASD. This score is calculated based on the presence of numerous common genetic variants, each contributing a small effect to the overall risk[45]. The polygenic score is derived from GWAS, which identifies SNPs associated with ASD. Each SNP is assigned a weight based on its association with ASD, and the polygenic score is the sum of these weighted SNPs present in an individual's genome. The polygenic score estimates how frequent genetic variations in the population contribute to the development of autism[46]. A higher polygenic score indicates a greater genetic predisposition to ASD and a higher probability of being diagnosed with autism. However, it is important to note that a polygenic score is not deterministic; it only provides a risk estimate based on genetic factors[47]. Environmental influences and gene-environment interactions also play significant roles in the development of ASD. Polygenic scores can be used in research to understand the genetic architecture of ASD and to identify individuals at higher genetic risk[48]. These scores might eventually aid in early detection and personalized intervention strategies in clinical settings, although their use in routine clinical practice is still under research and debate. Individuals can be stratified based on their polygenic scores into different risk categories. This stratification can help identify those who might benefit from more intensive monitoring or early intervention[49]. Several common variants have been associated with ASD, though each variant's individual contribution to the disorder is small.

Rare genetic variants: The genetic architecture of ASD is highly heterogeneous, involving a combination of common and rare genetic variants. While common variants each contribute a small effect size, rare genetic variants can have a substantial impact on the risk of developing ASD[39]. These rare variants often exhibit high penetrance, meaning they significantly increase the risk of ASD in carriers. Examples of such mutations include those found in genes like *CHD8*, *SHANK3*, and *MECP2*[50]. These mutations are frequently associated with severe forms of ASD and comorbid conditions such as intellectual disability, epilepsy, and specific syndromic features. The presence of rare genetic variants contributes to the phenotypic variability seen in ASD. Different mutations can lead to diverse clinical presentations, even within the same gene. For instance, mutations in *SHANK3* can result in a range of phenotypes from severe intellectual disability to milder social deficits[51]. Additionally, rare variants can interact with environmental factors, influencing the onset and severity of ASD symptoms. This highlights the importance of considering both genetic predisposition and environmental exposures in understanding ASD[52].

Many rare genetic variants implicated in ASD affect synaptic proteins, which are crucial for synapse formation, function, and plasticity[53]. Genes like *SHANK3*, *NRXN1*, and *NLGN4* are essential in synaptic signaling and neuronal connectivity. Genetic variations such as *CHD8* and *MECP2* affect chromatin remodeling and gene expression regulation, which are critical for proper neuronal development and function[54]. Rare variants also impact neurotransmitter systems, including glutamatergic, GABAergic, dopaminergic, and serotonergic pathways, which are vital for maintaining the balance of excitatory and inhibitory signals in the brain[55]. Advances in sequencing technologies have facilitated the identification of rare genetic variants in individuals with ASD. Whole-exome sequencing (WES) and WGS are instrumental in discovering novel mutations and understanding their functional consequences[56]. Experimental approaches, including animal models and cellular assays, are used to characterize the functional impact of rare variants. These studies help elucidate the biological pathways affected by these mutations and their role in ASD pathology[57].

The identification of rare genetic variants can inform genetic testing and diagnosis, enabling personalized approaches to managing ASD. Genetic counseling can also provide valuable insights to families regarding the inheritance patterns and risks of ASD[58]. Understanding the specific genetic and molecular mechanisms underlying ASD can lead to the development of targeted therapies. For example, drugs modulating synaptic function or neurotransmitter systems may offer potential treatment options for individuals with specific genetic mutations[59].

DNMs: DNM are mutations found in the genomes of autistic or non-autistic children but not in the genomes of their parents. DNMs are new genetic changes that arise spontaneously in the germ cells of parents or early in embryonic development and are not inherited from either parent. They play a significant role among the genetic contributors to ASD [60]. DNMs are particularly important in the context of ASD for several reasons. They are often found in genes critical for brain development and function. Studies have shown that individuals with ASD have a higher burden of DNMs compared to their unaffected siblings. These mutations can occur in coding regions of the genome, disrupting the structure and function of proteins involved in neural development, synaptic signaling, and other key processes[61,62]. One of the key aspects of DNMs is their high impact on the risk of developing ASD. Unlike common variants that contribute small incremental risks, DNMs can have large effects[63]. For instance, mutations in genes such as *CHD8*, *SCN2A*, and *SYNGAP1* have been identified as high-confidence ASD risk genes due to the significant disruptions they cause in neurodevelopmental processes. These genes are involved in critical pathways, including chromatin remodeling, synaptic function, and ion channel activity, highlighting the diverse biological mechanisms through which DNMs can influence ASD[64].

The identification of DNMs has been facilitated by advances in next-generation sequencing technologies, such as WES and WGS[65]. These technologies allow for the comprehensive analysis of the entire genome coding sequence, uncovering rare and potentially pathogenic mutations that may not be detected through traditional genetic testing methods[66]. Research has identified hundreds of genes that harbor DNMs associated with ASD, underscoring the genetic complexity of the disorder. In terms of phenotypic consequences, DNMs are often associated with more severe forms of ASD[67]. Children with DNMs may exhibit profound intellectual disabilities, severe communication deficits, and a higher incidence of comorbid conditions such as epilepsy. This contrasts with ASD cases linked to common genetic variants, which may present with milder symptoms[68].

Furthermore, DNMs provide insights into the genetic architecture of sporadic ASD cases-those without a family history of the disorder. Since these mutations are new and not inherited, they can explain the occurrence of ASD in families with no previous instances, helping to understand the sporadic nature of many ASD cases[69]. This also has implications for genetic counseling, as the recurrence risk of ASD due to DNMs in subsequent pregnancies is generally low, although slightly elevated compared to the general population. Understanding the role of DNMs in ASD has significant implications for both research and clinical practice. It highlights the importance of early genetic screening and diagnosis, which can lead to timely interventions and personalized treatment strategies[70]. Additionally, ongoing research into the functional impact of specific DNMs can identify potential therapeutic targets, paving the way for developing novel treatments to mitigate the effects of these genetic alterations[71].

Some of the well-studied genetic mutations observed in patients with ASD

This section highlights some of the well-studied genetic mutations observed in patients with ASD. Table 1 shows some notable loci, including *CHD8*, *CNTNAP2*, and *SHANK3*. Figure 4 shows some of the important genes liable for mutations in ASD: Their functions and localization of representative molecules.

***CHD8*:** A vital chromatin regulator enzyme during fetal development) gene is a significant genetic factor associated with ASD, located at chromosome 14q11.2, and encoding a protein crucial for chromatin remodeling and gene expression regulation[72]. *CHD8* influences neurodevelopment, neuronal differentiation, and synaptic function, and its disruption can lead to widespread effects on brain structure and function pertinent to ASD. DNMs in *CHD8*, which arise spontaneously and are not inherited, are strongly linked to ASD[25]. These mutations often result in macrocephaly, gastrointestinal issues, specific facial dysmorphisms, and core ASD symptoms such as deficits in social communication and repetitive behaviors[73]. Additionally, *CHD8* mutations are associated with intellectual disability or cognitive impairments, particularly in language and motor skills. Studies have shown that *CHD8* regulates a large network of genes implicated in ASD, and its mutations can disrupt multiple neurodevelopmental pathways[74]. Animal models with *CHD8* mutations exhibit similar features to humans, providing insights into the mechanisms contributing to ASD. Research also explores gene-environment interactions involving *CHD8* to identify intervention periods and therapeutic targets[75]. Potential therapies could involve modulating disrupted pathways, emphasizing the importance of genetic testing and personalized medicine. Understanding *CHD8* mutations helps tailor interventions and support services to individual needs, advancing the development of targeted therapies to mitigate the impact of these genetic mutations.

***CNTNAP2*:** Gene variant is a significant genetic factor implicated in ASD, playing a crucial role in the development and function of the nervous system, particularly in cortical areas related to language, cognition, and social behavior[76]. The *CNTNAP2* gene is the largest gene in the human genome, located at chromosome 7q35, and one of the few known human genes essential for language development. *CNTNAP2* encodes a protein involved in brain cell adhesion and neuronal communication, which is essential for synapse formation, nerve signal transmission, interactions between neurons and between neurons and glial cells, and the clustering of potassium channels[77]. Variants in *CNTNAP2*, including both common and rare mutations, have been linked to ASD and associated with core symptoms such as social communication deficits, repetitive behaviors, language delays, and intellectual disability[78]. Gandhi *et al*[79] showed that disruptions in *CNTNAP2* Lead to altered neural connectivity and signaling, contributing to ASD pathogenesis. Animal models with *CNTNAP2* mutations exhibit behaviors analogous to human ASD, providing valuable insights. Studies also explore how

Table 1 Genes implicated in autism spectrum disorder

No.	Gene symbol	Full gene name	Location	Function	Implication in ASD	Frequency in ASD patients
1	*CHD8*	Chromodomain helicase DNA binding protein 8	Chr. 14q11.	Crucial for chromatin remodeling and gene expression regulation	Regulates network of genes in ASD pathways. Disruption is linked to ASD, macrocephaly, gastrointestinal issues, facial dysmorphisms, social deficits, repetitive behaviors, and intellectual disability	0.2%-0.3%
2	*CNTNAP2*	Contactin-associated protein 2	Chr. 7q35	Essential for brain cell adhesion, synapse formation, and nerve signal transmission. Key role in language and cognition	Altered neural connectivity, language delays, social communication deficits, repetitive behaviors, intellectual disability	0.5%-1%
3	*SHANK* family	SH3 and multiple ankyrin repeat domains protein	SHANK: Chr. 19, SHANK: Chr. 11, *SHANK3*: Chr. 22q13.3	Postsynaptic scaffolding proteins are critical for glutamatergic synapse function. Mutations linked to ASD	Synaptic dysfunction affects the structural integrity of synapses, causing social deficits, repetitive behaviors, and intellectual disability	1%-2%
4	*AVPR1A*	Arginine vasopressin receptor 1A	Chr. 12q14-15	Regulates social behavior and communication	Variants linked to ASD impair social recognition, bonding, social cognition deficits, and repetitive behaviors	0.10%
5	*OXTR*	Oxytocin receptor	Chr. 3p26.2	Key in social cognition and emotional regulation	SNPs and deletions impact receptor function. Variations affect oxytocin binding, which is linked to ASD social deficits	0.1%-0.2%
6	*DRD1*, *DRD2*	Dopamine receptors D1 (DRD1), D2 (DRD2)	DRD1: Chr. 5q35.2, DRD2: Chr. 11q22-23	Crucial for reward processing, motivation, and social behaviors	Impact on synaptic transmission, neural circuits in social interaction. Repetitive behaviors, social deficits, and altered dopaminergic pathways	0.10%
7	*DRD3*	Dopamine receptor D3	Chr. 3q13	Modulates neural circuits related to movement, emotion, and cognition	Variants and CNVs impact dopamine signaling, potentially contributing to ASD features	0.10%
8	*MECP2*	Methyl-CpG-binding protein 2	Chr. Xq28	Regulates gene expression critical for neuronal development	Mutations associated with Rett syndrome and some cases of ASD	1%-2% in females with Rett syndrome
9	*NRXN1*	Neurexin 1	Chr. 2p16.3	Presynaptic cell adhesion molecule crucial for synapse formation	Mutations associated with social communication deficits and cognitive impairments in ASD	0.3%-1%
10	*NRXN2*	Neurexin 2	Chr. 11q13.1	Presynaptic cell adhesion molecule involved in synaptic transmission	Mutations associated with social communication difficulties and ASD traits	Rare, precise frequency unknown
11	*NLGN4X*	Neuroligin 4X	Chr. Xp22.32-p22.31	Postsynaptic cell adhesion protein is involved in synaptic function	Mutations associated with synaptic connectivity disruptions and ASD features	0.5% in males
12	*NLGN4Y*	Neuroligin 4Y	Chr. Yq11.221	Homolog of *NLGN4X* on the Y chromosome	Mutations contribute to synaptic dysfunction and ASD traits in males	Rare, precise frequency unknown
13	*PTCHD1*	Patched domain-containing protein 1	Chr. Xp22.11	Protein is crucial for brain neuronal development and synaptic function	Mutations associated with deficits in social communication, repetitive behaviors, and cognitive flexibility in ASD	0.5% in males
14	*SLC6A4*	Serotonin transporter	Chr. 17q11.2	Regulates serotonin levels in the brain	Variations linked to alterations in social behavior, repetitive behaviors, and sensory processing in ASD	0.1%-0.2%
15	*DLG4*	Discs large homolog 4	Chr. 17p13.1	Scaffolding protein is essential for organizing neurotransmitter receptors at synapses	Mutations associated with synaptic plasticity deficits and behavioral symptoms in ASD	Rare, precise frequency unknown
16	*GABRG2*	Gamma-2 subunit of GABA(A) receptor	Chr. 5q34	Mediates inhibitory neurotransmission in the CNS	Mutations associated with synaptic excitation/inhibition imbalance and ASD symptoms	0.10%
17	*GRM7*	Metabotropic glutamate receptor 7	Chr. 3p26.1	Modulates synaptic transmission and plasticity	Mutations associated with altered glutamatergic signaling and ASD traits	Rare, precise frequency unknown

18	*BDNF*	Brain-derived neurotrophic factor	Chr. 11p14.1	Promotes neuronal growth, survival, and synaptic plasticity	Mutations associated with cognitive and behavioral symptoms of ASD	Rare, precise frequency unknown
19	*NRCAM*	Neuronal cell adhesion molecule	Chr. 7q31.1	Involved in synaptic plasticity and neural connectivity	Mutations associated with altered neural circuitry and behavioral traits in ASD	Rare, precise frequency unknown
20	*HTR2A*	Serotonin receptor 2A	Chr. 13q14.2	Regulates serotonin signaling pathways in the brain	Mutations associated with social behavior deficits and cognitive impairments in ASD	Rare, precise frequency unknown
21	*CX3CR1*	Chemokine receptor 1	Chr. 3p22.2	Involved in brain immune response and neuroinflammatory processes	Variants associated with microglial dysfunction and synaptic connectivity issues in ASD	Rare, precise frequency unknown
22	*CHRNA7*	Alpha-7 nicotinic acetylcholine receptor	Chr. 15q13.3	Integral to cholinergic signaling in the CNS	Mutations associated with cognitive deficits, social impairments, and ASD symptoms	Rare, precise frequency unknown
23	*GRIN2A*	GluN2A subunit of NMDA receptor	Chr. 16p13.2	Essential for synaptic plasticity and learning	Mutations associated with cognitive impairments, seizures, and ASD features	Rare, precise frequency unknown
24	*PTGS2*	Prostaglandin-endoperoxide synthase 2	Chr. 1q31.1	Synthesizes prostaglandins involved in inflammation and immune responses	Potential role in immune dysregulation related to ASD; further research needed	Rare, precise frequency unknown
25	REELN	Reelin	Chr. 7q22	Guides neuronal migration and synaptic plasticity during brain development	Rare mutations associated with altered neuronal migration and synaptic connectivity in ASD	0.1%-0.2%
26	*FOXP2*	Forkhead box P2	Chr. 7q31.1	Important for language development and speech production	Rare mutations linked to speech and language deficits in individuals with ASD	Rare, precise frequency unknown
27	*SNAP25*	Synaptosome associated protein 25	Chr. 20p12.2	Facilitates neurotransmitter release at synapses	Rare genetic variants implicated in synaptic dysregulation in ASD	Rare, precise frequency unknown
28	*CACNA1G*	Calcium voltage-gated channel subunit alpha1 G	Chr. 17q21.33	Part of voltage-gated calcium channels regulating neuronal excitability and synaptic plasticity	Rare mutations associated with altered neural connectivity and behavior in ASD	Rare, precise frequency unknown
29	*GABRA5*	Gamma-aminobutyric acid type A receptor alpha5 subunit	Chr. 15q12	Subunit of GABA-A receptor critical for inhibitory neurotransmission	Rare variants linked to disrupted GABAergic signaling in ASD	Rare, precise frequency unknown
30	*GRIN2B*	Glutamate ionotropic receptor NMDA type subunit 2B	Chr. 12p13.1	It is a subunit of NMDA receptor involved in synaptic plasticity and excitatory neurotransmission	Rare mutations associated with altered synaptic signaling pathways in ASD	Rare, precise frequency unknown
31	*GRIK2*	Glutamate ionotropic receptor kainate type subunit 2	Chr. 6q16.3	Subunit of kainate receptor modulating synaptic transmission and plasticity	Rare genetic variants implicated in synaptic dysfunction and behavioral traits of ASD	Rare, precise frequency unknown
32	*HOMER1*	Homer protein homolog 1	Chr. 5q14.1	Postsynaptic density protein is involved in synaptic signaling and plasticity	Rare mutations linked to synaptic dysfunction and behavioral traits of ASD	Rare, precise frequency unknown

The frequency values provided are approximate and can vary depending on the specific study or population examined. Some genes have "Rare, precise frequency unknown," indicating that while they are implicated in autism spectrum disorder, their mutation frequency is less clearly defined. ASD: Autism spectrum disorder; CNS: Central nervous system; CNV: Copy number variation; NMDA receptor: N-methyl-D-aspartate receptor; SNPs: Single nucleotide polymorphisms.

CNTNAP2 variants interact with environmental factors, which could identify critical intervention periods and therapeutic targets[80]. These findings underscore the importance of genetic testing and personalized medicine, as understanding *CNTNAP2* mutations allows for tailored interventions and support mechanisms, advancing the development of more effective treatments for individuals with ASD.

***SHANK*:** Several large-scale genomic studies have established a strong association between ASD and mutations in the *SHANK* family of genes, specifically *SHANK1*, *SHANK2*, and *SHANK3*[81]. These genes encode a family of postsynaptic scaffolding proteins that are critical for the proper functioning of glutamatergic synapses in the central nervous system (CNS). The SHANK proteins play pivotal roles in synaptic structure and signaling, ensuring the stability and efficiency of

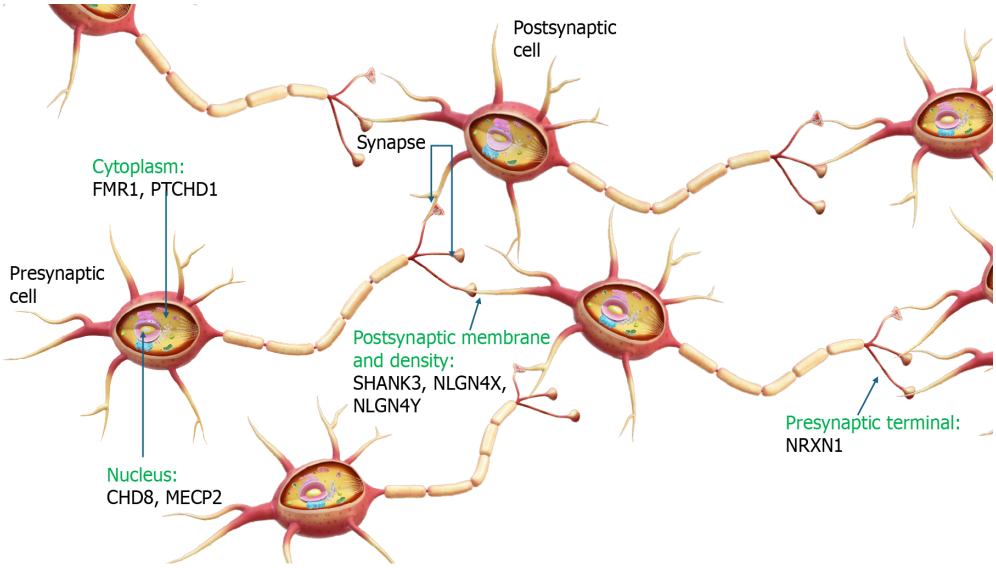

Figure 4 Genetic mutations in autism spectrum disorder: Functions and localizations of representative molecules. This figure provides an overview of representative molecules and their roles in synaptic function, focusing on the structure of a synapse, including the presynaptic terminal (containing neurotransmitter vesicles), the postsynaptic density (containing receptors and signaling proteins), and the synaptic cleft (space between presynaptic and postsynaptic terminals). Key molecules include *CHD8* (chromatin remodeling, gene expression regulation; nucleus; mutations disrupt gene expression, affecting synaptic development), *SHANK3* (postsynaptic scaffold protein; postsynaptic density; mutations affect synaptic signaling and plasticity), *MECP2* (DNA methylation regulation, transcriptional repression; nucleus; mutations affect neuronal function), FMR1 (regulates synaptic protein synthesis; cytoplasm, dendrites; mutations affect synaptic strength and plasticity), NRXN1 (cell adhesion, synaptic transmission; presynaptic terminal; mutations impair synaptic adhesion and neurotransmitter release), *NLGN4X* (cell adhesion molecule; postsynaptic membrane; mutations disrupt synaptic signaling and connectivity, especially in males), *NLGN4Y* [similar to *NLGN4X*; postsynaptic membrane; variations contribute to sex differences in autism spectrum disorder (ASD)], and *PTCHD1* (involved in the Hedgehog signaling pathway; cell membrane and cytoplasm; mutations linked to ASD and intellectual disabilities, more pronounced in males). The synaptic diagram illustrates the overall structure with labeled components, and molecule annotations place symbols representing each molecule at their respective localizations within the synapse, using arrows or lines to indicate their functional roles and the impact of mutations. Additional notes include color coding for different molecules to distinguish their roles and localizations and a legend explaining the symbols, colors, and impact of mutations. This figure underscores the importance of synaptic proteins and pathways in maintaining proper signaling and plasticity, with genetic mutations leading to impaired synaptic function central to ASD pathology.

synaptic connections, which are essential for learning, memory, and overall cognitive function[82].

Mutations in the *SHANK1* gene have been linked to ASD, particularly in males. *SHANK1* encodes a protein contributing to glutamatergic synapses' postsynaptic density (PSD), influencing synaptic strength and plasticity. Individuals with *SHANK1* mutations may exhibit milder ASD symptoms compared to mutations in *SHANK2* and *SHANK3*, but they still present with notable social communication deficits and repetitive behaviors[83]. Mutations in the *SHANK2* gene are associated with a range of neurodevelopmental disorders, including ASD. The SHANK2 protein plays a role in synaptic signaling and the structural integrity of synapses. Variants in *SHANK2* can lead to significant disruptions in synaptic function, resulting in the core symptoms of ASD, such as social communication challenges, repetitive behaviors, and sometimes intellectual disability[84]. Studies have shown that both inherited and DNMs in SHANK2 can contribute to the development of ASD[85].

The *SHANK3* gene is a significant genetic factor associated with ASD, encoding a protein crucial for the development and function of synapses, which are essential for neuronal communication. This protein, also known as ProSAP2, acts as a scaffolding protein in the PSD of excitatory synapses, ensuring synaptic connections' structural and functional integrity [86]. Mutations in *SHANK3* are strongly linked to ASD, particularly in cases related to Phelan-McDermid syndrome, which results from deletions or mutations on chromosome 22q13, where *SHANK3* is located[87]. Individuals with *SHANK3* mutations often exhibit severe expressive language delays, intellectual disability, and significant social communication and behavioral deficits, hallmark features of ASD. These mutations, which can be de novo or inherited, include point mutations, deletions, and duplications that disrupt SHANK3 protein function[88]. Zhou *et al*[89] indicate that *SHANK3* mutations lead to synaptic dysfunction, impairing neuronal communication and resulting in the neurological and behavioral manifestations observed in ASD. Animal models with *SHANK3* mutations exhibit behaviors similar to human ASD symptoms, such as social deficits, repetitive behaviors, and anxiety, offering valuable insights for studying underlying mechanisms and potential interventions[90]. The role of *SHANK3* in synaptic function makes it a critical target for therapeutic research, with efforts underway to develop treatments that can compensate for the loss of *SHANK3* function or restore its normal activity through gene therapy, small molecule drugs, and other innovative approaches[91]. Understanding *SHANK3* mutations in ASD not only aids in diagnosing and managing individuals with these specific genetic alterations but also provides broader insights into the synaptic and neurobiological mechanisms underlying ASD, essential for developing targeted therapies to improve the quality of life for those affected.

***AVPR1A*:** The *AVPR1A* gene, encoding the arginine vasopressin receptor 1A, has been implicated in ASD due to its

critical role in regulating social behavior. This receptor, part of the vasopressin-oxytocin signaling system, influences social bonding, communication, and various social behaviors by initiating signaling cascades essential for neuronal activity and synaptic plasticity[92]. Studies have identified several polymorphisms, such as *RS3* in the *AVPR1A* gene, linked to ASD, as well as rare CNVs affecting gene dosage and receptor function[93]. Variations in *AVPR1A* can lead to significant differences in social behavior, including deficits in social recognition, reduced ability to form social bonds, and impaired communication, which are core aspects of ASD[94]. Animal models have shown that altered *AVPR1A* expression results in notable changes in social interaction, providing insights into similar human behaviors[95]. Clinical studies have associated specific *AVPR1A* alleles with social cognition deficits and repetitive behaviors, highlighting the gene's role in ASD susceptibility[96]. Understanding *AVPR1A*'s impact on ASD opens potential therapeutic avenues targeting the vasopressin-oxytocin pathway and suggests that genetic variants in *AVPR1A* could serve as biomarkers for personalized interventions, enhancing social functioning in individuals with autism.

OXTR: *OXTR* gene mutations have been scrutinized for their potential involvement in ASD, given the pivotal role of oxytocin in social behavior and bonding, processes often disrupted in individuals with ASD. The *OXTR* gene on chromosome 3 encodes the oxytocin receptor protein primarily expressed in brain regions crucial for social cognition, emotional regulation, and reward processing[97]. Various mutations in *OXTR*, including SNPs, insertions, deletions, and structural variants, can alter oxytocin receptor function. These mutations may impair oxytocin binding affinity and downstream signaling pathways, influencing social behavior and communication skills relevant to ASD[98]. While specific *OXTR* mutations have not been conclusively linked to ASD, genetic studies suggest associations between *OXTR* variations and susceptibility to social deficits characteristic of ASD. Regulatory variations in *OXTR*, affecting gene expression levels in brain regions critical for social functioning, further contribute to ASD risk[99].

Dopamine receptor: Dopamine receptors D1 (*DRD1*) and D2 (*DRD2*) are integral components of the dopamine system, crucial for regulating various neurological functions such as reward processing, motivation, and motor control. Mutations or variations in the genes encoding these receptors have been implicated in ASD, suggesting a role in the disorder's neurobiological underpinnings[100]. *DRD1*, the predominant dopamine receptor in the CNS, influences neuronal growth, cognitive flexibility, and social behaviors, all of which are commonly impaired in individuals with ASD. Genetic variants affecting *DRD1* expression or function may disrupt dopaminergic pathways, contributing to ASD symptoms like repetitive behaviors and social deficits[101]. Similarly, *DRD2*, involved in modulating synaptic transmission and reward mechanisms, has also been linked to ASD. Variants in the *DRD2* gene may alter dopamine signaling, impacting neural circuits crucial for social interaction and communication[102]. Animal studies support these findings, demonstrating that changes in *DRD1* and *DRD2* expression can lead to behaviors resembling those seen in ASD, providing insights into potential therapeutic strategies targeting dopamine receptors to mitigate symptoms associated with autism[103].

The *DRD3* gene encodes the dopamine receptor D3, which is crucial in modulating neural circuits related to movement, emotion, and cognition. Variants in the *DRD3* gene have been explored for their association with ASD due to dopamine's significant role in social behavior, reward processing, and executive function[104]. Specific polymorphisms, such as the Ser9Gly variant, and CNVs in *DRD3* can affect receptor function and dopamine signaling, potentially contributing to ASD's behavioral and cognitive features. Alterations in dopamine signaling through *DRD3* receptors can influence social behaviors, affecting social motivation, reward processing, and social interactions[105]. Animal studies have shown that manipulating *DRD3* expression impacts social behavior, repetitive behaviors, and cognitive flexibility relevant to ASD symptoms[106]. Human studies have found mixed results regarding the association between *DRD3* variants and ASD, with some suggesting a link to increased risk of autism and specific traits like repetitive behaviors and social communication difficulties[107].

***MECP2*:** The *MECP2* gene encodes the methyl-CpG-binding protein 2, a critical regulator of gene expression in the brain, playing a crucial role in neuronal development and synaptic plasticity. Mutations in *MECP2* are primarily associated with Rett syndrome, a severe neurodevelopmental disorder, but are also implicated in some cases of ASD. These mutations can include missense, nonsense, insertions, deletions, and duplications, leading to a loss or abnormal function of the MECP2 protein[108,109]. Clinically, individuals with *MECP2* mutations may exhibit impaired social interaction, communication difficulties, and repetitive behaviors, overlapping with core ASD features. The phenotypic effects of *MECP2* mutations can vary widely, contributing to a spectrum of neurodevelopmental conditions[110]. Research has identified *MECP2* mutations in a subset of individuals with ASD, highlighting the gene's contribution to the genetic heterogeneity of autism[111]. Animal models with *MECP2* mutations exhibit similar neurological and behavioral traits to humans, providing insights into these disorders' underlying mechanisms[112].

***NRXN1* and *NRXN2*:** Mutations in *NRXN1* and *NRXN2* genes, which encode neurexins, are implicated in ASD and other neurodevelopmental disorders. Neurexins are presynaptic cell adhesion molecules crucial for synapse formation, synaptic transmission, and neural circuit development. *NRXN1* mutations include deletions, duplications, and point mutations, often resulting in a loss of function[113]. Individuals with *NRXN1* mutations frequently exhibit ASD features such as social communication deficits, repetitive behaviors, and restricted interests. These mutations are also linked to intellectual disability, schizophrenia, and epilepsy. Although *NRXN1* deletions are relatively rare, they are significant genetic risk factors for ASD[114]. *NRXN2* mutations, involving similar types of genetic alterations, are associated with social communication difficulties, cognitive impairments, and repetitive behaviors, also contributing to the genetic heterogeneity of ASD. Both *NRXN1* and *NRXN2* mutations impair synaptic transmission and plasticity, leading to deficits in learning, memory, and behavior[115]. Research on these genes underscores their importance in synaptic function and highlights potential therapeutic targets. Large-scale genomic studies and animal models have further elucidated the

impact of these mutations, suggesting that restoring normal synaptic function could mitigate the effects of these genetic disruptions and improve outcomes for individuals with ASD[116].

***NLGN4X* and *NLGN4Y*:** Mutations in the *NLGN4X* and *NLGN4Y* genes, which encode neuroligin (NLGNs)-4 proteins crucial for synaptic function, have been implicated in ASD. *NLGN4X*, located on the X chromosome, and *NLGN4Y*, its Y chromosome homolog, play essential roles in synaptic organization and neurotransmission[117]. Mutations in *NLGN4X*, including missense mutations and deletions, disrupt synaptic connectivity and function, contributing to ASD features such as impaired social communication, repetitive behaviors, and intellectual disability[118]. These mutations are primarily inherited in an X-linked recessive manner, affecting males more severely due to the lack of *NLGN4Y* compensation on the Y chromosome. *NLGN4Y* mutations, although less studied, similarly affect synaptic function and may contribute to ASD and other neurodevelopmental disorders in males[119].

***PTCHD1*:** *PTCHD1* gene mutations have garnered attention in ASD research due to their implications for neurodevelopmental processes. Located on the X chromosome, the *PTCHD1* gene encodes a protein crucial for brain neuronal development and synaptic function[120]. Various mutations in *PTCHD1*, including deletions, duplications, and missense mutations, disrupt its normal function, potentially affecting synaptic plasticity and neurotransmitter signaling pathways. These disruptions are implicated in the pathophysiology of ASD, contributing to deficits in social communication, repetitive behaviors, and cognitive flexibility observed in affected individuals[121]. *PTCHD1* mutations are more prevalent in males due to their X-linked inheritance pattern. Research into *PTCHD1* aims to elucidate how these mutations alter neuronal connectivity and synaptic transmission, providing insights into ASD's genetic mechanisms[122].

***SLC6A4*:** *SLC6A4* (also known as the serotonin transporter) gene plays a critical role in regulating serotonin levels in the brain by facilitating serotonin reuptake from the synaptic cleft back into presynaptic neurons[123]. Serotonin is a neurotransmitter involved in various physiological processes, including mood regulation, emotional processing, and social behavior, all of which are implicated in ASD[124]. Mutations in *SLC6A4*, encompassing various forms such as SNPs and structural variants, can impact serotonin transporter function and serotonin reuptake efficiency. These genetic alterations may disrupt serotonin signaling pathways, influencing neuronal development, synaptic plasticity, and the formation of neural circuits essential for social cognition and emotional processing[125]. While specific *SLC6A4* mutations have not been definitively linked to ASD, variations in the gene have been associated with alterations in social behavior, repetitive behaviors, and sensory processing observed in individuals with ASD[126].

***DLG4*:** *DLG4* gene (also known as Discs Large Homolog 4 or PSD-95) is a critical gene involved in synaptic function and neuronal development. It encodes a scaffolding protein essential for organizing and stabilizing neurotransmitter receptors and signaling proteins at excitatory synapses, particularly those involved in glutamatergic transmission in the CNS[127]. Mutations in *DLG4* can disrupt its function, affecting synaptic plasticity, neurotransmitter signaling, and neuronal circuitry, potentially contributing to the cognitive and behavioral symptoms observed in individuals with ASD [128]. These genetic changes, which may include missense mutations, deletions, or other structural variants, can lead to deficits in synaptic plasticity and an altered excitatory/inhibitory balance in the brain, associated with impairments in social communication, repetitive behaviors, and sensory processing in ASD[129]. Research into *DLG4* underscores the importance of synaptic proteins in ASD pathophysiology, providing insights into the molecular mechanisms underlying synaptic dysfunction and neuronal connectivity deficits[130].

GABRG2: The *GABRG2* gene, which encodes the gamma-2 subunit of the GABA(A) receptor, is critical in mediating inhibitory neurotransmission in the CNS. Mutations in *GABRG2* have been implicated in several neurological and developmental disorders, including ASD. GABA(A) receptors are pivotal in maintaining the balance between excitation and inhibition in the brain, which is essential for normal cognitive and behavioral functions[131]. In the context of autism, mutations in *GABRG2* can disrupt the function of GABA(A) receptors, leading to an imbalance in synaptic excitation and inhibition. This disruption can contribute to the core symptoms of ASD, such as social communication difficulties, repetitive behaviors, and restricted interests. Individuals with *GABRG2* mutations may exhibit a range of phenotypic manifestations, reflecting the gene's role in the broader neurodevelopmental landscape[132]. Studies have shown that *GABRG2* mutations can result in altered receptor function, affecting synaptic transmission and plasticity and leading to hyperexcitability of neural circuits, which is often observed in individuals with ASD[133]. Additionally, *GABRG2* mutations have been linked to co-occurring conditions frequently seen in autism, such as epilepsy, intellectual disability, and anxiety disorders, further complicating the clinical presentation and management of ASD[134].

***GRM7*:** *GRM7* gene, which encodes the metabotropic glutamate receptor 7 (mGluR7), modulates synaptic transmission and plasticity in the brain. Mutations or variations in *GRM7* have been associated with ASD, highlighting the gene's significance in neurodevelopmental processes. mGluR7 plays a crucial role in inhibitory neurotransmission by regulating the release of neurotransmitters at presynaptic terminals[135]. Dysregulation of glutamatergic signaling due to *GRM7* mutations can contribute to ASD symptoms, including social communication deficits, repetitive behaviors, and restricted interests[136]. Animal model studies have shown that *GRM7* expression or function alterations can result in autism-relevant behaviors, such as impaired social interactions and increased repetitive actions[137]. Genetic studies in human populations have identified associations between SNPs in *GRM7* and an increased risk of developing ASD. This suggests that genetic variation in this receptor may influence susceptibility to the disorder[138]. The involvement of *GRM7* in ASD points to potential therapeutic targets, with current research exploring the development of mGluR7 agonists or antagonists to restore normal glutamatergic signaling and mitigate autism symptoms[139]. Overall, *GRM7* mutations and their impact on glutamatergic signaling represent a significant area of interest for understanding the genetic and

molecular basis of autism and for developing new therapeutic approaches.

***BDNF*:** *BDNF* is a crucial protein involved in neurons' growth, maintenance, and survival, playing a significant role in synaptic plasticity essential for learning and memory. Mutations or variations in the *BDNF* gene have been implicated in ASD, suggesting that *BDNF* dysfunction may contribute to the neurodevelopmental abnormalities characteristic of autism [140]. *BDNF* influences several aspects of neuronal function, including dendritic growth, synapse formation, and neurotransmitter release, which are vital for proper brain development and function[141]. In individuals with ASD, alterations in *BDNF* levels or activity can disrupt these processes, leading to deficits in social communication, repetitive behaviors, and restricted interests typical of the disorder[142]. Studies have shown that individuals with ASD often have altered *BDNF* expression levels, with some research indicating that lower levels of *BDNF* may be associated with more severe autism symptoms[143]. Specific SNPs in the *BDNF* gene have been linked to an increased risk of developing ASD, as these genetic variations can affect *BDNF* production or function, contributing to the pathophysiology of autism[144]. Animal models have been instrumental in elucidating the role of *BDNF* in ASD, with mice exhibiting altered *BDNF* expression showing behaviors reminiscent of autism, such as impaired social interactions and increased repetitive behaviors[145]. These models provide valuable insights into the mechanisms by which *BDNF* dysfunction may lead to ASD symptoms and offer a platform for testing potential therapeutic interventions. The link between *BDNF* and ASD also opens up potential therapeutic avenues, as strategies aimed at modulating *BDNF* levels or enhancing its activity could potentially alleviate some of the symptoms associated with autism. For instance, certain pharmacological agents, physical exercise, and dietary interventions have been shown to increase *BDNF* levels and may hold promise as adjunct therapies for ASD[146,147].

***NRCAM*:** *NRCAM* is a crucial protein involved in the development and function of the nervous system, particularly in the formation and maintenance of synapses[148]. Mutations or variations in the *NRCAM* gene have been associated with ASD, highlighting its potential role in the disorder's pathogenesis. *NRCAM* belongs to the immunoglobulin superfamily of cell adhesion molecules and plays a significant role in axonal guidance, synaptic plasticity, and neural connectivity, all of which are critical for proper brain function and development[149]. In individuals with ASD, *NRCAM* mutations may lead to altered neural circuitry and connectivity issues, which are common neuropathological features of the disorder. Studies have shown that *NRCAM* is involved in processes such as dendritic spine development and the regulation of synaptic strength, both of which are essential for cognitive functions like learning and memory. Disruptions in these processes can contribute to the core symptoms of ASD, including social communication deficits and repetitive behaviors [150]. Research has indicated that *NRCAM* interacts with other synaptic proteins and receptors, influencing neurons' structural and functional plasticity. For instance, *NRCAM*'s interaction with the L1 family of cell adhesion molecules is vital for neurite outgrowth and axonal pathfinding, which are often disrupted in ASD[151,152]. Additionally, animal models with *NRCAM* gene knockouts exhibit behavioral phenotypes reminiscent of ASD, such as social interaction impairments and increased anxiety-like behaviors, further supporting the gene's involvement in autism[130]. Overall, the association between *NRCAM* mutations and ASD underscores the importance of cell adhesion molecules in neurodevelopment and synaptic function.

***HTR2A*:** The *HTR2A* gene encodes the 5-hydroxytryptamine (serotonin) receptor 2A, a critical receptor in the brain involved in neurotransmission pathways. Mutations or variations in the *HTR2A* gene have been linked to ASD, suggesting that disruptions in serotonin signaling could play a role in the disorder's pathophysiology[153]. Serotonin is essential for regulating mood, anxiety, and social behavior, and abnormalities in serotonin signaling have been implicated in various psychiatric conditions, including autism. Studies indicate individuals with ASD often exhibit altered serotonin levels in the brain and peripheral tissues[124]. The *HTR2A* receptor is distributed in brain regions associated with cognitive functions, such as the prefrontal cortex and hippocampus. Mutations in the *HTR2A* gene can change the receptor's expression or function, disrupting serotonergic signaling crucial for social behavior and cognitive processing [154]. Genetic studies have identified polymorphisms in the *HTR2A* gene associated with increased ASD risk, where certain SNPs in the promoter region can affect gene expression levels[155]. Functional studies in animal models demonstrate that alterations in *HTR2A* signaling can affect social behavior and anxiety, mirroring ASD symptoms. The *HTR2A* receptor also plays a role in neurodevelopmental processes, including synaptogenesis and neural differentiation, with disruptions potentially leading to brain development and connectivity abnormalities characteristic of ASD[156].

***CX3CR1*:** The *CX3CR1* gene encodes the chemokine receptor 1, which is involved in the brain's immune response and neuroinflammatory processes[157]. Mutations or polymorphisms in *CX3CR1* have been implicated in ASD, suggesting that disruptions in immune signaling pathways may contribute to ASD pathogenesis. *CX3CR1* is expressed in microglia, the brain's resident immune cells, which are crucial for synaptic pruning, neuronal connectivity, and neuroinflammation [158]. Proper microglial function is essential for normal brain development and neural circuit maintenance. Research indicates that *CX3CR1* variants can alter microglial function, impairing synaptic pruning and increasing neuroinflammation, resulting in abnormal synaptic connectivity and contributing to the neurological deficits seen in ASD[159]. Studies show that certain *CX3CR1* polymorphisms are linked to increased microglial activation and exaggerated brain inflammatory responses, disrupting neuronal communication and plasticity, which are key to cognitive and social behaviors[160]. Animal models with *CX3CR1* mutations exhibit ASD-like behaviors, such as social interaction deficits and repetitive behaviors, providing insights into the gene's impact on brain development and function[161]. Genetic studies in humans have identified associations between specific *CX3CR1* variants and increased ASD susceptibility, highlighting the potential role of immune dysregulation in the disorder[162].

***CHRNA7*:** The *CHRNA7* gene encodes the alpha-7 nicotinic acetylcholine receptor (α7nAChR), a key component of cholinergic signaling in the CNS. This receptor is crucial for neurodevelopmental processes such as synaptic plasticity, neurotransmitter release, and cognitive function[163]. Mutations or polymorphisms in *CHRNA7* have been linked to ASD, suggesting that disruptions in cholinergic signaling may play a role in autism's pathophysiology. The α7nAChR is highly expressed in brain regions involved in cognition, memory, and social behavior, including the hippocampus, cortex, and amygdala, and it modulates the release of neurotransmitters like glutamate, GABA, and dopamine[164]. Research indicates that *CHRNA7* mutations can reduce receptor function or expression, impairing cholinergic signaling and affecting synaptic formation, neuronal differentiation, and network connectivity. This can result in cognitive and social deficits typical of ASD[165]. Studies have found associations between *CHRNA7* gene variants and autism, including CNVs causing partial deletions or duplications of the gene, which disrupt α7nAChR function[166]. Animal models with *CHRNA7* mutations exhibit autism-like behaviors, reinforcing the gene's role in neurodevelopment and autism. Additionally, α7nAChR regulates brain anti-inflammatory responses, and its impaired signaling may increase neuroinflammation, which is implicated in ASD etiology[167].

***GRIN2A*:** The *GRIN2A* gene encodes the GluN2A subunit of the NMDA (N-methyl-D-aspartate) receptor, which is essential for synaptic plasticity, learning, and memory. Mutations in *GRIN2A* are linked to various neurodevelopmental disorders, including ASD, epilepsy, and intellectual disability[168]. These mutations can lead to either a gain or loss of NMDA receptor function, disrupting synaptic signaling and neural circuitry[169]. Individuals with *GRIN2A* mutations often exhibit language deficits, intellectual disability, seizures, and autistic behaviors, highlighting the gene's complex role in brain development and function[170]. Research using animal models has shown that disruptions in NMDA receptor signaling due to *GRIN2A* mutations affect the development of neural circuits involved in social behavior, communication, and cognition[171]. Potential therapeutic approaches include pharmacological agents that modulate NMDA receptor activity and genetic therapies to correct specific mutations.

***PTGS2*:** *PTGS2* gene, also known as COX-2, plays a pivotal role in synthesizing prostaglandins, which are important mediators of inflammation and immune responses in the body[172]. While *PTGS2* mutations have been extensively studied in relation to inflammatory diseases and cancer, their direct association with ASD is not well-established in the current research literature. Studies exploring the role of immune dysregulation and inflammation in ASD have suggested potential links between immune system abnormalities and the development of autistic symptoms[173]. Prostaglandins, synthesized by *PTGS2*, are involved in regulating immune responses that could impact neurodevelopmental processes [174]. However, specific evidence directly implicating *PTGS2* mutations in ASD pathogenesis remains limited. Further research is necessary to determine whether variations in *PTGS2* influence inflammatory pathways that might contribute to the development or severity of ASD traits in affected individuals.

***Reelin* (*RELN*):** *Reelin* (*RELN*) is a pivotal protein in brain development, crucial for guiding the migration and positioning of neurons during the early stages of development[175]. Located on chromosome 7q22, the *RELN* gene encodes an extracellular matrix protein that interacts with receptors like VLDLR and ApoER2 to regulate neuronal migration and synaptic plasticity. Mutations in *RELN* have been implicated in various neurodevelopmental disorders, including ASD [176]. Research indicates that disruptions in *RELN* expression or function can lead to altered neuronal migration patterns and abnormal synaptic connectivity, potentially contributing to the cognitive and behavioral impairments seen in ASD [177]. While rare mutations in *RELN* have been identified in some individuals with ASD, they are not universally present across all cases. Animal models with *RELN* mutations exhibit behavioral deficits akin to autism, supporting its role in neurodevelopmental processes[75]. Understanding how *RELN* mutations impact brain development and function is crucial for developing targeted therapies and interventions for ASD, highlighting the need for further research into its specific mechanisms and therapeutic implications.

***FOXP2*:** *FOXP2*, located on chromosome 7q31, is a gene crucial for language development and speech production. Mutations in *FOXP2* are associated with speech and language disorders, particularly developmental verbal dyspraxia, which affects speech coordination[178]. Beyond its role in language, *FOXP2* mutations have also been studied in relation to ASD. While rare, mutations in *FOXP2* have been identified in individuals with ASD, suggesting a potential link between *FOXP2* dysfunction and the broader ASD phenotype, particularly affecting language and communication skills [179]. Animal studies and genetic research indicate that *FOXP2* mutations may disrupt neural circuits involved in language processing and social communication, contributing to ASD symptoms[180]. Further investigation is needed to elucidate the precise role of *FOXP2* in ASD pathogenesis and to explore its implications for developing targeted therapies aimed at improving language abilities and social communication skills in individuals with ASD.

***SNAP25*:** *SNAP25* is a gene located on chromosome 20p12.2 that plays a pivotal role in neurotransmitter release at synapses, essential for efficient neuronal communication[181]. Mutations and variations in *SNAP25* have been implicated in various neurodevelopmental and neuropsychiatric conditions, including ASD[182]. Research indicates that alterations in *SNAP25* function can disrupt synaptic transmission, impacting neural circuitry and potentially contributing to the development of ASD symptoms. While *SNAP25* mutations in ASD are less common compared to other disorders like ADHD or schizophrenia, studies have identified rare genetic variations in individuals with ASD[183]. Animal models with *SNAP25* mutations exhibit behaviors relevant to ASD, such as impaired social interactions and repetitive behaviors, reflecting its importance in neural development and behavior regulation[184]. Further investigation into how *SNAP25* disruptions specifically influence ASD pathophysiology could provide insights into underlying mechanisms and potential targets for therapeutic interventions tailored to ASD-related synaptic dysregulation.

***CACNA1G*:** *CACNA1G* is a gene that encodes a subunit of the voltage-gated calcium channels, which are crucial for regulating calcium ion influx into neurons. These channels play a vital role in neurotransmitter release, neuronal excitability, and synaptic plasticity in the brain[185]. Mutations or variations in *CACNA1G* have been implicated in various neurological and neuropsychiatric disorders, including ASD[186]. Studies have identified rare genetic variants in *CACNA1G* among individuals with ASD, suggesting a potential link between *CACNA1G* dysfunction and ASD susceptibility[187]. Animal models with *CACNA1G* mutations display behavioral traits relevant to ASD, such as altered social interaction, repetitive behaviors, and impaired communication skills. These findings indicate that disruptions in *CACNA1G* function may contribute to ASD pathophysiology by affecting neuronal excitability and synaptic transmission [188]. Further research is needed to elucidate the specific mechanisms by which *CACNA1G* mutations impact ASD risk and to explore potential therapeutic targets aimed at modulating calcium channel activity to mitigate ASD-related symptoms.

***GABRA5*:** *GABRA5* is a gene that encodes a subunit of the GABA-A receptor, which is integral to inhibitory neurotransmission in the brain. GABAergic signaling regulates neuronal excitability and maintains the balance between excitation and inhibition within neural circuits[189]. Mutations or variations in *GABRA5* have been implicated in several neurological and psychiatric disorders, including ASD[190]. Studies have identified rare genetic variants in *GABRA5* among individuals with ASD, suggesting a potential link between *GABRA5* dysfunction and ASD susceptibility[132]. Animal models with *GABRA5* mutations exhibit behavioral characteristics associated with ASD, such as altered social behaviors, repetitive behaviors, and impaired communication skills[191]. These findings suggest that disruptions in *GABRA5*-mediated inhibitory neurotransmission may contribute to the neurodevelopmental abnormalities observed in ASD.

***GRIN2B*:** *GRIN2B* is a gene that encodes a subunit of the NMDA receptor, a critical receptor involved in excitatory neurotransmission and synaptic plasticity in the brain[192]. Mutations or variations in *GRIN2B* have been associated with various neurodevelopmental and neuropsychiatric disorders, including ASD[193]. Studies have identified rare genetic variants in *GRIN2B* among individuals with ASD, suggesting a potential link between *GRIN2B* dysfunction and ASD susceptibility[194]. Animal models with *GRIN2B* mutations exhibit behavioral characteristics relevant to ASD, such as altered social interactions, repetitive behaviors, and impaired cognitive functions[195]. These findings underscore the importance of NMDA receptor function in neurodevelopment and the potential role of *GRIN2B* mutations in disrupting synaptic signaling pathways implicated in ASD pathophysiology.

***GRIK2*:** *GRIK2* is a gene that codes for a subunit of the kainate receptor, which is involved in synaptic transmission and plasticity in the brain. Kainate receptors are a type of ionotropic glutamate receptor that modulates excitatory neurotransmission and plays a role in regulating synaptic development and function[196]. Stolz *et al*[197] showed that mutations or variations in *GRIK2* have been implicated in several neurodevelopmental disorders, including ASD. Studies have identified rare genetic variants in *GRIK2* among individuals with ASD, suggesting a potential link between *GRIK2* dysfunction and ASD susceptibility[198]. Animal models with *GRIK2* mutations exhibit behavioral traits associated with ASD, such as altered social interactions, repetitive behaviors, and cognitive impairments[199]. These findings highlight the significance of kainate receptor-mediated synaptic signaling in neurodevelopment and underscore *GRIK2* as a candidate gene contributing to the genetic complexity of ASD.

***HOMER1*:** *HOMER1* is a gene that encodes a family of PSD proteins involved in synaptic signaling and neuronal plasticity in the brain. These proteins play a crucial role in regulating the structure and function of synapses, particularly at glutamatergic synapses, where they interact with various neurotransmitter receptors and signaling molecules[200]. Mutations or variations in *HOMER1* have been implicated in several neuropsychiatric and neurodevelopmental disorders, including ASD. Studies have identified rare genetic variants in *HOMER1* among individuals with ASD, suggesting a potential role in ASD susceptibility[201]. Animal models with *HOMER1* mutations exhibit behavioral characteristics relevant to ASD, such as altered social interactions, repetitive behaviors, and cognitive deficits[202]. These findings underscore the importance of *HOMER1*-mediated synaptic function in neurodevelopment and synaptic plasticity, implicating *HOMER1* as a candidate gene contributing to the genetic underpinnings of ASD.

Chromosomal disorders in patients with autism

ASD is characterized by a wide range of genetic etiologies, including various chromosomal disorders. These chromosomal abnormalities, which involve alterations in chromosome number or structure, can significantly impact neurodevelopment and contribute to the manifestation of ASD symptoms. While less frequent than DNMs, chromosomal disorders represent another critical genetic piece of the puzzle in understanding ASD[203]. There are two main categories of chromosomal disorders observed in patients with ASD: Numerical abnormalities and structural abnormalities. Numerical abnormalities involve having an atypical number of chromosomes, such as Down syndrome (extra chromosome 21) or Turner syndrome (missing X chromosome). Structural abnormalities refer to changes in chromosome structure, like deletions, duplications, or translocations[204]. Studies suggest that chromosomal abnormalities are present in around 7.4% of individuals with ASD, a higher percentage compared to the general population. These abnormalities can sometimes contribute to more severe forms of ASD, particularly when intellectual disability and developmental delays are also present[205]. Individuals with ASD and chromosomal abnormalities may also experience a higher prevalence of co-occurring conditions like epilepsy and behavioral issues[8].

Fragile X Syndrome (FXS) is the most common inherited cause of intellectual disability and is often associated with ASD. FXS results from a mutation in the *FMR1* gene located on the X chromosome, which leads to the silencing of the gene and a deficiency in the fragile X mental retardation protein[206]. Approximately 30%-50% of individuals with FXS

meet the criteria for ASD, exhibiting symptoms such as social anxiety, repetitive behaviors, and language impairments [207]. Duplications of the 15q11-13 region, often referred to as Dup15q syndrome, are among the most common chromosomal abnormalities linked to ASD. This region contains several genes critical for brain development, including *UBE3A*[208]. Individuals with Dup15q syndrome typically exhibit severe developmental delays, intellectual disability, epilepsy, and a high prevalence of ASD, with features such as social communication deficits and repetitive behaviors [209].

22q11.2 deletion syndrome, also known as DiGeorge Syndrome or Velocardiofacial Syndrome, involves deleting a small piece of chromosome 22. This syndrome is associated with a broad spectrum of clinical manifestations, including congenital heart defects, palatal abnormalities, immune deficiencies, and neuropsychiatric disorders[210]. Approximately 20%-40% of individuals with 22q11.2 deletion syndrome exhibit ASD-like behaviors, including social communication challenges and restricted interests[211]. Turner syndrome affects females and is characterized by the complete or partial absence of one X chromosome (45, X karyotype). While Turner syndrome is primarily associated with physical features such as short stature and gonadal dysgenesis, there is also an increased prevalence of neurodevelopmental disorders, including ASD. Girls with Turner syndrome may exhibit social difficulties, attention deficits, and learning disabilities[212, 213].

Klinefelter syndrome (47, XXY) is a chromosomal disorder that affects males and is characterized by the presence of an extra X chromosome. Individuals with Klinefelter Syndrome often have mild cognitive impairments, speech and language delays, and social difficulties[214]. There is an elevated risk of ASD in males with Klinefelter Syndrome, with symptoms such as social communication deficits and repetitive behaviors[215]. Down syndrome, caused by the presence of an extra chromosome 21 (trisomy 21), is the most common chromosomal disorder associated with intellectual disability. Although not typically classified under ASD, a significant proportion of individuals with Down syndrome exhibit autistic traits, including social interaction challenges and repetitive behaviors[216]. The co-occurrence of ASD and Down syndrome highlights the overlap between different neurodevelopmental conditions[217]. Various other chromosomal abnormalities, such as duplications, deletions, and translocations, can also contribute to the development of ASD. For instance, abnormalities in chromosomes 1q21.1, 16p11.2, and 17q12 have been implicated in ASD, with each region harboring multiple genes involved in neurodevelopmental processes[218].

Identifying a chromosomal disorder can be achieved through karyotyping, a standard genetic test that analyzes chromosomes for abnormalities. Early diagnosis of a chromosomal disorder can lead to earlier diagnosis of ASD and the implementation of appropriate therapies and support systems[219]. Additionally, understanding the specific chromosomal abnormality can inform genetic counseling for families, providing information about potential recurrence risk in future pregnancies[220]. The identification of chromosomal disorders in patients with ASD has significant implications for diagnosis, management, and genetic counseling. Chromosomal microarray analysis and other advanced genetic testing methods have become crucial tools in identifying these abnormalities, enabling early diagnosis and tailored interventions[221]. Understanding the role of chromosomal disorders in ASD provides valuable insights into the genetic architecture of the disorder and underscores the importance of comprehensive genetic evaluations for individuals with ASD[222]. This knowledge not only aids in developing targeted therapies but also enhances our ability to provide personalized care and support for affected individuals and their families. However, it is crucial to recognize that chromosomal disorders are just one contributing factor to ASD in a subset of individuals. Most ASD cases have a more complex genetic architecture involving a combination of genetic and environmental factors[223].

Gender differences in autism symptomology: Sex chromosome effects?

ASD shows notable sex differences in its prevalence and symptomatology, with males being more frequently diagnosed than females. The reported male-to-female ratios vary from 1.33:1 to 15.7:1. Despite the general severity of autism not differing significantly between genders, notable differences exist in how ASD manifests, particularly when comorbid features are present[224]. Males with ASD often exhibit more externalizing behaviors, such as aggression, repetitive movements, and hyperactivity. In contrast, females are more prone to internalizing behaviors, including anxiety and depression. Furthermore, females with ASD tend to have more pronounced cognitive impairments, with the male-to-female ratio nearing 1:1 among those with severe intellectual disabilities[225]. These observations raise the question of whether these gender differences in ASD are due to distinct biological mechanisms or diagnostic biases influenced by the patient's presentation. Typically, ASD is diagnosed as a categorical condition rather than a continuum, which may significantly interact with behavioral and cognitive differences between males and females[26]. For instance, the less disruptive and less overt behaviors in girls with ASD might mean that only those with severe impairment are brought to diagnostic attention[226]. Recognizing these differences is crucial for clinical management, including screening for specific comorbidities and therapeutically targeting the most debilitating symptoms.

Some researchers believe that regardless of diagnostic biases, certain sex-specific biological mechanisms contribute to the gender disparity in ASD[227]. The female-protective effect (FPE) is a leading theory in this regard, suggesting that specific factors protect females from developing ASD, thereby requiring them to have a higher threshold to reach clinical impairment[228]. Evidence supporting this hypothesis includes studies indicating a greater genetic load related to ASD in females compared to males and in clinically unaffected female relatives compared to unaffected male relatives of individuals with ASD[229]. For example, a study of dizygotic twins by Attermann *et al*[229] using the Childhood Autism Spectrum Test and the Autism-Tics, Attention Deficit Hyperactivity Disorder, and Other Comorbidities inventory found higher autism symptom scores in siblings of female probands compared to those of male probands[230]. Similar findings were observed in another large-scale study by Van't Westeinde *et al*[231], which focused on repetitive and restricted behavior differences between male and female dizygotic twins. Females used more compensation and masking camouflage strategies than males. A related argument supporting the FPE is that males are more likely to meet clinical criteria for ASD than females, given the same genetic risk[232]. For instance, individuals with a *SHANK1* microdeletion

were rigorously assessed, revealing that males more frequently met the clinical criteria for ASD, while females with the same mutation exhibited anxiety but not ASD[83].

The FPE mechanisms likely involve genes on the sex chromosomes and sex hormones. Although ASD is not linked to the X chromosome, it is suggested that the Y chromosome may pose a risk or that a second X chromosome may offer protection, as indicated by higher ASD rates in Turner syndrome (XO) and 47, XYY syndrome[233]. The role of sex chromosomes and related molecules has been increasingly recognized in contributing to these differences. Understanding these molecular mechanisms is crucial for developing sex-specific diagnostic and therapeutic approaches. The *MECP2* gene on the X chromosome is a well-known player in neurodevelopmental disorders. Mutations in *MECP2* are primarily associated with Rett syndrome, a condition that predominantly affects females and shares some phenotypic overlap with ASD. *MECP2* is involved in the regulation of gene expression through binding to methylated DNA. Its dysfunction can lead to widespread gene expression changes and neural development abnormalities[234]. Since males have only one X chromosome, mutations in *MECP2* can have more severe consequences, potentially explaining some of the observed sex differences in ASD prevalence and severity. NLGNs are a family of postsynaptic cell adhesion molecules critical for synapse formation and function[25]. *NLGN4X* and *NLGN4Y* are located on the X and Y chromosomes, respectively. Mutations in *NLGN4X* have been linked to ASD, with affected individuals showing impairments in synaptic function and neural connectivity[117]. The presence of *NLGN4X* on the X chromosome means that females with two X chromosomes may have a protective effect if one copy is mutated, whereas males with only one X chromosome are more vulnerable. *NLGN4Y*, on the Y chromosome, has a similar but not identical function to *NLGN4X*, and its role in ASD is less clear. However, variations in these genes can contribute to the differences in ASD manifestation between males and females [118]. *PTCHD1* is another gene of interest located on the X chromosome, which encodes a protein involved in the Hedgehog signaling pathway, essential for brain development. Mutations or deletions in *PTCHD1* have been implicated in ASD, intellectual disability, and other neurodevelopmental disorders. Like *MECP2* and *NLGN4X*, *PTCHD1* mutations may have more pronounced effects in males due to the lack of a second X chromosome that could compensate for the defective gene[120]. The inclusion of sex chromosome-related molecules in the study of ASD is vital for uncovering the nuances of sex differences in the disorder. By investigating the roles of *MECP2*, *NLGN4X*, *NLGN4Y*, and *PTCHD1*, researchers can better understand the genetic and molecular basis of these differences. This knowledge will pave the way for more tailored and effective therapeutic strategies that account for sex-specific variations in ASD presentation and progression[235].

Hormonal differences between males and females may also play a role. The differences in the vasopressinergic system in males and females might explain the male prevalence of ASD[94]. The role of sex hormones, particularly testosterone, in early brain development in children with ASD has garnered considerable interest. Several studies have found correlations between fetal testosterone levels, systematizing traits, social impairments, and reduced empathy[236]. Additionally, adults with ASD have been found to have higher levels of testosterone metabolites compared to unaffected individuals[226]. Future research should focus on developing gender-specific measures to better understand the influence of gender-specific factors on diagnosis and treatment. To date, no treatment studies have specifically targeted females with ASD based on hypothesis-driven approaches. Understanding these gender differences is vital for creating more effective and personalized interventions for individuals with ASD. Table 2 summarizes these gender differences in patients with ASD.

Advances in genomic technologies

Recent advances in genomic technologies have significantly enhanced our ability to diagnose ASD. High-throughput sequencing methods, such as WGS and WES, have enabled the identification of numerous genetic variants associated with ASD[237]. These technologies allow for a comprehensive analysis of the entire genome or the coding regions, respectively, providing insights into both common and rare genetic factors contributing to the disorder. Additionally, microarray-based comparative genomic hybridization (aCGH) has facilitated the detection of chromosomal abnormalities, such as CNVs, which are often implicated in ASD[238]. Integrating these advanced genomic tools into clinical practice holds promise for earlier and more accurate diagnosis, personalized treatment strategies, and a deeper understanding of the genetic architecture underlying ASD[239].

WES: Exome sequencing has made significant contributions to identifying risk genes in patients with ASD. This technology focuses on sequencing the exonic regions of the genome, representing about 1%-2% of the entire genome but containing the vast majority of known disease-related genetic variations[240]. By concentrating on these regions, exome sequencing provides a more cost-effective and efficient means of uncovering the genetic underpinnings of ASD[241]. One of the major contributions of exome sequencing to ASD research is the identification of DNMs-mutations that are not inherited from either parent but occur spontaneously. These mutations have been found to play a critical role in the development of ASD[242]. Studies utilizing exome sequencing have revealed that a significant proportion of individuals with ASD have unique DNMs in various genes, which might not have been identified through traditional genetic testing methods. These discoveries have expanded our understanding of the genetic diversity and complexity of ASD[243].

Exome sequencing has also facilitated the discovery of rare, high-impact variants contributing to the disorder. By analyzing the exomes of large cohorts of individuals with ASD and comparing them to control groups, researchers have identified numerous rare variants in genes that are crucial for brain development and function[244]. These findings have highlighted the importance of genes involved in synaptic function, neuronal communication, and other neurodevelopmental processes in the etiology of ASD. Furthermore, exome sequencing has identified several novel ASD risk genes. For instance, genes such as *CHD8*, SCN2A, and *SYNGAP1* have been implicated in ASD through exome sequencing studies [245]. These genes are involved in critical biological pathways, including chromatin remodeling, ion channel function, and synaptic signaling. Identifying these risk genes has provided new insights into the molecular mechanisms underlying

Table 2 The differences in autism symptomology and related factors between males and females

Aspect	Males with ASD	Females with ASD
Prevalence	Higher prevalence, male-to-female ratio 1.33:1 to 15.7:1	Lower prevalence
Behavioral manifestation	More externalizing behaviors (aggression, repetitive movements, hyperactivity)	More internalizing behaviors (anxiety, depression)
Cognitive impairments	Less pronounced cognitive impairments	More pronounced cognitive impairments, with a male-to-female ratio nearing 1:1 among those with severe intellectual disabilities
Diagnostic bias	More likely to be diagnosed due to overt behaviors	Less likely to be diagnosed unless severe impairment is present due to less disruptive behaviors
Genetic load	Lower genetic load	Higher genetic load in affected females and unaffected female relatives compared to males
Compensation and masking strategies	Less frequent use	More frequent use
Clinical criteria meeting	More likely to meet clinical criteria for ASD given the same genetic risk	Less likely to meet clinical criteria, may exhibit related issues such as anxiety
Sex chromosome influence	Y chromosome may pose a risk	The second X chromosome may offer protection, as indicated by higher ASD rates in Turner syndrome (XO) and 47, XYY syndrome
Hormonal influence	Differences in the vasopressinergic system, higher fetal testosterone levels associated with ASD traits	Potential protection from the second X chromosome, hormonal influences not as clearly defined
Camouflage strategies	Less frequent use	More frequent use to mask symptoms
Research and treatment	Focused mainly on males	Lack of hypothesis-driven treatment studies targeting females

This table highlights the key differences in the manifestation, diagnosis, and underlying biological mechanisms of autism spectrum disorder between males and females. Understanding these differences is essential for improving diagnostic criteria and developing gender-specific treatments. ASD: Autism spectrum disorder.

ASD and has opened up potential avenues for targeted therapeutic interventions[246].

Another significant advantage of exome sequencing is its ability to uncover gene-disrupting mutations in individuals with ASD who do not have a family history of the disorder. This capability is crucial for understanding sporadic cases of ASD, where the genetic basis might be less apparent[247]. By pinpointing specific genetic mutations in these cases, exome sequencing helps to clarify the genetic contributions to ASD in a broader population. Moreover, exome sequencing has proven valuable in studying the genetic architecture of ASD in diverse populations. It allows researchers to explore the genetic variations and mutations that may be more prevalent in certain ethnic or geographic groups, contributing to a more comprehensive understanding of the global genetic landscape of ASD[248].

WGS: WGS has revolutionized the field of genetics by comprehensively analyzing an individual's entire genome, encompassing both coding and non-coding regions. This technology has significantly advanced our understanding of the genetic basis of ASD in several keyways[249]. First, WGS has facilitated the discovery of rare genetic variants that were previously undetectable with older methods. These rare variants often have a large effect size and can be crucial in understanding the genetic underpinnings of ASD[250]. By analyzing the entire genome, WGS can identify mutations in non-coding regions that may regulate gene expression, adding a new layer of complexity to our understanding of ASD genetics[251].

Second, unlike targeted sequencing or WES, which focus only on specific parts of the genome, WGS provides a complete picture. This includes single nucleotide variants, insertions, deletions, CNVs, and structural variants. The ability to detect a wide range of mutation types helps identify novel genetic contributors to ASD[252]. Third, a significant portion of the human genome is non-coding, and mutations in these regions can affect gene regulation and expression. WGS allows researchers to investigate these regions and understand how they may contribute to ASD. For instance, mutations in regulatory elements, enhancers, and promoters can disrupt normal gene function and lead to ASD[253]. Moreover, through WGS, researchers have identified numerous new genes associated with ASD that were not previously linked to the disorder. These discoveries expand the list of potential targets for therapeutic intervention and provide new insights into the biological pathways involved in ASD[254]. ASD is known for its genetic heterogeneity, meaning many different genetic factors can contribute to it. WGS helps elucidate this complexity by identifying the diverse genetic mutations across different individuals with ASD. This understanding can lead to more personalized approaches to diagnosis and treatment[54].

Additionally, WGS enables large-scale genomic studies and the creation of extensive databases of genetic information. By comparing the genomes of thousands of individuals with and without ASD, researchers can identify patterns and commonalities that provide deeper insights into the genetic architecture of the disorder[243]. WGS is particularly useful in family-based studies, where the genomes of affected individuals and their relatives are sequenced. This approach can identify inherited mutations and DNMs (new mutations do not present in the parents) that contribute to ASD, helping to

pinpoint specific genetic risk factors[255]. Overall, WGS has dramatically advanced our understanding of the genetic basis of ASD by providing a detailed and comprehensive view of the genome. This technology continues to uncover new genetic insights, paving the way for better diagnostic tools, personalized treatments, and a deeper understanding of the complex genetic landscape of ASD[256].

CNVs: CNVs have a substantial impact on the risk of developing ASD. CNVs refer to structural changes in the genome that result in the duplication or deletion of large segments of DNA. These variations can encompass one or multiple genes and significantly alter gene dosage, disrupting normal cellular functions[257]. One of the key contributions of studying CNVs to our understanding of ASD is the identification of specific genomic regions where duplications or deletions are associated with increased risk for the disorder[258]. For example, deletions and duplications at the 16p11.2 Locus have been repeatedly implicated in ASD. Individuals with deletions in this region often exhibit neurodevelopmental issues, including ASD, intellectual disability, and language impairments[259]. Conversely, duplications at the same locus are also associated with ASD but may present with differing clinical features, underscoring the complex relationship between gene dosage and neurodevelopmental outcomes[260].

The presence of CNVs can disrupt the function of multiple genes simultaneously, leading to widespread effects on brain development and function. This is particularly relevant for genes involved in synaptic connectivity, neuronal communication, and brain signaling pathways[261]. CNVs that affect these genes can lead to abnormalities in the formation and maintenance of synapses, which are critical for proper brain function and development[262]. For instance, CNVs affecting the *NRXN1* gene, which encodes a protein essential for synaptic function, have been associated with ASD, highlighting the importance of synaptic integrity in the disorder. Furthermore, the study of CNVs has revealed that individuals with ASD often carry a higher burden of rare, large CNVs compared to the general population[263]. These rare CNVs can significantly affect gene function and are often de novo, meaning they are not inherited from the parents but arise spontaneously. The identification of such de novo CNVs in individuals with ASD supports the idea that these structural variations are critical contributors to the genetic architecture of the disorder[264].

Research has also shown that certain CNVs are more prevalent in individuals with ASD who also exhibit additional comorbid conditions, such as intellectual disability or epilepsy[265]. This suggests that CNVs not only contribute to ASD risk but may also influence the broader clinical phenotype, leading to a range of neurodevelopmental outcomes depending on the specific genes and pathways affected. The impact of CNVs on ASD risk is further highlighted by their contribution to the genetic heterogeneity of the disorder[266]. ASD is known for its diverse genetic landscape, and CNVs add another layer of complexity by introducing large-scale genomic changes that can vary widely among affected individuals. This genetic diversity underscores the need for personalized approaches to diagnosis and treatment, as the specific CNVs present in an individual can influence the manifestation and severity of ASD symptoms[267].

Gene-environment interactions and their effects on autism development

Gene-environment interactions play a crucial role in the development of ASD. This concept refers to the dynamic interplay between genetic predispositions and environmental factors, where the combined effects can influence the onset and progression of ASD. Understanding these interactions is essential for unraveling the complex etiology of autism and developing more effective prevention and intervention strategies[268]. Certain genetic variations can increase an individual's susceptibility to ASD, but these variations alone may not be sufficient to cause the disorder. For instance, mutations in genes such as *CHD8*, SCN2A, and *SHANK3* have been identified in individuals with ASD, highlighting a genetic predisposition[223]. However, not all individuals with these mutations develop ASD, suggesting that other factors, including environmental influences, play a role in triggering or exacerbating the condition[52].

Environmental influences, particularly those occurring during prenatal and perinatal periods, have been increasingly recognized as significant factors that may interact with genetic predispositions to influence the risk of developing ASD [269]. Numerous studies have explored how various environmental exposures can contribute to ASD, offering insights into the complex etiology of the disorder. Several studies have established a link between maternal infections during pregnancy and an increased risk of ASD in offspring[270]. For example, a study by Atladóttir *et al*[271] found that maternal infection during the first trimester was associated with a higher risk of ASD. The proposed mechanism involves the maternal immune response, which can produce inflammatory cytokines that cross the placenta and potentially disrupt fetal brain development. The use of certain medications during pregnancy has been linked to an increased risk of ASD. For instance, Christensen *et al*[272] reported that maternal use of valproate, an antiepileptic drug, was associated with a significantly increased risk of ASD and other neurodevelopmental disorders. The study suggests that valproate can alter neurodevelopment through its effects on folate metabolism and histone deacetylase inhibition.

Prenatal exposure to environmental toxins, such as pesticides and heavy metals, has been implicated in the development of ASD. Research by Roberts *et al*[273] indicated that living near agricultural areas where pesticides are used during pregnancy was associated with a higher risk of having a child with ASD. These toxins can disrupt neural development by interfering with signaling pathways critical for brain development. Maternal nutrition, particularly the intake of essential nutrients like folic acid, has been shown to influence ASD risk. A study by Schmidt *et al*[274] found that adequate maternal folic acid intake around conception was associated with a reduced risk of ASD. Folic acid is crucial for DNA methylation and neural tube development, and its deficiency during critical periods can adversely affect fetal brain development.

Perinatal complications such as preterm birth, low birth weight, and hypoxia have been associated with an increased risk of ASD. A meta-analysis by Gardener *et al*[275] found that several perinatal factors, including low birth weight and preterm birth, were significantly associated with ASD. These complications can result in hypoxic-ischemic injury to the developing brain, leading to neurodevelopmental disorders. Advanced parental age, particularly paternal age, has been linked to an increased risk of ASD. Reichenberg *et al*[276] demonstrated that children of older fathers had a higher risk of

ASD, potentially due to the accumulation of DNMs in the sperm of older men. These genetic mutations can interact with environmental factors, increasing the likelihood of ASD development.

Environmental factors can interact with genetic vulnerabilities to influence ASD risk. For example, individuals with certain genetic mutations may be more susceptible to environmental insults. Kinney *et al*[277] found that prenatal exposure to severe maternal stress was associated with a higher risk of ASD in children with a familial history of the disorder. This suggests that genetic susceptibility and environmental stressors can act synergistically to increase ASD risk. Environmental exposures can lead to epigenetic changes that affect gene expression without altering the DNA sequence. These modifications can influence the development of ASD. Dutheil *et al*[278] showed that prenatal exposure to air pollution was associated with changes in DNA methylation patterns in genes related to neurodevelopment, suggesting a potential mechanism for how environmental factors can impact ASD risk. Gene-environment interaction models provide valuable frameworks for understanding how genetic predispositions and environmental factors jointly influence the risk of developing ASD. These models illustrate the complexity of ASD etiology, emphasizing that neither genetic nor environmental factors alone can fully explain the disorder. Several models have been proposed to elucidate these interactions[41].

The diathesis-stress model: The diathesis-stress model is one of the most widely recognized frameworks for understanding gene-environment interactions in ASD. This model posits that individuals inherit genetic vulnerabilities (diatheses) that predispose them to ASD[279]. However, the expression of these genetic vulnerabilities depends on the presence of environmental stressors. For example, a child with a genetic predisposition to ASD may only develop the disorder if exposed to certain environmental factors such as prenatal stress, maternal infections, or exposure to toxins during critical periods of neurodevelopment. This model highlights the interplay between inherent genetic risks and environmental triggers in the manifestation of ASD[280].

The differential susceptibility model: The differential susceptibility model suggests that some individuals are more susceptible to environmental influences, both positive and negative, due to their genetic makeup. In this model, certain genetic variants make individuals more responsive to environmental conditions[281]. For instance, a child with specific genetic variants may be more adversely affected by prenatal exposure to toxins or maternal stress, increasing their risk of developing ASD[282]. Conversely, the same genetic variants might make the child more responsive to positive environmental interventions, such as enriched early learning environments or supportive caregiving, potentially mitigating ASD symptoms or improving developmental outcomes[283].

The biological sensitivity to context model: Similar to the differential susceptibility model, the biological sensitivity to context model proposes that genetic variations influence an individual's sensitivity to environmental contexts. This model focuses on the idea that some individuals are biologically more reactive to environmental stimuli due to their genetic makeup. In the context of ASD, this model suggests that children with certain genetic profiles may have heightened biological responses to environmental stressors or toxins, which could disrupt neurodevelopment and increase the risk of ASD. Alternatively, these children may also benefit more from positive environmental influences, highlighting the importance of supportive and enriched environments for at-risk individuals[284,285].

The gene-environment correlation model: The gene-environment correlation model explores how genetic and environmental factors can be correlated, meaning that genetic predispositions can influence an individual's exposure to certain environments. There are three types of gene-environment correlations: Passive, evocative, and active[286]. In the passive correlation, parents provide both the genes and the environment, such as a parent with ASD traits creating an environment that influences the child's development[287]. Evocative correlation occurs when an individual's genetic traits elicit specific responses from the environment, such as a child's social difficulties leading to social isolation[288]. Active correlation involves individuals seeking out environments that complement their genetic predispositions, such as a child with sensory sensitivities avoiding noisy settings[289]. These correlations can help explain how genetic predispositions and environmental exposures jointly contribute to the development of ASD.

Epigenetic models: Epigenetic models emphasize the role of environmental factors in modifying gene expression through epigenetic mechanisms such as DNA methylation and histone modification. These changes do not alter the DNA sequence but can profoundly affect gene expression and neurodevelopment[290]. Environmental factors such as prenatal nutrition, exposure to toxins, and maternal stress can induce epigenetic modifications that influence the risk of ASD[291]. For example, prenatal exposure to air pollution has been associated with changes in DNA methylation patterns in genes involved in neurodevelopment, suggesting a potential mechanism for how environmental exposures can impact ASD risk [292]. Epigenetic models underscore the dynamic interplay between genes and the environment in shaping developmental outcomes[293].

Integrative models: Integrative models combine elements from multiple frameworks to comprehensively understand gene-environment interactions in ASD. These models recognize that genetic predispositions, environmental exposures, and epigenetic mechanisms all contribute to the risk of ASD and interact in complex ways[294,295]. Integrative models often incorporate neurobiology, developmental psychology, and epidemiology insights to create a holistic view of ASD etiology. For example, an integrative model might consider how genetic vulnerabilities to neuroinflammation interact with prenatal exposure to maternal infections, leading to epigenetic changes that disrupt brain development and increase ASD risk[296].

These gene-environment interaction models (Table 3) offer valuable insights into the multifaceted nature of ASD. These models emphasize that the development of ASD is not solely determined by genetic or environmental factors but by their complex interplay. Understanding these interactions is crucial for identifying at-risk individuals, developing targeted

Table 3 Comparison between the different gene-environment interaction models in the context of autism spectrum disorder

Model	Key concept	Description	Examples
Diathesis-stress model	Genetic vulnerability plus environmental stressors trigger ASD	Inherited genetic predispositions (diatheses) interact with environmental stressors to manifest ASD	Prenatal stress, maternal infections, or toxin exposure in genetically predisposed individuals lead to the development of ASD
Differential susceptibility model	Genetic variants make individuals more responsive to environmental influences, both positive and negative	Certain genetic profiles heighten sensitivity to environmental conditions, affecting ASD risk and response to interventions	Genetically susceptible children may develop ASD with prenatal toxin exposure but show improvement with enriched early learning environments
Biological sensitivity to context model	Genetic variations influence sensitivity to environmental contexts	Some individuals have heightened biological reactivity to environmental stimuli due to their genetic makeup, impacting neurodevelopment and ASD risk	Children with specific genetic profiles may have increased stress responses to environmental toxins or benefit more from supportive caregiving
Gene-environment correlation model	Genetic predispositions influence exposure to certain environments	Genetic factors shape individuals' environments, through passive, evocative, or active correlations	Parents with ASD traits create environments affecting child development (passive); a child's social difficulties lead to isolation (evocative); a child avoids noisy places (active)
Epigenetic models	Environmental factors modify gene expression through epigenetic mechanisms	Environmental influences like nutrition, toxins, or stress-induced changes in gene expression *via* DNA methylation or histone modification affect neurodevelopment and ASD risk	Prenatal air pollution exposure causes DNA methylation changes in neurodevelopmental genes, influencing ASD risk
Integrative models	Combines genetic, environmental, and epigenetic factors for a holistic understanding of ASD risk	Integrates multiple frameworks, considering genetic vulnerabilities, environmental exposures, and epigenetic mechanisms in ASD development	Interaction of genetic neuroinflammation susceptibility with prenatal maternal infections leads to epigenetic changes and increased ASD risk

This table provides a comparative overview of the key concepts, descriptions, and examples of how each model explains the interaction between genetic and environmental factors in autism spectrum disorder development. ASD: Autism spectrum disorder.

interventions, and informing preventive strategies.

Epigenetic mechanisms

Epigenetic modifications play a crucial role in regulating gene expression without altering the underlying DNA sequence, significantly contributing to the development of ASD. These mechanisms include DNA methylation, histone modification, and non-coding RNA molecules, which can either activate or silence genes, thereby influencing neural development and function[297,298].

DNA methylation typically suppresses gene expression and can be influenced by environmental factors such as prenatal stress, toxins, or nutritional deficiencies. In ASD, aberrant DNA methylation patterns have been observed in genes associated with synaptic function and neurodevelopment[299]. For example, hypermethylation of the *MECP2* gene, critical for brain development and associated with Rett syndrome (an ASD-related disorder), has been identified in some individuals with ASD[300].

Histone modifications alter the chromatin structure and gene accessibility, playing a critical role in gene expression regulation. These modifications can be influenced by external factors such as maternal diet or exposure to pollutants, potentially leading to atypical neural circuitry linked to ASD[301]. Studies have shown that individuals with ASD often exhibit altered histone acetylation and methylation states, disrupting chromatin structure and gene expression, particularly in genes implicated in neural connectivity and plasticity[302].

Non-coding RNAs, including microRNAs, regulate gene expression post-transcriptionally and have been implicated in modulating genes involved in neural connectivity and plasticity. Dysregulation of specific microRNAs that regulate neural development and synaptic function has been found in individuals with ASD, leading to the misregulation of critical brain function genes[303].

Research on epigenetic changes in individuals with ASD has uncovered several key findings. Perini *et al*[304] revealed abnormal DNA methylation patterns in genes involved in synaptic function and neural development, suggesting that epigenetic dysregulation contributes to the neural anomalies observed in ASD. Another study highlighted that individuals with ASD often exhibit altered histone acetylation and methylation states, disrupting chromatin structure and gene expression[305]. Additionally, research into non-coding RNAs, such as microRNAs, has emphasized their role in ASD. Dysregulation of microRNAs that regulate neural development and synaptic function leads to misregulating crucial brain function genes[306]. These studies underscore the importance of epigenetic mechanisms in ASD and suggest that both inherited and environmentally induced epigenetic changes can significantly impact gene expression, contributing to the disorder's pathogenesis[291]. Understanding the interplay between genetic predispositions and epigenetic modifications offers valuable insights into the complex etiology of ASD and highlights potential avenues for early intervention and therapeutic strategies. These findings pave the way for further exploration into epigenetic therapies that could potentially reverse or mitigate some of the effects of these epigenetic alterations in ASD.

Therapeutic implications

The growing understanding of the genetic underpinnings of ASD is revolutionizing therapeutic strategies, moving towards more personalized and targeted approaches. Traditional treatments for ASD have been mainly one-size-fits-all. Still, as we uncover more about the genetic diversity and complexity of ASD, it becomes clear that a more individualized approach is essential[307]. This section explores how these genetic findings are being translated into personalized treatment modalities, offering hope for more effective management and improved outcomes for individuals with ASD.

Personalized medicine: Advancements in genetic research are transforming the treatment landscape for ASD by enabling personalized medicine approaches. Personalized medicine involves tailoring medical treatment to the individual characteristics of each patient, particularly their genetic profile[308]. This approach is highly promising for ASD and is known for its complexity and heterogeneity. Discoveries in genetics have pinpointed numerous genes and genetic variations linked to ASD. These insights allow for the development of targeted therapies that address specific biological pathways disrupted in different individuals[309]. For example, mutations in the *CHD8* gene, associated with certain ASD cases, suggest that therapies modulating chromatin remodeling and gene expression, *e.g.*, using Baf53b, could be beneficial [310]. Similarly, therapies targeting synaptic function may be developed for individuals with *SHANK3* gene disruptions [311].

Pharmacogenomics, which studies how genes affect an individual's drug response, is a critical aspect of personalized medicine. By analyzing a patient's genetic profile, clinicians can predict which medications will be most effective and which might cause adverse reactions[312]. In the context of ASD, this could mean more precise management of co-occurring conditions like anxiety, depression, and ADHD, as well as core autism symptoms. For instance, variations in the serotonin transporter gene (*SLC6A4*) may inform the choice of antidepressants, leading to more effective and tailored treatment plans. Identifying biomarkers-measurable indicators of a biological state or condition-can greatly aid in the early diagnosis and personalized treatment of ASD[313]. Genetic and epigenetic biomarkers provide insights into the severity and specific characteristics of ASD in an individual, guiding personalized intervention strategies. Specific DNA methylation patterns or histone modifications, for example, might serve as biomarkers for particular ASD subtypes, helping to effectively tailor therapeutic approaches[314].

Personalized medicine also extends to non-pharmacological interventions, such as behavioral therapies, dietary adjustments, and environmental modifications. Genetic insights can inform the selection of behavioral therapies that are more likely to be effective[315]. For instance, individuals with mutations in genes affecting social cognition may benefit more from social skills training and interventions focusing on enhancing social interactions[316]. While the promise of personalized medicine is substantial, there are challenges to overcome. The genetic architecture of ASD is highly intricate, involving numerous genes and environmental factors[317]. Comprehensive genetic testing and sophisticated interpretation are necessary to implement personalized approaches effectively[318]. Additionally, ethical considerations, such as genetic privacy and potential discrimination, must be carefully addressed[319]. Future research should aim further to clarify the genetic and epigenetic landscape of ASD, develop advanced tools for genetic testing, and design targeted therapies based on these findings. Collaboration among geneticists, clinicians, and researchers is crucial to translating genetic discoveries into practical, personalized treatment strategies that improve outcomes for individuals with ASD[320].

Current and future therapies: Exploring the genetic underpinnings of ASD is paving the way for innovative therapies that could significantly enhance treatment efficacy. Current therapies for ASD include behavioral interventions, pharmacological treatments, and nutritional strategies[321]. ABA is a widely used behavioral therapy that focuses on improving specific behaviors such as communication, social skills, and adaptive learning skills. Genetic insights can help tailor ABA programs to target specific deficits associated with particular genetic profiles[322]. Social skills training interventions are also essential, especially for individuals with ASD-related genetic variations affecting social cognition[323]. Pharmacological treatments such as antipsychotics and SSRIs are commonly used to manage irritability, aggression, anxiety, and depression in individuals with ASD[324]. Genetic research helps identify those who might benefit most from these medications while minimizing side effects. Nutritional and dietary interventions, such as gluten-free and casein-free diets, are used by some individuals with ASD[325]. Genetic predispositions related to metabolic processes can inform nutritional adjustments to improve gastrointestinal and behavioral symptoms[326].

Future therapies, including gene therapy and epigenetic interventions, hold exciting possibilities. Targeted genetic interventions could potentially correct or mitigate the effects of specific genetic abnormalities, such as those in the *CHD8* or *SHANK3* genes[327]. Epigenetic therapies, such as DNA methylation modulators and histone deacetylase inhibitors, could correct epigenetic dysregulation observed in ASD, potentially reversing abnormal chromatin states and restoring normal gene expression patterns[297]. Pharmacogenomics promises highly personalized medication regimens that maximize efficacy and minimize adverse effects. Understanding variations in the serotonin transporter gene can guide the use of SSRIs and other psychotropic medications[328]. Non-coding RNA-based therapies, such as microRNA modulation, could correct dysregulation in neural development and synaptic function associated with ASD[329].

Recent genetic studies suggest a link between neuroinflammation and ASD. Targeting inflammatory pathways genetically associated with ASD could offer new therapeutic avenues to reduce neuroinflammation and improve neurological outcomes[330]. Stem cell therapy is a burgeoning field with the potential to regenerate or repair neural tissue affected by genetic mutations associated with ASD. Research is ongoing to determine the feasibility and safety of using stem cells to address neurodevelopmental deficits in ASD[331]. Continued research is essential to translate genetic findings into practical therapies. This includes clinical trials to evaluate the efficacy and safety of new genetic and epigenetic therapies, biomarker discovery to track treatment responses and tailor interventions, and interdisciplinary collaboration between geneticists, neuroscientists, and clinicians to integrate genetic data into therapeutic practices[332].

Genetic research is driving significant advancements in the treatment of ASD, offering hope for more effective and personalized therapies. Current treatments informed by genetic insights are already improving outcomes, while future interventions hold the promise of addressing the underlying genetic causes of ASD[283]. As research progresses, these innovative therapies will continue to evolve, providing more targeted and individualized care for individuals with ASD.

Future directions and research challenges

Unresolved questions: Despite significant advances in understanding the genetic basis of ASD, many questions remain unresolved, highlighting crucial areas for future research. Identifying these gaps is essential for guiding ongoing and future studies to deepen our understanding of ASD and improve diagnostic and therapeutic strategies. One key question revolves around the full spectrum of genetic variations contributing to ASD. While numerous risk genes and mutations have been identified, many cases of ASD cannot be explained by known genetic factors alone. This suggests that there are still undiscovered genetic components, possibly rare variants or non-coding regions, that play a critical role in ASD[42]. WGS and advanced bioinformatics tools are needed to uncover these hidden genetic elements.

Another significant gap is the lack of understanding of the precise mechanisms by which identified genetic mutations lead to ASD. Although specific genes and pathways have been implicated, the detailed biological processes linking these genetic changes to ASD symptoms remain unclear. This includes elucidating how genetic mutations affect neural development, synaptic function, and brain connectivity. Advanced imaging techniques and animal models can provide valuable insights into these mechanisms[333]. Another area requiring further exploration is the interaction between genetic and environmental factors in ASD development. While studies have shown that environmental factors such as prenatal stress, exposure to toxins, and nutritional deficiencies can influence ASD risk, the exact nature of these interactions is not well understood[334]. Longitudinal studies and integrative approaches combining genetic, epigenetic, and environmental data are needed to clarify these complex relationships.

Additionally, there is a need to investigate the heterogeneity of ASD. ASD is a highly variable condition with a wide range of symptoms and severities. Understanding the genetic basis of this heterogeneity is crucial for developing personalized treatment approaches. Research should focus on identifying genetic and epigenetic markers that can predict symptom profiles and treatment responses in individuals with ASD[19]. The role of epigenetic modifications in ASD is an emerging field with many unanswered questions. While aberrant DNA methylation, histone modifications, and non-coding RNAs have been linked to ASD, more research is needed to understand how these epigenetic changes are regulated and interact with genetic predispositions[298]. Identifying specific epigenetic alterations associated with different ASD subtypes can provide new targets for therapeutic interventions.

Finally, translating genetic research into clinical practice poses significant challenges. While genetic testing can identify risk factors and guide personalized treatments, the accessibility and cost of such tests remain barriers. Developing affordable and widely available genetic tests is essential for integrating genetic insights into routine clinical care[36]. Moreover, ethical considerations related to genetic testing, such as privacy, consent, and the potential for genetic discrimination, must be addressed[335]. Future research must address these unresolved questions and gaps in knowledge to advance our understanding of ASD. Collaborative efforts integrating genomics, neuroscience, environmental sciences, and clinical research are crucial for unraveling the complex etiology of ASD and improving outcomes for individuals with the disorder[307].

Emerging technologies

Emerging technologies such as CRISPR and advanced bioinformatics tools hold immense potential to address the existing gaps in ASD research and pave the way for groundbreaking discoveries and treatments. These innovative approaches can help unravel the complexities of ASD, offering new insights and therapeutic opportunities[336].

CRISPR-Cas9, a powerful genome-editing tool, enables precise modification of DNA sequences, allowing researchers to investigate the functional consequences of specific genetic mutations associated with ASD[337]. By creating animal models or cell lines with targeted genetic alterations, scientists can study the resulting phenotypic changes and understand how these mutations contribute to ASD[338]. This technology can also be used to correct genetic defects *in vitro*, providing a potential pathway for developing gene therapy approaches for ASD. Additionally, CRISPR can be employed to explore the role of non-coding regions of the genome, which are often overlooked but may contain regulatory elements crucial for neural development and function[339].

Advanced bioinformatics tools are essential for analyzing the vast amounts of genomic data generated by next-generation sequencing techniques such as WGS and WES[340]. These tools can identify novel genetic variants and potential risk genes associated with ASD by integrating and comparing data from multiple studies. Machine learning algorithms and artificial intelligence can enhance the interpretation of complex genetic data, uncovering patterns and correlations that may be missed by traditional analysis methods[341]. Bioinformatics approaches can also facilitate the study of gene-environment interactions by integrating genomic, epigenomic, and environmental datasets, providing a comprehensive understanding of the multifactorial nature of ASD[342].

scRNA-seq is another emerging technology that offers insights into the brain's cellular heterogeneity. Researchers can identify specific cell types and states affected by ASD-associated genetic mutations by analyzing gene expression at the single-cell level. This technology can reveal how different cell populations contribute to the pathology of ASD and highlight potential cellular targets for therapeutic interventions[343]. Furthermore, developing organoids (three-dimensional cultures derived from stem cells) allows for the modeling of human brain development *in vitro*. Brain organoids can mimic the early stages of neural development, providing a platform to study the effects of genetic and environmental factors on brain formation and function[344]. These models can be used to screen potential drugs and evaluate their effects on neural development, offering a promising avenue for preclinical testing of new treatments for ASD.

In addition to these technologies, advancements in neuroimaging techniques, such as functional magnetic resonance imaging and diffusion tensor imaging, can enhance our understanding of the structural and functional connectivity in the brains of individuals with ASD[345]. Combining genetic data with neuroimaging findings can elucidate how genetic variations impact brain structure and function, leading to the identification of biomarkers for early diagnosis and targeted interventions[346]. Integrating these emerging technologies into ASD research promises to address key gaps in our knowledge and transform our approach to understanding and treating ASD. By leveraging CRISPR, advanced bioinformatics, single-cell analysis, organoids, and neuroimaging, researchers can unravel the intricate genetic and biological underpinnings of ASD, ultimately leading to more effective and personalized therapies for individuals affected by this complex disorder[347].

Collaborative research: Advancing our understanding of ASD and developing effective treatments necessitate a concerted effort that spans multiple disciplines and countries. The complexity of ASD's genetic underpinnings and its interaction with environmental factors demand a collaborative research approach, bringing together diverse expertise and resources[348]. The necessity of multidisciplinary collaborations in ASD research cannot be overstated, as they allow for integrating knowledge from various fields such as genetics, neuroscience, psychology, bioinformatics, and clinical medicine. Geneticists and molecular biologists can identify and characterize genetic mutations associated with ASD, while neuroscientists can study how these mutations affect brain development and function[349]. Psychologists and psychiatrists can provide insights into the behavioral and cognitive aspects of ASD, helping to link genetic findings with clinical presentations. Bioinformaticians and data scientists can manage and analyze large datasets, revealing patterns and correlations that are critical for understanding the genetic architecture of ASD[350]. Clinicians can translate these findings into diagnostic tools and therapeutic interventions, ensuring that research outcomes benefit patients directly. The necessity of this collaborative effort is clear, and it is through such integration that we can truly advance our understanding and treatment of ASD.

International collaborations are equally important, enabling researchers to access larger and more diverse populations. Genetic studies require extensive data to identify rare variants and to ensure findings are applicable across different ethnic and genetic backgrounds. International consortia, such as the Autism Genome Project, have already made significant strides by pooling resources and data from research groups worldwide[351]. These collaborations can enhance the statistical power of genetic studies and lead to more robust and generalizable findings. Moreover, sharing data and methodologies across borders can accelerate the pace of discovery and avoid duplication of efforts[243]. Collaborative research also facilitates the sharing of advanced technologies and expertise. Institutions in different countries may have unique strengths and capabilities, and pooling these resources can lead to more comprehensive and innovative approaches to ASD research. For example, a research group with expertise in CRISPR technology can partner with a team skilled in neuroimaging to investigate the effects of specific genetic mutations on brain structure and function[352]. Similarly, collaborations with pharmaceutical companies can help translate genetic discoveries into new treatments, leveraging their expertise in drug development and clinical trials[353].

Furthermore, collaborative efforts can address the ethical, legal, and social implications of genetic research on ASD. Multidisciplinary teams can work together to ensure that research practices are ethical and that findings are communicated responsibly to the public. International collaborations can help harmonize regulatory standards and ensure that advances in genetic research benefit individuals with ASD globally[354]. To facilitate these collaborations, funding agencies and research institutions must prioritize and support initiatives that promote teamwork and data sharing[355]. Grant programs encouraging multidisciplinary and international projects can provide researchers with the necessary resources and incentives to work together. Establishing centralized databases and biobanks accessible to the global research community can also enhance collaboration and data integration[356].

Study limitations

This review, while comprehensive in its scope, has several limitations that must be acknowledged. Firstly, the rapid pace of advancements in genetic and epigenetic research means that some of the findings and technologies discussed may quickly become outdated as new discoveries emerge. Additionally, the review relies heavily on studies with varying methodologies, sample sizes, and population demographics, potentially leading to inconsistencies in the reported findings. The complexity and heterogeneity of ASD also pose significant challenges; the review attempts to cover a wide range of genetic and epigenetic factors, but this breadth may come at the expense of depth in some areas. Furthermore, the review predominantly focuses on genetic and epigenetic aspects, potentially underrepresenting other crucial factors such as environmental influences and their interactions with genetic predispositions. While efforts have been made to include various aspects of ASD research, selecting studies and sources might have introduced a bias, potentially overlooking relevant findings from smaller or less-publicized research efforts. The review also touches upon emerging therapies and personalized medicine. Still, the practical implementation and accessibility of these advancements are not fully addressed, which could limit the applicability of the discussed interventions in real-world settings. Finally, while mentioned, ethical considerations surrounding genetic testing and personalized medicine are not explored in depth. Issues such as genetic privacy, consent, and the potential for discrimination require more comprehensive discussion to ensure the responsible application of genetic insights. In conclusion, while this review provides a broad overview of the genetic and epigenetic underpinnings of ASD and their therapeutic implications, it is constrained by the rapidly evolving nature of the field, potential methodological biases, and the need for a more in-depth exploration of certain areas and ethical considerations.

CONCLUSION

This systematic review highlights significant advancements in understanding the genetic and epigenetic underpinnings of ASD and their therapeutic implications. Genetic discoveries, such as mutations in *CHD8* and *SHANK3*, and epigenetic factors like DNA methylation and non-coding RNAs, reveal the complex mechanisms contributing to ASD. These insights pave the way for personalized medicine, enhancing the precision of current treatments and informing future therapies like gene editing and epigenetic modulation. Emerging technologies, including CRISPR and advanced bioinformatics, accelerate research, offering deeper insights into genetic mutations. Collaborative efforts across disciplines and countries are crucial for advancing our understanding and translating findings into clinical practice. Despite these advancements, challenges remain, including the complexity of ASD's genetic architecture, gene-environment interactions, and ethical considerations of genetic testing. Continued research and collaboration promise more effective, personalized, and comprehensive approaches to managing ASD, improving outcomes and quality of life for those affected.

FOOTNOTES

Author contributions: Al-Biltagi M coordinated the project, contributed to the design, supervised the literature search, and ensured data integrity; Saeed NK was involved in the methodology, literature screening, data extraction, and manuscript writing; Bediwy AS participated in the literature search, data extraction, preliminary analyses, and manuscript drafting; Bediwy EA oversaw technical aspects, quality control, and statistical analysis and contributed to the manuscript, particularly in the analysis sections; Elbeltagi R addressed ethical considerations, contributed to the literature search and data extraction, and provided insights during data synthesis. All authors critically revised the manuscript and approved the final version, agreeing to be accountable for all aspects of the work. Al-Biltagi M and Saeed NK contributed equally to this work as co-first authors.

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LETTER TO THE EDITOR

Transabdominal intestinal ultrasound and its parameters used in the assessment of pediatric inflammatory bowel disease

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Abstract

This article extends on the use of transabdominal intestinal ultrasound in diagnosing pediatric inflammatory bowel disease. Some of the more essential features used in assessing bowel inflammation, such as hyperemia and wall thickness on ultrasound, are expanded upon from the publication on imaging and endoscopic tools in pediatric inflammatory bowel disease.

Key Words: Inflammatory bowel disease; Intestinal ultrasound; Limberg score; Hyperemia; Bowel wall thickness

Core Tip: This letter to the editor discusses some of the most important parameters of intestinal ultrasound used in assessing inflammatory bowel disease in children.

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TO THE EDITOR

I read with interest an important focused review by Hudson *et al*[1] that mentioned the use of intestinal ultrasound (IUS) and some of its characteristics in assessing pediatric inflammatory bowel disease (IBD). Items used to assess bowel inflammation on IUS include echostratification, motility, hyperemia, and bowel wall thickness (BWT)[1,2]. Of these, BWT and hyperemia are of the most significance.

Table 1 Mean bowel wall thickness modified from van Wassenaer *et al*[5]

Age in years	Jejunum	Ileum	Cecum	Ascending colon	Transverse colon	Descending colon
0–4	1.0 [0.4]	1.3 [0.2]	1.1 [0.2]	1.1 [0.2]	1.0 [0.2]	1.1 [0.2]
5–9	0.8 [0.1]	0.9 [0.1]	1.1 [0.1]	1.1 [0.2]	1.2 [0.2]	1.2 [0.2]
10–14	0.8 [0.1]	1.0 [0.2]	1.4 [0.2]	1.3 [0.3]	1.3 [0.2]	1.3 [0.2]
15–19	0.9 [0.1]	1.1 [0.1]	1.6 [0.2]	1.4 [0.2]	1.4 [0.2]	1.4 [0.2]

Data are mm [standard deviation].

Table 2 Limberg classification of bowel wall vascularity in inflammatory bowel disease

Grade	Description
0	Normal bowel wall with no thickening, well-delineated mural stratification, no color Doppler signal
1	Wall thickening (hypoechoic wall thickening and partially obscured mural stratification) and absent mural flow
2 (hypo-flow)	Wall thickening with intermittent (or spot) increases in vascularity
3 (hyper-flow)	Wall thickening with protracted regions of increased vascularity
4 (hyper-flow)	Color Doppler flow signals in both the bowel wall and surrounding mesenteric fat

BWT

BWT is considered the most important characteristic of IUS because bowel wall swelling indicates inflammation[3,4]. In healthy children, BWT ranges from approximately 0.8 mm to 1.9 mm in the small bowel and 1.0 mm to 1.9 mm in the colon, according to a pooled meta-analysis (Table 1)[5]. In children with IBD, cutoff values range from 2.5 mm to 3 mm; however, a consensus value is yet to be established by the scientific community[6]. Another study by Chiorean *et al*[7] revealed that children with Chron's disease had an increased thickness of the ileocecal bowel wall (> 3 mm) compared to healthy age-matched controls. With these existing data, the optimal cutoff value may be defined at 2–2.5 mm.

For the most accurate value of BWT, it is recommended to begin measurement at the lumen-mucosa interface and stop at the hypo-hyperechoic interface between the muscularis propria and the serosa[8]. BWT should always be measured by IUS in clinical suspicion of IBD as it predicts the severity of disease activity by visualizing all five layers of the bowel wall [6,8,9]. It is important to note that despite the importance of BWT, it is not pathognomonic for IBD[7,8]. A large spectrum of other diseases, such as vascular, neoplastic, or infectious conditions, should also be considered. Physicians should use clinical correlation in conjunction with imaging findings to arrive at the correct diagnosis.

HYPEREMIA

Hyperemia is a sign of active disease in an inflamed intestine and is the second most common parameter used to evaluate bowel wall vascularity[9,10]. It is measured with Doppler sonography, which shows increased vascular signals in the submucosa that penetrate the muscularis propria in the clinical context of IBD[11,12]. An increased signal on Doppler predicts disease severity in both pediatric and adult populations[5,11,12].

Hyperemia can be scored semi-quantitatively or dichotomously using the modified Limberg score (Table 2), which measures vascularity[13,14]. This score differentiates four grades of hyperemia with an abnormal score of 2 or above[15]. Getting a Limberg value on IUS is recommended as it correlates well with endoscopic and histopathologic disease severity[16]. Given the semi-quantitative nature of the scoring system, there is a potential for inter-rater variability[17]. Additionally, Doppler sonography can be compromised by occasional tissue motion artifacts[18]. Due to the combination of these events, other advanced quantitative measurements have been proposed. It is recommended to set the color Doppler pulse repetition frequency to 5–7 cm/s to maximize the capture of flow in small vessels/capillaries with a set gain to remove motion artifacts[2]. Although there is no standard protocol for the measurement of color Doppler in children, it is important and should be measured given its ability to predict disease severity.

CONCLUSION

IUS has revolutionized the way physicians assess and monitor pediatric IBD. It is less expensive and invasive than endoscopic procedures and is a valuable tool to evaluate disease activity, complications, and response to therapy. BWT and hyperemia are the two most important features used in assessing bowel inflammation on ultrasound. Emerging

research in the field suggests comparable specificity and sensitivity regarding IUS and colonoscopy. Although more extensive prospective data are needed, IUS is expected to provide a shift away from invasive procedures used in the assessment and management of pediatric IBD.

FOOTNOTES

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